Regulation of the Pharmaceutical-Biotechnology Industry

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Introduction

Pharmaceuticals and human biologic products are regulated in virtually all aspects of the product life-cycle: safety, efficacy and manufacturing quality as a condition for market access; promotion; and pricing. Since the regulatory structure developed for pharmaceuticals has largely been extended to human biologic medicines, we hereafter use “pharmaceuticals” to include biologics, and we note explicitly where biologics are treated differently. The rationale for heavy regulation of pharmaceuticals is not intrinsic natural monopoly, since any market power enjoyed by individual products derives ultimately from government-granted patents. Rather, regulation of market access, manufacturing and promotion arise because product efficacy and safety can be critical to patient health but are not immediately observable. Evaluating safety and efficacy as a condition of market access and monitoring manufacturing quality and promotion accuracy over the product life-cycle are public goods that can in theory be efficiently provided by an expert agency such as the Food and Drug Administration (FDA). By contrast, price regulation is best understood as a response by public insurers to the fact that insurance makes consumers price-insensitive. When consumers are heavily insured, producers of patented products face highly inelastic demand and hence can charge higher prices than they would in the absence of insurance. Price regulation and other reimbursement controls are a response of government payers to this interaction of insurance and patents.

Although these considerations suggest that regulation of the pharmaceutical industry is potentially welfare enhancing, designing the optimal structure of such regulation is not simple. Market access regulation entails both resource costs and foregone patient benefits in terms of

fewer drugs and delay of those that do launch. Measuring these costs, designing the optimal regulatory structure and finding the best balance between costs and benefits has been the subject of both academic research and policy debate and experimentation. Optimal regulation of promotion is a relatively recent extension of this debate. On the pricing side, regulation should ideally constrain pricing moral hazard while preserving insurance coverage for patients and sufficient patent power to assure incentives for appropriate research and development (R&D). Much has been learned from the experience with different price regulatory regimes, mostly in countries with national health insurance systems. But designing regulatory structures that are both theoretically sound and empirically practical remains an important theoretical and policy challenge.

In this paper, Section I describes the technological characteristics of the pharmaceutical sector and the primary objectives of regulation. Sections II provides an overview of safety and efficacy regulation in the US and abroad. Section III reviews the empirical evidence, lessons learned and proposals for change in safety and efficacy regulation.

Section IV discusses patents, focusing on those aspects of pharmaceutical patenting that interact with regulation, which include patent extension policy, regulation of generic entry, the extension of patents to developing countries and affordability concerns.

Section V describes regulation of pricing, reimbursement and profit; the evidence on effects of this regulation; and evidence on industry structure and competition. Section VI summarizes evidence on pharmaceutical promotion, focusing mainly on direct to consumer advertising (DTCA), which has become far more important over the last decade, following changes in regulatory oversight that remain contentious and unsettled. The final section concludes on lessons learned and areas for future research.

I. Technological Background and Objectives of Regulation

The pharmaceutical industry is characterized by unusually high costs of R&D. The US research-based industry invests about 17 percent of sales in R&D, and the R&D cost of bringing a new compound to market was estimated at $802m. in 2001, an increase from $138m. in the 1970s and $318m. in the 1990s (DiMasi et al. 2003). This high cost per new drug approved reflects high costs of pre-clinical testing and human clinical trials, high failure rates and the opportunity cost of capital tied up during the 8-12 years of development. To some extent, this high and rising cost of R&D reflects regulations that exist in all industrialized countries, requiring that new compounds meet standards of safety, efficacy and manufacturing quality as a condition of market access. The main initial focus of regulation since the 1930s was safety, and this has reemerged recently as a critical issue. Since the 1960s most countries also require pre-approval evidence of efficacy, monitor manufacturing quality throughout the product life, and regulate promotion and advertising to physicians and consumers.

The economic rationale for these requirements derives from the fact that the risks of benefits of pharmaceuticals are non-obvious, can differ across patients, and can only be known from controlled studies in large patient populations. Gathering and evaluating such information is a public good, and a regulatory agency that has both medical and statistical expertise can more accurately and efficiently monitor and evaluate the evidence from clinical trials than can individual physicians or patients. However, regulation that requires extensive pre-launch clinical trial data on safety and efficacy increases the R&D costs incurred by firms, increases delay in launch of new medicines, and may reduce the number of drugs developed and the extent of competition. The size and duration of clinical trials required to detect remote risks or cumulative risks from long term therapies can be large. The rising costs of R&D, combined

with new technologies for evaluating information, have prompted recent initiatives to accelerate approvals and optimally integrate evidence from pre-approval clinical trials with post-approval observational experience. In the US, the statutory regulation of pharmaceuticals through the Food and Drug Administration (FDA) is in addition to – and uncoordinated with -- the increasing level of indirect regulation through tort liability. Critical unresolved issues in market access regulation are: (1) how much information on risks and benefits should be required prior to launch; (2) what is the appropriate trade-off between benefits and risks, given that some risks are inevitable; and (3) what is the appropriate mix of pre- and post-launch monitoring of risks, what methods should be used, and what is the appropriate mix of regulation by an expert agency (such as the FDA or an independent agency) and tort liability?

A second important characteristic of the pharmaceutical industry is the critical role of patents, which results from its research intensity. Given the cost structure with high, globally joint fixed costs of R&D and low marginal costs of production, patents are essential to enable innovator firms to recoup their R&D investments. However, patents work by enabling innovator firms to charge prices above marginal cost, which raises issues of appropriate levels of prices and profits and appropriate structure and duration of patents. Concern that prices may be excessive is one rationale for price regulation in many countries (although, as discussed below, insurance coverage is probably an equally important determinant of pricing decisions).The regulatory criteria for admitting post-patent generic entrants is a contentious issue, even for traditional chemical compounds. More complex and yet to be resolved by regulatory agencies are the conditions for approving “biogenerics”, that is, alternative versions of large molecule, biotechnology products such as proteins, monoclonal antibodies etc. As the number and utilization of these expensive biologics expand, so does concern to establish a low-cost

regulatory path for approval of generic biologics without full scale clinical trials, in order to stimulate post-patent price competition.

The global nature of pharmaceutical products has also raised contentious questions over optimal patent regimes in developing countries and cross-nationally. The WTO's Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS) requires all member countries to recognize 20 year product patents by 2015. However, in response to concern that patents would make drugs unaffordable in low income countries, TRIPS permits member states to issue compulsory licenses in the event of a "national emergency." TRIPS also leaves decisions on parallel imports to the discretion of individual member states. In most industrialized countries including the US, the traditional rule has been national exhaustion of patent rights, which means that a patent holders can bar the unauthorized importation of the patented product (parallel trade) from other countries. Proposals in the US to legalize parallel trade, including drug importation by mass wholesalers, would undermine the traditional rule of national exhaustion of patent rights. If enacted, this would undermine manufacturers' ability to price discriminate between countries, which could have serious welfare consequences as discussed below.

A third characteristic of the pharmaceutical industry is the dominant role of third party payment through social and private health insurance. Like any insurance, third party payment for drugs creates moral hazard, with incentives for consumers to overuse and/or use unnecessarily expensive drugs. In addition, by making demand less elastic, insurance creates incentives for firms to charge higher prices than they would in the absence of insurance. In response to these insurance-induced distortions, since the 1980s government-run health systems in most countries have adopted elaborate regulatory systems to control pharmaceutical expenditures, through regulation of manufacturer prices or reimbursement, limits on rate of

return on capital, on total drug spending or on company revenues. Private insurers in the US also use formularies of covered drugs, co-payments and negotiated prices, but because these private insurers must compete for market share, their controls lack the leverage of public payer controls. The controls adopted by both public and private insurers have significant effects on demand for pharmaceuticals, on the nature of competition and hence on profitability, incentives for R&D and the supply of new medicines.

Because pharmaceuticals are potentially global products and R&D incentives depend on expected global revenues, national regulators face free rider incentives. Each country faces a short run incentive to adopt regulatory policies that drive its domestic prices to country-specific marginal cost, free riding on others to pay for the joint costs of R&D. But if all countries pay only their country-specific marginal cost, R&D cannot be sustained. The global nature of pharmaceuticals and the long R&D lead times – roughly 12 years from drug discovery to product approval, on average – make the incentives for short run free riding by individual countries particularly acute. While there is widespread consensus in support of differential pricing between the richest and poorest nations, no consensus exists on appropriate price levels for these countries or between high and middle-income countries. In practice, the ability of pharmaceutical firms to price discriminate is diminishing as more countries adopt national price regulatory policies that reference prices in other countries and/or legalize drug importation (also called parallel trade or international exhaustion of patent rights). These cross-national price spillovers in turn create incentives for firms to delay or not launch new drugs in low price markets, if these low prices would undermine potentially higher prices in other markets. Thus the design of each country's price regulatory system can affect not only their domestic

availability of drugs but also availability in other countries through price spillovers in the short run, and through R&D incentives in the long run.

Unlike some other industries, regulation of the pharmaceutical industry has not diminished or undergone fundamental changes over recent decades, although focus of market access regulation has shifted between concerns for safety vs. cost and delays, and the structure of price/profit regulation has become more complex. The motivations for regulation of pharmaceuticals -- imperfect and/or asymmetric information for market access regulation, patents and insurance-related moral hazard for price/profit regulation – remain and have, if anything, increased over time. These are summarized in Table 1. Regulatory trends over time within the US and cross-national differences provide a wealth of useful experience from which some lessons can be learned. This review will focus primarily on US issues and evidence, reflecting the dominance of US-based literature. Moreover, US regulatory policy has a disproportionately large effect on the industry, because the US market accounts for almost fifty percent of global pharmaceutical revenues. However, we draw extensively on experience from other countries for evidence on price and reimbursement regulation, cross-national spillover effects and access to pharmaceuticals in developing countries.

Insert Table 1 here

The appropriate economic model of the pharmaceutical industry is either monopolistic competition or oligopoly with product differentiation. However, both positive and normative analysis must also take into account the roles of physician prescribing and third party payment as key factors is demand elasticities and cross-price elasticities. Moreover, models of optimal pricing must recognize the importance of R&D and fixed costs. In this context, welfare conclusions about optimal levels of R&D, product variety or drug use are problematic. Most

analysis to date and most of our discussion are therefore positive rather than normative. Although the industry is characterized by high fixed costs, models in which firms endogenously choose sunk costs, either in the form R&D or promotion to retain competitive advantage and deter competition / entry (Sutton, 1991), do not seem appropriate and appear to be clearly refuted by the evidence of entry over the last two decades by thousands of small firms. We return to this below.

II. Overview of Safety and Efficacy Regulation

1. The US

The first comprehensive federal legislation regulating food and drugs in the US was the Pure Food and Drug Act of 1906 (The Wiley Act) which required that product labels and packaging not contain false statements about curative effects, but stopped short of requiring manufacturers to provide evidence to prove safety or efficacy (Palumbo, 2002). The 1938 Food, Drug and Cosmetics Act (FDCA), which replaced the Wiley Act, required any firm seeking to market a new chemical entity (NCE) to file a new drug application (NDA) to demonstrate that the drug was safe for use as suggested by the proposed labeling. The Food and Drug Administration (FDA) had 180 days to reject the NDA. As new forms of print and radio advertising had emerged since the Wiley Act, the FDCA established jurisdiction over drug advertising, but policing was left to the Federal Trade Commission (FTC) rather than the FDA. This Act also established the requirement that patients obtain a prescription from a physician in order to obtain retail drugs.

The 1962 Kefauver-Harris Amendments to the 1938 FDCA were the outcome of hearings that were initiated due to concern over the proliferation, pricing and advertising of

drugs of dubious efficacy. The final legislation also reflected concern to strengthen safety requirements, following the thalidomide tragedy that caused hundreds of birth defects in Europe whereas the drug was still under review in the US. The 1962 Amendments define the regulations that largely still operate today. They strengthened safety requirements; added the requirement that drugs show proof of efficacy, usually by double blind, randomized controlled trials of the drug relative to placebo; removed the time limit (previously 180 days) within which the FDA could reject an NDA; extended FDA regulation to cover clinical testing and manufacturing; and restricted manufacturers' promotion to approved indications. Basic requirements for promotional materials were defined, including that such materials cannot be false or misleading; they must provide a fair balance of risks and benefits; and they must provide a "brief summary" of contraindications, side effects and effectiveness. Regulatory oversight of promotional material was ceded back to the FDA from the FTC.

The presumption underlying the requirement for proof of efficacy was that imperfect and possibly asymmetric information prevented physicians and consumers from making accurate evaluations, leading to wasted expenditures on ineffective drugs and other associated costs, and excessive product differentiation that undermined price competition. Although Phase III trials, involving double-blinded, randomized placebo-controlled trials in large patient populations, were initially intended to establish efficacy, over time these trial requirements have been expanded to detect remote risks and/or cumulative treatment risks of chronic medications. The size and duration of clinical trials, together with increased regulatory review time, added to delay in the launch of new drugs, leading to foregone benefits for consumers, shorter effective patent life and foregone revenue for firms, albeit with the intent of avoiding potentially larger costs for consumers. [1] Moreover, since some regulatory costs are fixed, independent of

potential market size, such regulation raises the expected revenue threshold required to break even on a new drug, leading to higher break-even prices, *ceteris paribus,* and fewer drugs, particularly drugs to treat rare diseases with small potential market size.

Subsequent legislation has addressed several of these cost-increasing effects of the 1962 Amendments. The Orphan Drug Act of 1983 (ODA) significantly increased incentives to invest in orphan diseases (defined as conditions that affect less than 200,000 individuals in the US) by increasing revenues and decreasing costs: drugs that receive orphan status are granted market exclusivity for seven years (that is, similar compounds will not be approved to treat the same condition) and receive a 50% tax credit for expenses accrued through clinical testing. Orphan drugs may also benefit from research grants from the NIH and accelerated or Fast Track FDA approval (see below). Following the ODA, the number of orphan drug approvals has increased significantly. Between 1979 and 1983, orphan drug approvals increased at approximately the same rate as other drugs. However by 1998, there were more than five times as many orphan drugs as in 1979, but fewer than twice as many non-orphan drugs (Lichtenberg and Waldfogel, 2003).

An important initiative to reduce delay in the FDA review of regulatory filings was the Prescription Drug User Fee Act (PDUFA) of 1993.[2] Under PDUFA, pharmaceutical firms agree to pay substantial user fees to enable the FDA to hire more reviewers and hence expedite drug review.[3] In fiscal year 2004, the $251 million in fees accounted for 53% of total processing costs at the FDA (FDA 2005d). In addition to user fees, the PDUFA created a system that classifies new drug applications that target unmet medical needs as “priority review”, as opposed to “standard review”, with target duration of 10 months for standard review and 6

months for priority review drugs. Prior to 1992, the FDA classified drugs into either A,B or C categories, and an AA category was developed to speed the review of AIDS products.

The 1997 FDA Modernization Act (FDAMA) renewed the priority review system and created Fast Track status to potentially expedite the entire clinical trial process for novel drugs (FDA 2005b), by additional meetings, correspondence and review programs with the FDA. Products may receive fast track designation if they are "intended for the treatment of a serious or life-threatening condition" and "demonstrate the potential to address unmet medical needs for the condition"(FDA 1997; FDA 2004b). In addition, "Accelerated Approval" status refers to FDA acceptance of approval on the basis of a surrogate endpoint that "is reasonably likely to predict clinical benefit" rather than a clinical benefit. Accelerated approval is one of the potential review processes for which fast track drugs may qualify. Fast track has reduced overall development times by approximately 2.5 years (Tufts Center for the Study of Drug Development (2003)), but some have argued that fast track and priority review are associated with increased prevalence of post-approval adverse events (see below).

The increased time taken by clinical trials and regulatory review not only increases the out-of-pocket cost of R&D but also reduces effective patent life. To address this, the 1984 Patent Term Restoration and Competition Act (hereafter the Hatch-Waxman Act) granted innovator firms an extension of patent term for up to five years.[4] However, as a quid pro quo, the 1984 Act expedited post-patent entry by generic manufacturers. Specifically, generic manufacturers are permitted to work on the active ingredient before the patent expiry (the Bolar exemption) and generics can be approved with an Accelerated New Drug Application (ANDA), which requires only that the generic prove bioequivalence and chemical equivalence to the originator product, without new safety and efficacy trials. Hatch-Waxman conferred a five year

maximum data exclusivity period after the innovator's NDA approval (three years for other data not submitted in support of an NCE approval), after which generic firms are free to use innovator clinical trial data to prepare their ANDA (the EU allows 10 years of data exclusivity) (Kuhlik, 2004). Moreover, Hatch-Waxman grants to the first generic firm to successfully challenge a patent (a paragraph IV filing) 180 days as the exclusive ANDA-approved generic in the market, after the originator's patent expiry (Kuhlik, 2004). In recent years, originator firms have been accused of "evergreening" their drugs by late filing of follow-on patents on minor aspects of the compound; excessively litigating challenges to patents; entering collusive agreements with generic manufacturers; and developing follow-on products that resemble that original product except for minor changes that nevertheless may suffice for a new patent e.g. single isomer versions. The FTC has taken antitrust enforcement action against agreements between originator and generic firms to delay the launch of generics (FTC, 2002). The 2003 Medicare Modernization Act includes changes to deter these practices, but this remains an unsettled area.

The Hatch-Waxman Act laid the necessary foundation for fast and cheap generic entry immediately after patent expiry in the US. Generics account for over 50 percent of prescriptions filled, compared to 19 percent in 1984 when Hatch-Waxman was enacted (FTC, 2002); but generics account of only about 10 percent of drug expenditures, reflecting their low prices. However, the rapid and comprehensive generic erosion of originator market shares that now occurs also reflects state-level legislation authorizing pharmacists to substitute generics for originator drugs (unless the physician notes "brand required") and insurance reimbursement incentives to pharmacies and patients to accept generic substitution (see section V). The speed of generic entry, generic market shares and prices differ significantly across countries,

reflecting regulatory differences in market access and in reimbursement incentives for pharmacists and patients (Danzon and Furukawa, 2003). Empirical evidence related to Hatch-Waxman as well as cross-national differences are discussed below.

The FDAMA also initiated significant change in promotion regulation, by permitting companies to inform physicians of potential unapproved ("off-label") uses of drugs through the distribution of peer reviewed journals. It also permitted companies to issue economic analyses to payers, provided that the analysis "shall not be considered to be false or misleading…the health care economic information directly relates to an [approved] indication…and is based on competent and reliable scientific evidence"(FDA 1997).

The regulations governing direct to consumer advertising (DTCA) were subject to revised interpretation in an FDA Draft Guidance issued in 1997. Previously, product claim advertisements that named both the drug and the condition it treated were required to disclose all the risks and contraindications within the content of the advertisement (Wilkes, Bell et al., 2000). The 1997 FDA guidance still required firms to present a "fair balance" between risks and benefits and not mislead with false advertising; however, broadcast ads could meet the requirement for disclosure by providing several other sources to obtain the full label, including a toll-free number, an internet site, a print ad or a "see your physician" advice (US GAO 2002a). The 1997 draft guidance (formalized in 1999) stimulated the growth of DTCA, especially broadcast ads. Total DTCA spending grew from $266m. in 1994 to $2.47b. in 2000, while spending on television advertising increased from $36m. to $1.57b. over the same time period.

2. Other Industrialized Countries

Each country has its own drug approval process, although in practice smaller countries frequently review and reference approvals granted by other major agencies such as the US FDA or the European Medicines Agency (EMEA). Following the thalidomide tragedy and the strengthening of safety and efficacy requirements in the US in 1962, the UK tightened safety regulations in 1964 and added efficacy requirements in 1971. Other industrialized countries adopted similar regulations, although some, such as France and Japan, have less stringent efficacy requirements (Thomas, 1996).

In 1995 the European Union established the European Medicines Agency (EMEA) as a centralized approach to drug approval for EU member states. The EMEA offers two tracks to drug approval. The centralized procedure involves review by the EMEA and provides simultaneous approval of the drug in all countries of the EU. Alternatively, a firm can use the mutual recognition approach, seeking approval by one rapporteur country with reciprocity in other EU countries, subject to their review and objection. The EMEA is the required approval route for biotech products and is optional for other new drugs. National systems remain for products that seek approval in only a few countries.

Since the 1990s the regulatory authorities and the industry in the three major pharmaceutical markets – the US, the EU and Japan – have worked through the International Commission on Harmonization (ICH) to harmonize their regulatory requirements for safety, efficacy and manufacturing quality. As a result of the harmonization measures, companies can, to a significant degree, compile a single dossier for submission to the EMEA, the US FDA and Japan. However, some important differences in regulatory requirements remain and each agency still makes its own evaluation based on their own risk-benefit trade-off. For example,

the EMEA typically requires trials of new drugs relative to current treatment whereas the FDA more often uses a placebo comparator, except where use of placebo would imply unethical treatment of patients. Japan still requires some trials on Japanese nationals.

The EMEA and the UK Medicines Agency have adopted user fee programs to expedite review, and the EMEA has adopted an Orphan Drug Law. As a result of harmonization and other measures, differences in market approval requirements are no longer a major source of difference in timing of drug launch between the US and "free pricing" countries in the EU, notably the UK and Germany (until 2004). Larger differences remain in the approval process for generics. Measures similar to the US Hatch-Waxman provisions have been proposed for the EU but so far have not been adopted by the EMEA or by all EU countries' national regulatory agencies.

3. Developing Countries

More problematic is the appropriate regulatory agency and standards for drugs intended primarily for use in developing countries. Since disease incidence, competing risks, costs and benefits of treatment may be vastly different in these countries, decisions based on FDA or EMEA risk-benefit trade-offs may be inappropriate. For example, in 1999 Wyeth withdrew its rotavirus vaccine, Rotashield, from the US market due to concern that the risk of severe (but infrequent) intussuception would be unacceptable relative to the vaccine's benefit, given the relatively low risks from rotavirus in the US. The vaccine became unavailable in developing countries, which expressed no interest in using it, although their benefit-risk ratio would have been very different, given their much higher incidence and higher death rates from rotavirus (Hausdorff, W. 2002).

More generally, if willingness to pay high R&D and delay costs in order to reduce drug risks is income elastic, then requiring that drugs targeted at developing countries meet the standards of the FDA/EMEA may impose inappropriately high regulatory costs in developing countries. On the other hand, anecdotal evidence indicates that the developing countries themselves are unwilling to accept drugs that are not approved for marketing in the US or the EU. Moreover, inappropriately high costs of regulatory compliance are probably less important than low potential revenues in discouraging R&D for drugs to treat diseases prevalent only or predominantly in less developed countries, such as malaria, TB or leischmaniasis. Various "push" and "pull" subsidy mechanisms have been proposed and some have been implemented, to increase financial incentives for investment in these LDC-only drugs (see, for example, Kremer (2002); Mahmoud et al. (2006). Ridley et al. (2006) propose a transferable voucher for accelerated review by the FDA that could be used for any other product. While this might be politically more feasible than a subsidy financed by a broader tax, the efficiency and distributional consequences could be less desirable.

III. Effects of Safety and Efficacy Regulations: Evidence and Issues

1. Costs of Regulation

Much of the early economic analysis of pharmaceutical regulation focused on effects of the 1962 Kefauver-Harris Amendments on R&D costs, delays in launch of new drugs, decline in the number of new drug introductions and changes in industry structure that occurred in the 1960s and 1970s, raising questions of causation (for example, Peltzman, 1973; Grabowski, Vernon et al., 1978; Baily, 1972; Wiggins, 1981).

Number of new drug launches Grabowski, Vernon et al. (1978) report that the number of NCEs fell from 233 in the five-year period 1957-1961 to 93 in 1962-1966 and 76 in 1967-1971. Some decline would be consistent with the intent of the legislation, if some of the prior introductions were ineffective. However, the percentage of total ethical drug sales accounted for by new NCEs declined roughly in proportion to the number of drugs, from 20.0 percent in 1957-1961 to 5.5 percent in 1967-1971. The authors contend that this finding is inconsistent with the argument that only the most insignificant drugs were eliminated.[5]

Grabowski et al. also attempt to measure the marginal reduction plausibly attributed to the 1962 Amendments after controlling for other possible contributing factors, including the depletion of new product opportunities; the thalidomide tragedy that may have made manufacturers and physicians more risk averse, hence reduced demand for new drugs; and pharmacological advances that may have raised R&D costs independent of regulation. They compared trends in NCE discoveries in the US relative to the UK, an appropriate comparator country because of its strong and successful research-based pharmaceutical industry. This is a quasi-natural experiment since the UK did not adopt efficacy requirements until 1971 and its 1963 safety requirements were statistically unrelated to the flow of new discoveries. Grabowski et al. find that research productivity, defined as number of NCEs per (lagged) R&D expenditure, declined sixfold between 1960-61 and 1966-1970 in the US, compared to a threefold decline in the UK, and that the 1962 Amendments increased the cost per new NCE in the US by a factor of 2.3. They conclude that these differentials are plausibly attributable to regulation, since the UK would have been equally affected by exogenous changes in scientific opportunities and testing norms and by any thalidomide-related change in demand. In fact, these estimates based on using the UK as a benchmark are probably conservative estimate because

regulatory changes in the US, as the largest single pharmaceutical market, would influence incentives for innovative R&D for all firms, regardless of country of domicile, and hence could have contributed to the decline in NCE discoveries in the UK.

R&D Cost per NCE There is little doubt that regulation has contributed to the increase in R&D cost per new drug approved, but the relative contribution of regulation vs. other factors is uncertain. Baily (1972) and Wiggins (1981) concluded that the 1962 Amendments led to a large increase in the R&D cost per new drug approved, but with significant variation across therapeutic categories. More recent evidence shows that the cost of developing new drugs has continued to outpace the CPI, despite no major change in explicit regulatory requirements, although undocumented changes in regulatory requirements may have occurred. DiMasi et al. (2003) found that capitalized cost per approved NCE, measured in present value at launch, grew from $138M in the 1970s to $318M in the 1980s and $802M in the 1990s. Roughly half of this total cost is out-of-pocket expense, including spending on drugs that ultimately fail; the remainder is foregone interest or opportunity cost of capital. The inflation-adjusted rate of growth of out-of-pocket costs has remained relatively constant (7.0% 1970-1980, 7.6% 1980-1990). Interestingly, despite – or because of – the major advances and investments in microbiology, combinatorial chemistry, high-throughput screening, robotics, bioinformatics, and genomics, that revolutionized drug discovery in the 1980s and 1990s, pre-clinical costs related to drug discovery have grown at a slower annual rate (2.3% in the 1990s) than the costs of clinical trials (11.8%) which reflect shifts in medical care technologies, rather than drug discovery technologies. The clinical cost growth rate in the 1990s includes an increase in number of trial participants, more procedures and higher cost per participant, the latter partly reflecting new medical care technologies. [6] Besides changing regulatory

requirements, other contributing factors include: change in types of drugs and diseases pursued, as R&D effort shifts towards more difficult diseases once the "low hanging" diseases have been addressed; increased focus on chronic diseases which require longer trials to detect cumulative effects; collection of economic as well as clinical data, to satisfy growing payer demands for evidence of cost-effectiveness; and possibly growing public demand for safety that might lead firms to invest voluntarily in larger/longer trials in order to detect rare effects.

For certain types of drugs, particularly those used by large populations of relatively healthy subjects, such as vaccines, reluctance to tolerate even remote risks is increasing the size and duration of trials in order to detect very rare adverse events. For example, recent trials for the rotovirus vaccine involve 70,000 patients. In a qualitative survey Coleman et al. (2005) report that vaccine manufacturers attribute vaccine shortages and reduced incentives for discovery, in part, to the high safety standards that are required by the FDA.[7] Danzon et al. (2005c) show that both regulatory requirements and competition have contributed to exit of vaccine manufacturers.

On the other hand, regulatory changes (such as use of biomarkers rather than survival as the endpoints, Fast Track status etc.) which expedite drugs that treat life-threatening diseases for which no effective therapies exist have no doubt reduced costs and delay, contributing to the recent dramatic growth in number of drugs approved and in development for cancer, inflammatory diseases etc. in recent years. Other factors such as advances in science and relatively generous reimbursement under Medicare Part B have also contributed to the proliferation of R&D, particularly biologics for these high priority conditions, making it hard to identify the net effect of regulatory changes on R&D. However, it seems safe to conclude that, given PDUFA, FDAMA and other measures that have been adopted to expedite trials and

review for high priority drugs, the balance has shifted and there is now less concern over undue costs and delay at least for these high priority drugs, and perhaps more concern over adequate proof of safety and efficacy.

Lags in Launch Several analyses find that the 1962 Amendments increased delay in launch of new drugs in the US relative to other countries (for example, Wardell (1973); Wardell and Lasagna (1975); Grabowski and Vernon (1978); Grabowski (1976); Wiggins (1981)). Grabowski and Vernon (1978) compare introduction dates in the US and the UK for drugs discovered in the US between 1960 and 1974. The proportion of drugs introduced first in the US declined significantly between 1960-1962 and 1972-1974, while the proportion introduced later in the US increasing significantly. The authors conclude that increased regulatory scrutiny in the US caused multinational companies to introduce new products abroad before their US launch. Similarly, Grabowski (1976) finds that many more drugs were introduced first in Europe despite most being discovered in the US or by US-based firms. Dranove and Meltzer (1994) estimate that the average time from a drug's first worldwide patent application to its approval by the FDA rose from 3.5 years in the 1950s to almost 6 years in the 1960s and 14 years in the mid 1980. They also found that, beginning in the 1950s, more important drugs - especially drugs that proved to be successful in the marketplace - have been developed and approved more rapidly than less important drugs. They attribute this differential to actions of drug companies as much as to regulatory priority setting.[8]

However, evidence from the 1990s indicates that the US no longer lags and may lead the major EU markets in number and timing of major new drug launches (Danzon, Wang and Wang, 2005). Given the coordination of standards and similarity of regulatory requirements in the European Medicines Agency (EMEA) and the US FDA, differences in launch timing

between the US and the EU appear to be driven less by differences in market approval requirements and more by price and reimbursement regulation in the EU, including the fact that price spillovers create incentives for manufacturers to intentionally delay launch in low-price markets. One exception is Japan which has relatively high launch prices and unusually long launch lags due to its unique market approval requirements, including country-specific trials.

2. Benefits of Safety and Efficacy Regulation

Compared to costs, there are many fewer studies of the benefits to consumers from regulation. The only significant attempt to weigh both the benefits and costs of the 1962 Amendments is Peltzman's (1973) study. He attempts to measure the benefit associated with the new efficacy standards by comparing the growth of market shares of drugs launched prior to 1962 to those launched after 1962. The assumption was that new products would capture greater initial market share after 1962 if the Amendments increased the average efficacy of new drugs relative to drugs already on the market (Peltzman 1973). He concludes that the benefits were minimal and were far outweighed by the costs of regulation, which he estimates as foregone consumer surplus due to the reduced flow of NCEs. These conclusions depend critically on the methods for estimating costs and benefits, which have been questioned (for example, Temin (1979)). In particular, benefits may be understated and costs may be overstated by ascribing the decline in NCEs solely to the regulation. Nevertheless, this is an important study because it offers a theoretical and empirical framework for evaluating the net benefits of the 1962 efficacy requirements.

Several recent studies have examined the benefits and costs of the priority review policy introduced by PDUFA in 1992. Undoubtedly, PDUFA expedited the time to market for

"priority" drugs. Between 1993 and 2003 the median time to approval declined from 14.9 to 6.7 months, while review times for "standard" products only decreased from 27.2 to 23.1 months (Okie, 2005). Olson (2000) uses data from 1990-92 and 1992-95 to examine the difference in the effects of firm characteristics on review times before and after the 1992 PDUFA. She finds that firm characteristics were not associated with review times after 1992, suggesting that the regulatory change helped eliminate firm advantages that existed prior to 1992. PDUFA was also subsequently amended to reduce filing fees for smaller firms.

Olson (2004a) also attempts to quantify the safety impact of PDUFA and compare the costs of faster approvals to the benefits. She finds that post-launch reports of adverse drug reactions (ADRs) are more likely for drugs that the FDA rates as "priority", after controlling for drug utilization, disease characteristics, patient characteristics, drug review time and year specific effects. Controlling for these factors, she concludes that there are 60-84% more serious ADRs, 45-72% more ADRs that result in hospitalization and 61-83% more ADRs that result in death due to PDUFA. In order calculate benefits from reduced delay, Olson uses Lichtenberg's estimate of how the increase in the stock of priority review drugs for particular therapeutic categories increased life expectancy for persons with those conditions (Lichtenberg, 2002). She finds that under the most conservative assumptions (biasing against safety) the safety impact reduces net benefit by just 8% (measured in expected gain in life years). A large share of the benefit is attributed to the faster launch of new drugs with priority review status. This figure increases to 11% if ADRs are under-reported by 30%. Subsequent research has found that ADRs gathered through the FDA post-marketing surveillance mechanisms generally underreport ADRs, but the degree is not well established (Brewer and Colditz, 1999; Bennett, Nebeker et al. 2005). Whereas Olson finds significant negative safety effects of accelerated

review, the General Accounting Office (US GAO, 2002b) found that drug withdrawals rates differed insignificantly between the period before and after the PDUFA; however, this study did not control for other factors that may have influenced drug withdrawals rates.

None of these studies estimate the savings to firms from accelerating the R&D process, including lower capitalized costs of R&D and increased effective patent life. DiMasi (2002) estimates that a 25 percent reduction in phase length for all phases of clinical trials would reduce the average cost per NCE by $129M, or by 16.1% assuming a base cost of $802M. Since this estimate is based on a random sample of 68 drugs that entered clinical trials between 1983 and 1994, it probably overstates the dollar savings for the types of drugs that receive fast track status, however the percentage effect may be valid.

3. Discussion and Proposals for Change in Regulation of Safety and Efficacy

Despite the reduction in regulatory review times under PDUFA, total R&D time remains high primarily due to duration of Phase III trials.[9] Concern to reduce launch delay without sacrificing risk information has led to growing interest in supplementing pre-launch randomized controlled trials (RCTs) with post-launch observational evidence, from either controlled or uncontrolled studies. Advances in data collection from routine care and in statistical methods for analyzing such data to adjust for possible nonrandom assignment of patients to different treatments offer a potentially rich and relatively cheap source of information that could supplement clinical trial data, providing larger sample sizes, detail on subpopulations and evidence on long term effects. The Center for Medicare and Medicaid (CMS) is undertaking such studies in order to evaluate effectiveness of alternative treatment regimens for the Medicare Drug Benefit. Integrating such findings with FDA's pre-launch data from RCTs could

significantly enhance the information base available for post-launch decisions – for example, on labeling changes by the FDA and/or reimbursement decisions by CMS -- and could potentially affect the relative role of the FDA vs. CMS.

The net benefit to consumers from a shift towards earlier approval of drugs based on biomarkers (such as tumor shrinkage) depends in part on whether post-launch studies are in fact completed, in order to validate that biomarker results are predictive of longer term efficacy in clinical outcomes (such as survival) and safety. An FDA survey as of September 30, 2005 reports 1,552 post-approval studies assigned to industry that have not been completed, of which 59% have not been started (FDA, 2005e). Details were not reported on when the follow up studies were initially requested or the firms involved. This limited evidence suggests that the optimal mix of pre- and post-launch monitoring will depend on political will for enforcement as well as statistical feasibility.

Although models of producer vs. consumer capture are no doubt relevant to understanding the regulation of pharmaceuticals, current events and crisis also play a major role in the shifting emphasis between safety and speed to market. For example, public and Congressional concerns focused on speeding up access to new drugs in the 1980s and 1990s, partly in response to the AIDS crisis. More recently, post-launch evidence on risks of some widely used drugs, including the COX-2 inhibitors for arthritis and pain, notably rofecoxib (Vioxx) and valdecoxib (Bextra), and the SNRI anti-depressants, have led to a range of proposals to enhance regulatory protection of safety. The FDA's expanded MedWatch program reports adverse events on an FDA website as soon as reported (Longman, 2005; FDA 2005c), enabling consumers to draw their own conclusions. In February 2005 the FDA created a Drug Safety Oversight Board (DSOB) to review safety issues on approved drugs. Critics argue that

such an effective oversight board should be independent of the FDA, as the approving agency, and/or that the FDA is captured by industry (Okie, 2005). Counter arguments are that co-ordination within the FDA of pre-launch review and post-launch monitoring permits greater consistency in decision-making and takes advantage of expertise and economies of scale in reviewing data. Others have called for requiring public disclosure of results from all industry supported clinical trials. Some journals have made public release a condition of publishing results, and some firms have voluntarily committed to release data (Longman, 2005). These policies should increase the information available to physicians and patients. On the other hand, increased risk of post-launch regulatory review, possibly by an agency using different risk-benefit criteria than the FDA, would increase post-launch risk for firms and could reduce incentives to invest in drugs with novel mechanisms or for new targets.

Some argue that drugs should be available for prescription after successful completion of phase II trials with the stipulation that firms are mandated to continue with phase III trials. In such a system, patients and physicians would make their own evaluations as to whether expected benefits outweigh risks (Madden, 2004).[10] The counterargument is that the limited safety and efficacy data available after phase II trials are seriously inadequate for informed decision-making, which requires the more comprehensive data collected in phase III trials that are powered to provide statistically meaningful results. Moreover, the FDA has specialized expertise and provides a public good in evaluating the evidence on safety and efficacy, including imposing minimum standards with respect to each of these factors, before launch. Such information would be underprovided in a free market regime and costly to assimilate for individual physicians and patients. Although health plans can -- and do -- serve as intermediaries who assess the relative merits of individual drugs, consumers may view health

plans as imperfect agents, given their financial stake in controlling drug spending. Independent reviewers such as Consumers Reports lack access to the full clinical information which is essential to identify drug effects, controlling for patient condition and other treatments.

Moreover, the social benefit of a regulatory review process that establishes minimum standards for marketed drugs has plausibly increased with the growth in number of drugs and with insurance coverage. At the time of the 1962 Amendments, there were far fewer drugs on the market and virtually all consumers paid out of pocket. Hence the main potential benefit from a regulatory requirement for efficacy was to protect consumers from wasteful spending on useless drugs, including delayed recovery and other medical costs. At that time, the drugs available were few and mostly well known, hence the information burden on physicians or consumers was relatively modest. Since then, there has been a vast expansion in number, complexity and potency of drugs available, and with many consumers, especially seniors, take multiple prescriptions. Consequently, the potential frequency and severity of adverse drug reactions and interactions has increased, as has the information burden of staying informed and the potential cost from being misinformed. Moreover, the growth of insurance coverage has undermined individual consumer's financial incentives to avoid ineffective drugs which could exacerbate wasteful spending on drugs that are of low or only minor benefit. Thus in our view, the case remains strong for a regulatory agency such as the FDA to establish minimum standards of safety, efficacy and quality as a condition of market access. However, the optimal integration of post-launch data with the pre-launch RCT data remains an important issue to be resolved.

A second critical regulatory issue is the optimal mix and coordination of agency regulation and tort liability. The theory of optimal policy to control safety when markets suffer

from imperfect information generally views regulation and tort liability as alternatives. In theory, since the FDA is an expert agency that employs specialists in the design and evaluation of clinical trials and is guided by advisory panels comprised of external medical and statistical experts that review and evaluate comprehensive data on risks and benefits, their decisions should be better informed and more consistent across drugs than decisions of lay juries, made in the context of an adverse outcome to an individual patient who may have had many competing medical and life-style risk factors in addition to taking the drug at issue. The FDA approves drugs on the basis of population risks and benefits, which by definition are average effects, but it is intrinsically difficult to apply such trade-offs to individual patients in tort cases. For example, if the FDA decided that a 1 percent risk of an adverse outcome from a drug was acceptable in view of its benefits, how does a jury decide whether an individual patient's adverse event is within this 1 percent, in which case the producer should not be found liable, or lies outside the 1 percent, in which case the drug may be less safe than expected and the firm should be liable? More generally, the concept of a "defective product", which is the basis of product liability, is problematic when applied to drugs that necessarily entail risks and/or are ineffective for some patients. Unclear standards lead to erratic and unpredictable liability rulings, in which case incentives for safety are likely to be excessive (Craswell and Calfee, 1986). Moreover, tort decisions made ex post, after a drug has been on the market, are at risk of applying current information retroactively, that is, holding a firm liable for rare or cumulative adverse events that only emerge after widespread or long-term use, which the firm could not reasonably have foreseen and for which the FDA did not require testing. Given the extensive pre-market regulation of drugs, one proposal is that if a drug is in full compliance with FDA requirements, including full information disclosure by the company to the FDA, then FDA

compliance should be a bar to tort claims except on grounds of gross negligence, or at least a bar to punitive damages.

A more extreme proposal would replace tort liability for negligence or product defect with a no-fault compensation fund, to provide compensation to patients injured by drugs without regard to producer negligence or product defect, funded by a tax on drugs. The model for this proposal is the workers' compensation system or the Vaccine Compensation Fund (VCF), which was established in 1984 to provide compensation on a no-fault basis for injuries caused by vaccines, replacing tort liability on manufacturers, and funded by a tax on vaccines. However, the VCF model is relatively simple to administer because vaccine injuries are rare, they occur in otherwise healthy individuals and causation is usually clear. By contrast, patients take therapeutic drugs because they are sick; these drugs claim to increase the probability of cure but with no guarantees and with some risk of side effects. In these circumstances, if an individual patient is not cured by the drug or suffers an adverse effect, determining whether their condition is inappropriately caused by the drug or is simply the inevitable progression of their disease is problematic, both conceptually and empirically. Thus implementing a no-fault compensation system that accurately assigns liability if and only if an adverse outcome is caused by a drug, which is a necessary condition for appropriate deterrence signals to producers, is far more problematic for therapeutic drugs than for vaccines or workplace injuries.

IV. Patents

Given the high cost of pharmaceutical R&D, patents are essential to induce sustained investment and few, if any, industries rely on patents to the extent that the pharmaceutical industry does. The pharmaceutical industry benefits from the same patent provisions (20 years

from filing) available to firms in any industry, except for the special patent term restoration granted for pharmaceuticals under the 1984 Hatch-Waxman Act, to restore time lost in clinical trials (see section II). However, pharmaceutical product patents are more readily enforceable and harder to circumvent than patents in many other industries, including medical devices. Consequently, many originator pharmaceuticals enjoy an economic life until the patent expires and generic entry occurs. By contrast, the economic life of a medical device is at most a few years, because imitative entry occurs long before patent expiry, leading to continual incremental product improvement. Because of the necessity and value of pharmaceutical patents, the pharmaceutical industry has been at the forefront of international negotiations over WTO patent provisions.

There is an extensive general economics literature examining the tradeoff between the duration/scope of patents and optimal incentives for innovation (Gilbert and Shapiro, 1990; Klemperer, 1990; Lerner, 1994; Levy, 1999). Early research attempted to quantify the impact of patents by surveying pharmaceutical managers. Based on a survey of 100 R&D managers, Mansfield (1986) reported that between 1981-1983 60% of pharmaceutical products would not have been developed and 65% would not have entered competitive markets without the benefit of patent protection. Similar research among R&D directors in the UK reported that pharmaceutical investment in R&D would be 65% lower without patents (Taylor C.T., 1973; Silberson,Z. 1987). While these survey estimates may be useful benchmarks, they do not necessarily provide an accurate estimate of the counter-factual level of R&D effort in a world without patents. Although a full review of pharmaceutical patents is beyond the scope of this paper, issues that intersect with regulation are briefly reviewed here.

1. Patent Length and Conditions for Generic Entry

The effective patent life of pharmaceuticals is less than the statutory 20 years because patents are usually filed early in the discovery process but drug development and approval takes many years. Analysis of 126 products introduced in the 1990-1995 period shows average patent life of 11.7 years, with a right skewed tail (Grabowski and Vernon, 2000; Grabowski, 2002; Kuhlik, 2004). The Hatch-Waxman Act provides for patent term restoration on a 1:1 basis for NDA review time and 0.5:1 basis for clinical testing time, up to a maximum of 5 years restored and total effective patent length of 14 years.

The Hatch-Waxman compromise counterbalanced these patent extensions with an Abbreviated New Drug Application (ANDA) process for generics, which requires that generics show chemical and bio-equivalence to the originator drug, but permits them to reference the safety and efficacy data of the originator product. Moreover, the Bolar Amendment permitted companies to start work on generics before the originator patent has expired, thereby enabling prompt generic entry as soon as patents expire. By reducing the cost of regulatory approval, these measures increased the number of generic entrants, which in turn increases competitive pressure on prices.

In addition, during the 1970s-1980s, all states repealed anti-substitution dispensing laws and established default rules which allow pharmacists to substitute an AB-rated (FDA-approved bioequivalent) generic for a brand drug unless the physician specifies that the brand is required. By 1984, generic substitution had already expanded from 7.3 percent of eligible prescriptions in 1980 to 16 percent in 1984 (Levy, 1999). In the 1980s and 1990s the reimbursement strategies used by pharmacy benefit managers (PBMs), HMOs and Medicaid established strong financial incentives for pharmacists to substitute generics, where available. These third party payers treat

generics and brands as fully substitutable. They use a form of generic reference pricing (see below) in reimbursing pharmacies for multisource drugs. Specifically, they typically pay pharmacies a Maximum Allowable Cost (MAC), which is based on the acquisition price of a low-cost generic, regardless of which generically equivalent product is dispensed. Since pharmacies capture the margin between the MAC and their acquisition cost, they have strong incentives to substitute the cheapest generics, and this in turn creates incentives for generic suppliers to compete on price. If patients want the brand, they must pay the difference between the MAC and the cost of the brand (plus any other co-payment). Thus the main customers of generic firms are the large pharmacy chains, including mass merchandisers such as Walmart, and the wholesalers that supply the independent pharmacies; these customers are highly concentrated and highly price sensitive, and generics compete on price, not brand image. In contrast to this pharmacy-driven generics market model in the US, generics markets in many other countries, including the EU and Latin America, have been physician-driven, with higher-priced, branded generics. For example, until recently countries such as France, Spain and Italy paid pharmacists a percentage of the price of the drug and/or did not permit generic substitution by pharmacies unless the physician prescribes by generic name. In this environment, generic producers market to physicians, competing on brand rather than price, and generic market shares are smaller and generic prices are higher than in the US (Danzon and Furukawa, 2003). Several EU countries have recently changed their regulation of generics, to encourage lower prices and larger generic shares. In the US, the generic share of total prescriptions dispensed grew from 38.3% in 1999 to 50.1% in 2005, while the generic share of sales grew from 7.4% to 8.9%.[11] The higher generic share of prescription than sales reflects the low generic prices, relative to brands. This generic share of total scripts understates the share of eligible, off-patent

scripts that are filled generically, which can exceed 80% within 3 months of patent expiry in the US. The growth of generic share of scripts reflects not only increased generic penetration of compounds that are off-patent but also the growing number of major drugs that are off-patent.

Several research-based pharmaceutical firms attempted to enter the generics market in the 1990s, but most have divested their generic activities. Since generic firms compete for the business of large pharmacy chains and wholesalers by their breadth of product line, prompt availability of new generics inventory management and low prices, it is hardly surprising that originator firms were unable to compete simply by offering generic versions of their own drugs and most now focus on other post-patent strategies, except that some originator firms do produce "authorized generic" versions of their own drugs (see below). One major exception is Novartis, whose Sandoz generic division is a broad scale and global generic producer, particularly after the purchase in 2005 of Eon and Hexal. The Israel-based generics company Teva produces the largest volume of US prescriptions, with 364m. retail prescriptions filled in 2005, compared to 324m. for Pfizer (IMS data, from unpublished presentation).

Originator brands respond to the rapid generic erosion of brand share after patent expiry by a range of strategies, including: raising price to maximize profit from the shrinking, relatively price-inelastic brand-loyal segment (Frank and Salkever, 1992); shifting patients to a follow-on product, such as a delayed release version of the original drug (Procardia XL vs. Procardia) or a single isomer version (Nexium vs. Prilosec), which requires heavy marketing, sampling and discounting before the patent expires on the original drug; switching the drug to over-the-counter status, which may require clinical trials to show that it is safe and effective under patient self-medication; or filing additional patents, challenging generic entrants and/or producing an "authorized generic."

The growth in litigation around patent expiry was fueled by several provisions of the Hatch-Waxman Act that have been partly amended in the 2003 Medicare Modernization Act (MMA). Specifically, Hatch-Waxman provided that if a generic challenged an originator patent, the originator could file for a 30 month stay that blocked generic entry for 30 months or until the case was resolved, whichever came first. Originator firms could thus delay generic entry indefinitely by filing for additional patents on ancilliary features of the drug, and then file successive 30 month stays when generics challenged these patents. The MMA limited the number of 30 month stays to one per ANDA. FTC and class action suits against firms that have allegedly filed frivolous patents have also reduced incentives for such behavior.

In addition, Hatch-Waxman provided for a 180-days of market exclusivity for the first generic firm to successfully challenge a patent and show that it invalid (a Paragraph IV ANDA filing). Whether the increase in Paragraph IV filings -- from just 2% of expirations in the 1980s to 20% between 1998-2000, and higher for high-revenue products (Kuhlik, 2004) – reflects increased aggressiveness by generic companies seeking payoffs in settlement or increased filing of frivolous patents by originators, is debatable. While the intent of the 180 day exclusivity was to reward and therefore encourage costly challenges to dubious patents, the competitive effects are unclear. In some cases, originator firms colluded with the generic manufacturers that received the 180 day generic exclusivity period, paying them to delay launch of the generic, which effectively stayed entry by other potential generic producers of the compound (FTC 2002). The incentive for such collusion has been greatly reduced both by FTC challenges and by the MMA reforms, which provide that the 180 exclusivity period is forfeited if not used in a timely manner. However, the circumstances in which originators can legally settle with generic challengers remains unresolved and there are valid arguments on both sides: some originator

and generic firms argue that settling patent disputes is a legitimate and efficient means to resolve uncertainty as to ultimate court decision on patent challenges, and that settlement reduces litigation expenditures and enables both sides to pursue long term investment strategies; on the other hand, the FTC tends to view such settlements as anti-competitive, which would be correct if the challenged patents are clearly invalid and settlement were solely a means to delay competitive entry.

A final area of litigation is over the originator strategy of marketing an authorized (i.e. licensed) generic version of the brand product during the Paragraph IV180-day exclusivity period. Absent an authorized generic, the sole generic during a 180-day exclusivity period generally captures significant market share at a price only slightly below the brand price. Competition from an "authorized generic" generally reduces the price, quantity and profit earned by the generic owner of the 180-day exclusivity, and hence may reduce incentives of generic firms to challenge patents. Clearly, if the US Patent Office could rule instantly and accurately on all patent filings, originator firms would have no incentive to file dubious patents and there would be no social value in patent challenges by generics. But since patent filings are reviewed only with delay, and higher courts may overturn decisions by lower courts, incentives for frivolous filings remain and hence there may be some social value in encouraging generic patent challenges. Whether generic incentives to challenge patents are closer to optimal with or without authorized generics is an unresolved empirical question.

As costs of generic entry and hence the number of generic entrants depend, in part, on the ability to reference data and results from studies conducted by originator firms, data exclusivity policies are an important determinant of effective patent protection. Hatch-Waxman granted data exclusivity for five years from the NDA approval (and three years for data not used

in clinical trial), and these exclusivity provisions have been relaxed by subsequent rulings (Kuhlik, 2004). Differences across countries in effective patent life in part reflect differences in these data exclusivity provisions, as well as differences in regulatory requirements for generic approval and substitution by pharmacies, and reimbursement incentives for pharmacists and patients to prefer generics.

Empirical studies of generic entry have shown, not surprisingly, that generic prices are inversely related to number of generic competitors (Grabowski and Vernon, 1992); generic entry is more likely for compounds with large markets (measured by pre-expiry brand revenue), chronic disease markets and oral-solid (pill) form (Scott Morton, 1999; Scott Morton, 2000). Caves and Whinston (1991) find that total volume does not increase after patent expiration, despite the significant drop in price due to generic entry, indicating that the price effect is offset by the negative promotion effect, because incentives for promotion cease at patent expiration. Similarly, Scott Morton (2000) finds no significant generic deterrent effect of incumbent advertising via detailing or journal advertising from 2-3 years prior to generic entry. This is unsurprising, given that the generic switching decision is made mainly by pharmacists and patients, in response to their financial incentives, not by physicians who are the target of detailing and journal advertising.

Originator firms can seek FDA regulatory permission to switch a prescription (Rx) branded product to over-the-counter (OTC) status (which makes it available to patients without prescription) at any time, but this is usually done around patent expiry, to avoid cannibalization of the Rx version and possibly to pre-empt generic erosion. If the OTC switch involves a change of formulation, strength or indication, the FDA requires additional clinical trials to show safety and efficacy under patient self-medication. To encourage these costly investments, the

FDA grants three years of market exclusivity to a successful OTC switch, which delays entry of generic (private label) versions of the OTC formulation, but not of the Rx version. OTC approval is more likely for drugs to treat conditions that are easily self-diagnosed, the potential for abuse or misuse is low, labeling can reasonably communicate any risks and medical oversight is not required for effective and safe use of the product. Prices of OTC products are lower than Rx medicines, possibly reflecting lack of insurance coverage for OTC products. Social welfare is likely to increase, unless the OTC entails significant patient risk or preempts a potentially cheaper generic Rx version (Temin 1983). Keeler et al. (2002) estimate a demand function for nicotine replacement drugs and combine this with epidemiological evidence of medical and quality of life benefits to determine a net social benefit of approximately $2 billion per year for OTC conversion of these drugs.

2. Patents, "Access", and Static Efficiency: Industrialized vs. Developing Countries

Pharmaceutical patents raise the standard issue of static efficiency loss, if prices to consumers exceed marginal cost and result in suboptimal consumption. However, for most industrialized countries that have comprehensive health insurance coverage for drugs with at most modest patient co-payments, this patent-induced tendency for underconsumption is mitigated by an insurance-induced tendency for overconsumption. Probably a greater concern in these contexts is that health insurance reduces the demand elasticity facing the firm and hence creates incentives to charge prices that are significantly higher than would occur due solely to patents. Public insurers' response to this by price regulation is discussed below.

However, the potential for significant static inefficiency and welfare loss due to patent-induced underconsumption remains a serious concern for developing countries, where insurance

is limited and most consumers pay out of pocket for drugs. Under the WTO TRIPS requirements, all WTO members must adopt a patent regime with 20 year product patents (from date of filing) by 2015, with the proviso that governments may grant a compulsory license to generic producers in the event of a "national emergency".[12] The scope of this compulsory licensing provision remains disputed, both with respect to the health conditions and the countries to which it applies, and whether it is *de facto* being undermined by bilateral trade agreements initiated particularly by the US, that stipulate stricter patent provisions.

In practice, it is an empirical question whether product patents in developing countries would result in a significant welfare loss due to high prices and underconsumption (see for example, Fink, 2001; Watal 2000; Chaudhuri et al. 2006). If demand facing a patent holder is highly price-elastic due to low willingness or ability to pay, then a firm's profit-maximizing strategy may be to charge prices close to marginal cost, despite the patent. In fact, some companies have not bothered to file patents in several African countries that (in theory at least) would enforce them (Attaran, 2004), suggesting that they perceived little value in patents due to some mix of highly elastic demand, costs of filing and weak enforcement. If demand is highly elastic such that, even with enforceable patents, profit-maximizing prices in low income countries would be close to marginal cost, then the welfare loss due to patents is small but so is the incentive to invest in R&D to treat diseases endemic to these countries. Chaudhuri et al. (2006 forthcoming) estimate demand elasticities and supply parameters in the anti-infective market for quinolones and conclude that patents would result in a welfare loss to consumers of $305m. per year, compared to a gain to patent holders of only $20m., and a reduction of "generic" firm profits of $35m. However, the welfare loss estimates are obviously sensitive to demand elasticities and might be reduced by price discrimination.

In designing an optimal regulatory framework for pharmaceuticals for developing countries, it is important to distinguish between two classes of drugs, global vs. LDC-only drug. For global drugs that treat diseases such as diabetes, cardiovascular conditions or ulcers, that are common in both developed and developing countries, market segmentation and differential pricing can in principle reconcile affordability in LDCs with incentives for R&D: firms can recoup their R&D investments by pricing above marginal cost in high income countries while pricing close to marginal cost in LDCs. In this context, price discrimination across countries is likely to increase output and static efficiency, while also enhancing dynamic efficiency, through quasi-Ramsey pricing of the R&D joint assets.[13] In practice, actual cross national price differences diverge from ideal Ramsey differentials, for many reasons including the risks of external referencing and parallel trade (Danzon and Towse, 2003, 2005), and possibly incentives for regulatory free riding by large purchasers in regulated markets (see below).

Although actual price differentials are not ideal, the theoretical case is strong for establishing regulatory frameworks that support price discrimination and limit cross-national price spillovers through external referencing and parallel trade. Under these conditions, patent regimes could function to stimulate R&D for drugs with a significant industrialized market potential, without significant welfare loss in developing countries if firms choose to set low prices due to elastic demand.[14] As a modification, Lanjouw (2002) proposes a regime in which firms could opt for patents in either developed or developing countries. Assuming that most firms would opt for developing country patents, the main benefit of such a system would be to reduce uncertainty with respect to patent enforcement and prices in developing countries.

However, for drugs to treat diseases that are endemic only in developing countries, patents are likely to be an ineffective mechanism to achieve the dynamic efficiency goal of

stimulating investment in R&D, because consumers cannot pay prices sufficient to recoup R&D investments. In that case the question of static efficiency loss is moot. The very low level of private sector R&D for LDC-only diseases, despite patent regimes in most low income countries, tends to confirm that patents are ineffective in inducing R&D for LDC-only drugs.

In response to the great need but low levels of private sector investments in drugs to treat LDC-only diseases, there has been a recent spate of "push" and "pull" subsidy proposals and some initiatives to find new institutional solutions. In particular, a highly diverse set of public private partnerships (PPPs) has developed that combine government and philanthropic funds with private industry expertise and resources, to address diseases such as malaria (Medicines for Malaria Venture), tuberculosis (the Global Alliance for TB) , an AIDs vaccine (the International AIDs Vaccine Initiative, IAVI), and many others. The basic issues are outlined in Kremer (2002); for a review of PPP initiatives see the Health Partnership Database (Research 2006). The G8 countries have recently committed to fund an Advance Market Commitment (AMC) that commits to paying a pre-specified price to purchasing vaccines that meet specified conditions, with details still to be determined. While the optimal mix of push and pull mechanisms remains to be determined, the extent of donor funding and range of current initiatives is very encouraging, with several promising candidates in late stage development. LDC governments and international agencies such as the Global Fund are appropriately reluctant to pay for drugs that have not passed regulatory review of safety and efficacy. Thus as more of these drugs reach clinical trials, the case for developing an regulatory review agency or pathway that is appropriate for LDC drugs (see section II) will become more pressing.

V. Regulation of Prices, Insurance Reimbursement, Profits etc.

1. The Rationale for Price and Profit Regulation

Regulation of pharmaceutical prices is *a priori* anomalous because the pharmaceutical industry is structurally competitive, with relatively low concentration overall. Although concentration within specific therapeutic categories is greater, the market is contestable, as evidenced by the growing share of new products discovered by relatively new biotechnology firms. Patents grant exclusivity on a specific compound for the term of the patent. But a patent on one compound does not prevent competition from other compounds to treat the same condition. Competitive entry is initiated long before the first compound in a new class reaches the market. Competitor firms can obtain information on each others' drugs in development from patent filings, scientific conferences and other sources that are collated in publicly available databases, while techniques of rational drug design facilitate the development of close substitute compounds in new therapeutic classes.

Acemoglu and Linn (2004) show that entry of new drugs responds to expected demographic market size. Specifically, they find that a one percent increase in expected demographic demand results in a four percent increase in entry of NMEs / non-generic drugs and a six percent increase in total number of drugs, including generics. DiMasi and Paquette (2004) find that entry of follow-on compounds has reduced the period of market exclusivity of first entrants to a new therapeutic class from 10.2 years in the 1970s to 1.2 years in the late 1990s. Lichtenberg and Philipson (2002) compare the effect on a drug's net present value at launch of within molecule (generic) competition vs. between molecule (therapeutic) competition. They conclude that the reduction in discounted drug lifetime value from therapeutic competition (most of which occurs while the drug is on-patent) is at least as large as

the effect due to post-patent generic entry. Of course, a much higher discount factor is applied to generic erosion because the NPV is measured at launch; still, this study provides an interesting measure of therapeutic competition.

The limited market power that results from patents is reinforced by two other institutional characteristics of pharmaceuticals. First, in industrialized countries patients must obtain a physician's prescription in order to get most drugs. If physicians are uninformed about drug prices and/or are imperfect agents for patients and are not themselves at risk for drug spending, the separation of prescribing from consumption reduces demand elasticity.

Second, insurance coverage for pharmaceuticals makes patients less price-sensitive, hence makes the demand facing manufacturers less elastic which would lead them to charge higher prices, in the absence of controls. Co-payments can mitigate the insurance effect, but because co-payments also reduce financial protection, in practice most public insurance plans include only very modest co-payments. To counteract this price-increasing tendency of insurance, both private and public insurers set limits on the prices that they pay for all insured services including drugs, physician and hospital visits. In the US, private insurers negotiate drug prices with manufacturers as a condition of formulary placement and insurance coverage; although large private payers such as Kaiser have significant bargaining power, none have monopsony power and suppliers can and do choose not to supply a particular plan if its offered prices are unacceptably low.

Most industrialized countries other than the US have either a universal national insurance scheme, with the government as sole insurer, or a system of mandatory quasi-private social insurance funds that are regulated by the government. Controlling prices as a way to control supplier moral hazard applies to all services, including pharmaceuticals. For example,

Japan has a single fee schedule that sets fees for all medical services, including drugs. Consistent with this view of pharmaceutical price regulation as fundamentally an insurance strategy to control supplier moral hazard, price controls in most countries apply only if drugs are reimbursed by the public health plan. A firm is free to market a drug at unregulated prices once registration requirements are met. It is only if the firm seeks to have its product reimbursed by the public insurance that the price must be approved by the price regulatory body.

In the US, the Medicare program for seniors and the disabled did not cover outpatient prescription drugs until the new Medicare Part D drug benefit, authorized in the 2003 Medicare Prescription Drug, Improvement and Modernization Act (MMA) was implemented in January 2006. Following intense debate over the design of the program, the 2003 MMA stipulates that the Medicare drug benefit is to be delivered through private prescription drug plans (PDPs) using negotiated formularies similar to those negotiated by private sector pharmacy benefit managers (PBMs). The federal government is specifically barred from negotiating drug prices. However, if expenditures under this program exceed original projections, future legislation could renounce this non-interference clause and establish a government run plan, making the US government the purchaser for roughly 50 percent of US drug spending. Estimates for the Medicare drug benefit have already increased from $404B for 2004-2013 (CBO 2004(a)) to $724B for 2006-2015 (Kaiser Family Foundation 2005(b)).

Other government drug purchasing programs in the US include the federal-state Medicaid program and several smaller federal programs. The 1990 Omnibus and Reconciliation Act requires originator drugs to give Medicaid the lower of (a) the “best price” offered to any non-federal purchaser or (b) a 15.1% discount off AMP (average manufacturer price). To deter

the incentive to increase private price in response to the best price provision, an "excess-inflation" rebate is also required for price increases that exceed the CPI. For 2003, the combined effect of these mandatory discounts resulted in a 31.4% discount for Medicaid, relative to AMP (CBO June 2005b). Similarly, for the Big Four Federal programs (the Department of Defense, the Department of Veterans Affairs, the Public Health Service and the Coast Guard) the Federal Ceiling Price mandates a discount of 24 percent off non-federal average manufacturing price, plus an excess inflation rebate. In 2003, the average Big Four price was roughly 38 percent below the AMP (CBO 2003a). Thus public purchasers in the US have regulated prices by mandatory discounts off private sector prices. This has resulted in relatively low prices for public programs, but has also reduced the discounts firms grant to private plans and possibly increased list prices. This inflationary effect on private prices of best price requirements by public payers is expected to be significantly reduced after 2006, because the MMA transferred seniors who are eligible for both Medicaid and Medicare ("dual eligibles") from the Medicaid program to the privately administered Medicare Part D program. This reduced the effective Medicaid best price "tax" on discounts granted to private purchasers.

Empirical evidence confirms that these rules tying Medicaid rebates to "best" private sector prices lead to a decline in discounts to private payers. GAO (1993) found that median best price discounts to HMOs declined from 24.4 percent before the law went into effect in 1991, to 14.2 percent in 1993 (GAO 1993); CBO (1996) found similar evidence. Because discounts are confidential, academic studies have focused on the effects of the Medicaid best price provision on available measures of prices, which are gross of buyer-specific discounts. Using transactions prices from IMS, Scott-Morton (1997) found no effect for drugs which did not have generic competition, but modest price increases in product categories with generic

competition after the enactment of the Medicaid best price policy in 1991. In a similar study, Duggan and Scott Morton exploit the variation in the Medicaid market share for the top 200 selling products in the US to estimate the effect of the Medicaid legislation on average prices. They conclude that a ten percent increase in Medicaid market share resulted in a 7 to 10 percent increase in their measure of average price.[15] Whether the reduction in Medicaid market-share following the 2006 transfer of dual eligibles led to a reversal of this effect remains to be tested. Widespread awareness that tying public prices to private prices leads to increases in private prices is one reason this approach was not adopted for Medicare Part D.

3. Pricing and Competition in Unregulated Markets

On-Patent Brands The early literature provides some evidence on competition in pharmaceutical markets before the advent of widespread insurance coverage and associated price controls. Opinion in the economic and policy literature was divided on extent and welfare effects of competition. Some viewed closely substitutable, patented products as wasteful 'me-toos', arguing that patent protection leads to excessive product differentiation and higher prices (for example, Comanor, 1986; Temin, 1979). Under this view, the 1962 Amendments, by requiring proof of efficacy and restricting drug advertising, may have restricted "excessive differentiation". The alternative view is that the availability of more substitute products prior to 1962 increased price competition and benefited consumers. To assess the impact of the 1962 Amendments on prices, Peltzman (1973) examined average price changes from 1952 to 1962 and a cross sectional analysis for 1958-1961, prior to the 1962 regulations. He found no evidence that the number of NCEs had any net impact on drug price inflation and concluded that, if anything, drug price growth increased after the 1962 Amendments, contrary to the

"wasteful competition" hypothesis.

Other studies have examined launch prices and price trends over a drug's lifecycle. In a study of launch prices of drugs introduced between 1958 and 1975, Reekie (1978) found that new drugs that offer significant therapeutic advance were priced above existing drugs but tended to lower price over time, whereas imitators were priced lower initially but tended to increase prices. Similarly, Lu and Comanor (1998) using data for 144 new drugs launched in the US between 1978 and 1987 found evidence of a skimming strategy for innovative drugs and a penetration strategy by imitators. This evidence is consistent with some degree of competition but imperfectly informed buyers, such that sellers offer a low initial price to encourage use and build reputation or loyalty, then raise prices over time (Schmalensee, 1982).

In the US, the nature and extent of competition in pharmaceutical markets has changed with the growth of managed drug coverage in the 1980s and 1990s, as practiced by HMOs, pharmacy benefit managers (PBMs) and the prescription drug plans (PDPs) that manage the Medicare drug benefit.[16] PBMs typically establish formularies of preferred drugs that are selected on the basis of price and effectiveness. Tiered co-payments and other strategies are used to encourage patients and their physicians to the use "preferred" drugs in the class. Such strategies are designed to increase the cross-price elasticity of demand between therapeutic substitutes and between generic equivalents. By using formularies to shift market share between therapeutically similar on-patent drugs and hence increase the demand elasticity facing manufacturers, PBMs are able to negotiate discounts in return for preferred formulary status. These discounts are confidential, hence detailed analysis is not available. However, anecdotal evidence confirms the theoretical prediction that discounts are larger to purchasers that have tight control over drug use, such as Kaiser, and in classes with several close substitute products.

Evidence that new drugs are launched at list prices below the price of established drugs in the same product class and that the discount is greater, the greater the number of existing drugs in the product class (Boston Consulting Group, 1993) indicates that competition does reduce prices even for unmanaged consumers.

Although discounting through confidential, electronic rebates to PBMs, as agents of payers and consumers, has no doubt stimulated price competition, it has been attacked on several grounds. First, because it is essentially a system of price discrimination, those who pay higher prices feel aggrieved and indeed the results would strike many as inequitable. Specifically, the largest discounts go to plans with tightly controlled formularies that tend to attract relatively healthy, privately insured non-seniors, whereas uninsured and other cash-paying customers face the highest prices. This differential in manufacturer prices is amplified for retail prices because PBMs also negotiate discounts in pharmacy dispensing margins, relative to unmanaged dispensing fees pharmacies charge to cash-paying customers. Combining the manufacturer and pharmacy discounts, consumers with managed drug benefits face approximately 20% lower drug costs (GAO, 1997; GAO, 2003) compared to uninsured patients, including many seniors before the 2006 implementation of Medicare Part D.

Second, discounting has been challenged by retail pharmacists in antitrust litigation alleging collusive pricing and price discrimination by drug manufacturers (Scherer, 1997; Danzon, 1997). Dispensing pharmacies do not receive the same discounts given to PBMs because pharmacies cannot - and arguably should not – independently influence a physician/patient's choice between therapeutic substitutes. This litigation conspicuously excluded off-patent, multisource drugs, because for these drugs the discounts go to the pharmacies, because they are the decision-makers in choosing between generically equivalent

versions of a prescribed compound. Under the settlement of this litigation, manufacturer discounts were to be made available on the same terms to all purchasers; however, because PBMs design the formularies that drive therapeutic substitution, they remain the main recipients of discounts on on-patent drugs, although wholesalers do receive modest prompt payment and volume-related discounts.

Third, as noted earlier, incentives for discounts to private payers have been reduced by the matching requirement, that manufacturers of brand drugs give to Medicaid the "best price" given to private payers or a 15.1% discount off Average Manufacturer Price, whichever is lower. This best price provision effectively imposes a significant tax on discounts to private payers, because Medicaid demand is totally inelastic with respect to this discount. Theory suggests that this best price provision would reduce best price discounts to private payers and this is confirmed by evidence from several studies (CBO, 1996; GAO, 1994).

Finally, because the discounts are confidential, payers who contract with PBMs as agents accuse the PBMs of pocketing rather than passing on the discounts. Since the Medicare drug benefit will be delivered by competing, private "prescription drug plans" similar to PBMs, both Medicare (that will heavily subsidize the benefit) and seniors (who contribute to premiums, pay significant co-payments and must choose between competing plans) have demanded "price transparency". However, CBO (2004) estimated a significantly higher cost for a variant of the Medicare drug benefit that required price transparency, under the assumption that transparency would erode drug manufacturers' competitive incentives to discount and hence would lead to higher drug prices. The final MMA legislation requires PDPs to reveal discounts in aggregate but not drug-specific prices.

Generics In most US health plans, reimbursement for multisource drugs (off-patent drugs with at least one generic, in addition to the originator) is designed to create strong incentives for decision-makers to prefer generics over their brand equivalents. These regulatory and reimbursement structures in turn generate intense generic price competition and large generic market shares. Specifically, most HMOs, PBMs and Medicaid plans cap pharmacy reimbursement for multisource drugs at the price of a low priced generic, the MAC or maximum allowable charge for that compound. If the patient wants the originator brand, he or she must pay the difference between the brand price and the MAC (or a third-tier co-pay, in some tiered formularies). Since the 1980s, most states have overturned traditional anti-substitution laws and now authorize pharmacists to dispense any bioequivalent generic, unless the physician explicitly requires the brand.

Since pharmacists capture any margin between the MAC and their acquisition cost, pharmacists have strong incentives to seek out cheap generics. For generic drug manufacturers, the primary customers are large pharmacy chains and group purchasers for independent pharmacies. This highly concentrated and price-sensitive pharmacy demand creates incentives for generics to compete on price. If the 1984 Hatch-Waxman Act opened the door to cheap and prompt generic entry in the US, generic substitution programs adopted by PBMs, HMOs and Medicaid in the late 1980s and 1990s stimulated generic market shares while MAC reimbursement drives generic price competition. Masson and Steiner (1985) show that for a sample of 37 multisource drugs in 1980, pharmacists obtained the generic at an average price 45 percent lower than the brand, but the difference at retail was only 24.3 percent, because the pharmacist retained a higher average absolute margin on the generics. Similarly, Grabowski and Vernon (1996) show that for 15 drugs whose patents expired between 1984 and 1987, the

average absolute margin was roughly 40 percent higher on the generic. More recent anecdotal reports confirm that pharmacy margins are higher on generics than on on-patent brands.

Most studies of generic drug markets focus on the effects of the 1984 Hatch-Waxman Act on generic entry and on the effect of generics on prices, promotional activity and market shares of brand drugs. Since market conditions have evolved in the 1990s with the growth of managed drug benefits, the findings of these studies should be viewed as context-dependent. Grabowski and Vernon (1992), using data on patent expirations that spanned the 1984 Act, find that generic prices were significantly inversely related to number of generic competitors, but some brand prices increased after generic entry. Frank and Salkever (1992) show that a brand manufacturer may rationally increase the brand price following generic entry, as a response to market segmentation in which generics attract the price elastic consumers, leaving the brand with the price-inelastic, brand-loyal consumers. Brand advertising may decrease, since much of the benefit accrues to generics due to substitution; conversely, generics have no incentive to advertise if they are viewed as substitutable.

Caves, Whinston and Hurwitz (1991) analyze post-patent pricing and promotion for 30 drugs whose patents expired between 1976 and 1987. They find significant reduction in brand promotion even before patent expiration. The net effect of less promotion and lower generic prices is that quantity sold does not increase significantly after patent expiration, despite a lower weighted average price for the molecule. All of these studies underestimate generic penetration since the growth of managed drug benefits in the 1990s. Whereas Caves, Whinston and Hurwitz (1991) find that pharmacists were quite conservative in exercising their right to substitute a generic, for recent patent expirations the originator may lose over 80 percent of the market within several weeks of patent expiry in the US.

Summarizing, conclusions on competition in the brand and generic pharmaceutical industries depend on the context, in particular, on the insurance arrangements, reimbursement and price regulatory structure and resulting incentives for physicians, pharmacies and patients, which interact to determine manufacturer demand elasticities and hence optimal manufacturer pricing strategies. Similarly, estimates of demand elasticities depend on the context, including such factors as whether the drug is on-patent or generic, whether the measure of price is the co-payment to the patient, the full transaction price to the payer, or a list price, and on relevant pharmacy and physician incentives.

3. Forms of price and reimbursement regulation

Design of the optimal structure of price regulation or other controls on pharmaceutical spending is a complex problem that has not been adequately addressed in the literature. The one clear conclusion is that no country has an ideal solution. As noted earlier, market power of pharmaceuticals derives from patents and from comprehensive insurance coverage, hence standard regulatory models of price regulation for natural monopolies are inappropriate. Standard models of optimal insurance contracts are also inadequate. These tend to focus on the design of consumer co-payments to constrain moral hazard (for example, Pauly, 1968; Zeckhauser, 1971; Ma and Riordan, 2002). Since higher co-payments reduce financial protection, optimal co-payments for drugs may be too low to provide much constraint on pricing, especially for chronic and expensive drugs, given the concentration of spending by patients with multiple prescriptions. Optimal provider cost-sharing has been analyzed for physician and hospital services (for example, Ellis and McGuire, 1991) but not for pharmaceuticals. Moreover, the optimal insurance/reimbursement contract for drugs must deter

not only insurance-induced overuse by patients/physicians but also excessive prices by manufacturers, while paying prices sufficient to reward appropriate R&D, taking into account the global scope of pharmaceutical sales.

In practice, the structure of pharmaceutical price and reimbursement regulation differs across countries and continually evolves. This review focuses on the main prototypes and evidence of their effects. As noted earlier, regulation applies only if the drug is reimbursed. Effectively, the regulated price is the maximum reimbursement; it may also (but need not) be the maximum price that the firm may charge to insured patients.

Direct Price Limits

Under direct price regulation, as used in France, Italy, Spain, Japan etc. the initial launch price and any price increases must be approved as a condition of reimbursement, and price decreases may be mandated. Most countries use one or both of two criteria in setting prices: (1) comparison with other, established drugs in the same class, with potential mark-ups for improved efficacy, better side effect profile or convenience, and sometimes for local production (hereafter "internal benchmarking"); and (2) comparison with the price of the identical product in other countries (hereafter "external benchmarking").[17]

Internal benchmarking. Effects of regulation through internal benchmarking differ depending on the details of each country's system, including mark-ups for innovation and other factors. Hypothesized effects of price regulation on supply decisions include: adjustments to the price profile (Anis and Wen, 1998); distortions of R&D level and focus; and distortions of location of R&D and/or manufacturing plants, if prices are related to investment in the local economy.

If post-launch price increases are not permitted, a drug's real price declines over its life-

cycle. Consequently, if follow-on products are benchmarked to an old drug, the real launch price declines for successive entrants in a class. This downward trend of prices over the life-cycle is most extreme in Japan, where physicians traditionally dispense drugs and capture any margin between a drug's reimbursement and its acquisition cost. In such contexts, manufacturers have an incentive to discount the acquisition price in order to increase the physician's margin and hence gain market share.[18] The Japanese government audits acquisition prices bi-annually and reduces the reimbursement price to leave only a 1-2% margin, until the next rounds of competitive price cuts. This system of declining post-launch prices allegedly traditionally created incentives for Japanese pharmaceutical firms to focus their R&D on frequent, minor improvements of existing products in order to obtain higher prices, rather than invest in the major innovations necessary to achieve global competitiveness.[19]

Such price regulatory systems are also widely alleged to be used to promote industrial policy, by rewarding locally produced products with higher prices, despite the 1989 EU Transparency Directive which requires that regulations be 'transparent' and neutral with respect to country of origin. Such biased regulation creates incentives for nonoptimal location and/or an excessive number of manufacturing plants, if these excessive production costs are "offset" by higher prices (Danzon and Percy, 1996).

Although secondary (processing and packaging) manufacturing facilities may plausibly be located disproportionately in countries that reward domestic manufacturing through their regulated prices, the opposite charge is made with respect to R&D. Specifically, the pharmaceutical industry sometimes argues that price regulation discourages investment in R&D, due to low and uncertain prices countries that regulate prices. In theory, price regulation could reduce R&D due to both the incentive effect of lower expected profits and the financing

effect of lower retained earnings. It is empirically true that most R&D is located in countries with relatively free pricing, mainly the US and the UK. However, the causal relationship is unclear. In theory, given the potentially global market for innovative drugs, and extensive in- and out-licensing networks that enable small firms to reach global markets regardless of their location, there is no necessary connection between domestic price regulation and firms' location of R&D. Access to world class scientific research and a large pool of human capital may be more critical. As governments in many countries are establishing tax-subsidies to try to attract pharmaceutical and biotechnology R&D, more may be learned about the relative importance of financial vs. other factors in R&D location.

External benchmarking Whereas internal benchmarking compares the price of the new drug to the prices of competitor products in the domestics, external benchmarking uses as the comparator the mean, median or minimum price of the same drug in a designated set of countries. For example, Italy uses an average European price, Canada uses the median of seven countries (five European countries plus the US and Japan), etc.

External benchmarking limits the manufacturer's ability to price discriminate across countries. Predicted effects include convergence in the manufacturer's target launch prices across linked markets, with launch delays and non-launch becoming an optimal strategy in low-price countries, particularly those with small markets. Parallel trade, which is legal in the EU, has similar effects to external referencing, except that it generally only affects a fraction of a product's sales. Several studies provide evidence consistent with these predictions (Danzon, Wang and Wang, 2004; Kyle, 2005; Lanjouw, 2005; Danzon and Epstein, 2006 forthcoming).

Welfare effects of regulatory pressures for price convergence across countries are theoretically ambiguous but likely to be negative. Analyses of price discrimination vs. uniform

pricing show that price discrimination increases static efficiency if output increases. That differential pricing increases drug use seems plausible, given the evidence of delays and non-launch of new drugs in low price countries. Moreover, Ramsey pricing principles suggest that differential pricing also contributes to dynamic efficiency (Ramsey, 1927; Baumol and Bradford, 1970).[20] So far, external referencing and parallel trade apply mostly between countries at fairly similar levels of income, notably within Europe. Welfare losses would likely be much larger if referencing or importation were authorized directly between high and low income countries, or indirectly via middle income countries. The proposed US Health Security Act of 1994 would have limited drug prices in the US to the lowest prices in a group of 22 other countries, including several with much lower incomes than the US. More recently, the US has enacted a proposal to legalize drug importation from a broad group of countries, but implementation is stalled because required safety and savings conditions have not been met. Aside from the safety issues raised by drug importation, linking the dominant US market to other smaller, lower income markets could have serious negative effects on price and availability of drugs in those countries. From a global welfare perspective, forms of price regulation that are country specific are likely to yield lower welfare loss than regulatory systems that attempt to control one country's prices by referencing prices or importing drugs from other countries.

Reference Price Reimbursement Limits

Some countries, including Germany, the Netherlands and New Zealand, have established reference price (RP) reimbursement systems that limit the reimbursement for drugs in designated groups but leave prices uncontrolled. Under RP, products are clustered for

reimbursement based on either the same compound (generic referencing) or different compounds with similar mode of action and/or same indication (therapeutic referencing). All products in a group are reimbursed the same price per daily dose – the reference price (RP). The RP is usually set at the price of say the cheapest (or the median, the thirtieth percentile etc.) of drugs in the group. Manufacturers may charge prices above the RP, but patients must pay any excess. In practice, manufacturers typically drop their prices to the reference price, suggesting that demand is highly elastic when patients must pay.

Reference price reimbursement resembles price regulation with internal benchmarking to similar products, but with critical differences that make RP potentially more constraining. First, whereas informal benchmarking may permit higher reimbursement for drugs with superior efficacy or fewer side-effects, under RP the reimbursement is the same per daily dose, for all products in a group, and obtaining higher reimbursement for a more effective drug requires establishing a separate class within the same therapeutic category. The RP classification system is therefore critical, and assignment of individual drugs is often litigated. Second, therapeutic RP systems typically cluster compounds without regard to patent status. Consequently, if the RP is based on the cheapest product in the cluster, once one patent expires and generic entry occurs, reimbursement for all products in the group drops to the generic price, thereby effectively truncating patent life for the newer products in the group, unless patients are willing to pay surcharges. The magnitude of this patent-truncating effect is greater, the broader the definition of reimbursement clusters and the more price-competitive the generic market. Therapeutic RP is predicted to reduce incentives for R&D in general, if the patent-truncating effect is large. Negative effects on R&D incentives are likely to be greatest for follow-on products or line extensions of existing drugs. Whether any such reduction would be a welfare-

enhancing, by eliminating wasteful R&D, or a welfare-reducing, by eliminating potentially cost-effective new drugs and reducing competition in a class, is obviously context-specific and cannot be predicted a priori. More generally, because incentives for R&D depend on global expected revenues, the effects of RP so far are not expected to be large because so far no major market has long experience with therapeutic RP. Thus the experience to date is insufficient to predict the likely effects on R&D if the US, with its large share of global revenues and highly price-competitive generic market, were to adopt therapeutic RP (Danzon and Ketcham, 2004).

Although Germany adopted RP for some classes starting in 1989, new patented drugs were exempt from 1996 to 2004. Moreover, in interpreting the German experience with RP and extrapolating to other countries such as the US, it is important to note that generic prices are lower, both absolutely and relative to brand prices, in the US than in Germany.[21] Moreover, Germany -- like all other countries with RP or price regulation – adopted multiple price and spending controls simultaneously. Identifying the separate effects of RP and other constraints is therefore problematic.

The early literature on RP is summarized in Lopez-Casasnovas and Puig-Junoy (2000). Early evidence from Germany confirmed that brand drugs generally dropped their prices when RP was introduced, as theory predicts (Maasen, 1995). However, both theory and evidence suggest that dynamic price competition over time is weak under RP, because firms have no incentive to reduce prices below the RP, unless other provisions make pharmacists price sensitive. Zweifel and Crivelli (1996) analyze firms' response to RP using a duopoly model; however, since RP generally applies to classes with multiple products, oligopoly or monopolistic competition models may be more relevant. Danzon and Ketcham (2004) provide empirical evidence on effects of RP in Germany, the Netherlands and New Zealand, the three

most comprehensive RP systems. This evidence suggests that RP had little effect on average drug prices or drug availability in Germany or the Netherlands, but that effects on prices and availability were significant in New Zealand, which used broader classes and where the regulatory agency explicitly required RP-reducing price cuts as a condition of admitting new drugs to reimbursement.

In theory, since RP limits only the insurer's reimbursement, patients may be willing to pay a surcharge if a drug truly offers greater therapeutic benefits. But patients may be imperfectly informed about the risks and benefits of individual drugs, and physicians may be reluctant to spend the time required to inform patients, since such time is unreimbursed and may have a significant opportunity cost. Some manufacturers may choose to charge prices above the RP, despite high demand elasticities, to avoid price spillovers to other markets. For example, when British Columbia adopted RP, some manufacturers retained prices above the RP, plausibly to avoid undermining potentially higher prices in other Canadian provinces. If manufacturers do charge surcharges, patients may face significant co-payments, with possible effects on drug choice and health outcomes. The evidence on patient health outcomes under RP is mixed: some studies find no evidence of adverse effects, while others find an increase in adverse outcomes, possibly because patients switched to less appropriate drugs to avoid surcharges. The risks of such adverse effects depend on the degree of substitutability between drugs, which varies across therapeutic classes. For this reason, Australia and British Columbia only apply RP to a select set of therapeutic classes in which drugs are considered highly substitutable for most patients. PBMs in the US rarely use therapeutic RP, preferring the more flexible tiered formularies.

Drug Budgets and Expenditure Controls

Price or reimbursement controls alone do not control the growth of drug spending, which is also driven by prescription volume and "mix", that is, switching from older, cheaper drugs to newer, higher priced drugs. Most countries that initially controlled only price or reimbursement have added other measures to limit total drug spending. Specifically, from 1993 - 2003, Germany had a drug budget (limit on aggregate spending), with physicians and the pharmaceutical industry nominally at risk for successive tiers of any overrun. Physicians responded initially by reducing the number of prescriptions and switching to cheaper drugs, leading to a 16 percent reduction in drug spending in the first year of the budget (Munnich and Sullivan, 1994). Schulenburg et al.(1994) report that referrals to specialists and hospitals increased, because the drug budget excluded inpatient drugs. Thus the overall budget saving was less than the saving in outpatient drug costs. Germany's aggregate drug budget was abolished in 2003, because enforcing the repayment of overruns was practically and politically problematic. Some regions have adopted physician-specific budgets. Whether payers have sufficient information to achieve appropriate risk-adjustment of physician-specific budgets based on each physician's patient population remains to be seen – if not, such controls could create incentives for physicians to avoid high-risk patients and/or constrain their drug choices. France has a limit on total drug spending that is enforced by limits on each company's revenues. Overruns are recouped by price cuts or mandatory rebates on companies and therapeutic classes that exceed allowed targets, and on companies that exceed promotion guidelines. Similarly, since 2001 Italy limits drug spending to 13 percent of health spending; overruns have been recouped by price cuts in major therapeutic classes.

Since expenditure caps that are enforced by price cuts imply a price-volume trade-off

for manufacturers, one potential – and intended – effect is to reduce manufacturers' incentives to expand volume through promotion. However, penalties that apply collectively to all firms have only weak effects on firm-specific incentives in the absence of collusion. Company-specific revenue limits, as in France, create more powerful incentives to constrain promotion but also undermine incentives for R&D. As with price and reimbursement controls, these R&D incentive effects are negligible as long as controls apply in markets that are a small share of global revenue. Such effects would be more significant if drug spending caps enforced by price-volume offsets were adopted in the US or EU-wide.

Profit or Rate-of-Return Controls

The UK is unique among industrialized countries in regulating the rate of return on capital, leaving manufacturers (relatively) free to set the price of individual drugs. The UK Prescription Price Regulation Scheme (PPRS) is renegotiated every five years between the patented pharmaceutical industry and the government. The PPRS limits each company's revenues from sales to the UK National Health Service as a percent of their capital invested in the UK, with specified limits on deductible expenses to pre-empt incentives for expense padding. The allowed rate of return is around 17-21 percent; excesses can be repaid directly or through lower prices the following year. Companies with minimal capital in the UK can substitute a return-on-sales formula.

One simple theory predicts that pure rate of return regulation induces excessive capital investments relative to labor and hence reduces productivity (Averch and Johnson, 1962), although these predictions only hold under restrictive assumptions (Joskow 1974). For multinational companies, the costs of distortions may be small if capital in manufacturing plants

can be allocated across countries at relatively low cost in order to maximize revenues. Such flexibility may become more constrained as more regulatory systems link their prices or reimbursement to local investment. In a study of the effects of such biased regulatory schemes in the UK, France and Italy on labor productivity and total factor productivity, Danzon and Percy (1996) found that although the rate of growth of capital and labor in the UK pharmaceutical industry has been high, relative to other UK industry and relative to pharmaceuticals in other countries, it has not been biased towards capital relative to labor, possibly because the permitted company-specific rate of return on capital may partly depend on employment levels. Overall, the UK experienced relatively high total factor productivity growth, compared to other regulated and unregulated countries.

With respect to effects on drug prices, the UK is generally considered to have higher brand prices than those in the regulated markets of France, Italy and Spain. Consistent with this, the UK has a relatively large parallel import share, whereas the price regulated markets of France, Italy and Spain are parallel exporters. However, precise price differentials are sensitive to the sample of drugs, the time period and the exchange rate (see, for example, Danzon and Chao, 2000a; Danzon and Furukawa, 2003; Danzon and Furukawa, 2006 forthcoming). The UK's overall spending on drugs, either as a share of health spending or per capita, is not out of line with other EU countries, plausibly reflecting other characteristics of their health care system, including strong pharmacy incentives for generic substitution and physician reimbursement that creates incentives for cost-conscious prescribing.[22] The UK pharmaceutical industry has also contributed more significantly to the flow of new medicines than most other countries of comparable size. Nevertheless, following a recent review of the PPRS the UK Office of Fair Trade recommended that the UK move to a system of "value-based

pricing" regulation, in place of profit regulation (Office of Fair Trade, 2007; Danzon, 2007). Whether such a change will be implemented and its likely effects remain to be determined.

Cost-Effectiveness Requirements

Australia, Canada, New Zealand and the UK require a formal review of the cost-effectiveness of a new drug as a condition of reimbursement by national health systems; in other countries, such data are used as input to price negotiations. For example, in 1999 the UK established the National Institute for Clinical Excellence (NICE) to review the efficacy and cost of technologies expected to have major health or budgetary impact, including drugs, relative to current treatment, using standard metrics of the cost per quality adjusted life year (QALY). Cost reflects not only the price of the drug but also associated medical costs, such as reduced inpatient days or doctor visits. A similar expert body to review clinical effectiveness and now cost-effectiveness was established in Germany in 2004, and others are under debate in some other EU countries and in the US. Regulating prices indirectly through a review of cost-effectiveness is in theory more consistent with principles of efficient resource allocation than the other criteria for regulating drug prices reviewed here. In practice, such approaches are only as sound as the data and judgment used in implementation, of course. Still, the rapidly growing body of methodological and empirical literature on the measurement of cost-effectiveness offers some hope that this approach could provide one cornerstone to a more theoretically sound framework for drug price regulation.

4. Effects of Regulation on Prices

Cross-national comparisons of drug prices vary significantly, depending on the time

period, sample of drugs used, the price index methodology used, including unit for measuring price (grams, units, daily doses), consumption weights and exchange rates. Most price comparisons have been biased by use of very small, non-random samples including only branded drugs, and have not adhered to standard index number methods (for example, GAO, 1992, 1994). The exclusive focus on branded drugs tends to bias comparisons in favor of countries with strict price regulation. Regulation and competition are to some degree substitutes: less regulated markets tend to have higher brand prices but larger generic market shares and lower priced generics. Overall, countries that use direct price controls do not consistently have lower prices than countries that use other indirect means to constrain prices (Danzon and Chao, 2000a, b; Danzon and Furukawa, 2003, 2006). However, comparisons are very sensitive to the sample of drugs, weights, exchange rate and prices used.

5. Price Regulation: Lessons Learned and Future research

The research of the 1960s, 1970s and early 1980s focused on effects of regulation of market access, focusing more on measuring the costs of launch delay, with less success in measuring any benefits from reduced risks or more appropriate drug use. In the 1990s regulatory change has focused on the design of price regulatory systems, first to control prices and subsequently to control total drug spending, while preserving access for patients and incentives for R&D. Although much useful research has been done, there remain many unanswered questions on the optimal design of insurance and price regulatory systems to achieve appropriate use of existing drugs and prices that strike a reasonable balance between short run spending control and incentives for R&D for the future. Garber et al. (2006) consider the interaction between health insurance, patents, incentives for R&D and regulation.

Useful lessons have been learned on the specific effects of different regulatory strategies but many unanswered questions remain. The evidence on Germany's 1993 drug budget shows that placing physicians at financial risk is a potent weapon to limit drug spending. But an aggregate drug budget borne collectively by all physicians is contentious and ungrounded in welfare theory and Germany abandoned its drug budget in 2003. Physician-specific budgets provide stronger incentives but this may lead to undesirable cream-skimming if budget parameters cannot be appropriately risk-adjusted to reflect differences in patient characteristics. "Silo budgeting" which specific spending limits on individual medical services – drugs, hospitals, physicians – creates perverse incentives for cost shifting between the budgets, whereas cost-effective substitution between medical services is essential to achieve the maximum value from total health expenditures. Designing appropriate physician risk-sharing for drugs is an important issue for future research.

In theory, reimbursement limits that are based on cost-effectiveness offer more efficient incentives for R&D and for drug choices than price regulation using ad hoc internal benchmarking or reference price reimbursement. Under CE, more effective/safer drugs can charger higher prices and still be cost-effective relative to less effective/ less safe drugs. Moreover, if costs and effects are measured using appropriate guidelines, decisions can in theory reflect all relevant social costs and benefits and be more consistent across drugs than is likely with ad hoc price regulation. More appropriate regulatory mechanisms for reviewing prices could provide better incentives for both R&D and for prescribing.

Although CE offers a more appropriate criterion for drug price review than other widely used criteria, important details remain unresolved. One concern is that the data available for evaluating cost-effectiveness at launch are based on controlled, pre-launch clinical trials, which

may not accurately reflect the costs or effects of a drug in actual usage in broad patient populations. Updating the CE analysis with post-launch data from actual use is possible in principle; however, it is costly, is potentially less accurate due to non-random treatment assignments, and canceling reimbursement of a drug post-launch may be politically difficult. Nevertheless, integrating pre- and post-launch data is likely to become the norm as databases and statistical techniques improve. A second limitation of cost-effectiveness analysis is that it yields a ceiling or maximum price at which a drug is cost-effective, for a payer-specific CE threshold; however, CE alone does not yield the most appropriate price, because the drug would be even more cost-effective at a lower price. Thus although review of cost-effectiveness is becoming a necessary condition for reimbursement in an increasing number of countries -- and the US Medicare drug benefit may eventually follow -- CE evaluation has supplemented but not replaced other price and expenditure regulation in countries that seek to control drug spending.

6. Profitability and Rates of Return

The pharmaceutical industry is widely perceived to earn excessive profits. Accurate measurement of profits using standard accounting data is problematic for pharmaceuticals because capital investments are primarily intangible R&D investments made over 12+ years prior to drug launch, with value over a product life of 10-15 years in global markets. Several methods have been used to measure profitability. One approach attempts to adjust accounting rates of return to better account for investments in intangible capital of R&D and promotion. Standard accounting practices treat R&D and promotion spending as current expenses rather than as investments in intangible capital. This leads to upward bias in accounting rates of return

for industries with relatively high intangible investments. Clarkson (1996) illustrates the effects of these adjustments for firms in fourteen industries for the period 1980-1993. Before adjustment, the average accounting rate of return on equity for the fourteen industries is 12.3 percent; the pharmaceutical industry has the highest return of 24.4 percent. After adjustment for intangible capital, the average is 10.2 percent compared to 13.3 percent for pharmaceuticals, which is less than the adjusted return for petroleum, computer software and foods.

A second approach uses the Lerner index of price relative to marginal production cost. Caves, Whinston and Hurwitz (1991) estimate the ratio of the price of originator drugs relative to generic price several years after patent (a proxy for marginal cost) at roughly 5. However, this price ratio at patent expiry overstates the average Lerner index over the life-cycle in the US because prices of originator drugs rise and marginal costs decline with time since launch. More fundamentally, a one-year Lerner index based on short-run marginal production cost in one country is both theoretically and empirically inadequate as a measure of profit for global products with high and long-lived R&D investments.

A third – and conceptually more correct approach -- measures the rate of return on investment in a cohort of drugs, using discounted cash flow estimates of costs and returns. Grabowski and Vernon (1990, 1996, 2002) estimate the return on R&D for new drugs introduced in the 1970s, early 1980s and 1990s, respectively. Market sales data for the US are used to estimate a 20-year sales profile, with extrapolation to global sales using a foreign sales multiplier. Applying a contribution margin to net out other, non-R&D costs yields a life-cycle profile for net revenue, which is discounted to present value at launch using the estimated real cost of capital (10 – 11 percent). This NPV of net revenues is compared to the estimated average capitalized cost of R&D per NCE, at launch. Grabowski and Vernon conclude that the

1970s drug cohort on average earned a return roughly equal to their cost of capital; the 1980s cohort on average yielded a positive net present value of $22.2m, or an internal rate of return of 11.1 percent, compared to the 10.5 percent cost of capital. Similarly, results for the 1990s cohort show a small, positive excess return. Given the large number of assumption, confidence intervals are not reported. In all three time periods, the returns distribution is highly skewed, such that only the top 30 percent of drugs cover the average R&D cost. This extreme result would be mitigated if the distribution of revenues were compared to the distribution of R&D costs, rather than to a single mean R&D cost per NCE, but the overall result would remain. An important implication of this skewed distribution of returns is that regulatory strategies that target these 'blockbuster' drugs while on patent could significantly reduce expected average returns and hence reduce incentives for R&D. By contrast, a competitive regulatory environment that permits high prices for patented drugs but then promotes generic competition after patent expiry has a much less negative effect on incentives for R&D, because loss in sales revenue that occurs late in the product life is more heavily discounted.

Although this cohort rate-of-return approach in theory provides the most accurate measure of returns to R&D, it is arguably of limited relevance for policy in an industry with low barriers but long lead times for entry and high unpredictability of science and market risk. In the absence of significant barriers to entry to R&D for new firms, if the expected return on R&D exceeded the cost of capital, competitive entry would occur until the excess expected profit is eliminated. Such competitive adjustments may not be instantaneous, due to risks and time lags in R&D, and the actual realization of returns may differ radically from that anticipated due to changes in market and regulatory conditions. But if the assumption of dynamic competition with free entry is correct – and all the evidence suggests that it is – then if analysts were to

estimate that returns either exceeded or fell short of the cost of capital over a particular time period, this would either reflect measurement error or market disequilibrium that will be corrected by competitive entry, rendering the analyst's estimate obsolete.

Since the evidence indicates extensive competitive entry to exploit R&D opportunities and hence that dynamic competition should reduce *expected* profits to competitive levels, the more important policy question is whether the resulting rate of R&D yields a level and mix of new drugs that is socially optimal. In this model, changes in the regulatory and reimbursement environment may affect profitability in the short run. But in the long run, the rate and mix of R&D readjusts such that normal returns are realized on average. Whether the resulting R&D expenditures entail significant duplicative investment is an important issue. Henderson and Cockburn (1996) provide some evidence against this hypothesis, but not a definitive rejection. The current trend of payers to demand evidence of cost-effectiveness relative to existing drugs as a condition for reimbursement, reinforces incentives for manufacturers to target R&D towards innovative therapies and away from imitative drugs. The great *ex ante* uncertainty as to the ultimate therapeutic value and timing of new drugs implies that *ex post* realizations will still yield some "me-too" drugs. Even the optimal number of me-toos is uncertain, given their value as a competitive constraint and in improving therapies for some subsets of patients. Although product differentiation can be excessive in models of monopolistic competition or oligopoly, in the pharmaceutical industry any such excess more likely results from generous insurance coverage and high reimbursed prices, rather than firm strategies to use endogenous investments in R&D or marketing as an (unsuccessful) entry barrier.

7. Industry Structure and Productivity: Regulation or Technology?

Several studies have examined the effects of regulation and other factors on industry structure. Grabowski (1976) and Grabowski and Vernon (1978) suggest that regulation-induced increases in R&D cost and risk created scale economies that resulted in the concentration of innovation in large firms. Temin (1979) analyzed the impact of regulatory and technological change on the structure of the US pharmaceutical industry from 1948 to 1973. He concludes that the size of drug firms increased dramatically during this period with much of the growth concentrated in large firms. Thomas (1990) shows that the decline in NCE introductions around 1962 was concentrated in the smallest firms, many of which ceased R&D. Thomas (1996) extends the argument that strict safety and efficacy regulation in the US and UK led to a shakeout of smaller, less innovative firms and concentration of innovative effort in larger firms.

However, since the 1980s and 1990s the biotechnology and genomics revolutions appear to have eliminated the advantages of size, at least for drug discovery, and this has dramatically changed the structure of the pharmaceutical-biotechnology industry. Previously, the chemistry basis of drug discovery implied an advantage for large firms that had large proprietary libraries of compounds, often created by their in-house chemists. Now, the basis for drug discovery has shifted to micro-biology and associated sciences, with comparative advantage in smaller firms that are often spun out from academic research centers. Large firms have continued to grow larger, mostly by acquiring other large firms in horizontal mergers or acquiring biotechnology companies or inlicensing their compounds, in quasi-vertical acquisitions. However, even the largest manufacturer (Pfizer, by global revenues in 2004) accounted for only about 10% of total sales. The FTC monitors the effect of mergers on competition within therapeutic categories, requiring merging firms to divest overlapping products if concentration would be unacceptably

high.

Although firms have often rationalized their horizontal mergers on grounds of economies of scale and scope in R&D, the empirical evidence does not support the claims (Danzon, Epstein and Nicholson, 2005) and in fact R&D productivity of large firms has declined relative to smaller firms. A growing share of new drug approvals is originated by smaller firms, including not only biologics but also some chemistry-based drugs. Conversely, large firms rely increasingly on in-licensing – both research tools and target compounds - from smaller firms. Initially these start-up small firms specialize in discovery research, sometimes forming alliances with larger firms that provide funding and expertise for late-stage clinical trials and marketing, where experience and size play a greater role (Danzon, Nicholson and Pereira, 2005). The growth of contract research, sales and manufacturing organizations has increased the outsourcing opportunities for small firms and hence reduced their need to rely on larger, more experienced partners. Many small firms also purchase human capital expertise, by hiring experienced personnel from larger firms. A growing the number of biotechnology firms have fully integrated capabilities, with Genentech and Amgen being the most successful. Thus if, as earlier studies suggest, the 1962 regulatory changes did contribute to increased industry concentration and disadvantage small firms, the regulatory changes of the 1990s do not appear to have harmed small firms, and technological change has certainly benefited them. Moreover, competition for promising products developed by smaller discovery firms is strong and prices paid for such products have risen over the last decade, reflecting the shifting of bargaining power from large to smaller firms (Longman 2004; Longman 2006).

It might be argued that the high rate of new start-ups in this industry reflects excessive entry as firms compete for profits in a differentiated products oligopoly, that such entry is

welfare reducing due to the repeated initial costs associated with achieving reasonable scale. However, the great majority of new start-ups are formed around new technologies, which face great scientific uncertainty that can only resolved by preclinical and clinical testing that takes time. The rate of discovery of new technologies is driven in part by NIH funding of basic research and the incentives under the Bayh Dole Act (1980) to commercialize such research, and possibly by favorable tax treatment of R&D, especially for orphan drugs. Whether or not NIH funding to basic research is excessive or suboptimal is an important subject for research. Thus in the current environment it does not appear that regulation of market access or endogenous investments in sunk R&D costs are major contributors to excessive product differentiation or monopoly power, with the possible exception of orphan drugs that by design receive five years of market exclusivity.

However, it is plausible that health insurance coverage for modestly differentiated on-patent drugs, when cheap generics are available for off-patent, therapeutic substitutes, contributes to product differentiation through slightly differentiated molecules and new formulations. Whether insurance creates incentives for excessive product differentiation, including extensions and new formulations, and/or reduces cross-price demand elasticities is an important subject for future research.

VI. Promotion

1. Trends in Promotion

Promotion by manufacturers is an important mechanism whereby physicians, consumers and payers learn about drugs. In 2003 the industry spent $25.3 billion on promotion or 17.1% of sales– similar to several other experience-good industries with significant product

differentiation such as toys and cosmetics (Frank RG 2002; Berndt 2005).[23] This estimate of total promotion spending omits the promotion-related components of pre- and post-launch clinical trials. On the other hand, the estimate is upward biased because almost two-thirds ($16.3 billion) reflects free samples distributed to physicians for patient use (Berndt 2005), and these samples are valued at either a list price or a retail price that significantly exceeds the economic cost to manufacturers.[24] The next largest components of promotional spending were physician detailing ($4.5 billion), direct to consumer advertising ($3.7 billion), hospital detailing ($819 million) and medical journal advertising ($448 million) (Berndt 2005).

Promotional spending overall has grown absolutely and as a percent of sales, from 14.1% in 1996 to 17.1% in 2003. Direct to consumer advertising (DTCA) grew most rapidly, from just $12 million in 1989 and $791M. in 1996 –prior to the 1997 FDA reinterpretation of the guidelines for broadcast DTCA -- to $3.2 billion in 2003 (Palumbo FB 2002; Berndt 2005). The 1997 FDA Guidance clearly increased the share of DTCA that is broadcast, from under 30 percent prior to 1997 to almost two-thirds in 2002 (Rosenthal MB 2002). DTCA is concentrated on the leading drugs in therapeutic categories that are particularly amenable to patient awareness and choice. For example, in the first six months of 2004 spending for the top 20 drugs accounted for 65.1% of all DTCA. The top five therapeutic categories for DTCA in 2000 were antidepressants, antihistamines, antihyperlipidemics, nasal sprays and proton pump inhibitors (Rosenthal MB 2002; Berndt 2005).

2. Regulation of Promotion: Background and Issues

As discussed in Section II, promotion of prescription drugs in the US has been regulated by the FDA since the 1962 Amendments, which remains the statutory base guiding the FDA's

regulation of promotion to both physicians and consumers. This statute restricts promotional claims to facts established in clinical trials; requires that risks as well as benefits be described in brief summary; and excludes promotion of unapproved indications. The FDA's 1997 Guidance relaxed the requirement that the full product label, which includes all known risks, be displayed in broadcast ads. Rather, the requirement for a brief summary of risks and benefits could be provided by giving a website, a toll free number, or reference to a print ad with the full label, in addition to advice to "see your physician." These changes were deemed to reflect the ways in which consumers currently get information.

The US constitutional right to freedom of speech has been interpreted to include commercial speech and hence to support limits on regulation of promotion by the FDA. The FDA cannot require pre-clearance of ads; however, once they appear the FDA can require changes, removal and even dissemination of corrective information. Promotion of information about off-label (unapproved) uses of drugs was not permitted until 1997, when companies were permitted to disseminate peer reviewed publications discussing off-label use. In its oversight of promotion, as for its other activities, the FDA is required by statute to consider risks and benefits; costs are not mentioned. Thus the FDA is concerned with the effects of promotion on patients and physicians; whether or not it results in unnecessary costs is beyond its purview.

3. Evidence on Effects of Pharmaceutical Promotion

The pharmaceutical industry's large expenditure on advertising is controversial, with policy concern over both magnitude and form. The economic literature outlines the issues and provides some evidence, but basic questions remain unresolved. The growth of DTCA since 1997, in particular, has prompted research to better understand its effects. The economic

rationale for promotion is that it provides information to physicians and consumers about the benefits and risks of drugs, which is necessary for appropriate prescribing and to encourage appropriate patient compliance. Critics contend that much promotional expenditure is in fact designed to persuade rather than inform; that it increases product differentiation, brand loyalty, market power and prices; and that it leads to inappropriate use, including use of high-price, on-patent drugs when cheap generics would be equally effective.

Promotion studies pre-1997 An early proponent of the anti-competitive hypothesis, Walker (1971) argues that large promotion expenditures raise entry barriers and increase market power, by requiring new entrants to make large outlays in order to attract attention to new products. The alternative view is that advertising may enhance competition by facilitating the introduction of new products and new firms. Schwartzman (1975) finds that more innovative firms spend larger sums on promotion. Telser (1975) finds that the extent of new entry into a therapeutic class is positively related to promotional intensity. However, it is unclear whether this positive correlation indicates that promotion enhances competitive entry or whether both are simply related to unobservable factors such as technological advance and market potential.

Leffler (1981) estimates a model across therapeutic categories with selling effort as the dependent variable and the number of new products introduced as the primary explanatory variable. He finds a significant positive effect which he interprets as suggesting that pharmaceutical advertising is at least partly informative. He also finds evidence, however, that advertising of established pharmaceutical products accomplishes 'reminder' and 'habit-formation' purposes. These results suggest that the impact of advertising is multidimensional and that the net effect on competition may differ, depending on the circumstances. The distinction drawn by Leffler between the 'persuasion' and 'information' roles of pharmaceutical

promotion is extended and supported by Hurwitz and Caves (1988). Berndt et al. (1995) find that promotional stocks of detailing, journal advertising and DTCA (pre-1997) significantly affect industry-level demand for anti-ulcerants but with diminishing returns, again suggesting the importance of reminder or loyalty-building promotion.

Beales (1996) uses the FDA policy restricting manufacturer advertising of unapproved indications as a natural experiment to test the importance of pharmaceutical marketing as a source of information for physicians. He analyzes the impact of promotional activity following FDA approval of second indications for existing drugs on the share of patients treated with the newly approved product, the total fraction of patients treated with drug therapy, and the average price level. He finds some evidence that seller provided information after approval results in increased market share for the new indication as well as lower average price per prescription of other products in the market, suggesting an increase in consumer benefits from increased manufacturer-provided information. However, identifying the impact of FDA approval itself vs. promotional expenditures is problematic.

Effects of direct to consumer advertising post-1997 Much of the analysis of DTCA has focused on its effects on drug sales in aggregate and on share of the individual brand. Although some of these studies use state-of-the-art methods, applied to the best data available and provide valuable evidence, important issues remain unresolved. This reflects both data and empirical challenges and the difficulty of weighing costs and benefits to drawing overall welfare conclusions.

One major empirical challenge is that DTCA is endogenously determined and just one of several types of a promotion a firm may use. Ignoring the endogeneity of DTCA and its correlation with other (often unobserved) forms of promotion can potentially lead to serious

biases in results. For example, both theory and evidence suggest that DTCA is likely to have a higher pay-off for best-in-class drugs. This assumes that physicians, as good agents, are more likely to write the prescription for the best-in-class product, even if the patient requests another advertised brand. In that case, an observed positive correlation between promotion and market share may reflect in part these incentives for market leaders to invest more in promotion, leading to upward biased estimates of the reverse effect of promotion on market share. Second, estimates of promotional effects must take into account lagged and future impact on information stocks, as physicians form prescribing habits and patients tend to stay with a particular brand for chronic medications, once they have found a drug that works for them. Third, the net effect of one firm's promotion depends on competitors' strategic responses.

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

The study of promotional effects in the antihistamine and antiviral categories by Narayan et al. (2005) is unusual in including data on DTCA, detailing, pricing, and other medical spending as alternative marketing mechanisms to influence sales; measuring both the

short and long run effects of promotion; and estimating cross-firm elasticities. All marketing mix variables are modeled as endogenous. This study finds that, of the four marketing variables, only DTCA has a positive but small effect on aggregate category sales. Each product's own DTCA also positively affects its own brand sales, but interaction effects with other brands' DTCA are negative. Own DTCA and detailing appear to be complements, rather than substitutes. The estimated return on investment is lower for DTCA than for detailing, suggesting that firms might gain by reallocating marketing budgets away from DTCA and towards detailing. Although it would be a mistake to generalize the findings of this study, which focused on only two therapeutic categories, it does illustrate the importance of including the full marketing mix and controlling for endogeneity of the marketing variables when estimating the effects of DTCA.[25]

In general, with the important exception of the Narayan et al. (2005) paper cited above, findings from other studies suggest that DTCA has a greater effect on category sales than on individual brand sales. Rosenthal et al. (2003) use data for five large therapeutic categories to estimate effects of DTCA, controlling for sampling and detailing.(Rosenthal MB 2003) They conclude that DTCA has a significant positive impact on class sales, with an average elasticity of roughly .1, but they find no evidence that detailing or DTCA has a significant effect on product-specific market shares.[26] The authors emphasize that failure to find brand-specific effects could reflect learning or unmeasured longer term effects. Wosinska (2002) finds that DTCA for the cholesterol reducing medications (statins) positively affects brand share only if the brand had preferred formulary status.(Wosinska 2002) Similarly, Iizuka and Jin (2005b) find that DTCA increases total category sales, but brand-specific share is only significantly shifted by physician promotion such as detailing and journal publications. The authors conclude

that a product should hold at least 58% market share of its therapeutic category sales in order to recoup DTCA investment. In fact, they find that 69% of DTCA spending is on drugs with at least a 60% market share. They also find that DTCA increases the number of doctor visits at which a drug is prescribed (Iizuka and Jin, 2005a), with some differences between patient types in their responsiveness to DTCA (young vs. elderly; private vs. public insurance). Donohue and Berndt (2004) find that DTCA has no significant effect on choice of product, but that it does motivate individuals to visit the physician.

A randomized control trial by Kravitz et al. (2005) supports the ambiguous conclusions reached in other studies that use observational data on medical. Standardized patients (who were not sick, but were scripted with dialog to feign depression or adjustment disorder) asked unsuspecting blinded physicians for either A) no medication B) a generic drug or C) a specific brand. For both disorders those who requested were significantly more likely to receive a drug (31% vs 76% vs 53% for depression, 10% vs. 39% vs. 55% for adjustment disorder), but not necessarily the suggested drug (in the case of those who requested one). Various conclusions can be drawn from these data, including that there is both over and undertreatment of depression, and that responses to patient requests differ across physicians. Policy implications for DTCA regulation are therefore very unclear. Moreover, welfare conclusions would also require data on costs and medical outcomes.

The effects of DTCA on quality of care and patients' compliance with prescribed regimens are examined by Donohue (2004) and Wosinska (2004). Donohue (2003) finds that patients in the top quartile of exposure to DTCA had 32% higher odds of initiating therapy. Conditional on any therapy, those in the top quartile of DTCA spending also had a 30% ($p<.05$) greater probability of adherence (measured as filling at least 4 prescriptions over the first six

months of therapy). Wosinska's examination of the Blue Cross and Blue Shield of California data for adherence to statin regimes finds a minor impact for total DTCA spending, but current and lagged own DTCA has no affect on product adherence (Wosinska 2004).

Iizuka (2004) finds that high quality drugs, as defined by whether a drug had "priority" status for FDA approval, have significantly more DTCA spending. The interaction term between the quality dummy variable and a dummy variable indicating that the drug was either first or second to market within a particular class also had positive significance. He also finds that DTCA spending decisions are significantly related to the potential market size but not the currently treated market size—a result which supports the hypothesis that DTCA has positive social value in that it targets consumers might potentially benefit from medicines rather than those who already take medicines.

4. International Regulation of Promotion

Several countries include in their price regulation systems features that are designed to discourage promotion. The UK PPRS limits the promotional expenditure that can be deducted as a cost in calculating the net rate of return. Germany's 1993 German global drug budget legislation placed the pharmaceutical industry at financial risk for budget overruns, second in line after physicians, in order to discourage promotion. Similarly, France penalizes "excessive" promotion, both directly through fines for exceeding allowed promotion limits and indirectly through penalties for overshooting target sales limits. Some countries prohibit samples; even where there is no prohibition, there may be little incentive to give free samples in countries where patient co-payments are low.

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

Studies of regulatory systems and their effects are more limited for promotion than for prices, in part because data on promotion spending is more limited and less informative across countries. For example, the content of a visit by a detail representative to a physician can be very different, depending on time spent, messaging allowed, whether sampling is permitted etc. Berndt, Danzon and Kruse (2006, forthcoming) provides some evidence on cross-national differences in promotion and in diffusion of new drugs.

5. Promotion to Managed Care

The growth of managed care has fundamentally changed the nature of marketing of pharmaceuticals. The autonomy of the physician has been reduced, with power shifting to payers or their pharmaceutical and therapeutics committees that make formulary decisions, in addition to consumers. This shift in the primary ‘customer’ from the physician to more cost-conscious decision makers has been accompanied by a dramatic increase in the importance of cost-effectiveness analysis, to demonstrate that a particular drug is more cost-effective than the

alternatives. Use of cost-effectiveness analysis by managed care organizations is summarized in Elixhauser, Luce and Steiner (1995) and Newman (2004).

In response to this trend, the FDA proposed regulations that would require that a pharmaceutical firm's cost-effectiveness claims be supported by 'sound' analysis. A debate ensued as to whether this requirement requires a double blind, randomized clinical trial (RCT) between the two drugs under comparison. Such a requirement would raise the same issues that were debated at the time of the 1962 Amendments: are the gains from reducing the risk of misleading claims outweighed by the costs of additional clinical trials? The social value of head-to-head RCTs as a requirement for cost-effectiveness claims is weaker than the case for RCTs for efficacy prior to launch, in part because the information on both costs and effects produced in RCTs is not necessarily an accurate measure of cost-effectiveness in actual use, because trials do not mirror actual practice. Moreover, for firms considering investing in such trials, the payoff diminishes as patent expiry approaches and the risks could be significant, if negative findings must be publicized. So far the FDA regulations fall short of requiring RCTs to support economic claims. Some managed care firms require that studies submitted to support marketing claims follow specified guidelines, including comparison of any new treatment with the standard of care for their patient population. If CMS develops guidelines for effectiveness studies for the Medicare Drug Benefit, the private sector may choose to free ride, in which case the government guidelines may *de facto* acquire the status of regulation for the conduct of cost-effectiveness studies and, potentially, for decisions on reimbursement.

6. Discussion of Promotion

Some of the effects of DTCA appear consistent with social welfare, while other evidence suggests some inappropriate effects. Given other evidence that there is both under and overuse of pharmaceuticals, relative to medical guidelines, it is not surprising that drawing welfare conclusions on effects of DTCA and of DTCA regulation is problematic. Moreover, the real policy decisions in the US are less about whether DTCA should be permitted but about the specific details of appropriate regulatory rules that may be too nuanced for empirical analysis.

Moreover, the effects of regulation depend not only on the rules but on enforcement. The staffing levels at the FDA's division of drug advertising, marketing and communications (DDMAC) are reportedly inadequate for the amount of material they must review, including television and print advertising (GAO 2002). The HHS policy since 2001 to review warning letters from the DDMAC has further inhibited enforcement (Gahart, Duhamel et al. 2003). While firms have generally complied with warning letters for infractions and no major disciplinary action has been required, in some instances multiple letters have been sent and the delay in enforcement may have effectively allowed commercials to influence public opinion before modification or withdrawal.

The recent withdrawals of widely advertised products and of some widely disseminated ads have prompted both the FDA and industry to address their policies related to DTCA (Dubois 2003). Industry has issued voluntary guidelines for DTCA which reinforce the "fair balance" standard and stipulate that firms provide copy of advertisements prior to, rather than concurrent with, planned public release(PhRMA 2005(b)). The guidelines also call for firms to abstain from DTCA for several months after launch of a new drug, in part to enable education of physicians about new products in advance of DTCA release.

VIII. Conclusions

Regulation of pharmaceuticals derives from intrinsic product characteristics, in particular, significant but uncertain risks and benefits to health, rather than to structural features of the industry, such as natural monopoly. Information about a drug's risks and benefits in humans can only be obtained from careful study in large numbers of patients with appropriate controls for patient characteristics and co-morbidities. There is a strong argument that structuring and interpreting such data analysis is a public good that is best delivered by an expert regulatory agency. The existence of regulatory systems to perform these functions and control market access in all industrialized and most developing countries is strong evidence for consensus opinion on this basic proposition. However, the regulatory details of what information to gather, whether relative to placebo or current treatment, from pre-launch or post-launch sources, and under what conditions to make a drug available to the public, raise questions of effects of different regulatory regimes and optimal regulatory structure. Economic analysis has shed considerable light on these issues, but many fundamental questions remain. Moreover, since the fundamental problem is imperfect information, the optimal regulatory structure may change over time, as technologies for data gathering and analysis change and consumers' willingness to bear risk and demand for information change with technology, income and other factors.

Early research on the 1962 Keffauver-Harris Amendments strongly suggests that it was one – but not the only – factor contributing to rising costs of R&D, reduction in number of new drugs and probably reduced market share for small firms. However, the evidence from the 1990s and 2000s suggest that, while some regulatory changes accelerated the review process and stimulated R&D for diseases with smaller market size, rising concern over drug

risks contributed to rising R&D costs. At the same time, the biotechnology and genomics revolutions have transformed drug discovery and transformed industry structure, with biologics accounting for an increasing share of sales and a rapidly growing share of new drugs in the pipeline. Thus regulation no longer appears to play a significant role in the size distribution of firms.

In contrast to the evidence on costs and delay, the debate over appropriate minimum standards for safety and efficacy and the optimal trade-off between them has generated more heat than light. Important topics for future research include the political economy questions, to shed light on economic reasons for the changes over time in FDA policy, and standard economic analysis of effects of various alternatives. Some advocate greater disclosure of all clinical trial results and stricter requirement for safety and efficacy relative to current standard of care, via larger trials and mandated registration of both pre-approval and post-marketing trials in publicly available registries, while others assert that greater autonomy of patients and physicians to select drugs which meet minimal safety standards would offer expanded choice and potentially increase net welfare. While the methodology of cost-effectiveness analysis has become increasingly sophisticated for use in reimbursement decisions, little progress has been made on the application of such concepts or other formal decision analytic tools to the weighing risks and benefits in drug approval decisions, or determining optimal thresholds for safety and efficacy.

Another important topic for future research involves identifying best practices and best data sources for integrating post-launch observational data with pre-launch clinical trial data, to evaluate safety and efficacy decisions on an ongoing basis as information accumulates. An important related question will be the effect of post-launch drug evaluation on costs and ex

ante risks and returns to firms, and hence on firm R&D investment decisions. Optimal integration of post-launch regulatory review with tort liability is a related issue.

The interface between patents and regulation is another important topic on which economic research has shed some light but many interesting questions remain. Although pharmaceuticals are subject to the same 20 year patent life as other products, effective patent life depends on regulation. FDA requirements for proof of safety and efficacy truncate early product life, but regulation also restores patent term and grants additional market exclusivities for new formulations, pediatric indications etc. Most important, regulatory requirements for market access of generics effectively define the end of patent life for originator products. Litigation between generic and originator firms has proliferated in recent years, indicating considerable uncertainty about patent validity and/or perverse incentives for strategic patent filing and patent challenges. More research is needed on how far new formulations and new indications for established drugs add to consumer welfare vs. serve as mechanisms for "evergreening" the original patent. Such research could be useful input into regulation and patent provisions for these follow-on products and could inform antitrust activity towards settlements between originator and generics firms. Clearer standards for patents could in turn help reduce wasteful litigation.

Defining appropriate regulatory provisions for approval of generic biologics is partly a scientific question but with important potential for economic impact. The regulatory details must consider safety and efficacy and the need to avoid biasing R&D incentives for or against biologics vs. chemical drugs. Moreover, the extent to which price competition occurs between similar biologic products will depend on reimbursement provisions and incentives for physicians who typically dispense these drugs. Reimbursement for physician-dispensed drugs

is in flux and current models have perverse incentives (Danzon, Wilensky and Means, 2005). Resolving these issues is essential if consumers and payers are to realize the potential for savings from generic biologics.

Regulation of price and reimbursement for pharmaceuticals differs from price regulation in other industries in that the rationale for regulation arises out of insurance and its effects on demand elasticity. Both private and public insurers adopt supply side policies, including limits on reimbursed prices, in order to control supplier pricing moral hazard, in addition to patient co-payments to control consumer moral hazard. Price regulatory systems are generally an ad hoc mix of historical policies that have evolved over time as a trade-off between controlling drug spending and assuring access for patients. Because the details of each country's system differ, attempts to measure effects of regulatory prototypes, such as "price controls" or "reference pricing" are fraught with confounding from other unmeasured country-specific details and non-regulatory factors. Moreover, effects on R&D are confounded by the fact that incentives for pharmaceutical R&D depend on global revenues. Nevertheless, understanding effects of different systems for controlling drug prices, reimbursement and expenditures is clearly an important subject for future research, including effects on prices, utilization, patient outcomes and firm R&D incentives. Such research is particularly important as some form of regulation becomes more likely in the US, as the federal government becomes a much larger purchaser of pharmaceuticals through the Medicare drug benefit, albeit so far through private administration.

Finally, regulation of promotion remains a relatively uncharted territory, with some useful studies but many remaining questions, particularly related to DTCA. Empirical issues are particularly challenging, given the number of promotional channels that are

simultaneously determined, and interdependence between firm strategies. The existing evidence on effects of DTCA is mixed, with quite strong evidence for category expansion and weaker evidence for improved compliance and product specific benefits. Effects on patient outcomes and on competition and overall costs have not been measured. Thus several of the components of a full welfare analysis remain to be developed.

In summary, although there is a large and growing literature on regulation of the pharmaceutical industry that has produced valuable information and useful lessons learned, large and important issues remain for future research. Models of regulation in other industries are either not relevant or require significant adaptation and extension, in order to fit this industry's peculiar characteristics --- in particular, high rates of R&D and technical change, with life-or-death effects, patents, insurance, and physicians, consumers, payers and pharmacists as potential customers. This industry remains a fertile area for future research.

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Table 1: Objectives and Types of Regulation of the Pharmaceutical Industry

Rationale for Regulation	**Type of Regulation**
Imperfect information about drug safety and efficacy	Market access requirements of safety, efficacy and quality Regulation of promotion Tort liability
High fixed costs of R&D	Patents and regulation of generic entry Orphan Drug Act Accelerated approval measures
Insurance-induced moral hazard	Regulation of prices, reimbursement, profits, expenditure/revenues

Endnotes

[1] In theory, firms may submit for OTC (over-the-counter or non-prescription) status, but the new product would have to be proven safe and effective under self medication, which could be a higher bar since some consumers may not use the product appropriately (Mahinka SP and Bierman ME, 1995). In contrast to medicines, dietary supplements are regulated under the Dietary Supplement Health and Education Act of 1994. Manufacturers of dietary supplements are responsible for assuring that their products are safe but they are not required to get FDA approval before marketing. However, they cannot make explicit health claims unless these claims have been demonstrated by clinical trials. The ability to make health claims and, most important, to be eligible for health insurance coverage probably makes prescription status the most attractive status, for any drug that (a) can potentially meet FDA standards for safety and efficacy and (b) is patentable and hence can expect to recoup the costs of clinical trials.

[2] This has subsequently been renewed twice as part of the Food and Drug Modernization Act (1997) and the Bioterrorism and Preparedness and Response Act (2002).

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

[4] The patent term restoration is 0.5 years per 1 year spent in clinical trials and 1-for-1 for years spent in regulatory review.

[5] Assuming that more important drugs typically have atypically high price or quantity, and therefore revenues, the percentage decline in revenue share of new drugs should be less than the percentage decline in number of new drugs, if the Amendments only eliminated minor drugs of dubious efficacy.

[6] Boston Consulting Group (BCG, 1993) reports that the mean number of subjects included in NDAs increased from 1576 for 1977–1980, to 1321 for 1981–1984, and 3233 for 1985–1988. DiMasi et al. (2003) report a mean number of subjects per NDA of 5,303 for trials completed in the late 1990s. DiMasi (2001) reports that total cumulative time from drug synthesis to approval increased from 8.1 years for 1963-1969 to 14.2 by 1990-1999.

[7] Finkelstein (2004) examines the effects on vaccine R&D of three plausibly exongeneous shifts in policy (the 1991 CDC recommendation to vaccinate infants against Hepatitis B, the 1993 expansion of Medicare to cover influenza vaccines and the 1986 introduction of the Vaccine Injury Compensation Fund) that plausibly increased expected revenues. She finds a lagged increase in vaccine clinical trials after these events, but no increase in early stage patent activity or preclinical trials.

[8] Dranove and Meltzer (1994) used several measures of drug importance, including citations in medical textbooks, in medical journals, and in subsequent patent applications; the extent of worldwide introduction; and US sales. To the extent that these *ex post* measures of importance

are noisy measures of *ex ante* forecasts of importance, their estimates of differential delay may be understated.

[9] DiMasi (2003) p.164-165 reports that total time from start of human testing to approval for a representative drug is 90.3 months in the 1990s, down from 98.9 in the 1980s.

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

[11] Data from IMS Health, unpublished presentation. Note that these figures include only unbranded generics, which compete on price rather than brand image. Branded generics, which include some old single source drugs, account for an additional 9.8 percent of prescriptions and sales.

[12] See Article 31
http://www.wto.org/english/tratop_e/trips_e/t_agm3_e.htm

[13] For a discussion of these issues, see for example Danzon (1997), Dumoulin (2001), Jack and Lanjouw (2003), Malueg and Schwartz (1994), Maskus (2001), Danzon and Towse (2003, 2005), Scherer and Watal (2002).

[14] Institutional arrangements that facilitate differential pricing between the low and high income subgroups within developing countries may also be necessary. Without such

segmentation, manufacturers may rationally choose a single price for a low-income country that is profit-maximizing given demand of the affluent minority of the population but is unaffordable for the lower-income majority.

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

[16] Some insurers contract with PBMs as specialized intermediaries to manage their drug benefit, while other larger plans manage their own benefit using similar techniques. Thus although PBMs are estimated to manage approximately 57 percent of the US population's drug benefit (Health Strategies, 2005) the share of the population that has managed drug benefits, including HMOs and seniors under Medicare Part D, is probably over 70 percent.

[17] Although some countries, including Italy, have attempted to base prices on costs, this approach is not widely used because of the difficulty of obtaining accurate measurement of costs. Measuring R&D cost is particularly problematic, because it occurs over many years, includes the cost of failures and foregone interest, and is largely a joint cost that must be allocated across global markets. In practice, price regulation based on costs has relied on transfer pricing rules which were designed for tax purposes, not price regulation.

[18] Similar incentives existed in the US under Medicare B which, until 2005, paid for physician-dispensed drugs based on a percent of Average Wholesale Price (AWP). Since

physicians captured the margin between AWP and their acquisition cost, manufacturers could increase physicians' financial incentives by discounting the acquisition price.

[19] Thomas (1996) discusses other factors, including weak efficacy requirements for drug approval, that may have contributed to the relatively weak international competitiveness of Japan's pharmaceutical industry, compared to its prowess in other high technology industries.

[20] For analysis of differential pricing in the context of developing countries, see Danzon and Towse (2003, 2005); Jack and Lanjouw (2003).

[21] In Germany, pharmacies were required to dispense the brand prescribed by the physician and could substitute a generic only if the script was written by generic name. Until 2004, German pharmacies were paid a percentage of the price of the drug they dispensed, hence they had neither legal authority nor financial incentive to seek out cheaper generics. Not surprisingly, in this system generics competed on brand rather than price, and generic prices were relatively high, compared to US generic prices (Danzon and Furukawa, 2003). In 2006 German sickfunds began contracting directly with generic suppliers in order to obtain lower generic prices.

[22]Primary care physicians in the UK are organized into primary care groups, by locality. Each group must serve all residents in its area and receives a global budget for their costs. Thus spending more on drugs means less money for other services. Physicians are trained to

prescribe generically and pharmacists in the UK can profit from substituting generics for brands, if the script is generically written.

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

[24] A more accurate measure of the true cost of samples to firms lies somewhere between the marginal production cost and the actual price the manufacturer might have received, had the patient filled the prescription and paid for the drug.

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

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