



Markets for Pharmaceutical Products¹

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Abstract

This chapter describes the market for pharmaceuticals, which exceeded \$500 million in sales in 2010. The industry is also characterized by extensive regulation of almost every activity, from product development through manufacturing and marketing, which we summarize. We next describe the industry's market structure. Large, fully integrated, multinational firms that develop and market new drugs have historically dominated the industry, but the emergence of smaller firms focused on the application of biotechnology to drug development as well as firms that specialize in low-cost production of off-patent "generic" drugs has had an important impact on the market structure of the industry. The last two decades have seen a shift towards vertical specialization as well as many horizontal mergers. We discuss trends in the productivity of pharmaceutical research and incentives for innovation. We then summarize the pricing and marketing of drugs in the US and several other countries.

Keywords: pharmaceuticals; market structure; regulation; innovation; productivity; competition

JEL Codes: L65; I11; L22; I18; D12; D43



1. INTRODUCTION

The pharmaceutical industry generated more than \$500 billion in sales in 2010, and sustained its position as one of the most research-intensive industries. Studies of the contribution of new pharmaceutical treatments to social welfare generally find that society has derived large benefits from these innovative efforts. However, the industry now faces concerns about access to new treatments and a potential decline in innovation.

The industry is also characterized by extensive regulation of almost every activity, from product development through manufacturing and marketing. Some of these regulations have unintended consequences as a result of strategic responses by firms. Increased globalization of research, development, and manufacturing poses new challenges to regulators, as the cost of monitoring compliance in facilities around the world is considerable, and regulations may have implications beyond the borders of the country for which they were adopted. In addition, changes in technology may necessitate adjustments to regulatory structures created to address market conditions several decades ago.

There is considerable heterogeneity across firms, both in size as well as business strategy. Large, fully integrated multinational firms that develop and market new drugs have historically dominated the industry, but the emergence of smaller firms focused on the application of biotechnology to drug development as well as firms that specialize in low-cost production of off-patent "generic" drugs has had an important impact on the market structure of the industry. The last two decades have seen a shift towards vertical specialization as well as many horizontal mergers.

This chapter describes the market for pharmaceuticals. We begin with a general summary of important regulatory features, and then present some statistics on pharmaceutical expenditures in major markets. We next describe the industry's market structure, including market definitions, the costs of drug development and marketing, the evolving vertical chain, and incentives for innovation. We then summarize the pricing and marketing of drugs in the US and several other countries. We conclude with a discussion of current regulatory challenges in the industry.



2. OVERVIEW OF REGULATION

2.1. Safety and Efficacy

Pharmaceuticals may be considered “experience” or “credence” goods, for which the consumer has less information about quality than the producer. A patient is usually unable to determine whether a pill is safe and effective just from examining it, and sometimes even after consuming it. As is well known in economics, this information asymmetry can lead to the “lemons problem” described by [Akerlof \(1970\)](#), wherein the quality of the product falls to inefficiently low levels. One solution to this market failure is the provision of information about a product's quality from a trusted third party, or, in the case of pharmaceuticals, a government agency's regulatory approval process.

In all developed countries, firms must receive regulatory approval to market a pharmaceutical product. The approval process generally involves demonstrating the safety and efficacy of a product. In the United States, this function is the responsibility of the Food and Drug Administration (FDA). The equivalent of the FDA in the European Union is the European Medicines Agency (EMA), though individual member states have their own authorities as well; in Japan, it is the Ministry of Health and Welfare (MHW). Over the last several decades, these agencies and their counterparts in other countries have harmonized their rules and regulations to some extent. For example, the EMA and FDA do work together on some issues such as Good Manufacturing Practices, post-marketing surveillance, and scientific advice, among others.² However, they do not always agree. The tolerance for Type I (approving a harmful drug) vs. Type II error (rejecting a beneficial drug) varies across agencies, and arguably over time within the same agency. Importantly, trade is generally prohibited between two countries even when both have approved the same pharmaceutical. Arbitrage of price differences across countries, or “parallel trade,” is prohibited by

² http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/09/news_detail_001112.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1

intellectual property law or regulatory safety concerns, with the exception of trade between EU member states. Each country may therefore be considered a separate market.

For the sake of brevity, we focus on the FDA approval process here rather than attempt a comprehensive description of all countries; as noted above, efforts at international harmonization mean that the process is not very different elsewhere. Firms that wish to market a chemical or biological product that has not previously been sold in the US must file a New Drug Application (NDA) or a Biologics License Application (BLA) with the FDA. The dossier includes information about the applicant, manufacturing, preclinical and clinical trial data, and labeling information. Clinical trials to demonstrate safety and efficacy are the most expensive component of the application, and we describe this process in greater detail in section 4. The review process can be quite long, and in response to industry concerns about regulatory delays, the US adopted the Prescription Drug User Fee Act (PDUFA) in 1992, which mandated performance goals for the FDA while allowing the FDA to charge fees to applicants. [Berndt et al. \(2005\)](#) find that PDUFA contributed significantly to the decline in review times (from an average of 24.2 to 14.2 months) observed since the early 1990s. However, [Olson \(2008\)](#) finds that faster reviews are accompanied by an increase in reported adverse events following the marketing of a new drug.

The process is different for so-called “generic” drugs that are no longer under patent protection.³ Prior to the passage of the Hatch–Waxman Act in 1984, all firms wishing to market a prescription pharmaceutical product were required to submit NDAs, even if the chemical had been previously approved for a different firm. Thus, even for off-patent drugs, winning regulatory approval required the full dossier of clinical trials. To encourage competition in off-patent (generic) drugs, the Hatch–Waxman Act established the Abbreviated New Drug Application (ANDA), which requires proof that the applicant’s product is bioequivalent to the original product approved as an NDA but does not require clinical trials to demonstrate safety and efficacy. In order to provide an incentive for generics to challenge weak brand patents, the Hatch–Waxman Act offers 180 days of exclusivity to the first generic to file an ANDA claiming that one of the brand’s patents is either not infringed by the generic or is invalid, which is referred to as a “Paragraph IV” challenge. Thus, the Hatch–Waxman Act sets up a race among generics to be the first firm to file and win the six-month “duopoly prize.”

Pharmaceutical companies that wish to enter the European Union market can choose to apply for marketing authorization for a new drug in two ways. The first, which is required for applications with a biologic component or that uses

³ The term generic refers to the practice of using the International Nonproprietary Name (INN) for the chemical, in contrast to a “branded” drug that is marketed with a shorter, trademarked name. For example, atorvastatin is the INN corresponding to Pfizer’s Lipitor.

recombinant DNA technology but optional for others, is a single application to the EMA for approval in all EU member states. The EMA has 210 days to evaluate the evidence and makes a decision to recommend approval or not to the European Commission.⁴ The second approach to market entry, known as the mutual recognition procedure, involves an application to the local authority in a member state. If a drug is authorized by that state's marketing authority, other member states should also grant authorization at the firm's request, unless they can justify an objection on scientific grounds. Indeed, one of the EMA's functions is to help arbitrate among states whose regulatory standards do not match up.⁵

Post-market surveillance of safety in both the United States and Europe is a key component of drug regulation. Given that clinical trials are only able to assess a drug's impact on a small subset of the population at large, many of a drug's side effects are not known until it is released into the market. The FDA and EMA both have a set of detailed post-marketing reporting requirements pharmaceutical companies must comply with. There is, however, an important distinction drawn by both agencies between, to use the FDA's terms, post-market requirements (PMRs) and post-market commitments (PMCs). The EMA uses the term "Specific Obligations" to describe PMRs and "Follow-up Measures" for PMCs. Post-marketing *requirements*, as their name suggests, are directives issued by the FDA that must be followed within the designated timeframe in order for a drug-sponsor to continue to be able to market and sell its drug. In contrast, marketing authorization does not require the completion of PMCs; unsurprisingly, some of the most recent criticism of FDA post-market surveillance is that so many PMCs go unfulfilled. A study by the Tufts Center for Drug Study and Development found that the average drug in the US has almost nine post-market study commitments attached to it, while the average European drug has almost 11, and the average Japanese drug almost two.⁶

Post-market surveillance is arguably most concerned with the safety of the approved drug, given that it is being used by a population much larger than that used in pre-approval clinical trials. The FDA requires all drug sponsors to support reporting systems where physicians or other providers can report adverse drug reactions and other reportable events. A survey of drug manufacturers found that mean spending on post-marketing safety per company was \$56 million (0.3% of sales) in 2003. The innovator must submit a report to the FDA within 15 days of a report of an adverse reaction to a drug. The FDA also maintains Medwatch, a website that allows consumers to submit complaints about the safety of drugs currently on the market. FDA officials investigate the claims and take action against drug sponsors accordingly. Criticism of post-marketing surveillance in the US has focused on the FDA's lack of

⁴ Details about the agency can be found at www.ema.europa.eu.

⁵ http://www.euro.who.int/document/e83015_5.pdf

⁶ <http://www.medicalnewstoday.com/articles/114749.php>

sufficient authority to ensure compliance with post-marketing requirements as well as the general underreporting of adverse effects. There are few economic studies in this interesting area. One paper by David et al. (2010) models and finds evidence for increased adverse drug reactions accompanying increased (less appropriate) promotion of a drug.

2.2. Pricing and Reimbursement

Outside the United States, there is a second regulatory hurdle to clear in developed markets and some developing countries. In order for a new drug to be eligible for reimbursement by national insurance programs, the firm must negotiate a price with the national government agency. This often requires presenting economic evidence on cost effectiveness or negotiating over price. We discuss several examples in more detail in section 5.

It is important to note that pricing and reimbursement policies vary much more across countries than do the standards required for marketing approval. There has been far less effort to harmonize regulatory approaches. In the EU, for instance, the EMA can approve a new drug for all member states, but a firm must still negotiate pricing and reimbursement with each individual country. This has a number of important consequences, to which we return later.

2.3. Restrictions on Marketing, Prescribing, and Dispensing

Demand for pharmaceuticals is complex for many reasons, not least of which is the involvement of multiple decision makers: physicians, pharmacists, insurers, and patients. Pharmaceutical firms, like firms in many other industries, engage in marketing efforts to persuade decision makers. Regulatory agencies recognize that an innovator firm is unlikely to be an unbiased source of information about its products and their merits compared to the competition. The FDA and its counterparts in other countries therefore strictly regulate what a firm can claim about a drug in its marketing efforts to ensure that the marketing is not false or misleading.⁷ The NDA for a new drug is approved with a label that contains the claims about efficacy that the FDA has approved, as well as side effects and warnings. A large component of promotional expenditure goes on “detailing,” short visits to physician offices by representatives of the firm who discuss a new or existing drug with the doctor. For a widely used drug, there would typically be hundreds of detailing representatives visiting thousands of physicians across the country. Each detailing representative is typically paid on a steep incentive scheme, whereby financial compensation is linked to increased sales

⁷ <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm> is the link to the Division of Drug Marketing, Advertising, and Communications (DDMAC) at the FDA.

in a geographic territory or among a set of physicians. In the US, promotional visits to the physician may not focus on the price of the drug because of concerns that this encourages inappropriate prescribing. In other countries, regulations limit the amount of time detailing representatives may spend with physicians. The combination of the incentives, the impossibility of direct monitoring, and the enormous amount of non-FDA approved information available on new drugs means that achieving perfect compliance with the FDA's regulations on detailing is a challenge. Direct-to-consumer advertising (DTCA) of pharmaceuticals is not permitted in developed countries with the exception of New Zealand and the US.

Most countries separate prescribing and dispensing to address potential agency problems. That is, dispensing is the responsibility of a pharmacist, so that the physician's choice between pharmaceutical treatments is not influenced by a profit motive. There are exceptions: US physicians who administer drugs in their offices are reimbursed, and in many Asian markets there is a tradition of physicians who dispense the drugs they prescribe. Separation of these practices does mean that physicians are often unaware of the prices of drugs they prescribe, so while they may have less incentive to prescribe treatments than would be the case if they profited directly from doing so, physicians do not necessarily have incentive to prescribe relatively inexpensive or cost-effective treatments.

Pharmacists must dispense the chemical, dosage form and strength specified in a physician's prescription. For drugs with generic competition, the pharmacist has some discretion. In order to encourage the use of generic drugs, many US states and some (not all) developed countries require the pharmacist to fill a prescription with a generic version if one is available; other jurisdictions may encourage but not require generic substitution. A pharmacist's incentive to supply the generic version with the lowest cost depends on additional country-specific regulations and practices. In many European countries, pharmacists are subject to profit controls. Some countries (for example, Germany and the Netherlands) use a system of awarding the entire national market for a drug to a single generic supplier that tenders the lowest bid, leaving the individual pharmacist no choice.



3. BASIC FACTS ON PHARMACEUTICAL EXPENDITURES AND PRICES

In the United States in the 1980s, pharmaceutical expenditure as a percentage of total health spending was about 5–6%. However, the proportion increased significantly during the 1990s and early 2000s. From 2004 onwards, pharmaceutical expenditure as a percentage of total health care spending in the United States has been

approximately 11 to 12 percent,⁸ five to six percentage points below the OECD member-nation average of 17 percent. In some countries such as Korea, Hungary, and Poland, however, pharmaceutical expenditure accounts for a far greater portion of total health spending. The modest share for the US is driven by a large denominator, not a low absolute expenditure on pharmaceuticals. If we examine a related measure, per capita expenditure on pharmaceuticals, the US in 2005 ranked the highest among OECD countries, spending USD PPP 792 per capita. Canada, the next highest ranking country, spent USD 589 per capita. Two years later, in 2007, the Commonwealth Fund reported that US prescription drug spending per capita had increased to USD 878. The high growth rates of biologic prices and usage will likely cause total US expenditure to continue growing. [Table 12.1](#) shows per capita pharmaceutical expenditures for OECD countries from 1990 to 2008.

The US is the largest market for pharmaceuticals, accounting for about half of global sales for most of the previous three decades. Historically, Japan has been the second, followed by Germany, France, and the United Kingdom; China now holds the number two position. Pharmaceutical industry sales growth averaged around 12–13 percent between 1987 and 1999 ([Berndt, 2002](#)). Since 2000, IMS Health reports that sales in the US, Japan, and Europe have been rather flat (less than 4 percent per year), though Latin America, China, and other emerging markets show much higher sales growth. There has been some work attempting to determine whether price increases, quantity increases, introduction of new products, or some other force has driven that growth. [Berndt \(2002\)](#) has shown that from 1994 to 2000, “. . .price growth accounted for only about one-fifth of revenue growth (2.7 percentage points out of 12.9%), with the remaining four-fifths reflecting volume/mix changes in utilization rates for incumbent drugs, as well as expenditures on new pharmaceuticals. Hence, in recent years, price increases have been relatively less important, and instead, quantity growth—greater utilization of incumbent and new products—has been the primary driver of increased spending” (p. 48). [Berndt](#) argues that increased quantity growth is a function of “increased drug insurance benefit coverage and enhanced marketing efforts.” Expenditures on new products may reflect the changing nature of medicine and science, which now allows many more diseases to be treated with pharmaceutical products. Indeed, the impetus for including prescription drug coverage in the Medicare Program (Part D) was financial risk to the elderly. When Medicare began in 1965, drugs were a small part of health care spending: 10.7 percent in 1960 and 8.2 percent in 1970, according to [Berndt \(2002\)](#). In the years since, expenditures on pharmaceuticals became a

⁸ <http://www.cbo.gov/ftpdocs/106xx/doc10681/DrugR&D.shtml>, <http://www.commonwealthfund.org/Content/Charts/Chartbook/Multinational-Comparisons-of-Health-Systems-Data-2008/P/Percentage-of-Total-Health-Care-Spending-on-Pharmaceuticals-1996-and-2006.aspx>

Table 12.1 Pharmaceutical Expenditures as Percent of Health Expenditures in OECD Countries

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Australia	12.2	12.4	12.7	13.3	13.8	14.8	15.1	14.5	15.0	14.8	14.3	14.3	14.3	
Austria	9.4	9.7	10.9	11.4	12.0	12.3	12.5	12.8	13.3	13.0	13.0	13.1	13.3	13.3
Belgium	16.2	15.5	15.8						16.0	16.4	15.9	16.5	15.0	15.1
Canada	13.9	14.1	14.8	15.3	15.6	15.9	16.2	16.6	17.0	17.3	17.2	17.3	17.2	17.2
Czech Republic	25.1	25.0	24.9	22.9	23.0	23.4	24.0	23.9	24.2	24.8	24.8	22.8	21.5	20.4
Denmark	9.1	8.9	9.0	9.0	8.7	8.8	9.2	9.8	9.1	8.7	8.6	8.5	8.6	
Estonia					19.5	22.3	25.2	26.5	24.0	25.4	23.9	23.5	21.4	20.7
Finland	12.7	13.2	13.6	14.0	14.8	14.7	15.0	15.2	15.3	15.5	15.5	14.3	14.1	14.4
France	15.0	14.8	15.0	15.5	16.0	16.5	16.9	16.8	16.7	16.8	16.7	16.5	16.5	16.4
Germany	12.8	13.0	13.1	13.5	13.5	13.6	14.2	14.4	14.4	13.9	15.1	14.8	15.1	15.1
Greece	15.7	16.1	16.2	13.9	14.4	18.9	18.0	18.8	20.4	22.0	21.5	22.7	24.8	
Hungary	25.0	26.0	25.9				28.5	27.6	27.5	28.8	31.1	31.7	31.1	31.6
Iceland	13.4	14.0	15.1	14.1	13.6	14.5	14.1	14.0	15.2	15.4	14.4	14.2	13.5	13.9
Ireland	11.4	12.1	11.9	12.4	13.2	14.1	14.3	14.5	14.9	15.6	16.5	17.4	17.7	17.3
Italy	20.7	21.1	21.2	21.5	22.1	22.0	22.5	22.5	21.8	21.2	20.2	19.8	19.3	18.4
Japan	22.3	21.6	20.6	18.9	18.4	18.7	18.8	18.4	19.2	19.0	19.8	19.6	20.1	
Korea	26.1	25.9	25.8	24.6	24.5	25.9	25.2	25.8	25.8	26.0	25.5	25.4	24.5	23.9
Luxembourg	12.0	11.5	12.6	12.3	11.9	9.1	10.0	9.3	10.1	9.5	9.2	8.8	9.1	9.1
Mexico					18.6	19.4	19.5	21.2	25.2	26.1	25.4	26.3	28.2	28.3
Netherlands	11.0	11.0	11.0	11.2	11.4	11.7	11.7	11.5						
New Zealand	14.8	14.5	14.4							10.4	10.4	11.0	10.2	9.6
Norway	9.0	9.1	9.1	8.9	8.9	9.5	9.3	9.4	9.2	9.4	9.1	8.7	8.0	7.6
Poland								28.4	30.3	29.6	28.0	27.2	24.5	22.6
Portugal	23.6	23.8	23.8	23.4		22.4	23.0	23.3	21.4	21.8	21.6	21.8		
Slovak Republic					34.0	34.0	34.0	37.3	38.5	31.4	31.9	29.7	27.9	27.6
Slovenia								20.9	20.5	20.7	20.6	20.5	19.8	18.7
Spain	19.2	19.8	20.8	21.0	21.5	21.3	21.1	21.8	23.2	22.7	22.3	21.6	21.0	20.5
Sweden	12.3	13.6	12.4	13.6	13.9	13.8	13.9	14.0	13.8	13.9	13.7	13.7	13.4	13.2
Switzerland	10.1	10.2	10.5	10.4	10.6	10.8	10.7	10.4	10.6	10.5	10.6	10.4	10.3	
Turkey					26.2	26.6								
United Kingdom	15.3	15.6	15.9			14.1	13.9	13.5	13.5	13.2	12.8	12.3	12.2	11.8
United States	8.7	9.0	9.5	10.0	10.8	11.3	11.7	12.0	12.1	12.2	12.0	12.2	12.0	11.9

significant burden on the elderly, as we see in the current 12 percent pharmaceutical expenditure share.



4. MARKET STRUCTURE

4.1. Supply Side

4.1.1. Drug Development and Production

The process of developing a new drug is long and expensive. New drugs do not result from R&D spending in a predictable way. Rather, innovation is stochastic. In addition, the productivity of R&D changes over time due to advances in basic science and research techniques. Thus, the enterprise of inventing innovative biopharmaceuticals is inherently risky. Its cost structure—large fixed and sunk costs of drug discovery and development and relatively low marginal costs of production, the details of which we describe below—is another important feature of the pharmaceutical industry. Imitation costs are also quite low: once a product is known to be safe and effective, it can be backward-engineered with little difficulty. If competition from imitators drives price down to marginal cost, as standard industrial organization models would predict, then firms would be unable to recoup the fixed and sunk costs of development and thus would not engage in risky innovative activities. Of course, many other industries share these features, such as movie production, book publishing, and software. A key difference between the pharmaceutical industry and these others is that the social cost of a bad drug brought to market is considerably higher than the cost of a bad movie, which is a justification for its extensive regulation. The cost structure and ease of imitation *ex post* also explain why patent protection is considered more important in the pharmaceutical industry than in any other (Cohen et al., 2000). We address alternative mechanisms for inducing innovation later in this chapter.

Over recent decades, drug discovery has evolved from random screening of chemicals to “rational drug design,” which is based on the understanding of a biological process. Drug candidates, once almost exclusively small molecules, now include large, complex molecules usually referred to as biologics. Once a drug candidate has been identified, preclinical work begins in animal subjects, followed by an Investigational New Drug (IND) filing with regulatory authorities if preclinical results are sufficiently promising (see Figure 12.1 for a diagram). The drug candidate is then tested in three phases of human clinical trials, with costs increasing at each phase. Phase I clinical trials involve a small number of healthy patients to establish safety and toxicity. If successful, Phase II trials are initiated. These involve a larger number of participants for the purpose of establishing efficacy, in addition to safety. Phase III trials are randomized controlled trials, often conducted in multiple centers or locations. The

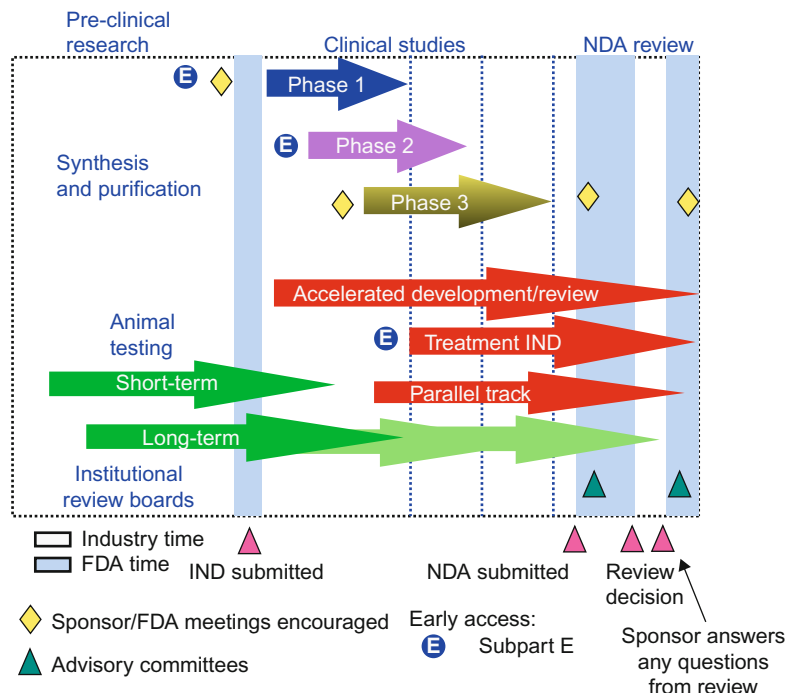


Figure 12.1 Drug development process. *Source: CDER handbook.*

length and cost of these trials varies by disease, since more time is required to assess the effectiveness of a cancer treatment than an antibiotic, for example. For each phase, clinical endpoints that are acceptable to regulatory authorities must be established *ex ante*, and this is not always straightforward. For example, should a cancer treatment be judged based on tumor shrinkage or survival? Failure is common: [Pammolli et al. \(2011\)](#) report that the average probability of reaching the market for a project at the preclinical stage is less than 5 percent for most disease areas. The results of these tests are submitted as part of the NDA to the FDA as proof of safety and efficacy.

Estimating the economic cost of inventing a few successfully marketed drugs is challenging. One must include the cost of examining all the drugs that failed, including the costs of the capital to carry out all the research, and the cost of development and approval—not just the actual expenditures on clinical testing. A 2003 study by DiMasi, Hansen, and Grabowski using a sample of drugs that were first tested on humans between 1983 and 1994 estimated the average cost of drug development to be \$802 million per successful molecule. [DiMasi and Grabowski \(2007\)](#) later update their estimate of the cost of invention of a new molecular entity to \$1.2 billion using the most recent part of the sample. That paper concludes that the fixed development cost for a biologic product is similar in total to that of a traditional chemical product.

However, the authors estimate the direct cost outlay of the biologic is somewhat lower, while the time cost of the expenditure is higher.

The DiMasi et al. work uses a proprietary database that covers primarily large US firms. In addition to concerns about the sample of firms used and the reliability of the self-reported expenditure data, their estimate depends critically on the assumed cost of capital. Adams and Brantner (2006) use a publicly available dataset on drug development projects to estimate drug development costs, and find that the cost to produce a new drug between 1989 and 2002 was \$868 million, with substantial variation across disease areas and firms.

Note that a firm that produces generic drugs does not need to engage in discovery of new drugs. Rather, a generic firm concentrates on accurately imitating an existing drug and producing it at the lowest possible cost. The market entry cost for a generic imitation of a previously approved drug is low compared to the cost of developing a new molecule. There is much less risk, since the safety and efficacy of the original molecule has already been established. In most countries, a generic firm need only show that its product is bioequivalent to the original product, and that it is safely manufactured.

For small-molecule drugs, production costs are low relative to the cost of drug development. For molecules with many generic competitors, in which we expect competition to drive price close to marginal cost, it is not uncommon to see generic prices less than 25 percent that of the branded version. For biologic drugs, manufacturing costs are a larger percentage of total cost, but the same general relation between fixed/sunk and marginal cost applies. While specific manufacturing costs are closely guarded, recent 10-K filings from biologic manufacturers list aggregate “product sales” and “cost of sales” in the range of 15–28 percent. As this number is generated for accounting purposes, it is probably an upper bound on marginal costs. Thus, even for biologics, most of the cost of producing an innovative pharmaceutical product is fixed and sunk.

4.1.2. Organizational Forms

Historically, the pharmaceutical industry has been divided into innovator firms that develop new treatments (also referred to as “brand name” or “ethical” firms) and imitator firms that produce generic copies of off-patent treatments. Prominent generic drug firms include Israel-based Teva, US-based Mylan Laboratories, and Indian-based Dr. Reddy’s. A small number of firms engage in both activities. For example, the Sandoz division of Novartis specializes in generic drugs. The generic sector in India has been of particular importance in recent years because of its role in producing HIV treatments for developing countries (Waning et al., 2010).

The organizational form of firms conducting biopharmaceutical discovery, development, and manufacture has been slowly changing over the last few decades.

Table 12.2 US Biotech Industry Statistics

Year	2010	2009	2008	2007	2006	2005	2004	2003
Sales (bn US\$)	52.6	48.1	\$57.00	\$52.70	47.7	42.1	33.3	28.4
Revenues	61.6	56.2	70.1	64.9	58.8	51.8	46	39.2
R&D expense	17.6	17.1	30.4	26.1	27.1	20.8	19.8	17.9
Net loss	4.9	3.7	-3.7	-4.2	-5.6	-3.6	-6.4	-5.4
Public firms	315	314	371	395	336	331	330	313
Total firms	1,726	1,703	1,754	1,758	1,452	1,475	1,346	1,444

Figures are billions of USD.

Source: Ernst & Young annual reports on biotech industry.

Table 12.3 EU Biotech Industry Statistics

Year	2010	2009	2008	2007	2006	2005	2004	2003
Revenues	13	11.6	15.3	13.6	13.3	11.8	11.3	11.3
R&D expense	3.4	3.2	6.8	6.6	5.7	5.3	6.2	6.4
Net loss	-0.5	-0.5	-2	-3.1	-2.5	-3.3	-2.1	-1.9
Public firms	172	167	178	185	156	122	98	96
Total firms	1,834	1,842	1,836	1,869	1,621	1,613	1,815	1,861

Figures are billions of euros.

2009–2010 figures are for public companies only.

Source: Ernst & Young annual reports on biotech industry.

Traditionally, “big pharma” firms were highly vertically integrated, with activities spanning basic research, development, clinical trials, the regulatory approval process, manufacturing, promotion, and post-marketing activities. Such firms still exist, but there has been a shift towards vertical specialization in each of these stages of production and increased use of “markets for technology” (Arora, 2001).

Perhaps the most well-known change in the organization of the pharmaceutical industry is the movement of innovative activity outside large vertically integrated pharmaceutical firms whose researchers have stronger incentives or greater expertise in new scientific areas: in more concrete terms, the “biotech industry.” (See Tables 12.2 and 12.3 for a profile of the biotech industry in the US and Europe.) If there are diseconomies of scope or poor incentives for discovery of new drugs inside a large firm, then it may be efficient for the large firm to contract with smaller firms who will be more productive on average. Smaller biotech firms often lack the capacity to manage large-scale clinical trials to manufacture and navigate the regulatory approval process. Typically the biotech firm will start with venture capital and then when it has some success will contract with a larger firm. The contract can take many forms: payments in stages as the innovation clears particular scientific hurdles,

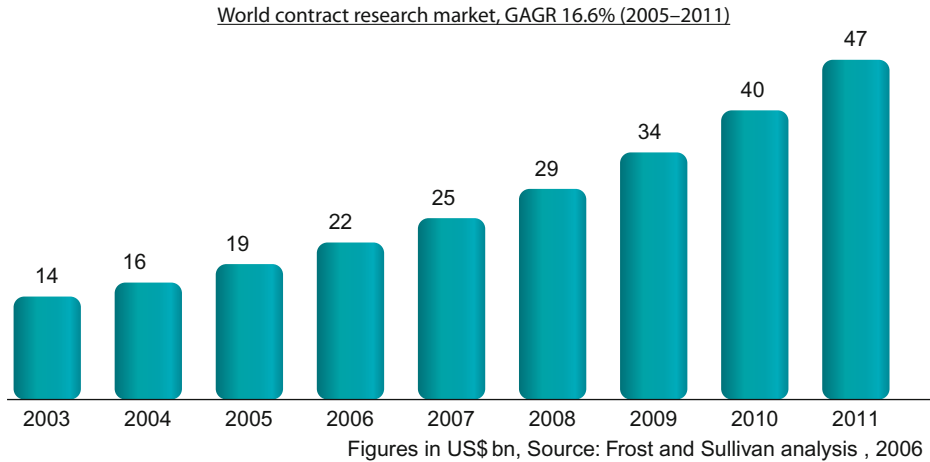


Figure 12.2 Growth of contract research.

licensing of the intellectual property on certain terms, purchase of the firm in stages as particular benchmarks are reached, or purchase of the small firm outright.

Clinical trials are another area where a firm may have capacity that is costly to increase or decrease, and where specialized firms known as contract research organizations (CROs) have emerged (see [Figure 12.2](#)). While CROs can create high-powered incentives to achieve specific goals, such as a time deadline or an enrollment number, they are not as good at capturing “softer” knowledge and retaining it in the firm. Clinical trials are increasingly conducted in emerging markets like India and Eastern Europe, where the cost of running trials in emerging markets is relatively low ([Thiers et al., 2008](#)). [Azoulay \(2004\)](#) shows that there are costs to outsourcing of clinical trials.

Outsourcing of functions further along the vertical chain has also increased (see [Figure 12.3](#)). There now exists a number of firms, particularly in emerging markets such as India, that specialize in contract manufacturing, and some “traditional” firms (such as Boehringer Ingelheim and Abbott) that contract out their excess manufacturing capacity. A firm may also outsource its marketing to the sales force of another. This will occur when the second firm has spare capacity and the first does not have the right type or quantity of sales force of its own. For example, if a firm has invented a product that is outside its traditional therapeutic areas, its own sales people may not be trained in the therapeutic area and may not have connections with the appropriate set of specialist physicians. Rather than spend the fixed costs to develop a sales force for one drug, it may instead contract for an appropriate sales force.

All of these organizational changes make particular sense given the stochastic nature of the innovative process in pharmaceuticals, which implies that a firm will often find its capacity for manufacturing, testing, or promoting to be too high or too

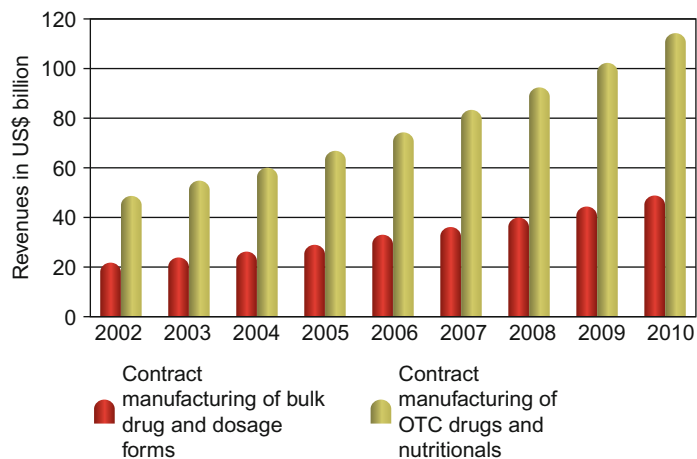


Figure 12.3 Growth in contract manufacturing.

low for its current portfolio of drugs. Sharing that capacity, or renting to other firms in the industry, is an efficient choice, particularly when the lessee is not a direct competitor on the product market. Technology and the frontier of science change rapidly and we should therefore not expect a single organizational form to be optimal across time and projects.

In addition to changes in vertical structure, the pharmaceutical industry has seen considerable (mostly horizontal) merger activity. [Table 12.4](#) shows the top firms ranked by 2009 revenues with examples of their recent mergers and acquisitions. [Grabowski and Kyle \(2008\)](#) report that the top ten firms' share of revenues increased from 28.3 percent in 1989 to 48.3 percent in 2004. Mergers may also be an attempt to bolster weak drug development pipelines ([Higgins and Rodriguez, 2006](#)), although the use of licensing could achieve the same purpose. Another motive for merger activity may be achieving sufficient size to realize economies of scale in activities for which outsourcing is not observed (such as managing the regulatory approval process or the development and protection of intellectual property). In the following section, we summarize the evidence on R&D productivity and its relationship with size, organizational type, and other characteristics.

4.1.3. R&D Productivity

In recent years, the productivity crisis in the pharmaceutical industry has been the topic of much discussion; see, for example, [Cockburn \(2007\)](#) and [Pammolli et al. \(2011\)](#). Certainly, the number of new drugs approved has fallen in recent years, as illustrated in [Figure 12.4](#). There are a number of hypotheses for this decline. One

Table 12.4 Top Pharmaceutical Firms by 2009 Revenues

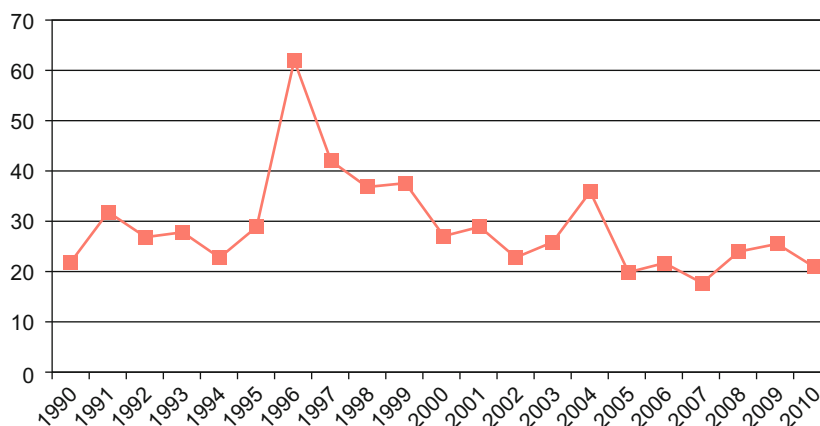
Firm	Headquarters	Revenues	Merger History
Pfizer	US	\$45,448	Warner-Lambert (2000), Pharmacia (2002), Wyeth (2009), King (2011)
Sanofi-Aventis	France	\$40,871	Sanofi merged with Synthelabo (1999), Rhone-Poulenc merged with Hoescht Marion Roussel to form Aventis (1999), Sanofi merged with Aventis (2004), Genzyme (2011)
Novartis	Switzerland	\$38,455	Ciba-Geigy merged with Sandoz to form Novartis (1996), Hexal (2005), Eon (2005), Chiron (2006)
GlaxoSmithKline	UK	\$36,746	GlaxoWellcome merged with SmithKline Beecham (2000), Block Drug (2001), Domantis (2007), Reliant (2007), Praesis (2007)
Roche	Switzerland	\$36,017	Boehringer Mannheim (1998), BioVeris (2007), NimbleGen (2007), 454 Life Sciences (2007), Genentech (2009)
AstraZeneca	UK	\$31,905	Astra merged with Zeneca (1999), MedImmune (2007)
Merck & Co.	US	\$26,929	Schering (2009)
Johnson & Johnson	US	\$22,520	Centocor (1999), Alza (2001), Tibotec (2002), Crucell (2011)
Eli Lilly & Co.	US	\$20,629	ICOS (2007), Imclone (2009)
Bristol-Myers Squibb	US	\$18,808	Medarex (2009), ZymoGenetics (2010)
Abbott Laboratories	US	\$16,486	Knoll (2001), Solvay (2010)
Amgen	US	\$14,642	Kinetex (2000), Immunex (2001), Abgenix (2006), BioVex (2011)
Takeda Chem Ind.	Japan	\$14,204	Syrrex (2005), Millennium (2008), IDM (2009), Nycomed (2011)
Boehringer-Ingelheim	Germany	\$14,027	microParts (2004)
Teva Pharma	Israel	\$13,814	Novopharm (2000), Sicor (2004), IVAX (2006), Barr (2008)
Bayer Schering	Germany	\$13,344	Bayer acquired Schering (2006)
Astellas	Japan	\$10,509	Yamanouchi Pharmaceutical and Fujisawa Pharmaceutical merged to form Astellas (2005), Agensys (2008)
Daiichi-Sankyo	Japan	\$9,757	Sankyo Co. and Daiichi Pharmaceutical Co. merged (2005)
Novo Nordisk	Denmark	\$9,566	
Eisai	Japan	\$8,441	Morphotek (2007), MGI Pharma (2008)
Otsuka	Japan	\$7,717	Taiho Pharmaceutical (2007)

(Continued)

Table 12.4 (Continued)

Firm	Headquarters	Revenues	Merger History
Merck Serono	Switzerland	\$7,454	Merck KGaA acquired Serono (2007)
Gilead Sciences	US	\$6,469	Nexstar (1999), Triangle (2003), Myogen (2006), CV Therapeutics (2009)
Baxter BioScience	US	\$5,573	Immuno International (1997), North American Vaccine (2000), Cook Pharmaceutical Solutions (2001)
Mylan	US	\$5,015	Generics division of Merck KGaA (2007)
Biogen Idec	US	\$4,247	Biogen merged with Idec (2003), Conforma (2006), Syntonix (2007)
Genzyme	US	\$3,562	Acquired by Sanofi–Aventis (2011)
CSL Ltd.	Australia	\$3,211	Aventis Behring (2004), Zenyth Therapeutics (2006)
Allergan	US	\$1,310	Inamed (2006)

Source: Contract Pharma. Figures are millions of USD.

**Figure 12.4** New drugs approved in the US, 1990–2010.

possibility is that discovery of new treatments is simply more difficult because the “low hanging fruit” has already been picked. Some blame increased costs of clinical trials and regulatory compliance. The decline in R&D productivity has coincided with the trends discussed in the previous section, suggesting that consolidation or outsourcing may have failed to yield efficiency gains.

Because of advances in science, we would expect productivity of R&D to change over time, thus making it difficult to predict current probabilities using old data. Moreover, success probabilities depend on which innovations are pursued, which are

endogenous choices of the firm. However, the long time lag in research and development does not allow analysis of outcomes until long after the initial discovery. A 1993 report by Office of Technology Assessment summarized two earlier studies that placed the probability of ultimate approval at 13 and 23 percent. [DiMasi \(2001\)](#) finds that about 21 percent of the drugs whose INDs were first filed between 1981 and 1992 had been approved for marketing in the United States by 1999. According to [DiMasi et al. \(2003\)](#), the cost of pharmaceutical drug development increased at 7.4 percent per year above inflation between 1984 and 1997. Their evidence suggests that the clinical component (human trials in particular) rather than the preclinical (bench science) is responsible for the marked increase in costs, and that increasing complexity of trials is driving this trend (p. 178). DiMasi et al. argue that trials may have become more expensive because of stronger FDA requirements, an increase in drugs being tested, and need for lengthier trials due to many drugs treating chronic conditions.

More recent work by [Pammolli et al. \(2011\)](#) estimates the probability of success from the preclinical stage (earlier than that in the DiMasi work) to market approval at less than 5 percent for most disease areas, based on data from 1990 to 2004. They find that much of the decline in productivity is the result of investing in more challenging disease areas, where the risk of failure is higher but where unmet need is greatest. This is not necessarily inconsistent with the DiMasi et al. results, but it does have different implications. If firms are rationally directing their research where social value is highest, then that is less worrisome than a productivity decline resulting from excessive regulatory burdens. However, this remains an open question for future research.

There is considerable academic literature on factors that explain variation in productivity across pharmaceutical firms. One factor is size: [Henderson and Cockburn \(1996\)](#) found that large pharmaceutical firms exhibited both economies of scale and scope in pharmaceutical research during the 1980s. This result suggests that the increased outsourcing (or licensing in) of R&D to smaller biotech firms is somewhat puzzling. One possibility is that the optimal organizational form has changed since the period of their study. As discussed earlier, economies of scale could also exist in later stages of drug development. [Grabowski and Kyle \(2008\)](#) provide some evidence consistent with the theory that large firms have an efficiency advantage in the management of large clinical trials. They find that the fraction of drug development projects that advance from Phase III to marketing approval is increasing in the number of projects a firm is managing.

Subsequent work by [Cockburn and Henderson \(1998\)](#) on the organization of research inside large pharmaceutical firms focused on the organizational culture and incentives that attract and stimulate good researchers, such as the ability to co-author externally and publish research findings. Such incentives may be easier to provide inside smaller firms, giving them an efficiency advantage over large firms in early-stage research and creating opportunities for licensing. But [Guedj and Scharfstein \(2004\)](#)

suggest that agency problems may contribute to differences in productivity across large and small firms. Because small firms have everything riding on a small number of projects, the decision to stop pursuing development of a drug candidate has far more serious consequences for firm survival than would be the case for a large firm with several hundred projects. For a marginal project, managers in small firms may therefore be more likely to continue development than managers in large firms. Using data on drug candidates for cancer, they show that small firms were more likely to have projects that advanced from Phase I to Phase II than larger firms, but had a higher failure rate from Phase II to Phase III.

Realizing the gains from vertical specialization requires that markets for technology work efficiently. There are a number of potential frictions in such markets, including search costs in finding a firm to transact with, uncertain intellectual property rights, and asymmetric information on the idea or drug candidate at issue. [Lerner and Merger \(1998\)](#), among others, have examined the structure of licensing contracts in biotechnology, but few papers address whether contracting costs and other frictions overwhelm the efficiency gains that are theoretically possible. Using a theoretical model supported by empirical evidence, [Allain et al. \(2011\)](#) focus on how information asymmetries can lead biotechnology firms to delay the stage at which they license their products. Such delays reduce the efficiency gains of vertical specialization.

Finally, another stream of research has focused on the relationship between location and R&D productivity. Research efforts often generate knowledge externalities. The desire to benefit from spillovers from other firms is one explanation for geographic clustering; the New Jersey–Pennsylvania–Maryland corridor and Basel, Switzerland, are examples of historical clusters of pharmaceutical activity. [Furman et al. \(2005\)](#) examine how geographic proximity to academic science and to other pharmaceutical labs affects R&D productivity. They find that productivity within a disease area, as measured by patent applications, is positively associated with proximity to universities, especially universities whose faculty publish many papers related to that disease. However, proximity to other pharmaceutical labs does not enhance productivity. Their results are consistent with relocation of pharmaceutical research to places like Cambridge, Massachusetts, and the San Francisco Bay area that has occurred in the years following the end of their data. [Fabrizio and Thomas \(2011\)](#) find that local demand, not just local technological spillovers, influences R&D performance. Firms located in countries with high demand for particular therapies are more likely to create new treatments for those therapies, and their innovative efforts are less sensitive to global demand than local demand.

4.1.4. Incentives for Innovation

The innovation we observe occurs in response to policy choices—both government spending on basic research and on drug development, and policies that affect the

financial rewards to innovation, whether that is a price level in the private sector or a financial prize from a non-profit. The financial inducement to innovate in the pharmaceutical industry is significant. Global annual sales of pharmaceuticals were \$837 billion in 2009⁹ while sales of biologics were \$112 billion.¹⁰ Additionally, there are significant sources of public and non-profit investment in research and development. For example, the National Institutes of Health in the US spend over \$30 billion annually on medical research.

Naturally, if societies rely on the for-profit motive to generate innovation, firms will invent therapies that have market demand. In some cases, this may not maximize social welfare. For example, where consumption of a treatment produces externalities, individuals will not account for the potential benefits to others and market demand will be too low. Vaccines are the most obvious case of this issue. [Kremer and Snyder \(2003\)](#) present a model of vaccine R&D, and explain why market forces will cause private firms to invest in drugs rather than vaccines. If individuals have high discount rates and thus place a lower value on the benefits of long-term prevention of a disease, or if insurers are reluctant to pay for disease prevention on policyholders who are not enrolled for a long time, then willingness-to-pay for treatment will be higher than for prevention. In addition, the presence of other market failures—the lack of health insurance markets, or an inability to finance treatments—can lead to situations where market demand is low despite high social need. Such market failures are especially prevalent in developing countries.

To date, the for-profit motive has resulted in therapies affecting large populations in the US, EU, and Japan, and therapies that treat rather than prevent illness. In addition to vaccines, there are two categories of disease that offer low profits to the private sector: orphan diseases, which affect a small population, and neglected diseases, which affect mostly poor people. The same WHO report referenced above finds that less than 5 percent of the R&D in 1992 was spent on diseases suffered by citizens of developing countries. [Glennerster, Kremer, and Williams](#) report that 1,233 drugs were licensed worldwide between 1975 and 1997. Of this group, only 13 treat tropical diseases.

As China, India, Brazil, Africa, and the rest of the developing world grow and become both richer and adopt greater protection of intellectual property, the needs of the citizens of these countries will create financial incentives for innovation also. The adoption of patent protection for pharmaceuticals is required for members of the World Trade Organization (WTO) under its TRIPS Agreement. [Kyle and McGahan \(2011\)](#)

⁹ <http://uk.reuters.com/article/idUKTRE63J0Y520100420>

¹⁰ Brill 3 (he got these figures from an FTC report: “Emerging Health Care Issues: follow-on biologic drug competition”; the \$112 billion figure is described as the “total global value of the biologics industry” and Figure 1.1 shows that top-selling biologic products in 2008 had sales <\$100 billion, so the \$112 billion figure might not be a bad approximation of 2009 sales).

examine whether the introduction of patent protection in developing countries is associated with an increase in drug development efforts targeting diseases that are most prevalent in poorer countries. They find that R&D responds to patent protection in rich countries, but even with patent protection, the profit potential in poor countries is too low to induce R&D. They argue that IP protection and income are both necessary to generate R&D tailored to local needs, and that alternatives to patents may be more appropriate.

An expansion of intellectual property rights through additional years of patent protection or market exclusivity can effectively increase the market size of a drug. To spur for-profit innovation for diseases suffered by small populations, the US Congress passed the Orphan Drug Act (ODA) in 1983. The Act gives innovators seven years of exclusivity (regardless of patent status) for approved orphan drugs, which are those that treat diseases affecting fewer than 200,000 people. Additional years of market protection can be offered by the regulator in exchange for services that benefit the public, such as clinical trials in children. In the US, an innovator may earn an additional six months of exclusivity if it performs pediatric studies. [Lichtenberg and Waldfoegel \(2003\)](#) find an increase in treatments developed for orphan diseases following the ODA, but [Yin \(2009\)](#) shows that some of this increase reflects the efforts by firms to redefine diseases as narrowly as possible, so that their treatments qualify for the ODA's benefits.

An important policy question is how innovative effort responds to market size. Estimation of this responsiveness presents a number of challenges. First, disaggregate R&D expenditures data are difficult to find, so the empirical literature does not usually consider the cost of inputs. Researchers have variously used data on patents, published papers, early stage trials, and drug launches as measures of innovative output. Similarly, measuring potential market size for treatments that do not exist is difficult, so market size is measured as revenues, mortality, or disability-adjusted life years (DALYs).¹¹ A second challenge is that innovative efforts are likely to respond to global market size. Isolating the impact of a policy change in a single country is therefore quite difficult. Many researchers focus on the large US market for this reason, but generally ignore changes in other markets that might also influence R&D investment choices. Fortunately, researchers are able to use variation over time and across disease areas or therapeutic classes, which facilitates identification.

[Dubois et al. \(2011\)](#) exploit the changing market size of a therapeutic class as the demographics and wealth in different countries change. These changes alter the financial returns to innovation in those therapeutic classes and this should alter the number of New Chemical Entities (NCEs) launched in the therapeutic classes.

¹¹ Examples of such papers include [Blume-Kohout and Sood \(2008\)](#), [Maloney and Civan \(2006, 2009\)](#), and [Lichtenberg \(2005\)](#).

The identification of the response of innovation to market size addresses the endogeneity of market size and innovation. Market size could call forth innovation, which is the relationship of interest, but a great innovation could generate a lot of revenue and therefore create market size, which is the reverse causality. Using instrumental variables, [Dubois et al. \(2011\)](#) find the estimated elasticity of new molecular entities to market size is 0.25; the estimate implies that a 1 percent increase in market size increases the number of new molecules launched by about 0.25 percent. On average, this means a market has to grow by about \$1.8 billion to induce entry of a new molecule. [Kyle and McGahan \(2011\)](#) also use variation across diseases and time, but across a larger number of countries. They employ a different dependent variable (new clinical trials) and measure of market size (mortality). They estimate a similar elasticity of innovation to patent-protected market size in relatively rich countries. These recent results are much smaller than the estimate in earlier work by [Acemoglu and Linn \(2004\)](#), who used data only on the US market. However, the order of magnitude of the more recent estimates is consistent with the DiMasi findings on the cost of innovation combined with marginal production and distribution costs on the order of 50 percent.

Alternatives to the traditional approach of using market exclusivity (patents) to provide incentives for innovation are an important area of academic research and policy experiments. As noted above, the patent system has neglected many high-burden diseases that affect poorer countries. Donors can help solve this problem by contractually creating a market for drugs needed in developing countries; these contracts are known as Advanced Market Commitments. Michael Kremer has written extensively about AMCs; examples include [Kremer et al. \(2006, 2011\)](#). A Gates Foundation press release succinctly describes the purpose of an AMC:

Normally pharmaceutical companies have little interest in investing in research, development and manufacturing of vaccines for the developing world because countries usually cannot afford them. Through an AMC, donors commit money to guarantee the price of vaccines once they have been developed and manufactured, thus creating the potential for a viable future market. In turn, companies that participate in the AMC will make legally binding commitments to supply the vaccines at lower and sustainable prices after the donor funds are spent.¹²

This mechanism has the advantage of solving the access problem: rather than relying on high prices to recover their R&D costs, firms receive a lump sum payment and the products can be sold at cost. Another policy intervention focused on incentives for neglected diseases is the Priority Review Voucher (PRV) described by [Ridley et al. \(2006b\)](#). A PRV allows a firm that wins approval on a new treatment for

¹² “Ministers of finance and global health leaders fulfill promise to combat world’s greatest vaccine-preventable killer of children,” Gates Foundation Press Release, June 12, 2009.

a neglected disease to receive priority review of another NDA under review by the FDA, or to sell the voucher to another firm. The first PRV was awarded in 2009 to Novartis, for its malaria treatment Coartem. Public–private partnerships such as DNDi and the Institute for Oneworld Health are another example of creative efforts to solve the neglected disease problem.

Analysis of alternative market designs to spur particular kinds of innovation is a promising area of research. Another area of research interest is the problem of eliciting information from private parties on the performance of drugs. For example, many drugs are used “off-label.” A physician may prescribe a drug for a use unapproved by the FDA (assuming the drug has been approved for a different use), which happens when the physician has a reason to think that the drug may be efficacious despite the lack of FDA approval. For example, relatively few drugs have been tested in children, so a great many pediatric prescriptions are off-label; obstetrics is also a specialty with a lot of off-label prescribing. Without a financial incentive, the innovator will not bear the expense of an additional clinical trial in order to prove the new indication is valid. This may occur if the new use is discovered when the patent has too few years remaining on it to allow for significant sales after time is allocated for trials and FDA approval. However, if the innovator lacks FDA approval for its new indication, it may not legally market the drug for that use. So the innovator faces a trade-off between the cost of the trial and the incremental gain from marketing the new use to physicians. The nature and amount of existing research evidence for the new use may also affect the trade-off.

When the innovator chooses not to carry out the trial, social welfare can be harmed because physicians either may not want to prescribe the drug absent guidance, or do prescribe the drug, but without the knowledge of efficacy, dosing, and side effects that would be gained from a large randomized clinical trial. In the US there are currently limited regulatory mechanisms to get around this problem. A new indication can be patented—and the indication can even have orphan drug designation—so that other versions of the molecule may not list that indication on their labels. However, that does not stop physicians from prescribing a generic for the patented indication and depriving the innovator of rents, because off-label prescribing is legal. In addition, an additional 20 years of patent protection for a new indication may be inappropriate, since the original product represents a more significant inventive step.

Subgroups of the population may benefit more or less from an approved drug. As with off-label use, there is no incentive for the innovator to conduct a trial to find those subgroups. This is because the firm is likely to lose sales from other subgroups when it determines which group of patients gains most from the drug. This is also an issue in the development of diagnostic tests to identify subpopulations. There is little academic work on the incentives in this system, and little on the design of regulatory mechanisms that might raise social welfare, either in a single-payer system or a market-based system like the US. Yet these are important topics.

4.2. Demand Side

4.2.1. Market Definitions

One reason the pharmaceutical industry has been extensively studied by industrial organization economists is the ease in defining a market. A narrow definition is the molecule itself, with competition between the originator product and generic imitators and between the generic imitators themselves. A broader definition is a disease area or therapeutic class, in which several different chemicals or biologics may compete for patients with the same or similar diseases. For example, metformin is a drug used to treat Type 2 diabetes. The narrow market considers competition between the branded version, called Glucophage, and bioequivalent generic versions. The broader definition includes other drugs that treat Type 2 diabetes, such as glimepiride (brand name Amaryl) and rosiglitazone (brand name Avandia). The broader market definition is often the most relevant to the physician's or insurer's choice, and the narrow market definition is often appropriate for decisions of the pharmacist.

Antitrust authorities have applied both of these market definitions in various cases. For example, the US Federal Trade Commission (FTC) used the molecule as the relevant market in complaints against Abbott Laboratories, Hoescht Marion Roussel, and Schering-Plough, and in merger challenges involving Baxter International-Wyeth, Glaxo Wellcome-SmithKline Beecham, and Pfizer-Pharmacia. But the FTC has also recognized the broader market definition when considering mergers between firms with different chemicals treating the same disease, and required divestitures in some of these cases (such as Pfizer-Warner Lambert, for which Warner Lambert divested its Alzheimer's treatment Cognex because of Pfizer's competing treatment Aricept).

As noted earlier, regulatory structures and the application of intellectual property laws limit pharmaceutical markets to country borders, with the exception of EU member states. In other words, a US physician cannot prescribe a drug approved in Mexico but not in the US. If the drug is marketed in both countries, wholesalers and pharmacists cannot purchase the product in Mexico and resell it in the US. In principle, therefore, the US and Mexican markets are separate and prices in Mexico should not affect US prices. (We return to this issue later in this chapter, in our discussion of international pricing.) The European Union's promotion of free movement of goods between member states has changed links between country markets there. While prices are regulated at the level of the member states, firms cannot prevent arbitrageurs from purchasing their products in countries with low prices and reselling them in higher-priced markets, a practice known as parallel trade. Treating countries as entirely independent markets within the EU is therefore inappropriate.

Most diseases have multiple chemically distinct treatments available. The newest treatments usually have patent protection, and are marketed under brand names. Usually, these markets are characterized as differentiated oligopolies, since it is rare to

observe more than 10 treatments still on patent at the disease level. Competition between versions of the same molecule tends to be more intense because there is less scope for differentiation. These versions may include the branded or originator's product, generic drugs, and parallel import versions in EU countries (which may have different packaging than the non-parallel import version of the originator). Arguably, the branded or originator version of a molecule could be perceived as having higher quality, or enjoy brand loyalty. Economists typically consider generic versions of the same molecule to be homogeneous goods. There are many studies that estimate demand for therapies within a disease market and the cross-price elasticities between treatments (branded and generic), which we discuss in the next section. We discuss competitive responses and antitrust considerations in section 5.

4.2.2. Estimates of Pharmaceutical Demand

As previously noted, pharmaceutical demand is rather more complicated than in most other settings due to the participation of multiple parties in the pricing and consumption decision. Large buyers, whether government agencies or insurance companies, negotiate a price for each treatment and in turn set a reimbursement rate or copayment for which the patient is responsible. A physician chooses among competing treatments to prescribe, but price is not necessarily part of his or her objective function. Pharmacists may select a particular manufacturer's product when there are multiple sources available. The patient, therefore, does not usually face the full price of a treatment (at least in developed countries), and does not really have the opportunity to choose between existing treatments without investing in learning about the alternatives and discussing them with the physician. Empirical work on estimating demand in pharmaceutical markets rarely models all these components explicitly. That is, the "consumer" at the heart of demand systems is a mix of physicians, insurers, pharmacists, and patients.

A typical approach is that used by [Ellison et al. \(1997\)](#). Using market-level data, they model the retail demand for a class of antibiotics as a two-stage budgeting problem using a representative consumer approach. In the first stage, the physician chooses between competing molecules, and in the second stage, the pharmacist (perhaps influenced by the patient and insurers, and constrained by laws on substitution) chooses between the brand and generic versions of that molecule. The top-level estimating equations are the log of each molecule's quantity as a function of total revenue in the class of drugs and weighted prices of each drug in the class. The estimating equation for the bottom level regresses the share of a molecule on the relative prices of the brand and generic versions and the dependent variable from the top-level equation. As with all demand estimation, the endogeneity of price is a concern, and the authors use changes in the number of firms in the market as an instrumental variable that is expected to trace

out the demand curve as well as prices in the hospital market. As expected, cross-price elasticities are higher between competing versions of the same molecule than between molecules, which are more differentiated. In addition, own-price elasticities are more negative for generic versions than for branded versions, suggesting that consumers of generic products are more sensitive to price.

The use of a representative consumer model precludes consideration of how insurance and patient heterogeneity affect patient demand for pharmaceuticals. Since patients with insurance coverage do not face the full price of the treatment, there is a potential moral hazard problem. The resulting increase in pharmaceutical consumption has obvious implications for pharmaceutical expenditures overall. Almost all prescription drugs in the US are now purchased using private or public insurance: between 1980 and 1999, the proportion of prescription costs paid out of pocket (OOP) by the consumer fell from nearly 70 percent to only 8 percent in 2010 (Danzon and Pauly, 2002; Berndt and Aitken, 2010). Using a demand response assumption of a -0.3 own-price elasticity, Danzon and Pauly (2002) conclude that demand response or moral hazard "...may account for one-fourth to one-half of growth in drug spending." Clearly, accounting for insurance coverage is important in estimating demand.

Cleanthous (2002) was among the first to estimate the effect of insurance coverage on pharmaceutical consumption in a paper estimating demand for antidepressants. He specifies a discrete choice model of demand in which each consumer's utility is a function of drug characteristics and prices, with individual heterogeneity. That is, different consumers can place different weight on each characteristic. Using aggregate market data on prices, market shares and drug characteristics combined with demographic data on insurance and income, Cleanthous estimates a random coefficient logit model using the approach of Berry et al. (1995). He finds a preference for branded versions over generic versions, and that consumers generally dislike characteristics such as side effects. But more importantly, incorporating information on insurance reduces the price sensitivity of patients to -1.1 from a range of -1.6 to -2.6 in models without this inclusion. He concludes that the moral hazard of insurance coverage in demand for antidepressants is indeed economically significant. Calculating the welfare gains of innovation in pharmaceuticals should therefore distinguish between private and social willingness-to-pay.

Moral hazard may differ across disease areas or be changing over time, however. Like Cleanthous (2002), Dunn (2010) uses a discrete choice model of demand for anti-cholesterol treatments, but exploits the information on individual patients available in the MEPS data. Patient characteristics matter: those with heart disease prefer Zocor, while younger patients prefer Lipitor and Crestor. Patients with health insurance and with pharmaceutical coverage have higher preferences for drugs overall. However, he finds that even patients with insurance coverage are sensitive to price, with an estimated elasticity of -1.81 .

The [Dunn \(2010\)](#) paper can only address how the existence of insurance coverage affects pharmaceutical demand, but not the specifics of that insurance such as reimbursement rates and co-payments, which can vary considerably across plans. While there are numerous papers in the literature that examine co-payment elasticities for medical care, they do not generally consider competition and the co-payments of alternative therapies. One exception is [Ridley \(2011\)](#), who examines pharmaceutical demand in two disease areas using data at the level of drug–insurance–group–month that includes co-payments. He estimates a log–linear demand system where total quantity of a drug demanded by an insurance group each month is a function of the co-payment and advertising for that drug in addition to the co-payments and advertising levels of competing drugs (he also allows for unobserved drug, patient, and insurance group characteristics). Instruments for co-payments and advertising include mean hourly earnings for pharmaceutical workers and advertising workers, a manufacturer’s sales in other disease areas, a manufacturer’s new product launches, and other firm-specific variables. [Ridley \(2011\)](#) finds that a drug’s sales are more sensitive to an increase in co-payment when the co-payments of substitute therapies are constant or falling, as would occur when the insurer moves the drug to a different tier on the formulary. When co-payments for all competitors move together (the co-payment for a formulary tier changes but the treatments remain in the same tiers), demand appears relatively insensitive to price. [Limbrock \(2011\)](#) finds that being the “most preferred drug” on the formulary, or the drug with the lowest out-of-pocket cost in the therapeutic class, has a positive incremental effect on market share even when controlling for absolute price levels.

The physician’s role in pharmaceutical demand, and in particular whether physicians consider price, has been addressed in a few papers. As discussed earlier, physicians in most countries do not have a financial incentive to prescribe one treatment over another. This is deliberate in many cases, in the hope that a physician’s choice reflects an objective assessment of each drug’s (clinical) suitability for a patient. However, a physician might be acting as a good agent by considering the economic circumstances of a patient when prescribing. Alternatively, the physician may perceive that he or she should act as an agent for an insurance company rather than a patient, and in fact regulators in some European countries have introduced incentives for physicians to consider price in their decisions in an effort to control expenditures. [Hellerstein \(1998\)](#) found that physicians were more likely to prescribe the generic version of a drug to patients who were members of HMOs, which suggests that HMOs were somewhat successful in increasing awareness of less expensive alternatives. The physician’s use of trade names or generic names is less important today, as pharmacists have greater freedom (or the obligation) to dispense generic versions even if the prescription is written using the trade name and insurers have become more aggressive in promoting generic substitution.

Little work exists on how the relative prices of competing molecules affect prescribing, and it usually involves cases in which physicians do have a financial incentive. Since chemotherapy drugs are administered in the physician's office, physicians are reimbursed by Medicare for providing such treatment. [Jacobson et al. \(2006\)](#) examined how Medicare reimbursement to physicians affected their chemotherapy choices, and found that physicians were more likely to administer chemotherapy regimens with more generous reimbursement. [Chou et al. \(2003\)](#) studied the Taiwanese market, which experimented with separating the prescribing and dispensing functions in the late 1990s. They found that post-separation, the probability of prescribing and total drug expenditure was lower at clinics without an on-site pharmacy (i.e. with no financial interest in prescribing) relative to control sites. In a study of the Japanese market, another in which physicians may sell the drugs they prescribe, [Iizuka \(2007\)](#) found that prescriptions were influenced by the (regulated) markup physicians could charge. However, he found that physicians were nonetheless sensitive to the potential out-of-pocket charges faced by their patients. Additional work on agency problems in pharmaceutical markets would be valuable in light of efforts to change physician behavior.

There is an important caveat that applies to data on pharmaceutical prices, especially in the US. Invoice prices to drugstores and wholesalers do not reflect performance rebates paid by the manufacturer to a PBM months later for purchases spread across different drugstores. Information about rebates is proprietary and is never disclosed publicly, since manufacturers use the confidentiality of prices to price discriminate among buyers. Rebates are believed to have increased in prevalence and magnitude over time, particularly in classes with close therapeutic substitutes. The most interesting prices in the industry are not available to researchers and therefore there is little evidence on the change in elasticities of demand over time. Datasets that do not include rebates (such as that of IMS Health, the most commonly used by economists) likely have significant measurement error in the price variable for at least some drugs.

4.2.3. Buyer Power

Going back a number of decades, insurance coverage for prescription drugs was relatively rare ([Berndt, 2002](#)) and most consumers paid the full price of a drug out of pocket. With insurance that subsidizes pharmaceutical purchases, consumers do not face the full price of pharmaceutical treatments and may therefore overconsume. In the case of a cash-paying consumer, this moral hazard problem is minimized, and a pharmaceutical firm with market power sets price in the standard way.¹³ As Berndt

¹³ Although there are interesting questions about externalities on other people through use or non-use of prescription drugs, and the impact of price on compliance of "behavioral" consumers, such as when the drug produces a benefit that is delayed or not observable to the patient.

shows clearly, once a patient has insurance, the optimal price for a firm with market power increases dramatically.

The insurer can take an active role in negotiating for the pharmaceuticals it subsidizes, however, and exploit countervailing buyer power. Large buyers have a number of advantages over individuals. Typically, a patient is uninformed about the efficacy of the drug and, in particular, the relative efficacy of the drug. The physician has little knowledge of drug prices, and may suffer from an agency or information problem that prevents him or her from fully internalizing the cost to the patient (Hellerstein, 1998). An informed buyer, like an insurer, can trade off the merits of competing treatments versus their prices. It is critical that some competition between treatments exists, and a large buyer can foster such competition by creating a formulary, or list of covered drugs, that may exclude cost-ineffective drugs. Elasticities in response to co-payments have been shown to be substantial, as noted in the previous section, so the formulary can create financial incentives for the patient to consume cost-effective products, such as generics. Empirically, countervailing power can be important for ex-manufacturer prices as well as consumption patterns. Ellison and Snyder (2010) showed that hospitals in the US are able to negotiate for larger discounts than drugstores because the former can impose restrictive formularies.

In countries with national health insurance, the buyer is the government. In the US, this role is played by private insurers, hospitals, and drugstores as well as the various government agencies that provide health insurance to subpopulations (Medicare, Medicaid, and the Veterans' Administration (VA)). In many cases, these buyers are monopsonists with respect to their covered populations. For example, the VA is a monopsonist when it comes to buying for VA patients and can use its power to extract price concessions from a monopolist. Because drug development costs are sunk, pharmaceutical firms are exposed to *ex post* expropriation by buyers. That is, conditional on having invested R&D, a pharmaceutical firm should be willing to supply a product at any price that covers its marginal costs. In the long run, of course, the firm cannot cover its fixed costs with such pricing. This threat of expropriation is particularly severe in the case of government buyers, who in the extreme have the option of invalidating patents and issuing compulsory licenses.¹⁴ For example, in 2006 the government of Thailand announced it would institute compulsory licensing of Kaletra (efavirenz), an HIV drug, and several other products of Abbott Laboratories. In 2001, after the anthrax attacks in the United States, there was discussion of overriding the Bayer patent on its anthrax drug in order to quickly and cheaply obtain large amounts of ciproflaxin. A further difficulty in this context is the public good nature of R&D. Each country or private insurance firm prefers to shift the burden of paying for R&D to others, i.e. that other countries or insurers pay prices high enough to

¹⁴ Compulsory licensing is permitted under the TRIPS Agreement in the case of public health emergencies.

compensate firms for their innovative efforts but to pay close to marginal cost themselves. This is especially true for small countries, whose individual populations are too small to have significant impact on R&D investment choices.

The extent to which buyers anticipate the long-term consequences of their purchasing strategies has not been studied extensively. Critics have blamed the downturn in the vaccines industry on the US government's exploitation of its power as a large purchaser. Similar concerns have been raised about the move towards "pooled procurement" of treatments for developing countries, an arrangement in which a single buyer such as the Global Fund to Fight AIDS, Tuberculosis and Malaria negotiates on behalf of many low-income countries. [Danzon and Pereira \(2011\)](#) found that the increased volume of vaccine sales associated with government purchasing largely offset the price reductions extracted. This remains a vital area for future work.



5. COMPETITION

5.1. Generic Entry

5.1.1. US

The 1984 Hatch-Waxman Act encouraged a great deal of generic entry in the late 1980s and 1990s. Many blockbuster drugs experienced dozens of generic entrants and the ensuing price competition was fierce. [Frank and Salkever \(1997\)](#) and [Reiffen and Ward \(2005\)](#) demonstrated that markets with more generic firms have lower generic prices relative to the branded price.¹⁵ In the Frank and Salkever dataset, which contains drugs experiencing generic entry in the 1980s, generic price is 70 percent of the brand's price at launch, declines to 50 percent with four entrants, 30 percent with 12 or more, and falls to around 10 percent with 18–23 entrants. Price competition appears to be confined to the generic segment, with little price response by brands ([Regan, 2008](#)). A recent paper by [Berndt and Aitken \(2010\)](#) calculates average generic prices relative to the brand price at the time of initial generic launch using data from 2005 to 2009.¹⁶ They find that after six months, the index is at 78 (its initial value at the time of generic launch is 100), falling to 50 at one year post-generic entry, 23 at two years, and then less than 10 more than two years after generic entry.¹⁷ [Figures 12.5 and 12.6](#) illustrate the intensity of generic competition in the US.

In addition to declining with entry, generic prices move with supply and demand. For example, events such as closure of a factory due to fire, flood, or violation of

¹⁵ Richard Frank and David Salkever (1997) Generic entry and the pricing of pharmaceuticals. *Journal of Economics and Management Strategy*, 6(1): 75–90.

¹⁶ Ernst Berndt and Murray Aitken (2010) Brand loyalty, generic entry, and price competition in pharmaceuticals in the quarter century after the 1984 Waxman-Hatch legislation. NBER Working Paper.

¹⁷ In this dataset, at two years after entry there are on average 12 generic entrants.

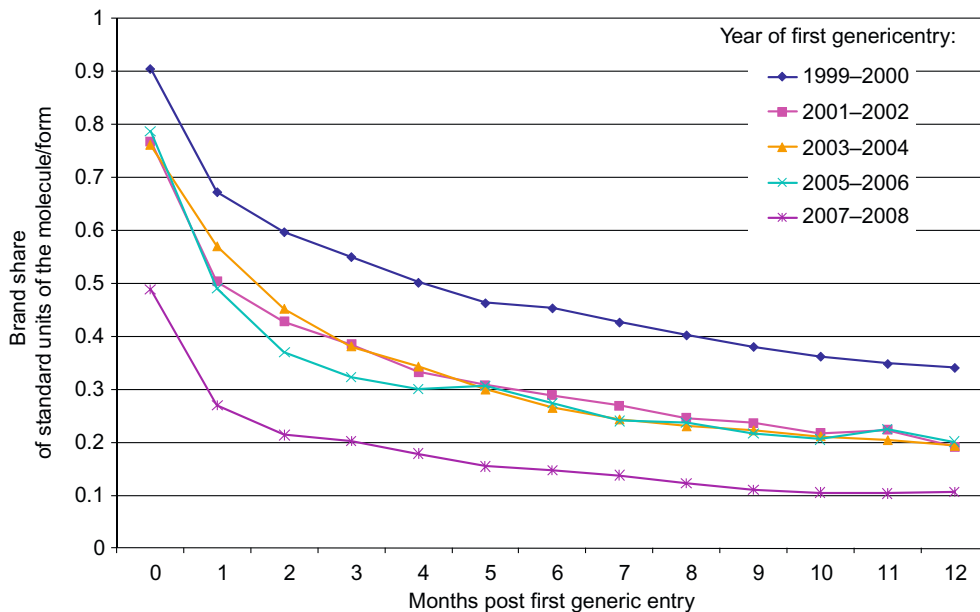


Figure 12.5 Brand share for drugs facing generic entry (all drugs with sales >\$250 M). *Source: Grabowski et al. (2011).*

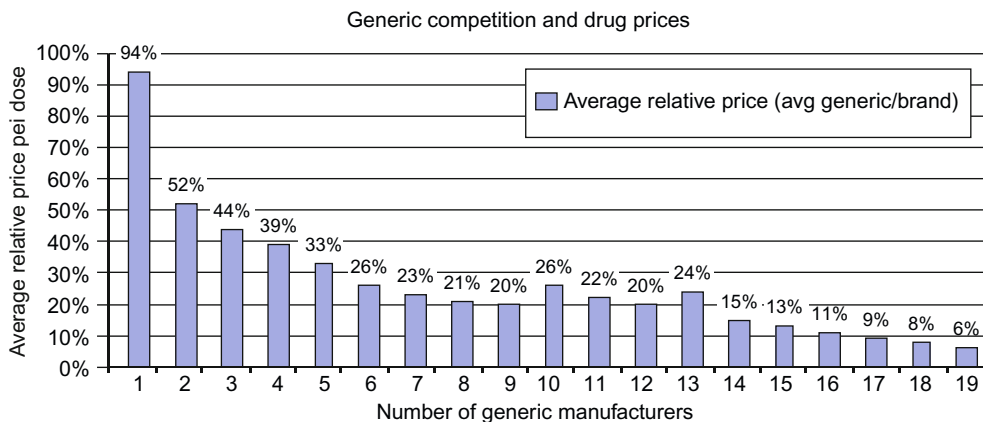


Figure 12.6 US generic competition and drug prices.

current Good Manufacturing Practices will drive up prices, at least temporarily, because of the supply shortage. As the molecule declines in popularity—perhaps due to new treatments becoming available—generic manufacturers tend to leave the market. When there are sufficiently few manufacturers and therefore less competition,

prices often rise. There is little research into the nature and extent of generic price fluctuations or models of their determinants, though this is becoming a more important research topic as the share of prescriptions filled with generics grows.

Pharmacies search across generic firms in order to buy from the one with the lowest contract price. Payments for generic drugs to pharmacies from insurers are often at a fixed price, implying that the pharmacist has a profit incentive to find the lowest price source. Small pharmacies band together into buying groups or join a wholesaler's "sourcing program" to obtain access to the prices that wholesaler has negotiated. The constant change in the generic marketplace—entry, exit, price movements—means that insurers trying to pay pharmacies for a generic drug cannot typically use industry list prices to approximate market prices, as they often do with brands. Instead, insurers and pharmacy benefit managers (PBMs) invest in creating generic price lists called Maximum Allowable Cost (MAC) lists. An MAC list simply has on it each drug along with the dollar amount the insurer will pay the pharmacy. It is updated over time to reflect changes in the market, and is proprietary, as it reflects the PBM's investment in learning about market supply and demand. Most generic drug payments in the US today are paid based on an MAC price. This stands in contrast to payments for branded drugs, which are often based on the list price of the brand, wholesale acquisition cost (WAC), or average wholesale price (AWP). When insurers do not want to create an MAC list, they can use a list price formula, such as AWP-60%, to pay pharmacies for generic drugs.

Because the entry game in the US generic industry is simultaneous, generic firms have a difficult problem choosing which markets to enter. [Scott Morton \(1999\)](#) shows that generic firms tend to enter where they have prior expertise either in distribution or manufacturing. When there are more (fewer) entrants *ex post* than expected in the market, the firm can adjust its output down (up)—including down to zero—if desired. Exit is distinct from zero production, as exit requires a withdrawal of the ANDA by either the firm or the FDA. A useful way to think about the firm's problem is to consider the generic firm as having a filing cabinet containing many ANDAs and a factory containing many manufacturing machines; each month it optimizes what it produces according to demand.

The brand and its generics are sufficiently homogeneous so that price competition in these markets is intense. Low marginal costs and price competition result in very low prices—as discussed above. Such low prices attracted the attention of insurers and policy makers, who began to encourage consumption of generics instead of brands in the late 1980s. Consumers took time to get used to the idea that a generic was as high quality as its reference brand. Additionally, the process of institutional change to favor generics took time. For example, state laws that allow a pharmacist to substitute a generic in place of a brand were not universal in 1984, and financial incentives for patients to consume generics have become more sophisticated over time. The US

generic fill rate, or what [Berndt and Aitken \(2010\)](#) term the “efficiency rate,” increased from 84 percent in 2003 to 92 percent in 2009.

However, even if 100 percent of prescriptions that could be filled with generics were filled with generics, the generic share is limited by sales of brands under patent protection. Because of relatively unproductive or unlucky pharmaceutical R&D in the last decade, there have been fewer blockbuster new molecules approved by the FDA. Hence, while medications have lost patent protection steadily during the decade, new brands are not fully filling that space. The share of prescriptions “accessible to generic substitution” has increased from 64 percent in 2003 to 81 percent in 2009 ([Berndt and Aitken, 2010](#)). In addition, aggressive formulary management has tended to move prescriptions away from brands and towards molecules with a generic option. Continuing with the statin example above, suppose one of the four brands were going to lose patent protection before the others. A PBM would use its tools to start patients on the early-expiring brand and to switch patients from other brands to the early-expiring brand. Then, upon generic entry, the PBM would automatically convert all its patients on the expiring brand to a generic. [Aitken, Berndt, and Cutler \(2008\)](#) describe this pattern when generic versions of Zocor (simvastatin) and Pravachol took prescriptions away from branded Lipitor in 2007. Simvastatin prescriptions rose by 75 percent while prescriptions of Lipitor fell by 12 percent.

The net result in the US today is that the proportion of prescriptions filled with a generic has risen to 74.5 percent from only 19 percent in 1984 ([Berndt and Aitken, 2010](#)). The extensive use of generics in the US creates a massive and continuing social welfare gain, as these products will be available at close to marginal cost if demand is sustained and the generic markets remain competitive. PBMs’ aggressive promotion of generics, as well as other contributing factors such as mandatory substitution laws, means that the branded product typically loses 75 percent or more of its market share very quickly—often in the first year after generic entry. This cliff-like pattern of revenue may be creating strong incentives for innovation by the former monopolist as suggested originally by [Arrow \(1962\)](#).

5.1.2. Other Countries

Generic entry rates in other countries are typically much less impressive than those in the US market. Smaller economies may have less competition because their markets cannot sustain as many generic firms. However, more importantly, many other nations do not have a system that generates strong price competition among generic producers. For example, regulation of pharmacy profit margins at fixed levels is common in Europe, meaning the pharmacist has no incentive to purchase from the least expensive supplier. This may be one reason why generic drugs are much more expensive, on average, outside the US and why they achieve lower market penetration ([Danzon and](#)

Table 12.5 Generic Shares Across Selected Countries
EXHIBIT 5

Originator Versus Generic Market Shares for Drugs, 2005								
Country	Share of Unit Volume				Share of Sales			
	Originator		Generic		Originator		Generic	
	Single-source	Multi-source	Branded Generic	Unbranded Generic	Single-source	Multi-source	Branded Generic	Unbranded Generic
US	20.2%	8.5%	18.2%	53.1%	70.2%	10.4%	9.6%	9.8%
Canada	16.2	8.4	45.1	30.3	55.5	12.5	24.3	7.8
France	23.0	16.3	44.7	16.0	56.4	14.7	21.1	7.9
Germany	10.0	15.4	43.8	30.8	42.6	14.5	29.3	13.6
Italy	23.7	26.0	39.7	10.5	49.6	20.9	24.9	4.6
Spain	20.6	27.3	35.4	16.7	48.0	23.1	21.4	7.4
UK	11.8	19.5	21.3	47.4	47.3	16.0	13.3	23.4
Japan	19.3	25.6	42.3	12.7	50.0	27.1	18.8	4.1
Australia	20.1	20.2	49.5	10.2	55.0	18.0	24.2	2.8
Brazil	4.9	24.6	46.3	24.2	18.4	25.2	37.3	19.2
Chile	1.9	7.5	37.7	52.9	9.2	20.3	49.1	21.3
Mexico	7.5	25.5	51.4	15.6	25.9	38.8	31.4	3.9

Source: Authors' calculations based on data from IMS Health MIDAS database, 2005. Source: Danzon, P. M. Furukawa, M. F. (2008). International prices and availability of pharmaceuticals in 2005. *Health Affairs*, 27(1), 221–233.

Furukawa, 2008). Table 12.5 provides a summary of how generic shares compare across major markets.

Payment policies also likely inhibit competition. For example, Canadian provinces fix prices for generic drugs at a percentage (such as 45 or 50 percent, but formerly much higher) of the branded price (Bell et al., 2010). More than half the market is supplied by two generic drug firms. In Quebec and some other provinces, the government payment to the pharmacist for any generic version is the lower of the percentage described above or the lowest price paid by any other province, which weakens a manufacturer's incentive to reduce price and tends to create a price floor across the nation. British Columbia pays the actual acquisition cost to the pharmacy of the lowest priced generic in the province. This rule means that the generic firm that may have cut its price in order to sell to a pharmacy will find that it has in fact created no advantage for itself, since every rival product will cost the pharmacy the same lower amount. And, due to the most-favored-nation (MFN) rule in other provinces, the low price will set a new national floor. Generic manufacturers do not have an incentive to compete on price in such an environment.

While some generic firms such as Teva (the largest generic manufacturer) sell in many countries, many generic firms operate in one country or region. Often, these

are relics of industrial policies that favored domestic producers: prior to 1987, for example, Canada used compulsory licensing to bolster its local producers. The fact that generic manufacturers are the “local” firms in most countries outside the US, and both they and the local pharmacies benefit from less vigorous price competition in that country, may partly explain the durability of some of the regulations limiting price competition among generics outside the United States.

5.2. Biologic Drugs and Biosimilars

Biologic drugs represent about a quarter of total US spending on pharmaceuticals and are forecast to be close to 40 percent by 2020. Biosimilars are still a relatively new technology, and because their regulations have not been established and there are no entrants, existing academic work is largely speculative. Such work would be very valuable and is likely to be a frontier area in health economics in the coming decades.

Biologics differ considerably from small-molecule drugs (SMDs) in off-patent competition. Biologics, some of which have been on the market since the 1980s, face very little direct competition from imitators producing an identical molecule. There is some dispute over whether such imitation would ever result in a biosimilar that is as close to the original version as a generic copy of a small-molecule drug is to its original version. Indeed, biologics produced by the same firm in different plants can demonstrate different characteristics, due to small differences in the manufacturing process. This debate underlies the 2010 Patient Protection and Affordable Care Act, which proposed two regulatory pathways for an imitative biologic. One is a biosimilar pathway, where the product is demonstrated to be very close to the reference product. The second pathway is for products seeking an interchangeable designation from the FDA, which means the products are identical and could be exchanged at the pharmacy level. Many observers feel that this second standard is not achievable with current technology. The FDA must create regulations delineating these pathways, accept an application into a pathway, and then approve the product before a biosimilar would be permitted to enter the US market.

Biosimilars are successfully competing in Europe, where they have been approved since 2006. To date the EMA has approved biosimilars in three areas: granulocyte colony-stimulating factor (stimulates production of white blood cells), erythropoietin (stimulates production of red blood cells), and somatropin (human growth hormone). In May 2010, the National Institute for Clinical Excellence (NICE) in the UK issued a report evaluating Sandoz’s biosimilar Somatropin and concluded that the biosimilar had the same safety and efficacy as the brand. NICE encouraged providers to choose the least expensive product among those that are therapeutically appropriate. There is no empirical work currently examining the impact of biosimilars on branded prices in Europe, but some facts have recently emerged. In both France and Germany,

biosimilars entered the market at a discount and the price of the original version fell also.¹⁸ However, some of this reduction is due to price regulations in these countries (discussed in section 6).

The critical aspect of regulations on biosimilars in the US is the extent to which they create a barrier to entry that reduces competition in the sector. The FDA could require tests that are only slightly less extensive than those required of the brand, which would mean entry costs for the biosimilar would be nearly as high as the brand's, or even potentially higher (Grabowski et al., 2007). Since each entrant must expect to cover its high fixed entry cost, few biosimilars would want to enter the market via the pathway and prices would not fall as dramatically as we have observed in SMDs. This would be true particularly for drugs with small patient populations. Alternatively, entry costs could be relatively low which would attract many entrants and drive prices lower. The extent to which entrant biosimilars would be able to put price pressure on brands is an open question. A pharmacist will not be able to substitute a biosimilar for the reference product without consulting a physician because the drugs are not identical. The extent of perceived heterogeneity will affect price competition. Consumers may not want to consume the biosimilar if they think it is different from the brand. Because of the differentiation among products and their complexity, biosimilar competitors may advertise in a way that we do not see in SMDs. The biosimilar's impact on prices may also be affected by whether a drug is taken chronically (the patient has switching costs) or for a short period of time. All of these issues are fertile areas for economic research in biologics.

FDA regulations are also important because they affect the nature and extent of technical progress in manufacturing, as Cockburn et al. (2006) describe. For example, if the biosimilar must carry out every aspect of production exactly as the brand described in the brand's original application, then the biosimilar entrant cannot use the latest manufacturing techniques or equipment. Since it could be 20 years or more since the brand's manufacturing process was designed, this may have significant productivity consequences. In particular, process innovation would likely reduce variable costs, which in turn is likely to affect equilibrium prices.

5.3. Parallel Trade

Parallel trade allows competition from the originator's product sold in another country. Parallel trade constitutes the resale of goods first purchased outside the country and without the authorization of the firm that owns the intellectual property rights pertaining to the goods. Typically, the originator (the innovator or patentholder) blocks competition from a third party engaged in resale of its products by invoking IP laws. If national IP laws consider the IP to be "exhausted" once the product has been

¹⁸ <http://www.gabionline.net/Biosimilars/General/The-hurdles-to-biosimilars-in-Europe>.

put on the market in another country, then the originator cannot prevent resale and parallel trade can occur. While not currently permitted in the US, relaxing rules on imports of pharmaceutical products from Canada and Europe, where prices are often lower, has been suggested as an effort to contain US prices. Australia, New Zealand, and Switzerland have considered similar adjustments. In the European Union, parallel trade in pharmaceuticals is permitted and is economically important in some countries.

Because parallel trade is effectively arbitrage of price differences, countries with relatively low prices (typically Greece, Portugal, and Spain) tend to be sources of parallel exports, which are then resold in countries where prices are high (such as the UK and Scandinavian markets). [Maskus and Ganslandt \(2004\)](#) examine parallel trade for best-selling drugs in Sweden, and find that entry by parallel traders resulted in price reductions by originators. However, as documented in [Kanavos and Costa-Font \(2005\)](#) and [Kyle et al. \(2008\)](#), competition from parallel imports has not resulted in significantly lower prices overall or in price convergence across countries. [Kanavos and Costa-Font \(2005\)](#) and [Kyle \(2011\)](#) explain that this outcome is due to a combination of regulations that dampen incentives for pharmacists and patients to switch to lower-priced parallel imports and strategic responses by firms.

5.4. Strategic Responses by Originators

Innovative (as opposed to generic) pharmaceutical firms have large gross margins and strong incentives to protect those margins from generic competition, price regulation, and threats to intellectual property protection. The low marginal costs of pharmaceutical firms and their long experience in global regulatory environments means their responses to laws and regulations are often strategic and very sophisticated. The pharmaceutical industry is an excellent place to carry out research on firm behavior and the unintended consequences of well-meaning regulation.

The responses of innovator companies to generic entry are particularly interesting. Brands often file multiple patents for attributes of the same drug, for example on the basic molecule, the process, the release mechanism, and even the shape of the pill. Waiting for all these patents to expire would create a long period of monopoly pricing. A feature of the Hatch-Waxman Act that seems to have been unanticipated was the ability of the generic to settle “Paragraph IV” patent litigation in a manner that arguably harms consumers. If there are, for example, a number of years left to run on the challenged patent at the time of litigation, and the generic wins, the brand will lose monopoly profit for that entire remaining time period. By contrast, the generic will only gain six months of duopoly profit as an exclusive generic and thereafter the market will become competitive with additional generic entry. The lost profit for the remaining years (less six months) accrues to consumers in the form of lower prices.

Given this situation, the generic is clearly better off by settling for a share of the monopoly rents of the brand and agreeing not to enter: a standard contract of this type would have the brand paying the generic to settle the patent litigation, and a condition of the settlement is that the generic does not enter the market.¹⁹ This strategy (sometimes called “pay for delay”) is generally profitable for both firms, but deprives consumers of early generic entry in cases where the brand patent is weak.

The FTC began taking these agreements, known as “reverse payments,” to court on the grounds that they violated the antitrust laws, but a series of judges since 2005 found in favor of the firms.²⁰ This issue is still one of active policy debate, as despite the adverse legal rulings, the FTC continues to sue in cases of reverse payments. An agency study found that agreements with compensation to the generic results in 17 additional months of patent protection relative to agreements with no generic compensation.²¹ The FTC currently considers a settlement negotiation over the entry date of the generic without a financial transfer to be pro-competitive. In such a settlement, each side’s assessment of the strength of the patent determines how far into the remaining patent term the generic is permitted to enter. Consumers then get the benefit of competition at a date that reflects the strength of the patent. Having settled (or won) in patent litigation, the generic may use its 180 days of exclusivity during which time no additional generic may enter the market.²²

A second strategic response to generic competition by innovators is the use of so-called “authorized generics.” Prior to patent expiration, innovators using this strategy choose to launch their own generic version or to sell a license allowing another firm to do so. This authorized generic version reaches the market earlier than would otherwise be the case, and thus has the potential to increase consumer welfare. However, this early entrant may deter subsequent competitors. [Appelt \(2010\)](#) examines the consequences of authorized generics in Germany. She found that the primary motive for the introduction of authorized generics appears to be earning generic profits without affecting the number of entrants or price, rather than entry deterrence.

Brands employ other strategies to retain their monopoly position by investing in incremental innovation, such as developing extended release formulations or over-the-counter (OTC) versions. [Berndt et al. \(2003\)](#) describe the effects of this practice for antiulcer treatments. Critics describe this as “evergreening,” though of course there may well be patients who benefit from this type of new product. The answer to whether the innovation is socially useful is often clearer when the product line

¹⁹ Sometimes the payments take the form of compensation for unrelated transactions such as marketing or manufacturing assistance provided by the generic (which may be a way to make reverse payments less transparent).

²⁰ Pay-for-delay: how drug company pay-offs cost consumers billions (January 2010) FTC Staff Study.

²¹ Pay-for-delay: how drug company pay-offs cost consumers billions (January 2010) FTC Staff Study.

²² For further analysis, see [Scott Hemphill and Mark Lemley \(2011\)](#) Earning exclusivity: generic drug incentives and the Hatch-Waxman Act. *Antitrust Law Journal*, forthcoming.

extension is put to a market test. If the new product is not sufficiently better than the old one, conditional on price, it may not be given good formulary placement by PBMs. OTC versions, because they do not require a visit to a doctor in order to obtain a prescription, may increase use of pharmaceuticals by the uninsured population. For example, OTC versions of smoking cessation products could reach a much larger population than the prescription versions. Naturally, the risk of inappropriate use (or abuse) is a first-order consideration to regulators considering whether to approve OTC versions. The application to market Plan B, the so-called “morning after pill,” was a high-profile example of this concern.

However, sometimes the introduction of new versions has more to do with regulatory features that reward product proliferation, albeit unintentionally. [Duggan and Scott Morton \(2006\)](#) show that launch prices are higher when the buyer (Medicaid enrollees) is inelastic. The same paper shows that when the government rebate grows over time the firm has an incentive to introduce new products in order to “reset” the inflationary component of the rebate. In Japan, launch prices are unconstrained but the government mandates steep price reductions each year. As a result, manufacturers in Japan introduce new products much more frequently than do firms in other jurisdictions ([Thomas, 2001](#)). [Kyle \(2011\)](#) shows that firms select packaging and dosage type in order to make parallel trade more costly in Europe.

[Scott Morton \(1999\)](#) provides evidence that when the federal government wanted to lower the cost of drugs in the Medicaid program, it did so in a way that benefited manufacturers, mandating Most Favored Nation protection for Medicaid purchases. Manufacturers and many industry observers forecast the likely effects of the MFN clause, and anticipated the dampening effect it would have on large price discounts which had been extracted by some buyers before the law. The year after the MFN took effect, the average price of branded drugs with high sales to Medicaid rose.



6. PRICING AND MARKETING

6.1. International Prices

While policy interest primarily focuses on prices, there is a surprising amount of variability in the portfolio of drugs sold across different countries also. [Kyle \(2011\)](#) documents a number of relevant facts, such as that only one-third of prescription drugs sold in one of the seven largest national markets in the world (US, Japan, Germany, France, Italy, UK, Canada) are also sold in the other six markets. Since marginal costs are low and fixed costs are high, innovators have a strong incentive to sell as much of their product as possible. Moreover, presumably governments would like their citizens to have access to as many effective treatments as possible. Lack of entry under these

conditions suggests that approval costs may be limiting competition in many markets. An interesting issue for further study is whether lowering entry costs might stimulate competition among additional products and lower drug expenditures.

There is a large literature examining the differences in the price of pharmaceuticals across countries. For example, [Danzon and Furukawa \(2008\)](#) present a comparison between rich countries (summarized in [Table 12.6](#)), and [Yadav \(2010\)](#) focuses on prices in developing countries. The consumption patterns of drugs vary considerably across nations. [Danzon and Chao \(2000\)](#) show that it makes a large difference to the calculation of relative price levels whether one weights with US quantities or own country quantities. Differences in the product mix and consumption patterns mean that direct price comparisons can be misleading, but there are two important stylized facts that have emerged from the literature. First, large price differences exist, even across high-income countries. Second, these price differences may not be large enough: on a purchasing-power parity basis, low-income countries pay relatively high prices and hence have lower access.

From the standpoint of economic theory, when a seller can price discriminate across markets, we expect to see higher prices in markets with lower demand elasticity. International data do not allow easy comparison across countries in terms of demand elasticity. We do, however, see a pattern of richer countries paying more, which may have to do with not just higher income, but with the insurance/reimbursement and regulatory structures in those countries. Most economists would argue that price discrimination favoring lower income countries should be encouraged in this context. Theory shows that price discrimination raises social welfare if it expands quantity consumed ([Varian, 1985](#)). Drugs sold at high prices in rich countries, but also sold at low prices to citizens of poor countries, seem very likely to be satisfying this condition and raising welfare. By contrast, if drugs were sold at a uniform price across all countries, that price would likely reduce access for lower-income people around the world.

[Danzon and Towse \(2003\)](#) argue that something close to optimal Ramsey prices could be achieved by basing prices on national income. The policy implication is that governments around the world should accept differential prices as welfare enhancing instead of engaging in reference pricing, or benchmarking their prices to those in other countries. Charging low prices to very poor countries like Sudan or Malawi is not controversial. Everyone appreciates that these consumers cannot pay for drugs and yet need them. Middle-income countries, particularly those that have been growing fast (e.g. Brazil, Turkey), may begin to object to differential pricing. These countries are used to paying low prices for pharmaceuticals but their incomes now justify higher prices; the policy response to international price discrimination as innovation and incomes change is an interesting area for future research.

Table 12.6 Comparison of Pharmaceutical Prices Across Selected Countries
EXHIBIT 6

Pharmaceutical Price Indexes, Relative to US Prices (US = 100), 2005

Country	Comprehensive Indexes ^a				Originator versus Generic ^{b,c,d}				
	Manuf. ^d at Exch. Rates ^c	Public ^e at Exch. Rates ^c	Public ^e at GDP PPPs ^f	Manuf. ^d Normalized by Income ^g	Originator		Generic	Rx versus OTC ^{b,c,d}	
					Single-source	Multi-source	Branded and Unbranded	Rx	OTC
US	100	100	100	100	100	100	100	100	100
Canada	81	81	79	103	74	60	133	79	189
France	74	91	78	100	64	37	108	69	262
Germany	75	90	95	106	74	65	151	77	192
Italy	67	87	82	94	55	68	150	63	527
Spain	59	69	71	93	62	40	109	57	377
UK	72	81	68	93	76	61	131	77	202
Japan	111	99	50	151	81	99	211	101	362
Australia	69	70	66	90	63	62	138	70	195
Brazil	69	80	68	336	62	109	128	64	186
Chile	56	65	119	206	56	55	138	58	312
Mexico	102	107	157	414	90	87	216	110	218

Note: ATC3 is Anatomical Therapeutic Classification.

^aBilateral matching with US by molecule-atc3.

^bBilateral matching with US by molecule-atc3-form-strength.

^cPrice converted to US dollars at exchange rates.

^dManufacturer prices.

^ePublic prices.

^fPrices converted to US dollars at gross domestic product (GDP) purchasing power parities (PPPs).

^gPrice index normalized by GDP per capita.

Source: World Development Indicators, 2005; and authors calculations based on data from IMS Health MIDAS database, 2005. Source: Danzon, P. M. & Furukawa, M. F. (2008). International prices and availability of pharmaceuticals in 2005. *Health Affairs*, 27(1), 221–233.

Differential pricing can be difficult to sustain for a number of reasons. Firms sell to monopsonist purchasers in most rich countries, and these large buyers have countervailing power (particularly relative to low-income countries, where government health coverage and purchasing may not exist). In addition, these large buyers either explicitly or implicitly reference prices used in other countries. As discussed earlier, parallel trade between countries undermines the ability of firms to price discriminate. While parallel trade is currently limited to the EU, the use of “international reference pricing” has the same effect of linking prices across countries and is widespread. For example, in France, government policy is to pay a price that is “similar” to that accepted by the manufacturer of an innovative product in a group of reference countries: Spain, Italy, UK, and Germany. Greek policy is to pay no more than the lowest price within Europe. Of course, the choice of which countries—high price or low price—are in the reference basket will have a large impact on the final negotiated price.

From the manufacturer’s point of view, the revenue earned from a country with reference pricing depends strongly on the prices the manufacturer sets or negotiates with peer countries. Therefore a manufacturer should want to negotiate over prices and launch new products in high-price countries first, so as to positively affect any reference price used by later countries. [Danzon et al. \(2005\)](#) show that countries with lower price levels experience longer launch delays (or fewer products launched), controlling for per capita income. [Kyle \(2011\)](#) finds that markets with regulated prices have less entry overall, and more entry delay when entry does occur. As predicted by economic theory, markets with lower prices tend to be harmed by policies that encourage uniform pricing. Interestingly, a product that has been launched earlier in a low-price market (or belongs to a domestic firm in that market) is less likely to be launched in additional markets compared to a drug that is marketed in high-price countries. This may arise because of implicit or explicit reference pricing by other countries that condition their prices on existing prices for the product, and therefore determine the profitability of additional entry.

Even without formal international reference pricing, low prices charged to others often create political pressure on branded pharmaceutical prices in richer countries. Politicians in the US have responded to high branded prices by proposing bills to allow importation of cheaper branded drugs from Canada. The likely result of any such policy would be to cause manufacturers to set higher prices in Canada, manufacturers to limit sales in Canada, the government to disallow exports to the US, or all three. In response to growth in cross-border trade enabled by internet pharmacies, in 2004 GlaxoSmithKline began to ration sales to Canadian pharmacies suspected of exporting products to the US. Several other large pharma firms followed suit. Economic theory demonstrates that well-intentioned efforts to increase transparency of drug prices in different countries, such as those spearheaded by *Medicins Sans Frontières*, have the potential to harm the populations they are meant to help.

The process of setting prices across different countries is difficult to describe concisely because the institutions vary across countries, there are many countries with significant pharmaceutical sales, and policies are always changing. Useful resources are PPRI, an information network providing Pharmaceutical Pricing and Reimbursement Information for EU countries and EU applicant countries (e.g. Turkey),²³ and Annex K to a 2007 report “International survey of pharmaceutical pricing and reimbursement schemes” from the Office of Fair Trading in the UK.²⁴ Another non-profit site that explains pricing and approval processes across various countries is the International Society for Pharmacoeconomics and Outcomes Research.²⁵ Kyle (2011) provides a one-page summary of different types of regulation across 25 markets, which MacGarvie and Koenig (2011) supplement.²⁶ Rather than provide an exhaustive summary of the information contained in these sources for many countries, we focus on several examples that illustrate general types of approaches: Germany for a strong reference price system, Australia for incremental cost effectiveness, France for strong state regulation of prices, and the UK for its clinical effectiveness institute. We also touch briefly on the Japanese market, the second largest in the world, which has a number of important differences from Western regulatory structures. There are many reports by agencies, consulting firms, and non-profits that examine these national schemes. A fruitful area of research going forward may be to model different national schemes and explicitly contrast their welfare consequences.

Launch prices are unregulated in Germany. When the EMA or the local German authority approves a new product, it is almost always covered by social insurance in Germany (those deemed insufficiently innovative are placed on the negative list). However, the reimbursement level is regulated by G-BA (Gemeinsamer Bundesausschuss). The Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), or the agency for “medical efficiency, quality, and effectiveness,” evaluates the drug and provides a recommendation to G-BA. G-BA devises reference drug categories and sets reimbursement levels. Usually, a reference group includes therapeutic substitutes as well as generic versions, if available. If the drug can be placed in an existing reference group, then its reimbursement is determined in the following way. The reference price is at the 33rd percentile of the price distribution of the group; it must also be a price at which 20 percent or more of the prescription (and volume) of the group can be purchased. The patient is responsible for the difference between the reference price and the price of the drug he or she consumes.

²³ <http://ppri.oebig.at/index.aspx?Navigation=r|0|2->

²⁴ http://www.offt.gov.uk/shared_offt/reports/comp_policy/oft885k.pdf

²⁵ <http://www.ispor.org/Default.asp>

²⁶ <http://www.cmj.hr/2002/43/4/12187524.pdf>

Germany has recently adopted a more formal cost-effectiveness approach, which is explained clearly by the International Society for Pharmacoeconomics and Outcomes Research (www.ispor.org) on their Germany page:

In January 2008 (updated to version 2.0 in March 2009), the IQWiG published their first draft of the “Methods for Assessment of the Relation of Benefits to Costs in the German Statutory Health Care System”. In contrast to other HTA agencies, . . . IQWiG did not use the incremental-cost-effectiveness-ratio (ICER) approach, but they introduce a different methodological instrument, the efficiency frontier. Within the efficiency frontier, all available compounds/agents have to be compared using their total benefit in relation to their total costs. This results in an efficiency frontier. New agents have to show comparable efficiency, compared to (a) the cost–benefit ratio of the alternative with the best available maximum benefit, or (b) compared to the mean cost–benefit ratio within the specific indication.

The German system and the US system are similar in the sense that a truly innovative new product does not face a regulated price. However, drugs that provide smaller benefits are lumped into a reference price group, which essentially treats them as undifferentiated. Drugs in a group can, in theory, charge consumers a premium. However, many manufacturers set their products’ prices at the reference price benchmark. [Pavcnik \(2002\)](#) considered how manufacturers respond to the introduction of reference pricing in Germany, and found that the increase in out-of-pocket expenditures created by this system induced firms to cut their prices, with the decline in brand-name prices being especially steep. [McGuire and Bauhoff \(2011\)](#) showed that the German reference price system was very effective in inducing substitution for Lipitor. [Brekke et al. \(2011\)](#) examined the reference price system in Norway, and found that its use significantly lowered prices of both brand-name and generic products as well as increased generic uptake.

In Australia, approval and pricing of new drugs either follows a “cost-minimization” track or a “cost-effectiveness” track. The former track is used by all generics and any brand that does not think it has a significant clinical advantage over other products in the therapeutic category. The Pharmaceutical Benefits Advisory Council (PBAC) identifies a reference group comprised of therapeutic substitutes; the lowest price (per dose) of the drugs in this group sets the benchmark price. All products are reimbursed at the benchmark, but a brand can add a premium to its price that the consumer must pay, provided there is another product in the therapeutic group that is available at the benchmark price. Innovative products that are improvements over the status quo follow the cost-effectiveness track and must present evidence of their clinical merits to PBAC in order to obtain the designation of cost effective. Then the Pharmaceutical Benefits Pricing Authority (PBPA) sets the reimbursement price, which depends on clinical effectiveness and other factors. A significant fraction of cost-effectiveness applicants are rejected, in the sense that the agency does not find

their product a significant improvement and they have to accept the benchmark price if they want to enter the market.

Australia also uses risk-sharing agreements to address total expenditure by the government. If a product is successful and sales are higher than a negotiated cap, the manufacturer must rebate some of its revenues. This technique preserves the list price for international reference pricing purposes, while still offering the Australian government a discount. In addition, it renders the contract similar to a lump sum payment by the government with small marginal payments for additional quantities, which is efficient (given low marginal costs). Lastly, some of the caps are for a therapeutic class rather than an individual drug, with rebates paid according to market share in the class. This gives manufacturers incentive to compete in price, because pure business-stealing will not trigger a rebate.

In France, there is no therapeutic reference price group and initially no cost effectiveness. First, the Haute Autorité de Santé (HAS) evaluates a new drug for its clinical attributes and the seriousness of the underlying condition, and assigns it a score relative to therapeutic substitutes. The Comité Economique des Produits de Santé (CEPS), a separate committee, is responsible for pharmaceutical prices. Low-scoring products must negotiate a price. High-scoring products may, in theory, freely choose a price, but this price may not exceed the average list price in Germany, Italy, Spain, and the UK (this is an example of explicit international reference pricing).

Risk sharing in France is similar to that in Australia in that firms must pay rebates if government spending in a category gets too high, growth rates exceed targets, or volume exceeds targets. However, rebates are also payable if volume of an individual, innovative, but expensive drug rises above a cap. Importantly, the government negotiates for special rebates for high-scoring, and therefore “unregulated,” drugs when it thinks the European average price is too high. Thus, high-scoring innovative products may have restricted pricing, despite the apparent pricing freedom provided in the launch regulation. The existence of the rebate means that net price is not easily observed, but will clearly be lower than the published price.

These measures have not controlled expenditures very effectively: France’s per capita spending on pharmaceuticals is one of the highest in Europe, despite its relatively low prices. Its regulatory system does not produce high rates of use of generics. According to the OFT report, generic prescriptions are 7 percent of French pharmaceutical spending. In addition, French consumers face very low co-payments and consequently tend to be quite insensitive to price.

In the UK, pharmaceutical prices are determined through a voluntary contract called the Pharmaceutical Price Regulation Scheme (PPRS), which is renewed periodically for a set number of years. Approved new products may be priced at the discretion of the manufacturer. Instead of directly regulating prices, the PPRS limits the profitability, or rate of return on capital, of the firms in the industry (21 percent

in 2009). Price increases are not allowed unless the firm can demonstrate its forecast of its return on capital is below 40 percent of the allowed rate. If the introduction of a popular new product raises, or is forecast to raise, the firm's return on capital above the limit, it must negotiate price reductions to bring firm-wide profitability down. Clearly, a firm's portfolio of products—some more successful than others—will affect its average return on capital. Products may be sold to other pharmaceutical firms, but their prices may not increase for three months after the sale. In this situation one would expect detailed rules for the method of calculating return on capital, and these are provided. The PPRS terms may call for an across-the-board price cut, an overall expenditure reduction requirement (which can be met with any combination of price reductions across products), mandatory generic substitution, or other terms that reduce price.

The UK's NICE reviews medications (new or existing) and issues opinions on whether local health authorities should purchase and administer those treatments. NICE does not publicly set prices, nor does it negotiate prices. It determines the value of medications—primarily through measurement of Quality Adjusted Life Years (QALYs), though it is permitted to account for other factors—and compares the drug's value to the price chosen by the firm. If the treatment is cost effective, NICE will issue a favorable recommendation. Originally, such a conclusion meant that all health authorities in the country had to offer that treatment, but recent (2010) changes by the government make the NICE decision non-binding on providers. If the price per QALY is too high, NICE will recommend against providing the treatment. Local health trusts may still make their own decisions about the treatment, but they are not obligated to offer it. While NICE does not publish a formal limit, observers note that treatments with costs above 30,000 GBP per QALY are less likely to be approved. The lack of price negotiation means that the manufacturer is playing a one-shot game that is high risk. A higher price raises profit conditional on acceptance; but a higher price lowers the probability of acceptance. The firm must choose a submission price balancing these forces and taking into account its expectations of NICE's own data, analytical process, and likely conclusion; see [Jena and Philipson \(2007\)](#) for a discussion.

A useful feature of PPRS 2009 is that the regulation allows the one-shot game to have a second stage in some cases. A manufacturer may adjust the price of a medication up (by as much as 30 percent) or down when new evidence on efficacy or additional indications becomes available. Another interesting feature to the scheme is that an additional indication may be priced above existing indications if it is more valuable than the original indications. This type of regulation addresses the problem of lack of incentives for additional knowledge gathering that were raised earlier in this chapter. A second innovation adopted by the PPRS is the option for performance-based contracts (known as "Patient Access Schemes"). This includes the conventional rebate, triggered by expenditure or usage, that we have seen in other countries. More

exciting provisions include agreements that the manufacturer may seek a price increase if subsequent studies (agreed to by NICE upon initial approval) produce evidence of higher quality. Analogously, a price may be accepted initially, but NICE may commit to revising it subject to data from further studies. In this case the manufacturer will forfeit funds if the treatment does not perform as expected. The implications of NICE policies for firm pricing strategies are a very interesting area for future research.

Lastly, and most interestingly, are sophisticated and novel risk-sharing contracts that bring down average costs and sharpen incentives for manufacturers. These are agreements where UK patient health outcomes determine the price of the treatment. For example, an agreement might specify that all appropriate patients receive a cancer drug, as would be the case in the US. However, only those patients whose tumors shrink will trigger payment from the NHS to the manufacturer. Such an arrangement allows the manufacturer and the government to hold different views on the efficacy of the drug, and for both to be satisfied with the contract. In particular, such a contract protects the government from paying for expensive medicines that do not perform as expected. Risk sharing is especially useful when considering expensive drugs that have heterogeneous effects in the population. The heterogeneity results in a small average effect and means that these products are likely to fail NICE's threshold test. In the example above, if some fraction of patients responds to the drug (e.g. 25 percent) while others do not, and the price of a dose is high, average price per QALY is high. When only 25 percent of doses are purchased, price per QALY falls to 25 percent of its former size and the NICE threshold may be passed. Because of the prevalence of international reference pricing, the fact that the list price remains constant is another advantage of the contract to the manufacturer.

The Japanese pharmaceutical market has a number of features that distinguish it from other markets in high-income countries. Some of these are not directly related to its pricing, but have implications for competition. There is also a tradition of protectionist policies. Clinical trials conducted on non-Japanese participants were not always accepted in applications for new drug approvals, and foreign firms had difficulty penetrating the market. Japan has the smallest shared set of drugs marketed in comparison with the six other largest markets (Kyle, 2011). We noted previously that there is a tradition in Asian markets that physicians both prescribe and dispense drugs. The system of approving and paying for pharmaceuticals in Japan has an important interaction with this practice. Because physicians earn a margin on each drug they prescribe, they have an incentive to write many prescriptions for each patient (Thomas, 2001) and to prescribe those for which they earn the highest margins (Iizuka, 2007). Further, the government does not limit introductory prices but does require frequent price reductions. The result is that many new products are introduced over time, but these are not generally new chemical entities. Instead, they are

mainly versions of existing drugs because releasing a new version allows the firm to set the launch price again.

6.2. US

With 45 percent of global pharmaceutical spending, the US is both the largest market and the least regulated in terms of price. However, between Medicare Part D, Medicaid, and other programs, the government buys more than 50 percent of drugs in the US directly or indirectly.²⁷ This means that the manufacturers face significant political pressure to keep prices down in the US, even in the absence of explicit price controls. [Ellison and Wolfram \(2006\)](#), examining the behavior of pharmaceutical firms when health care reform was considered in the early 1990s, found that these firms took steps to forestall price regulation such as limiting price increases.

6.2.1. Private Sector

The “free market” in the US means that buyers must negotiate to secure lower drug prices for their members. The use of buyer power in pharmaceutical markets was discussed in section 4.2.3. In the private sector, PBMs are the most important buyers: PBMs manage more than 70 percent of the prescriptions dispensed in the US. Though US prices are not regulated, the emergence of the PBM and the formulary has made demand more elastic. HMOs like Kaiser and the Yale Health Plan receive low prices from manufacturers because they are willing to drop a drug from their formulary unless the manufacturer’s price is low. In response to small price changes, these buyers switch large volumes among competing products ([Limbrock, 2011](#)). They create price competition among branded therapeutic substitutes by means of formulary tiers. Tier 1 drugs, usually generic drugs and perhaps a few inexpensive brands, have the lowest co-pay. Preferred brands are on the next tier, with perhaps a \$20 co-pay, and non-preferred brands are on tier 3 with a higher co-pay. Insurers also sometime have a fourth tier for “specialty pharmaceuticals” that are often expensive biologics. This tier typically has co-insurance rates of 30 percent or something similar. The PBM can also restrict consumption of particular brands to certain clinical subgroups to limit usage.

The process of identifying “preferred brands” is where the formulary is most useful in creating bargaining power for the insurer. This dynamic is nicely summarized in [Berndt et al. \(2011\)](#). Suppose there are four branded cholesterol-lowering drugs, none of which faces generic competition, and the insurer has decided they are very similar. An insurer can offer to prefer the manufacturer’s product with its group of customers in exchange for a lower contract price—or a higher rebate. “Preferring” the product means the insurer will increase its market share by using tools such as its formulary

²⁷ Other government purchasers include the Department of Defense, the Veterans’ Administration, and the Bureau of Indian Affairs.

and financial incentives. The manufacturer decides how much of a discount it is willing to offer for the business of the group which, because it represents lots of volume and is elastic across therapeutic substitutes, has more bargaining power than any individual consumer. The insurer holds what one can think of as an auction for access to its customers, and comes away with a preferred brand and a low price. Naturally, the more differentiated are the brands, the more difficult it is for the insurer to threaten to put all but one on a high tier and discourage their use. An insurer can have a preferred brand in a category, but allow a second brand to be on the first tier for particular patients or indications. For example, Mevacor might be a preferred brand for patients needing a statin for cholesterol, while Lipitor might be preferred only for patients with cholesterol levels above a certain cutoff. Sometimes the contract between the insurer and the preferred brand, call it Brand A, includes a performance requirement, and sometimes the discounts are geared to the level of performance by the insurer. For example, suppose Brand A had a 20 percent share nationally. The insurer might get a 5 percent discount regardless of usage, an additional 10 percent discount if the market share of Brand A—among all drugs in the therapeutic class—reached 30 percent, and a further 5 percent discount if the market share of Brand A was as high as 50 percent. Thus to obtain the lowest prices on branded drugs in the US, a buyer should be both large and able to effectively “move market share” across brands.

It is not as easy to move patients from one brand to a similar brand as it is to effect generic substitution. As described in section 2, pharmacists can or must substitute generics for brands without informing or obtaining permission from the doctor. However, changing the drug dispensed to a therapeutic substitute requires a different prescription from the physician. Insurers or PBMs must work with physicians, pharmacists, and patients using information, social norms, and financial incentives in order to shift prescribing behavior. A PBM can mail a letter describing the formulary to the physician, but since a physician typically has hundreds of patients belonging to dozens of insurance plans, each with a formulary that changes over time, this is often not very effective. Using a large dataset of statin (anticholesterol) purchases, [Limbrock \(2011\)](#) demonstrates that “preferred” status is associated with a much higher incremental market share gain for an HMO than for a standard indemnity insurer. However, he does not observe exactly what techniques the plan uses, outside of prices, to achieve this result. For example, location of physicians, concentration of insurers in the patient population, and structure of information are all plausible drivers of insurer performance. These issues form an important area for research in the intersection of health economics and organizational economics.

6.2.2. Public Sector

Because the US state and federal governments purchase a large share of pharmaceuticals, prices for government purchases are not totally unregulated. The various agencies

that administer drug benefits have considerable buyer power, and have implemented a variety of purchasing policies.

6.2.2.1. Medicaid

There are mandatory rebates for drugs sold to state Medicaid programs (approximately 17 percent of the pharmaceutical market). The federal government administers the rebate program; it requires each manufacturer to calculate and submit two summary pricing measures: AMP and best price. AMP stands for Average Manufacturer Price and is the average in a calendar quarter of sales to the retail class of trade, including discounts.²⁸ “Best price” is the lowest per unit price at which the firm has sold in the previous quarter to any non-public buyer—essentially a minimum price. Using these inputs, the Centers for Medicare and Medicaid Services (CMS) calculate a unit rebate amount. For brands, this has two parts. First, the greater of 23.1 percent (HR 3590 Sec. 2501 Patient Protection and Affordable Care Act) or the difference between AMP and best price. In this way, the rebate rule ensures that Medicaid receives the minimum price offered by the manufacturer if that generates a lower net price than the fixed percentage discount. This rebate rule is easy to recognize as a most-favored nation (MFN) provision. *Scott Morton (1999)* shows that, upon imposition, these rules raised minimum (and average) prices for pharmaceutical products in markets where Medicaid market share was high. In addition, the rebate has an inflation component, which has grown to be of significant magnitude. If a manufacturer increases prices faster than the rate of inflation (CPI-U), the additional increase must be returned to the state Medicaid programs as part of the rebate. Since drug prices have grown faster than general prices over the last 20 years, many drugs have significant inflation components. *Duggan and Scott Morton (2006)* find suggestive evidence that for high-Medicaid-share products the inflation component creates an incentive for manufacturers to launch new versions (pill versus capsule) of their drugs in order to obtain a new launch price (and reset the inflation calculation). The sum of the inflationary component plus the greater of the basic rebate or best price forms the rebate percentage. The head of the Congressional Budget Office testified in 2005 that the total rebate for branded drugs averaged 31.4 percent.²⁹ The rebate for generics is smaller because the basic rebate is lower for generics (11 percent, increasing to 13 percent in 2011) and the inflationary component is less significant since nominal prices tend to fall over time.

²⁸ The calculation of AMP is somewhat complex; the discounts and customers that are included or excluded from AMP calculations are provided in federal regulation.

²⁹ See Mr. Holtz-Eakin’s testimony for a summary of the Medicaid rebate and pharmaceutical pricing. <http://www.cbo.gov/doc.cfm?index=6564&type=0>

6.2.2.2. Medicare

Two components of Medicare now cover pharmaceutical purchases. Prior to the introduction of Part D, Medicare Part B (physician services) only reimbursed drugs delivered in a physician's office.³⁰ Physician-administered drugs are drugs that are not taken at home by the patient, but are administered—usually injected or infused—in a physician's office. Prior to 2006, Medicare paid the physician a percentage of a branded drug's list price and many private payers did the same. For example, a list price of \$100 would first be marked up by 25 percent (to create AWP), and then be reimbursed at 95 percent of \$125, or \$119. The patient is responsible for a 20 percent co-payment on the drug, or \$24 in this example. This system yielded a positive margin on the drug if the physician could collect the co-payment from the patient and purchased the drug near list price.³¹ However, in situations where there was therapeutic competition among physician-administered products, purchase prices of these drugs sometimes fell significantly below list prices. Because many of these products are expensive, the margin the physician earned for dispensing the drug grew large in dollar terms in these situations. In 2006, the Medicare Modernization Act (MMA) altered the Medicare payment for physician-administered drugs to 106 percent of the average sales price (ASP) of the product in the previous quarter, including all discounts and rebates. ASP is calculated by the manufacturer for each of its drugs and reported to CMS each quarter. ASP data became public beginning in 2005 through CMS. Many private payers changed their reimbursement procedures to match Medicare, so the ASP methodology is now very prevalent. The profit margin for the physician on the drug is proportional to the cost of the drug, which is appropriate if some of the physician's costs are inventory, for example. Furthermore, the physician has an incentive to search for low-cost sources of the drug, since he is reimbursed at a fixed price. If buyers create price competition that drives down market price, or price changes for any other reason, the next quarter's ASP will reflect those changes.

Payments to hospitals are made using fixed payments for diagnoses. Medicare pays hospitals a set rate for a patient with a particular condition (DRG, or diagnosis-related group). This leaves the hospital as residual claimant and so it has an incentive to minimize costs. Physician-administered drugs given in a hospital are therefore not reimbursed directly (using ASP or any other methodology) but the hospital must pay for them out of the bundled DRG payment. The hospital, however, has influence over

³⁰ This is also largely true in private sector health plans—the physician-administered drugs are included under the medical benefit rather than the pharmacy benefit. Interestingly, the management services of the PBM have not been used extensively in the medical benefit compared to their penetration in the pharmacy benefit. Rather than creating a formulary and establishing financial incentives to use particular products, as would be done by a PBM, payers often reimburse the physician for physician-administered drugs using a fixed-price contract.

³¹ Patients with supplemental insurance, such as Medigap, use that coverage to pay their co-payments. In a simple example like this, a physician can break even on drug costs even if a large fraction of his patients do not pay their drug co-payments.

the pharmaceutical treatments physicians can prescribe to patients in the hospital. The hospital can therefore bargain in the same manner as a PBM. It negotiates for the lowest price possible, and can threaten to use a therapeutic substitute if its price and quality are superior.

The share of pharmaceutical expenditure that is physician administered is growing because the biologic market is growing and many of these drugs are injectables. The problem of developing cost-effective procurement techniques for biologics and physician-administered drugs is unresolved and will be an interesting area for future research. For example, one physician likely sees patients from many different insurance plans, and those plans may contract with different competing physician-administered drugs. If there were several biosimilars on the market, it is hard to know how the physician would stock them all, handle the logistics, keep track of expiration dates, and afford the inventory cost. While the institutions that have grown to create competition among generic drugs and drive down prices do not generally exist for biologics, Medicare's significant share of the market implies that the regulations by which Medicare purchases or reimburses physicians for biologics will greatly affect incentives for price competition and entry.

The introduction of Medicare Part D expanded coverage of pharmaceuticals. Part D does not, at present, require rebates, though beneficiaries only pay about 25 percent of the cost of the basic Part D benefit, with federal subsidies making up the balance. Instead, private insurance companies negotiate over prices as usual with manufacturers. Critics thought this would result in high prices being paid by Part D and indirectly by taxpayers. In fact, [Duggan and Scott Morton \(2010, 2011\)](#) show that prices in Part D, at least for the first two years of the program, were lower than cash prices paid by seniors who were uninsured before the inception of the program. The analysis exploits variation across drugs in the share of patients eligible for Medicare in 2002/03, before the program was passed or begun. The drugs with higher sales to Medicare-eligible patients experience a drop in price (IMS revenue divided by IMS quantity) in 2006 relative to other drugs. Further, the drop moves with the drug's share of "uninsured in 2003, but Medicare eligible" patients. Lastly, the drop does not occur for drugs with market power due to their position on the CMS formulary. This suggests that insurer bargaining was ineffective in lower prices for drugs that had no therapeutic substitutes.

6.2.2.3. Other

Other government entities, such as the Veterans' Administration and the Department of Defense, also purchase drugs, and achieve some of the lowest transaction prices. These agencies purchase drugs off the Federal Supply Schedule and have some of the most aggressive and restrictive formularies in the country, especially the VA. This results in the Veterans' Administration purchasing at what are widely regarded as the

lowest prices in the US. Many comparisons are made to VA prices without adequate recognition that the VA restricts access by beneficiaries to many therapies that it considers cost ineffective. The VA and DoD are also helped in their negotiations by being exempt from the “best price” provision in the Medicaid rebate rules so that discounts made to them do not trigger an increase in a manufacturer’s rebates. Clearly, a buyer that has the ability to negotiate for a low price would prefer to be exempt from the Medicaid MFN so that the seller is not weighing the fact that all his Medicaid sales will also occur at the negotiated price. Many buyers would therefore like to be exempt from the best price rule. Since 1991, Congress has passed additional regulations that exempt progressively more buyers. The regulations are subject to interpretation, but many observers conclude that rebates to a PBM that does not take delivery of the product should be exempted from the best price calculation—and PBMs collectively serve a large share of the market. By contrast, a manufacturer’s price to a traditional HMO that runs its own pharmacies (e.g. Kaiser) does get included in the best price calculation. We see here an example of how the government’s price regulation favors certain organizational forms in the delivery of health care and penalizes others.

A recent clever pricing innovation from manufacturers that makes an interesting topic for future research is the impact of brand coupon cards. These are cards issued by a manufacturer that pay the difference between a patient’s generic co-payment and branded co-payment. That charge is borne by the manufacturer, which directly pays the pharmacy. By absorbing the difference between the products, the manufacturer removes the patient’s financial incentive to buy the generic. As explained above, this financial incentive is created purposefully by the PBM to drive consumption to more cost-effective products. Because the difference in the co-payment is typically much smaller than the difference in price of the two products, the insurer’s costs are higher when the consumer chooses the brand. The problem for the insurer is that typically it cannot tell that the consumer has used the coupon card because the data from the pharmacist only shows that the branded co-pay was paid—not how it was paid. This nicely demonstrates the strategic interaction between the PBM, who is trying to drive demand to low-cost products, and the branded manufacturer, who is trying to negate those incentives.



7. MARKETING OF PHARMACEUTICALS IN THE UNITED STATES

Because pharmaceutical firms spend as much on promoting their products as they do on research and development ([Gagnon and Lexchin, 2008](#)), drug advertising is a contentious issue in policy debates. Few products sell for the markups of price over marginal cost that characterize drugs. High margins also imply what a

manufacturer will spend on marketing to increase demand (Dorfman and Steiner, 1954). The net revenue return on marketing depends on the elasticity of quantity with respect to marketing and the margin of price over cost. Particularly for new products, marketing can introduce awareness and thereby increase quantity. However, marketing efforts that provide financial or non-pecuniary benefits to physicians may be less benign. Competition also drives advertising: if a rival invests in promotional efforts, a firm's best response is to increase its own marketing.

A significant fraction of all pharmaceutical firm promotional expenditure is spent on "detailing." Promotion of prescription pharmaceutical products directly to physicians appears to be effective in selling those drugs, though it is important to know whether the increase in sales is a result of information provision or the physician acting as an imperfect agent for patients. In a perfect world, physicians might choose which drugs to prescribe by reading professional journals where academic studies or new advances in the field were presented impartially, perhaps by experts in the area. Instead, a significant source of physician information about new pharmaceutical treatments is the manufacturers of the products themselves (Podolsky et al., 2008). While physicians may believe that their judgment is not affected by detailing, academic work on the use of generics suggests otherwise. In the few months before a brand loses patent protection, its manufacturer typically stops detailing it because the manufacturer anticipates much of the resulting sales will accrue to the generic drug. When the patent expires and the generic enters, the effective price of the molecule falls. However, Huckfeldt and Knittel (2010) show that on average, the total number of units of the drug consumed, both brand and generic, *also* falls noticeably around patent expiration, which is not what an ordinary model of demand would predict. They estimate a 20 percent drop in quantity prescribed on average from six months before patent expiration to six months after. The authors conclude that the reduction in detailing best explains the decline in the quantity sold of the molecule. The drug itself is unaltered and, indeed, has become cheaper. The effect of drop in marketing must on average outweigh any positive incentives due to the price fall.³²

This is only one example of imperfect agency; as physicians are people subject to the behavioral biases, one might expect there are other instances of the impact of promotion on prescribing. Empirically identifying the effect of promotion on prescribing is very difficult because almost all promotion of pharmaceuticals is accompanied by some scientific information, though one would expect for a drug promoted for 10 years or more during its patent life that the "new information" content would be minimal after its introduction. Determining the causal impact of the two separately is therefore very hard. A recent article finds that Japanese physicians surveyed "believed

³² The exception to this pattern is the entry of the first generic in a large therapeutic class with close substitutes, as in the example of Zocor and Lipitor above.

that they were unlikely to be influenced by promotional activities, but that their colleagues were more susceptible to such influence than themselves.” This asymmetry of beliefs is a recurring theme in this literature (Saito et al., 2010). The authors conclude that Japanese doctors are “at risk” from pharmaceutical promotions. The impact of promotion on prescribing behavior is an important area for more, and better, academic research. Another interesting area for future research is the optimal regulation of pharmaceutical promotion under different assumptions about physician behavior.

Another fertile area for both empirical work and economic modeling is the nexus between off-label prescribing and promotion. Dresser and Frader (2009) point out that a problematic interaction between off-label prescribing and detailing could easily arise. The detailing force has an incentive to promote the off-label use, as this will boost sales with low effort. (Additionally, off-label sales do not generate liability for the manufacturer, as it is the physician’s decision to prescribe off-label.) Further, detailing representatives are permitted to distribute academic literature that reports on off-label uses. Kirsch (2009) argues that the subset of clinical trial results that are published in the academic literature are chosen by the firm to be favorable to the product and therefore useful in marketing efforts. Osborn (2010) provides a legal treatment of regulations in off-label area and areas of potential improvement.

Promotion of pharmaceuticals is currently an active area for litigation and for new regulation. It is also an active area for self-regulation by both the medical profession and pharmaceutical firms. Many medical schools (and many HMOs) have recently significantly limited interactions with detailing representatives.³³ Medical schools and journals are also requiring more disclosure about financial ties a physician may have with a pharmaceutical firm.

Arguably, much of the impact of promotional tactics by pharmaceutical firms is likely to be business stealing and therefore zero sum. To the extent that firms are not expanding the market for the treatment but shifting shares among themselves, they may be in a prisoner’s dilemma. Each firm would like to detail less, but only if the others detail less. In 2009, the industry trade association PhRMA introduced a voluntary Code on Interactions with Healthcare Professionals. This code limits informational presentations to the workplace or similar settings, limits entertainment to “modest meals,” and prohibits trips to resorts, sponsored recreation, and gifts to the physicians, including little trinkets such as pens and pads with drug names on them. The Code requires the independence of continuing medical education (CME) content and the content of sponsored conferences. Companies may pay physicians to be speakers as long as the speakers are trained and their financial ties are disclosed. Manufacturers cannot agree among themselves to limit marketing without violating US antitrust laws. Nonetheless, the 2009 voluntary PhRMA code may be advantageous

³³ <http://www.amscorecard.org/> is an interesting website containing medical school policies.

for the industry in several ways: it lessens the possibility of regulation and restricts promotional competition among firms. It also arguably improves the quality of information received by medical professionals. The impact of these changes on the design of clinical trials, marketing choices by firms, utilization, and prices is an important area for future research.

There is a burgeoning literature on the effects of Direct-to-Consumer (DTC) advertising on drug consumption and cross-price elasticities of demand. DTC is often used to expand the market. Many of the therapeutic categories in which there is a lot of DTC are underdiagnosed or undertreated therapeutic areas, such as depression or seasonal. A person who sees an ad on TV may not have realized that there was a treatment for her problem and seek the advice of a doctor; [Iizuka and Jin \(2005\)](#) found that every \$28 of spending on DTC advertising led to an additional doctor's visit within 12 months. A second category of DTC advertising focuses on long-term treatments for which patients have poor compliance. The length of time for which a person newly diagnosed with a chronic disease takes his medication is approximately three years on average. [Wosinska \(2005\)](#) shows that seeing advertisements on TV will help the patient remember that the drug is doing him good and improve his compliance. Despite its visibility, DTC is a relatively small component of total pharmaceutical promotional expenditures.

The marketing of prescription drugs in the United States is an area of active regulation and active private sector policy change. For this reason, research in areas of optimal regulation of marketing, organizational and incentive design in physician groups, and strategy and incentives of firms would make significant contributions to the economics literature and to policy.



8. CONCLUSION

Past trends are likely to be an imperfect guide to the near future with respect to trends in drug pricing and costs. Although the underlying technology of drug treatments changes slowly, regulatory chance and patent-related events can have significant effects on market conditions. There are currently a number of blockbuster small-molecule products that have just lost, or are about to lose, patent protection ([Berndt and Aitken, 2010](#)), including the world's largest selling drug by sales, Pfizer's Lipitor. The prices of these medicines will fall as generic entry occurs and (with inelastic demand) overall expenditure on small-molecule drugs will also fall, at least for the drugs with generic competitors.

Biologics may have sufficient price and quantity growth to cause overall pharmaceutical spending to continue to rise smartly. For example, one consulting report

forecasts that biologic revenues will grow at a CAGR of 10 percent over the next 15 years.³⁴ Another sends the same message: “Big Pharma companies forecast about 60% of revenue growth to come from biologic products. The forecast revenue growth rate to 2010 for biologics is 13%, compared to 0.9% for small molecule products.”³⁵ As noted above, what remains unclear is the extent to which competition from biosimilars will check this forecast growth.

The US and most other countries face a serious problem with rising health care costs and will have to find some method to restrict expenditure growth. A system of paying for any treatment a physician determines is necessary, at any price the innovator chooses, is unsustainable. Research into the effectiveness of solutions used in various countries will be necessary and informative to the policy debates taking place in developed countries as well as emerging markets.

In particular, current pricing patterns and mechanisms to induce innovation will continue to be challenged. As countries like India, China, and Brazil achieve higher levels of development, they will have greater ability to contribute to the cost of providing incentives for new product development. But declining R&D productivity and concerns about the shortcomings of the patent system may require rethinking the model of drug development and marketing.

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³⁴ Biosimilars and follow-on biologics: the global outlook 2009–2024 (2010), visiongain LTD, London, England.

³⁵ <http://www.pharmameddevice.com/app/homepage.cfm?appname=100485&linkid=23294&moduleid=3162>

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