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THE EFFECTS OF PRICE REGULATION ON PHARMACEUTICAL R&D AND INNOVATION

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ABSTRACT

As rising health care expenditures focus government attention on slowing the growth, the pharmaceutical industry comes under increasing pressure to curb prices of ethical drugs. Pharmaceutical price regulations have been implemented in many countries to control pharmaceutical expenditures. Yet, creating innovative drugs requires enormous R&D costs, which in turn require adequate expected economic returns. Since price controls reduce profits and expected returns, as countries invoke stricter price regulations, firms will either move their R&D process into less regulated markets or move out of innovative R&D. This paper assesses the impact of drug price regulations in Japan compared to market-priced drugs in the US on pharmaceutical innovation.

INTRODUCTION

In the past few decades, hundreds of innovative new drugs have entered the marketplace. They help: improve quality of life; save millions of lives; increase labor productivity leading to more robust economies; and, provide cheaper, less invasive solutions to chronic diseases, such as heart disease. The improvements to quality of life and life expectancy have been significant. Studying US life expectancy between 1970 and 1991, Lichtenberg (1998) conservatively estimates a \$15 billion increase in pharmaceutical R&D expenditures saves 1.6 million life-years per year, valued at \$27 billion. Lichtenberg also finds pharmaceutical innovation decreases costs in other areas within the healthcare industry. For example, Lichtenberg (1996) estimates for every \$1 increase in spending on pharmaceuticals there is a subsequent decrease of \$3.65 in hospitalization costs, yielding a savings of \$2.65. Additionally, by reducing the age of utilized drugs from 15 to 5.5 years, pharmaceutical expenditures increase \$18, but yield a \$129 savings in non-drug expenditures for a net savings of \$111 (Lichtenberg 2002).

The worldwide pharmaceutical industry, as we know it today, is relatively young, having only become global in the last twenty years. Yet over a century of work by chiefly national pharmaceutical industries has enabled the industry to blossom globally. The countries leading the pharmaceutical industry into the global era laid the path to success through their domestic policies prior to globalization. Their intellectual property rights and domestic market environments, often coupled with public research funding,

enabled innovative pharmaceutical firms to prosper. From 1820 to 1990 these originator countries of the today's global industry created the overwhelming supply of new drug technologies. Between 1820 and 1990, 80% of globally marketed, innovative drugs for the world's seven leading indications came from just five countries: France, Germany, Switzerland, the United Kingdom, and the United States (Landau et al 1999). The five next most productive countries (Belgium, Denmark, Italy, the Netherlands, and Sweden) represented 19% of globally launched products, leaving only 1% coming from the rest of the world (Landau et al 1999).

The quantity of new products introduced per country is just one measure of innovation. Another is the dollar value of a country's pharmaceutical exports, since this figure highlights reaching out to a global market. While the countries noted above excel in exporting innovative drugs, the Japanese did not from 1820 to present. From 1820-1990, about 60 percent of the drugs in the Japanese market were only marketed domestically and the value of Japanese exports was relatively low (Landau et al 1999). Despite some improvement in exports, by 2000 Japanese drug exports still ranked eleventh in the OECD with exports of \$2.73 billion compared to \$13.13 billion for the US (JPMA 2003). Japanese drug exports to date have brought relatively little value to the global market, contrary to Japan's various world-class industries.

Patent protection in the Japanese market has lagged compared to that in other developed countries. Only processes, not compounds, were protected until 1976. Therefore Japanese firms could launch a product that was still under patent protection in other countries so long as they produced it through a different process. Thus, much of the research conducted in Japan prior to 1975 centered on the "adapting" of internationally developed products and not the development of novel products (Reich 1990). Fearing a disadvantage in innovative R&D, in 1987 the Japanese government began to direct funds toward innovative R&D. Much of this effort, however, was countered by the dramatic cuts in the government's national drug reimbursement prices (Reich, 1990). Prices were cut an average of 61.4% in the 1980's, dampening innovator's expected returns (Reich 1990).

Today, despite the fact that Japan is the second largest single market, its pharmaceutical industry continues to lag behind

the United States and Europe in terms of innovation. The Japanese market remains centered on domestic products, and the few successful Japanese R&D-based firms are increasingly concentrated in international markets. Companies like Takeda, Daiichi, and Sankyo continue to set up headquarters in many more innovation friendly markets, as Japan maintains less innovator friendly policies.

In contrast, Europe led the world in drug exports through the late 1980s and early 1990s, reflecting the market environment in which the industry developed (Landau, Achilladelis, and Scriabine 1999). A leading factor for this European predominance was early patent protection, encouraging R&D leading to innovation. The creation of new drugs coupled with strong, historical distribution chains enabled the European pharmaceutical firms to flourish.

The same link to patent protection and innovation holds true for the US where it is even more apparent in the biopharmaceutical arena. Currently, the US is benefiting greatly in the biopharmaceutical market because it has long been providing protection to both natural products (since 1947) and recombinant DNA (since 1985) (Achilladelis 1999). Biological research was initially conducted by private firms, not by the major publicly-held pharmaceutical companies. With the assurance of patent protection investors moved into the budding biologics industry, as other industries struggled (Achilladelis 1999). As the biologics industry began to move into pharmaceuticals in the 1980s, many European countries did not allow the genetic research needed to produce new biologic entities. Thus, both technological and intellectual capital moved to the US where they were able to pursue innovation (Scriabine 1999). Today the US continues to dominate this growing field of research. According to EFPIA (2004), the US represents 73.9% of biological R&D today, followed by Europe at 22.7%.

The dominance of the US and Europe in creating innovative drugs has continued since 1990, however, there has been a movement toward more of the innovations coming from the US. P.E. Barral (2004) focuses on new drugs authorized in at least four of the major world markets and shows the four European originator countries accounted for 61 new drugs produced between 1975-1979, compared to 54 for the US. By 1990-1994, European firms were the originator of 38 new drugs relative to the US's 40 (Barral 2004). Of the top ten selling drugs in the world today, US firms developed eight of them (Pharma Profile 2002).

Despite the growing evidence of the tremendous benefits of innovative drugs, great attention is drawn to their costs by consumers and governments; the pharmaceutical industry has come under increasing pressure to curb prices of ethical drugs. Between 1981-1994 drug prices rose an average of 9.6% annually compared to 5.1% average inflation (Santerre

and Neun 2000). The USA Today reported findings from an AARP study indicating a 27.4% average price increase in the leading 155 selling drugs from 1999-2003 relative to 10.4% general inflation (Welch 2004).

To bring a drug to market today, it takes approximately ten to fifteen years and \$1.7 billion in R&D costs (Launders 2003), as compared to \$231 million in 1987 (DiMasi *et al* 1991). Along with the significant financial outlay needed to create a new product also come the high risk of failure. Most compounds and biologics investigated for therapeutic use never make it to market. Of every 5,000 possible medicines investigated, five make it through to clinical trials and one becomes a marketable product generating revenues exceeding average R&D costs (PhRMA 2000). Firms engage in new drug development, but they need sufficient economic returns to continue the process.

Pharmaceutical price and/or profit regulations have been implemented in all OECD countries, except the US, to attempt to control pharmaceutical expenditures. In Germany, increased price regulations were implemented in 1992 through the Health Sector Act. By restricting prices, profits were diminished and companies saw much less incentive to conduct R&D in Germany. From 1992-1999, 23,000 jobs were eliminated in the German pharmaceutical industry, and by 2001 Germany had slipped from the number one to the number three position in European countries conducting innovative R&D (Kermani and Bonacossa 2003). The UK implemented profit restrictions, though they are not seen as restrictive as the German scheme (Kermani and Bonacossa 2003). R&D activity has not been as gravely affected in the UK compared to Germany.

Japan's government sets prices of new drugs based on older comparator drugs. Recently, price premiums have been permitted on truly innovative drugs, but even with the premium in place the introductory price is not higher than that of older drugs. Following a drug launch, the government decreases the price as the product matures; the highest price ever received is the first one. Prices fall by as much as two thirds from the original price within ten years. The low introductory prices, coupled with no inflationary price increases, discourage new product development (Phrma 2005).

The United States is the least regulated market in the industrialized world, and has seen R&D increase significantly. EFPIA reports that in 1990, Europe led the United States in R&D spending by more than 70%, whereas today R&D in the United States is greater than that in Europe (EFPIA 2002 *in* Kermani and Bonacossa, 2003). We contend that as countries increase the stringency of their price regulations, companies will either move their R&D processes into less regulated markets, or move out of innovative R&D.

In this paper we will provide insight into the factors leading to innovative drug production in the US. We also examine the impact of regulation on innovation in the world pharmaceutical market by comparing the US and Japan. Specifically, have the more restrictive drug regulations in Japan altered the innovation playing field and led to less innovation in Japan compared to the US?

INNOVATION

R&D in the pharmaceutical industry is the process by which innovative firms discover, test, and receive approval for ethical drugs. There are two main categories in which R&D falls; innovative and imitative. Imitative R&D primarily produces generics, me-too drugs, and line extensions. Therefore, it is the cheaper and "safer" form of R&D, but provides only incremental benefit to society. In contrast, innovative R&D produces novel products such as New Molecular Entities (NMEs) or New Chemical Entities (NCEs), which are one in the same. They are defined as, "any medication containing an active substance that has never before been approved for marketing in any form... Thus, new dosage forms, strengths, or indications of already approved drugs are not considered NMEs or NCEs." (CDER 2004). While generics, me-too drugs, and line extensions play important roles, innovative products represent the largest benefits for society and absorb the greatest portion of R&D efforts and expenditures. Thus, current trends in various stages in the novel R&D process can be used as metrics for innovation.

How to measure the output associated with R&D inputs is a subject of debate. Some use NME's or NCE's, suggesting these are ultimately the end product. One can also argue NCEs first in a therapeutic class is a better measure of output. Similarly, how many people are impacted by the NCE is also a viable measure. Traditionally, however, NMEs are used as a broad measure of R&D output.

In recent years, the productivity of R&D has become a concern. In Figure 1, US R&D expenditures per year are compared to number of NMEs entering the US market per year. While total R&D has risen every year since 1980, the number of NMEs launched per year has oscillated downward since 1996. For example, the number of NMEs in the US declined from 35 in 1999 to 21 in 2003.

In a recent report requested of the European Commission, Charles River Associates (CRA 2004) contends there is not a global crisis in innovative R&D. By analyzing historical swings in launches per year and tracking the movement between the different phases of development until a New Drug Application (NDA) is filed, CRA predicts authorizations are likely to grow in 2005 (CRA 2004). NDAs are submitted to the regulatory board of a country at the end of Phase III in the R&D process. The regulatory

board reviews the application to ensure all safety and efficacy requirements are met. If the drug is found to meet all requirements it is given marketing approval (PhRMA 2001). Therefore increases in submissions should generate an increase in approvals. CRA (2004) believes the downturn in launches due to fewer approvals was brought on by changes in the market rather than decreases in innovation. They suggest that by streamlining the regulatory process, providing standardized exclusivity, and allowing for faster market access, the number of drugs launched per year should increase (CRA 2004).

While CRA (2004) did not find there was a crisis in innovation, they did find there is a disproportionate amount of new products, especially biologics, coming from the US versus the EU and Japan. New biologic entities (NBEs) use biotechnology to produce a new drug. The process is described by Scriabine (1999) as, "genes that can generate the potential products are discovered, cloned, and introduced into bacteria, yeast, or mammalian cells capable of producing the desired products in large quantities." As noted earlier, the US gained an early advantage over the EU due to better patent protection and continues to attract relatively more resources to the biopharmaceutical arena.

New Active Substances (NASs) include NMEs and NBEs and serve as another metric for drug innovation. The origins of the companies producing NASs first launched in the world have shifted towards the US since 1980. According to Figure 2, NASs originating in US companies have increased from 5% between 1980-83 to 47% for 2000-03 (HHS 2004). Since 1994 the shift toward the US is dramatic. While this speaks positively for the R&D output in the United States, it is also noted that the total number of NASs produced per 4 year period has been slowly decreasing since 1987, again raising concerns about the productivity of the R&D dollars.

THE R&D PROCESS

In the R&D process, patents are sought even before a possible drug has entered clinical trials. When a firm determines a compound is likely to create a desired effect, the researching company seeks patents for a range of indications that the compound could possibly treat. It is essential that firms patent any innovation directly upon discovery so as to protect their investments in R&D on this compound, despite the fact that this limits the patent life remaining on a product at market launch. Once patents are granted, firms proceed with the R&D process by checking for the safety, toxicity, and metabolism of the compound through tests on animal subjects. If a drug is determined to have no severe side effects that could lead to complications in humans, the sponsor submits an Investigational New Drug (IND) application. If approved, the IND application gives sponsors the ability to proceed with clinical trials.

Clinical trials consist of three phases. Phase I is conducted on healthy volunteers to determine safety and dosage. In phase II, people with the given indication take the drug to test for efficacy and side effects. At the end of this phase, the sponsor meets with the regulatory board, the Food and Drug Administration in the US, to show data and receive clearance for end phase trials. Phase III trials use volunteers with the condition to test for long-term side effects. Upon completion of Phase III a sponsor compiles all their findings and submits a New Drug Application (NDA) referred to as Phase IV. If the drug is found to meet all regulatory board requirements it is given marketing approval.

The safety and efficacy standards firms must meet to receive regulatory approval are high. The trend of growing efficacy and safety burden-of-proof standards began following the Thalidomide tragedy in the late 1950s. When Thalidomide was found to cause birth defects, the public demanded more care be taken in determining whether or not a product was safe to market. The FDA increased regulatory stringencies to ensure safety in 1962, but the greater safety measures severely affected the launch of products within the US. The number of new drugs introduced in the United States fell 70% that year. The new regulations also increased the amount of time invested in R&D, thereby delaying submission of NDAs and shortening nominal patent life. Furthermore, fewer compounds made it through clinical trials and into the market. All these factors led to the US lagging behind France, Germany, and the UK in new drug introductions by 1.0, 1.6, and 2.1 years respectively (Achiladelis 1999). By 1970, US companies had begun to launch up to 60% of their products in Europe prior to launching in the US, thereby circumventing the burden of FDA approval. In the mid-1980s, Europe began to implement regulatory policies similar to those of the US, and thus US company first launches in Europe declined to between 20-25% (Achiladelis, 1999).

In Europe, the effects of increased efficacy standards in the mid-1980s were compounded by the fact that each country had its own regulatory board. The FDA represents the United States, and thus a major portion of the world pharmaceutical market. However, in Europe, each country had its own board and therefore its own efficacy standards. The creation of the European Agency for the Evaluation of Medical Products (EMA) was an attempt by the European community to harmonize its regulatory process and thereby allow manufacturers to have better access to the market. While this organization attempts to harmonize the European community, many national and local regulatory boards still exist throughout European countries (Kermani and Bonacossa, 2003).

Today, regulatory boards are now calling on companies to conduct more studies than before and requiring post-market commitments. Post-marketing commitments are clinical trials

mandated by the regulatory board in order for a particular drug to be approved temporarily with final approval subject to the results of the additional trials. The industry believes the new standards are often times unrealistic and even unachievable (Ruffolo, 2003). Today, this practice has become so wide spread that it accounts for 26 percent of clinical R&D out-of-pocket spending (Ruffolo, 2003). In 2003, Tufts Center for the Study of Drug Development (CSDD) increased its R&D cost per drug estimate from \$802 million, as stated in 2001, to \$897 million in 2003 to include the cost of post-approval studies (Tufts 2003).

Not only do supplementary trials cost a great deal, they also delay the market launch of drugs, which in turn hurts patients. Japan is best known for its supplementary trial demands. The country often refuses to accept trials conducted outside its borders, arguing Japanese bodies are intrinsically different from other races. While there may be some biological differences, most firms believe that the demands of the Japanese regulatory board are unreasonable. Thus, it is likely that many international firms will stop seeking regulatory approval in Japan (Ruffolo, 2003). Despite the fact the innovative pharmaceutical industry lies primarily in only three markets, the US, EU, and Japan, they lack harmonized systems of approval. Thus companies are forced to do at least three different types of clinical trials, effectively tripling clinical expenditures.

Japan's regulatory process is burdensome. Four consultations with the Ministry of Health are required during the approval process. Due to severe understaffing, the appointments are made several months in advance. In the event a meeting needs to be rescheduled because clinical trial data are not yet available, a six month delay occurs. Moreover, since Japanese doctors are not paid to undertake clinical trials, because hospitals receive payment, it is increasingly difficult to find consenting doctors. These actions further limit the incentives to do R&D in Japan (O'Neill 2005).

With the increased number of clinical trials required, there has been an increase in the cost of conducting clinical trials. In the last ten years the cost of conducting clinical trials has increased five-fold and the cost of preclinical development has increased 60 percent (CRA 2004). As the complexity of products grows, so do the complexity of trials needed to prove safety and efficacy. R&D today is concentrated on complicated, chronic diseases, in which it is harder to create a successful drug. The industry has already developed treatments and cures for most infectious diseases, and therefore they are now burning science and money on harder to treat indications (Ghosh 2003). The CRA (2004) finds there is clear evidence that the cost of R&D varies across therapeutic categories, therefore R&D costs are driven up as the industry moves into working on more complicated diseases.

EFFECTS OF PRICE REGULATION ON R&D

One can think of R&D as a pay-as-you-go process. Years of R&D expense are incurred prior to a drug's launch, yet these expenses are paid for with funds generated through current sales, retained earnings or investor monies. Thus, current funds pay for current research that may not come to fruition in terms of a NDA for many years to come. After FDA approval is given and the new drug is marketed, these receipts can be used to support new research endeavors. Whether or not the receipts over the coming years are great enough to cover or "recoup" the already expensed R&D has two implications. First, it is immaterial if the R&D costs are recouped because the costs have already been paid. The second, however, is more important. If receipts earned are less than what it cost to create the drug, management of the firm and the firm's investors will be displeased with losing the gamble and question current R&D decisions. With hindsight, the drug was a bad investment. In addition, there will be less than anticipated revenues available to generate new R&D.

Introducing price regulations hinders R&D. Take the hypothetical situation of a company. In year zero, the company has entities A through Z that could possibly create new drugs. Due to budgetary constraints and projected internal rates of return only six entities are selected for further exploration. Suppose in the fifth year of the R&D process, the country in which this company is conducting research implements unexpected price regulations, which effectively cut possible returns in half. As a result, two products are dropped from the R&D process, as they will no longer witness returns great enough to warrant further investigation. At year ten, when the remaining four products should have completed the R&D process, only three come to market assuming one has failed to meet efficacy and safety standards. Due to the decreased cash flow brought on by fewer marketed drugs, the new budget constraint only allows for three new entities to enter the R&D pipeline in year 10 instead of six as had been previously investigated in year zero. Perhaps two will make it to the market. Thus the effects of price controls are two-fold: an immediate decrease in R&D as prospective drugs witness diminished returns and long term declines as smaller returns facilitate less R&D.

However, pharmaceutical companies are likely to change their R&D process in certain ways to accommodate regulation, rather than allow R&D to dry up completely. They may respond by increasing the creation of imitative drugs, by moving their research and development processes to less regulated markets, or they may merge with or acquire other pharmaceutical and biotechnology firms.

In fact, there have been a significant number of "mega mergers" between companies. Firms are finding that under the increased pressure of R&D costs and the transition in the

types of drugs being investigated, they can no longer be competitive alone. Merging with another firm provides an opportunity to gain more capital with which to investigate new drugs, as well as more possible compounds to investigate. For example, the company known today as GlaxoSmithKline (GSK) was originally 9 smaller firms that combined into three firms, and now into one. Bristol-Myers Squibb was originally six other companies that combined to become four companies, and today represent only one. Wyeth is a combination of nineteen companies (Ruffolo, 2003). The mergers of GSK, Bristol-Myers Squibb, Pfizer, Aventis, and Wyeth have occurred in only the past 20 years. Originally representing 42 different firms, today there are only five. Ruffolo estimates that it takes at least 8 significant pharmaceutical firms to create one company that is competitive in today's market. That is an 88% decrease in the size of the pharmaceutical industry within the last 20 years (Ruffolo 2003). He attributes this collapse to the increase in R&D time and costs as well as declining success rates.

Price regulation of a country's pharmaceutical market not only affects that country, but the world as a whole. This is true because the revenues from one country directly affect the revenues for multinational research-based pharmaceutical companies. International price comparisons and parallel trade are the primary sources of regulatory spillover; many regulatory systems use price referencing as a benchmark for reimbursement prices. Reference pricing occurs when a country gathers price data from other countries to create comparative price analyses, allowing payers to set a reimbursement ceiling (O'Neill, 2003). Generally, lower prices from countries with highly price sensitive or highly regulated markets are being used as a benchmark, creating artificially low prices in the country using the reference pricing. These artificially low prices, especially prevalent in Japan, decrease the ability of pharmaceutical firms to earn sufficient revenues to maintain existing R&D projects.

REVIEW OF THE LITERATURE

In an older study, Jensen (1987) analyzed the effects of US safety and efficacy regulation stringency on pharmaceutical R&D. Her findings supported other studies which found the 1962 Amendments to the FDA guidelines for both efficacy and safety did have negative, significant effects on the number of new drugs being developed. She found, "the magnitude of this effect appears to be large: a one month decrease in each of the two regulatory delay variables would lead to an increase of approximately 15% in the number of NCEs discovered per year, *ceteris paribus*" (Jensen, 1987).

Troyer and Krasnikov (2002) use 1970-2000 data for US NCEs, New Drug Applications and New Drug Approvals to show how changes in FDA policies affected the three innovation measures. They find R&D expenditures and sales are highly correlated, thus they use changes in sales rather

than changes in R&D to predict changes in innovations. A one percent increase in sales growth currently and lagged one year accounts for a 2.65% in the growth of New Drug Applications, compared to a 2.89% increase in New Drugs Approved. The number approved was positively impacted in 1984 and 1992, following the FDA's extension in patent protection and shortened review times, respectively. Limiting sales growth via price regulation in the US would reduce pharmaceutical innovation (Troyner and Krasnikov 2002).

According to research conducted by Grabowski (1986) there are three structural factors that determine research expenditure: research productivity, product diversification, and the level of internally generated funds. These results are reiterated by Achilladelis and Antonakis (2001) showing annual R&D expenditures for ten global firms for 1950-1989 are determined by past R&D and cash flow. Grabowski's indicators predict a change in the hub of R&D as increased regulation occurs in one region relative to another. As European countries have increased their regulations on pharmaceuticals, manufacturers no longer see a promising future nor do they have sufficient retained earnings to encourage R&D investment. As a result, the R&D that once took place in these countries is predicted to decrease. The evidence of the 1990's supports this contention. By 1999, R&D investment within Europe was down 73% from 1990 while the R&D industry in the United States grew from a \$1 billion industry in 1970 to a \$32 billion industry by 2002 (Pharmaceutical Industry Profile, 2003).

Pammolli et al (2000) did an extensive study of the EU pharmaceutical industry to see if the European industry is falling behind that of the US. They find the EU firms have a comparative disadvantage in selling their innovative products, citing the number of NCEs created by US versus EU firms since 1990 is not much different, but the US sales of such are twice as high. They contend market demand for drugs grew demonstrably in the US, and that despite the multinational nature of the companies, firms still tend to concentrate sales in their home market. This advantaged the US firms, and subsequently several EU firms did move some R&D and sales efforts to the US. Since 2000, British GlaxoSmithKline, Swiss Novartis, Dutch Organon and German Schering AG have moved substantial parts of their businesses to the US. Additionally, Pammolli et al contend the US has witnessed more vertical consolidation of R&D efforts by firms, which coupled with the numerous biotech upstarts, have created an R&D advantage in the US over the EU (Pammolli et al 2000). One can infer the market demand comes from the relatively unregulated nature of the US market compared to the attempt to pare prices in the EU.

MacInnes *et al* (1993) conducted an international study of drug utilization in the international pharmaceutical industry. They studied NCEs and NBEs launched in the US, Europe,

and Japan from 1970-1992. They found Europe was initially responsible for introducing the most NCEs, but the data from 1990 to 1992 led them to believe this trend would not continue. They argue the decrease in European competitiveness can be linked to increasing price pressures being born by innovative firms. With sales and margins declining, companies are unable to earn sufficient monies to reinvest in R&D and therefore were forced to cut their budgets (MacInnes *et al*, 1993).

Scherer (2001) finds the US pharmaceutical industry is best represented as a virtuous rent-seeking industry. Using industry data from 1962-1996, he finds firms use profits to create additional R&D ventures, which in turn increase R&D costs until all supra-normal profits dissipate. Therefore attempts to reduce prices and profits will have deleterious impacts on future R&D.

As part of the Medicare Prescription Drug Act of 2003, Congress requested a study be undertaken, directed by the Commerce Department, to examine the effects of pharmaceutical price deregulation on R&D and innovation. In December 2004, the presented report stated estimated increases in revenues between \$17.6-\$26.7 billion annually, following price deregulation. The higher revenues are expected to increase R&D by \$5.3-\$8 billion annually, resulting in an average of 2.7-4.1 new drugs each year (Congress 2003). Once again, price regulations are seen as a detriment to innovation.

MODELS AND DATA

We investigate econometrically two interrelated phenomena. First, we posit R&D employees and domestic sales create innovative drugs, though with a lag. Second, price regulations hinder the number of new drugs coming to market; countries with drug price regulations will witness less innovative activity since the regulations reduce the returns to inventiveness. While those claims are not surprising, the difficulty in testing them lies in the availability of data. Ideally, we would like the dependent variable to be the number of first launches of innovative drugs (no me-too drugs) in the world per year based on the drug company's country of origin. For example, if fifteen new drugs appeared on the world market in 2004, regardless of where they first appeared, we would like to know how many of the drugs emanated from US firms, British firms, Japanese firms, etc. We predict the number of new drugs emanating from a country is directly related to R&D employment and domestic sales in the country.

Domestic sales are an independent variable for three reasons. First, firms will seek to create and market drugs where the expected return is greatest. Since industry data on net profits are not available, the proxy of sales is used. Second, using domestic sales, as opposed to total sales that include foreign

sales, suggests home country sales serve as the drawing card for innovation as suggested by Pammolli et al (2000). Third, R&D expenditures are needed to develop a drug and for post-marketing clinical trials. These pay-as-you-go R&D expenditures require sufficient sales, and domestic sales can provide the funding. Additionally, since R&D expenditures are highly correlated with R&D employment, the other independent variable, domestic sales serve as the proxy for R&D expenditures as proffered by Troyer and Krasnikov (2002).

R&D personnel are hired to create new drugs and get them approved. Though there is approximately a fifteen year time lag between pre-clinical research and new drug approval, there is a flurry of R&D activity required at Stage III trials. According to Phrma (2003), 35% of R&D researchers are involved in the basic, pre-clinical processes. The remainder, which account for 68% of the R&D expenditures, are involved in the drugs' approval stages. In fact, 23% of the R&D staff are involved at Stage III, which occurs about two years prior to approval. For these reasons we expect lagged R&D employment to predict new approvals.

Unfortunately, we are not privy to the data for the dependent variable. We use a suitable alternative measure of innovativeness: NCEs approved per year in each country. Our dependent variable is a reasonable alternative to our desired one for two reasons: the majority of the drugs introduced in a market originate from home country firms; and new drugs coming from foreign firms require some R&D activity in the approval country in order to pass regulatory muster. We use NCEs approved only, not biologics or vaccines, for two reasons. First, we are wary of not having corresponding R&D figures for the biotech firms. Second, for comparison purposes, the data from Japan only include NCEs.

The national trade associations of the major markets survey member firms annually and publish R&D employment and sales. In the US, Phrma has surveyed its members since 1968. The R&D figures represent 80% of the pharmaceutical and biopharmaceutical industry's R&D expenditures in 2004 (Profile 2005), though it was a higher percentage prior to the increase in biotech products. Unfortunately, R&D employment and expenditure figures are not available for the numerous small biotech firms that are not members of Phrma, which is why we concentrate on NCEs only, since they derive from pharmaceutical companies. JPMA conducts R&D surveys of firms operating in Japan and data are available from 1980. VFA is the German trade association conducting surveys, but the data begin in 1990. British, Swiss and French data are available for too few years, thus are not included. Lastly, we need data to span as many years as possible to incorporate trends.

Concentrating on the US market for 1980-2004, we expect more NCEs approved in the US over time as R&D employment in the US increases and as domestic sales rise. We use a multiple regression model (1) to estimate this relationship:

$$NCE_t = \beta_0 + \sum_{j=0}^m \beta_{t-j} * RDEMP_j + \sum_{j=0}^m \beta_{t-j} * DSALES_j + \beta_3 * TIME + \beta_4 * FDA + \epsilon_t \quad (1)$$

NCE_t is the number of NCE's approved in year t in the US. RDEMP_j represents R&D employment in the US pharmaceutical industry and we allow for lags (j) in employment to impact innovation. DSALES_j is US domestic sales, which also allows for lagging. The Prescription Drug User Fee Act (PDUFA) passed in 1992 led to a demonstrable increase in NCEs in 1996, thus FDA is a binary variable for 1996. TIME represents time intervals 1, 2...and its inclusion is addressed below.

R&D employment in the US generally increases each year as shown in Figure 2. NCEs approved each year in the US oscillate as shown in Figure 2, suggesting the time sensitive nature of NCEs, R&D employment, and domestic sales may lead to spurious results when estimating (1).

The second model we estimate uses NCEs approved each year in the US and Japan with the corresponding R&D employment for each country each year. We cannot include the other price regulating countries at this time due to insufficient data. We test whether Japan has fewer predicted NCEs given the regulated nature of its market relative to the US by including a binary variable JAPAN. We estimate

$$NCE_{it} = \beta_0 + \sum_{j=0}^m \beta_{t-j} * RDEMP_{ij} + \beta_2 * TIME + \beta_3 * TIME^2 + \beta_4 * JAPAN + \epsilon_t \quad (2)$$

where NCE_{it} represents NCEs in each country i per year t. R&D employment in country I in period t is RDEMP_{it}. To capture the quadratic shape of the NCEs, TIME and TIME squared are used. Domestic sales are only available for twelve years in Japan, thus we exclude them as an independent variable.

We have a complete data set for RDEMP, DSALES and NCEs for the US for 1980-2003. The NCEs only include innovative drug approvals, not me-too drugs. The RDEMP captures Phrma membership R&D employees in the US, which includes R&D employees working for foreign-based firms operating in the US and in Phrma's membership. JPMA reports two sets of NCEs each year, one entitled 'manufactured' the other 'imported'. The first is NCEs approved to firms manufacturing in Japan and the second represents drugs approved for import. We use the former since they are most closely related to Japanese R&D

employment in Japan. Japanese data are available from 1980-2002. Unfortunately our results are limited by small sample sizes.

US MARKET RESULTS

Estimating the US equation (1) may lead to spurious results given the time sensitive nature of the variables. Each time series variable is tested for unit roots using Ender's procedure (Enders, 1995). The Augmented Dickey Fuller test suggests NCEs, RDEMP and DSALES have unit roots. The same holds for the natural logs of R&D employment and domestic sales, LNRDEMP and LNDSALES, respectively. The first differences are stationary as shown in Table I.

Various lag structures were estimated using one and two period lags. The most robust results appear in (3). All p-values are given in parentheses.

$$\Delta NCE_t = -7.64 + 29.94*FDA + 51.1*\Delta LNRDEMP_{t-2} +$$

(.0009) (.0855)

$$35.58*\Delta LNDSALES_t \quad (3)$$

(.3572)

$$ADJ-R^2=.39 \quad \Delta NCE \text{ mean} = .136 \quad DW=2.117$$

The model captures 39% of the variation in the change in NCEs from one year to the next. Equation (3) suggests a 1% increase in the growth of R&D employment in year t accelerates NCE creation by 51, which is enormous relative to the annual mean change in NCEs of .136. R&D efforts take time and the payoff is great two years hence, which is not surprising given the influx of R&D activity at Stage III. The coefficient on FDA implies the PDUFA impact was an acceleration of almost 30 NCEs in 1996, which is consistent with the jump from 28 to 53 between 1995 and 1996. The coefficient on $\Delta LNDSALES$ is not statistically significant. In alternative estimations, time, foreign sales and total sales were included, but none were significant.

Replacing $\Delta RDEMP$ for $\Delta LNRDEMP$ yields equation (4):

$$\Delta NCE_t = -7.09 + 29.15*FDA + .000878*\Delta RDEMP_{t-2} +$$

(.0010) (.0767)

$$35.67*\Delta LNDSALES_t \quad (4)$$

(.3525)

$$ADJ-R^2=.40 \quad \Delta NCE \text{ mean} = .136 \quad DW=2.116$$

The results are very similar. The estimation implies a 1000 person change in R&D employment in year t accelerates NCEs by .878 two years later. This suggests a 1,140 person increase in R&D employment now accelerates the NCEs by one, two years from now. Witnessing the incredible increase from 51,588 to 77,459 R&D employees between 2000 and 2003 in the US suggests a rapid acceleration of NCEs approved in the US in the near future.

Regressing levels on levels from (1) is feasible if the variables are cointegrated and leads to non-spurious results. Equation (5)'s Tau test for cointegration is -3.86, which is significant at .01, implying non-spurious results. Using the runs test to test for serial correlation from the residuals in (5) enable us to reject serial correlation.

$$NCE_t = 10.12 + 26.12*FDA + .00042*RDEMP_{t-2} +$$

(.0003) (.0931)

$$-.00006*DSALES_t \quad ADJ-R^2=.5361 \quad (5)$$

(.2842)

The results suggest approximately 2,380 additional R&D employees in year t will increase NCE's by one in year t+2. An influx of R&D personnel into the US will reap innovative rewards. Domestic sales do not statistically significantly impact NCE's, contrary to Troyner and Krasnikov (2002).

US VS. JAPAN RESULTS

The second set of regression results concern price regulations. Until more data are available for the UK, Germany, Switzerland and France, the only comparison is between the US and Japan. Since total sales figures are limited for Japan, and domestic sales figures are not included as an independent variable. Equation (6) presents the estimated results from (2) using the Yule-Walker technique for correcting for autocorrelation. The Tau of -6.29 for the cointegration test for (6) suggests non-spurious results.

$$NCE_t = 11.23 + .6372*TIME + -.0449*TIME^2 +$$

(.5061) (.1623)

$$.0003*RDEMP_{t-2} + -7.44*JAPAN$$

(.1051) (.0741)

$$ADJ-R^2=.439 \quad DW=1.88 \quad (6)$$

Time and time squared are included to account for the quadratic nature of NCEs in both countries. The signs on these coefficients are as expected, but not statistically significant. The coefficient on R&D employment lagged two years implies an additional 1,000 people will increase NCEs by .3 two years later. Alternatively, 3,333 additional personnel will create one more NCE, ceteris paribus. The number of NCEs being approved in Japan is 7.5 less than that in the US, holding time trends and R&D employment constant. The regulations in Japan lead to fewer innovations, regardless of R&D employment.

CONCLUSION

R&D employment is a key factor in determining drug innovation. In the US, adding 2,380 R&D employees will

increase NCEs two years later by one on average. This positive impact also holds across the US and Japan. The regulations in Japan create an environment not conducive to innovation; about 7.5 fewer NCEs on average are approved in Japan compared to the US. If Japanese firms begin to shift R&D into the US, there will be a double impact on the reduction of NCEs approved in Japan. This bodes poorly for the Japanese drug industry.

There are several avenues available for future research. First, collecting additional data on EU countries would enable a more robust study. We are attempting to collect these data.

Second, finding the most recent data will not only elongate the sample size but will show the most recent trends. As soon as new US and Japanese data are available, the equations will be re-estimated. Third, capturing Japanese domestic sales data may enhance the US versus Japanese model. Fourth, trying to incorporate biologics and R&D employment in biologics may be feasible if data can be found. The shift to biologics, especially in the US, needs to be examined. Lastly, finding the more ideal dependent variable may be possible, which would cast a new and perhaps better light on drug innovation.

TABLE I – First Differences for Equation 1

Δ VARIABLE t-(t-1)	TAU VALUE
Δ NCE	-4.36****
Δ RDEMP	-3.84****
Δ DSALES	-2.92*
Δ LN RDEMP	-3.89****
Δ LN DSALES	-3.27**

where ****, **, and * denote p-values of .01, .05 and .1, respectively.

Figure 1.

US R&D Expenditures and R&D Employment vs. NCEs per Year

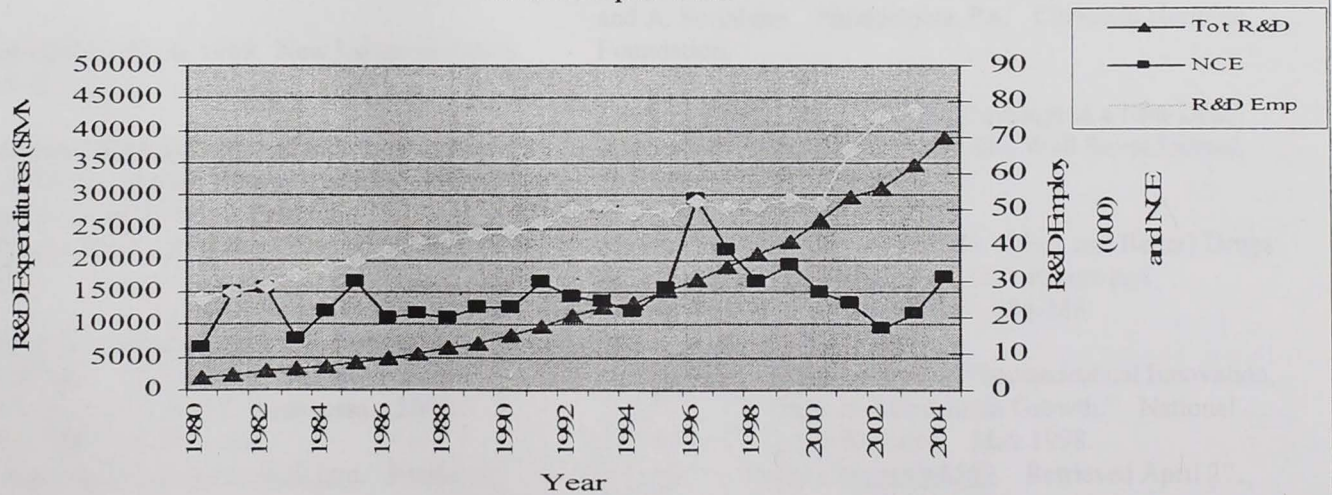
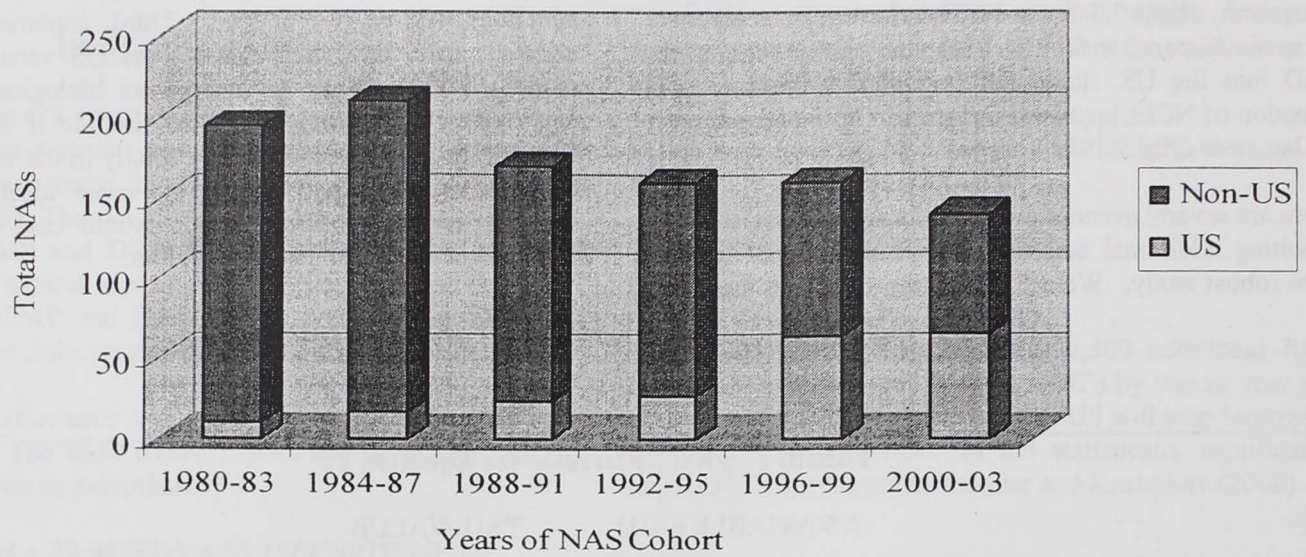


Figure 2.

US Share of New Active Substances First in World Market



Data From "HHS Task Force on Prescription Drug Importation." United States Department of Health and Human Services. <http://www.hhs.gov/importtaskforce/Report12-20.pdf> accessed 3/15/05.

REFERENCES

- Achilladelis, B. 1999. Innovation in the Pharmaceutical Industry. In *Pharmaceutical Innovation*, ed. R. Landau, B. Achilladelis, and A. Scriabine. Philadelphia, PA: Chemical Heritage Foundation.
- Achilladelis, B. and N. Antonakis. 2001. The Dynamics of Technological Innovation: The Case of the Pharmaceutical Industry. *Research Policy*. 30: 535-88.
- Barral, P.E., 1995. Twenty Years of Pharmaceutical Research Results throughout the World (1975-1994). Foundation Rhone-Poulenc Sante, Paris.
- Center for Drug Evaluation and Research (CDER1). 2004. FDA's Drug Review and Approval Times. <http://www.fda.gov/cder/reports/reviewtimes/default.htm>. Retrieved on April 6, 2004.
- Charles River Associates. 2004. Innovation in the Pharmaceutical Sector: A Study Undertaken for the European Commission. Nov. 8, 2004.
- Congress. 2003. Medicare Modernization Act. <http://www.cms.hhs.gov/medicarereform/MMAactFullText.pdf>. Retrieved on April 27, 2005.
- Di Masi, J., *et al.* 1991. The Cost of Innovation in the Pharmaceutical Industry. *Journal of Health Economics*. 10: 107-142.
- The Economist (US), May 6, 1989. New kid on the block, 311, 7601: 65-71.
- European Federation of Pharmaceutical Industries and Associations (EFPIA). 2004. Research and Development as a Percentage of Gross Domestic Product. http://www.efpia.org/6_publ/infigure2004e.pdf Retrieved April 27, 2005.
- European Federation of Pharmaceutical Industries and Associations (EFPIA). 2002. The Pharmaceutical Industry in Figures. *in* Kermani, F. and P. Bonacossa. 2003. *Pharma R&D in The U.S. & Europe*. <http://www.contractpharma.com/Sep033.htm>. Retrieved April 27, 2005.
- Ghosh, Krish. (personal communication, March 2, 2004)
- Grabowski, Henry G. 1986. The Determinants of Industrial Research and Development: A Study of Chemical, Drug, and Petroleum Industries. *Journal of Polit. Econ.* Mar./Apr. 1986. 76: 292-305.
- Grabowski, Henry. 2002. Patents, Innovation and Access to New Pharmaceuticals. http://levine.sscnet.ucla.edu/archive/grabow-patents_innov.pdf. Retrieved on April 27, 2005.
- HHS Task Force on Drug Importation. 2004. Report on Prescription Drug Importation. <http://www.hhs.gov/importtaskforce/Report12-20.pdf>. Retrieved April 27, 2005.
- Jensen, Elizabeth. 1987. Research Expenditures and the Discovery of New Drugs. *The Journal of Industrial Economics*. 36, 1, September 1987: 83-95.
- Japanese Pharmaceutical Manufacturers Association (JPMA). 2003. Fact Book 2003. Japanese Pharmaceutical Manufacturers Association (JPMA). Japan.
- Kermani, F. and P. Bonacossa. 2003. Pharma R&D in The U.S. & Europe. <http://www.contractpharma.com/Sep033.htm>. Retrieved April 27, 2005.
- Krasnikov, Alexander and Jennifer Troyer. 2002. The Effects of the Price Regulation on the Innovation in the Pharmaceutical Industry. *Journal of Applied Business Research*. 18, 4: 87-96.
- Landau, R., A. Desimone, and L.E. Gasorek. Pharmaceutical Taxonomy of Most Important Drugs. In *Pharmaceutical Innovation*, ed. R. Landau, B. Achilladelis, and A. Scriabine. Philadelphia, PA: Chemical Heritage Foundation.
- Landers, Peter. 2003. Cost of Developing a New Drug Increases to About \$1.7 Billion The Wall Street Journal. December 8, 2003. pp. B4 col.2.
- Lichtenberg, Frank R. 1996. Do (More and Better) Drugs keep People Out of Hospitals? *AEA Papers and Proceedings*. May 1996. 86, 2: 384-388.
- Lichtenberg, Frank R. 1998. "Pharmaceutical Innovation, Mortality Reduction, and Economic Growth." *National Bureau of Economic Research*. May 1998. <http://www.nber.org/papers/w6569>. Retrieved April 27, 2005.
- Lichtenberg, Frank R. 2002. Benefits and Costs of Newer Drugs: An Update. *National Bureau of Economic Research*. June 2002. <http://www.nber.org/papers/w8996>. Retrieved April 27, 2005.

- MacInnes, R., C. Lumley, S. Walker. 1994. New Chemical Entity Output of the International Pharmaceutical Industry from 1970 to 1992. *Clinical Pharmacology & Therapeutics*. September 1994. 56, 3: 339-349.
- O'Neill, Mike. 2003. Reference Pricing Systems: An Overview. (working paper).
- O'Neill, Mike. (personal communication, May 2005).
- Pammolli, F., A. Gambardella, L. Orsengio. 2000. Global Competitiveness in a European Perspective. A Report Prepared for the Directorate General Enterprise of the European Commission. November 2000.
- Pharmaceutical Research and Manufacturers of America (PhRMA). 2000. Why Do Prescription Drugs Cost So Much...and Other Questions About Your Medicine. Pharmaceutical Researchers and Manufacturers of America (PhRMA). Washington, DC.
- Pharmaceutical Research and Manufacturers of America (PhRMA). 2001. Pharmaceutical Industry Profile: 2001. Pharmaceutical Research and Manufacturers of America (PhRMA). Washington, DC.
- Pharmaceutical Research and Manufacturers of America (PhRMA). 2002. Pharmaceutical Industry Profile: 2002. Pharmaceutical Research and Manufacturers of America (PhRMA). Washington, DC.
- Pharmaceutical Research and Manufacturers of America (PhRMA). 2003. Pharmaceutical Industry Profile: 2003. Pharmaceutical Research and Manufacturers of America (PhRMA). Washington, DC.
- Pharmaceutical Research and Manufacturers of America (PhRMA). 2005. PhRMA Position on Current Pricing in Japan. Pharmaceutical Research and Manufacturers of America (PhRMA). Washington, DC.
- Reich, Michael R. 1990. Why the Japanese Don't Export More Pharmaceuticals: Health Policy as Industrial Policy. *California Management Review*. Winter 1990. 32, 2: 124-150.
- Ruffolo, Robert. 2003. R&D Productivity in the Pharmaceutical Industry: Issues and Challenges. Presented on August 12, 2003.
- Santerre, Rexford E., and Stephen P. Neun. 2000. *Health Economics: Theories, Insight, and Industry Studies*. Revised Edition. Orlando, FL: Dryden Press.
- Scriabine, A. 1999. Discovery and Development of Major Drugs Currently in Use. In *Pharmaceutical Innovation*, ed. R. Landau, B. Achilladelis, and A. Scriabine. Philadelphia, PA: Chemical Heritage Foundation.
- Scherer, F.M. 2001. The Link Between Gross Profitability and Pharmaceutical R&D Spending. *Health Affairs*. Sept/Oct. 2001. 20, 5: 216-220.
- Tufts University. 2003. Total Cost to Develop a New Prescription Drug, Including Costs of Post-Approval Research, is \$897Million. May 13, 2003. <http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=29> Retrieved April 27, 2005.
- Welch, William M. 2004. AARP: Drug Prices Soargin. *USA Today*. May 25, 2005. http://www.usatoday.com/news/washington/2004-05-25-drugs-lede_x.htm Retrieved April 27, 2005.