The Evolution of the Pharmaceutical Industry Over the Past 50 Years: A Personal Reflection

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ABSTRACT *The pharmaceutical industry has an outstanding record of innovative performance over the past 50 years. The R&D process has become more knowledge-based and a market for innovation has emerged between research start-ups, development-stage firms, and the larger, multinational companies. At the same time, R&D costs have increased several fold over time and generic products now dominate many traditional therapeutic areas. The current challenge for the industry is to discover new therapies for chronic diseases with high unmet needs like Alzheimer's disease and various auto-immune diseases and cancers that afflict an increasingly aging population. Recent advances in molecular biology and related fields provide a scientific foundation to undertake these R&D efforts, although the time path and outcomes remain subject to many risks and uncertainties.*

Key Words: Pharmaceuticals; Innovation; R&D; Biotechnology; Generics; Alliances.

JEL classifications: L65, L22, I11, I18.

1. Introduction

I first started doing research on the pharmaceutical industry in the early 1960s. I was in graduate school at Princeton University, and considering my dissertation topic. I wanted to do my thesis on research and development and innovation in the US economy.¹ I had been an undergraduate engineering physics major. Very early on in my PhD degree program I was attracted to the concept of Schumpeterian competition and the importance of new products and processes for long term growth and consumer welfare. In the empirical portion of my thesis, I selected pharmaceuticals as one of the industries to study because of its core competition around new product innovations and the role public policies play in shaping this industry.

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The pharmaceutical industry had become increasingly research-oriented in the immediate period after World War II. Many of the firms traced their origins back to chemical manufacturing firms located in Europe and the United States. The industry's structure in the 1960s was very different than the current one. The companies focused on a relatively small number of biological targets. The prevailing research style was to chemically synthesize and test a large number of compounds in a laborious trial and error manner to see if there was any biological response to these compounds (a process known as "random screening"). Nevertheless, the first few decades after World War II were characterized by many important new product introductions. Particularly notable was the introduction of several broad spectrum antibiotics such as the synthetic penicillins, streptomycin and tetracycline, and several new vaccines targeted to childhood diseases. Other therapeutic advances included the corticosteroids, the diuretics and beta blockers for hypertension, new classes of tranquilizers and antidepressants, as well as the first oral contraceptives. The industry was generally held in high regard for its innovative performance. However some critics like Senator Kefauver focused congressional hearings on the industry's high profit margins and promotional activities.

One of the IO issues receiving considerable attention by economists when I was a graduate student was the neo-Schumpeterian hypothesis that large-scale was an advantage in performing industrial R&D. Using panel data on a sample of drug firms for the 1958 to 1962 period, I did not find that size was an important determinant of research intensity in pharmaceuticals, at least beyond a threshold level. However, I did find support for the hypothesis that firm diversification across therapeutic areas led to higher research intensity (Grabowski, 1968). This result is suggestive of later research findings by Henderson and Cockburn (1996) on the importance of economies of scope in pharmaceuticals.

The prevailing organizational structure that dominated the industry from the end of World War II until the 1980s was the vertically integrated multinational company that encompassed R&D laboratories, production facilities, and marketing divisions. For the most part, these firms financed their R&D expenditures through internally generated funds and incurred relatively little debt (Grabowski, 1968; Grabowski and Vernon, 1981). This was viewed as a strategic response to the risks involved in developing new pharmaceuticals – in particular, long investment periods, high costs, and variable outcomes. The entry of biotech start-ups and development-stage firms with venture financing originated during the 1970s, but were still in their infancy compared to later decades. Generic competition also was confined to a few therapeutic areas and accounted for a very small share of total US prescriptions prior to the 1980s.

The industry has experienced an incredible amount of change since the 1960s associated with scientific advances, legislative enactments, new regulatory requirements and profound organizational changes in the broader health care system. In terms of the R&D process, scientific advances have led to a more knowledge-based approach to drug discovery, and played an important role in fostering the entry of hundreds of research-oriented start-up companies founded by entrepreneurial scientists. FDA regulations on new product approvals have changed significantly over time and transformed the drug development process. A landmark event was the passage of the 1962 Amendments to the US Food and Drug Act that established the requirement that all

new drug products demonstrate substantial evidence of efficacy based on double-blind placebo-controlled trials. Evolving FDA rules and guidelines since the 1962 Act have affected the length of the R&D process, the number of subjects in clinical trials, and other key aspects of the drug development process.

The generic industry also came of age after the passage of the 1984 Hatch-Waxman Act. This law created an abbreviated regulatory process that facilitated low-cost generic entry and also provided patent extensions to help compensate innovators for time lost during clinical trials and FDA review. Managed care organizations (MCOs) and pharmacy benefit management firms (PPMs) subsequently assembled electronic networks of retail pharmacies and encouraged generic utilization through formulary placements and pharmacy incentives. As noted elsewhere in this volume, generics now account for approximately three quarters of all US prescriptions (Berndt and Aitken, 2011). This compares to less than 20% generic utilization prior to the 1984 Act. More recently, prescription drug benefits were extended to Medicare recipients in 2006 through the Part D program. The passage of the Patient Protection and Affordable Care Act in 2010, also has expanded drug insurance coverage and created an abbreviated application process for biosimilars.

Outside the United States, most developed countries established comprehensive government payment programs for pharmaceuticals in the period after World War II. These generally involved some form of price regulation and constraints on reimbursement levels. However, cost containment measures have evolved and become much more stringent over time. Reference price reimbursement systems have been established in several European countries including Denmark, Germany and The Netherlands. In addition, controls on volumes and total expenditures have been superimposed on traditional price and reimbursement controls in many countries (Danzon, 1997).

In this article, I am going to focus on how the pharmaceutical industry has evolved in the face of all these changes and developments. My focus will be how these developments has transformed the pharmaceutical R&D process. I will also discuss some of the outstanding issues currently confronting the industry. My perspective is primarily a US one, but I also will comment on parallel or contrasting developments outside the United States where appropriate.

2. Changes in the Discovery and the Emergence of the Biotechnology Industry

2.1 Scientific Advances and the Drug Discovery Process

There have always been strong ties between academic research centers and pharmaceutical companies dating back to the pre-World War II discovery of penicillin (Scherer, 2010). Throughout the development of the research-oriented pharmaceutical industry, pharmaceutical firms have provided research grants to universities, utilized academic scientists as advisors, hired key scientists from universities to head up research projects, undertaken collaborative research projects, and authored many joint publications in scientific journals.

The role of academic science and the pharmaceutical industry has been largely complementary rather than competitive. A division of labor is generally recognized with academic scientists focusing on basic biomedical research while the pharmaceutical industry builds on this knowledge to create new

medicines for particular diseases. This is borne out by various studies. For example, based on interviews with heads of R&D laboratories, Mansfield (1998), found that close to half of all new drug product introductions in 1986–1994 period emanating from the interviewed companies received “very substantial aid” or “could not have been developed (without substantial delay) in the absence of recent academic research.” At the same time, an analysis of the source of new product introductions between 1990 and 1999 by DiMasi *et al.* (2003) found that 93% of the 284 new drug approved in the United States originated from industrial sources.

The approach to discovering new molecules has undergone a series of important transformations over the past several decades. Some have characterized the overall approach to discovery as “rational” drug design in contrast to the random screening of compounds of early eras. While there is still significant uncertainty and experimentation present in the R&D process, the industry has been able to utilize increases in medical knowledge about disease processes to target particular biological pathways and cell receptor sites. It has also incorporated new scientific techniques to facilitate the design of new drug candidates for these disease targets.

An important milestone for this new approach to drug discovery occurred in 1978 with the introduction of Tagamet (cimetidine) by SmithKline. Building on the knowledge that H_2 histamine played an important role in the secretion of excess stomach acid that could lead to ulcers, SmithKline researchers developed Tagamet as the first H_2 histamine receptor inhibitor. The analogy was that of a key that locked into the receptor site to block the H_2 histamine pathway. Within a few years of its introduction, Tagamet had become the largest selling drug worldwide (Grabowski and Vernon, 1990). Other important new classes of drugs that followed during the 1980s that focused on specific receptor targets with novel mechanisms of action included interleukin-2 inhibitors to prevent organ transplant rejection, the statins for cholesterol reduction, the nucleoside reverse inhibitors for HIV-AIDS, the serotonin reuptake inhibitor for depression, and proton pump inhibitors for GERD. DiMasi and Paquette (2004) have provided a detailed analysis of the new drug classes introduced since the 1960s. Many of the pioneering products and early movers in these classes quickly became leading products in terms of global revenues.

In addition, a number of new scientific techniques and methods were added to the drug discovery toolkit over time. One of the key developments was x-ray crystallography and nuclear resonance imaging for ascertaining the structure of receptor sites in the body. Firms can also use computer modeling to design three-dimensional structures of target molecules to mesh with a specific receptor site. Werth (1994) has described the important role this played in the discovery of cyclosporine, a pioneering drug product to inhibit organ transplant rejections. Other techniques have facilitated more efficient methods to screen large numbers of compounds simultaneously using chip technology rather than investigating one test tube or Petri dish at a time. Firms also have the ability to use combinatorial chemistry to combine fragments of molecules into large libraries of new and possibly interesting combinations that can be screened using these new methods. These advances have increased the productivity of chemists in synthesizing and screening the activity of particular compounds in the laboratory setting.

2.2 *The Emergence of the Biotechnology Industry*

Advances in molecular biology have played a key role in the evolution of the industry's approach to drug discovery. A key invention by Stanley Cohen at Stanford and Herbert Boyer at the University of California-San Francisco was the ability to synthesize therapeutic proteins by recombinant methods in the 1970s (Robbins-Roth, 2000). Subsequently, the mapping of the human genome and related advances in fields such as bioinformatics has led to an abundance of new disease targets and drug candidates. A dedicated biotechnology industry has emerged in the wake of these important breakthroughs. Biopharmaceuticals have accounted for several significant new drug introductions and are currently the source of many promising therapeutics currently under development.

The first firm to exploit recombinant DNA was Genentech in 1976. This firm was established by scientists from UCSF which venture capital funding and had its internal public offering in 1980. Several additional firms were subsequently established by scientists from Berkeley, Harvard, MIT, Columbia, and other leading academic institutions. Hundreds of small biotech firms were founded during the ensuing decades. These firms were typically located in close proximity to university research centers, had academic scientists as their founders and chief scientific officers, and received initial funding from private equity firms that also were often based near the same university research institutions (Robbins-Roth, 2000).

A market for innovation has emerged between the traditional pharma industry and these biotech and technology-driven development stage firms.² Today, large pharmaceutical firms increasingly look to alliances with development-stage firms to gain access to new technologies and buttress their R&D pipelines. This is a dramatic departure from the earlier era where major pharma firms looked to develop new products largely through their own R&D laboratories and often evidenced a "not invented here" syndrome to externally originated drug candidates.

The extent of integration at the R&D stage associated with these partnership agreements varies considerably. They range from true joint development agreements, to transfers of development-stage products through licensing deals, to marketing options in exchange for development-stage funding and future payments. Partnership agreements in turn often lead to subsequent acquisitions by the major pharma firms in order to obtain full ownership of the development-stage firm's R&D pipeline as well as the addition of key R&D staff members to its own R&D personnel. Prior partnership agreements also lessen the information asymmetries that can create problems for these acquisitions (Higgins and Rodriguez, 2006).

Arrow (1983) provided an economic rationale for alliances in terms of R&D specialization based on comparative advantages in research versus development. At the earlier stages of R&D, small research-oriented boutique firms may enjoy a number of advantages relative to their larger rivals. These include their proximity to the cutting edge technologies emerging from universities and publically supported basic research, willingness to take risks on disruptive technologies, and less bureaucratic organization structure (Scherer, 1999). By contrast, larger pharmaceutical and biotechnology firms have advantages in the more advanced stages of development, where large scale clinical trial design and co-ordination with regulatory authorities become important.

While alliances can pose challenging issues of governance and management, some initial empirical studies provide support for the hypothesis that there are comparative advantages at different stages of the R&D process. These studies have examined R&D project data from a large sample of companies, and find that alliances improve the probability of success of new drug candidates across different development phases (Danzon *et al.*, 2005; Arora *et al.*, 2007). A skeptical view is provided by Pisano (2006) who argues that licensing deals in the biotechnology area are susceptible to misaligned incentives due to asymmetric information and an adverse selection process.

2.3 *Emerging Trends and Policy Issues for Biologics*

A paper that I co-authored with Richard Wang (2006) investigated trends in the quantity and quality of new drug introductions worldwide between 1982 and 2003. We found that biologics accounted for a disproportionate share of first-in-class therapies over this period, with novel biological introductions for anemia, neutropenia, various types of cancer, multiple sclerosis and autoimmune diseases like rheumatoid arthritis and psoriasis. Biologics were the fastest growing component of new drug introductions, and US based firms originated more than half of all worldwide biological introductions over the 1982–2002 period.

A recent analysis by Tusheim *et al.* (2010) finds substantial differences in the market dynamics of biologics compared to small molecules. Biologics are twice as likely to be orphan drugs than small molecule drugs, are more likely to receive priority review at the FDA, and also have greater sales revenues after their initial uptake period. Biologics also now account for close to half of all drugs under investigation in clinical trials from all sources. There are currently more than 600 biotechnology drug candidates under development in different therapeutic areas, with more than 250 biotechnology drugs for cancer alone (PhRMA, 2008).

Pharmaceutical firms have been increasingly attracted to biologics not only for their potential to achieve breakthrough products, but also because of their favorable economic conditions. In particular, they command relatively high prices per course of therapy, are generally covered by insurers in their medical rather than pharmacy benefit programs, are typically selectively marketed to smaller groups of physician specialists, and to date have not faced generic competitors. These market conditions may be changing in the near future.

As part of the Patient Protection and Affordable Care Act passed in March 2010, Congress created an abbreviated pathway for “biosimilars” that will allow companies to rely, at least in part, on the safety and efficacy data of the reference brand product. Biosimilar products are not chemically identical to the reference products as in the case of AB related generic products. For the foreseeable future, they are not likely to be interchangeable with their reference brands. However, they may be close enough substitutes to provide significant competition to several leading biologics coming off patent in the near future. The experiences from Germany among the European Union countries suggest this may be the case. The new law also contains a provision designed to maintain the incentives for innovation in biologics by establishing a 12-year data exclusivity period for innovators before biosimilars can rely on their data to gain approval. There are currently many regulatory and reimbursement issues

associated with implementing this new law that will affect how market competition evolves in the future between biologics and biosimilars.³

3. Growth of Managed Care Organizations and Generic Competition

3.1 Demand Side Developments

The demand side of the market for pharmaceuticals has also experienced dramatic changes over the past several decades. In the period after World War II, most US insurance plans focused on physician and hospital coverage, and drug prescriptions were largely paid out of pocket. In 1965, more than 90% of prescription drug expenditures were paid out of pocket by consumers, and as late as 1980, the consumers' share was two thirds of these expenditures (Berndt, 2001). With the growth of managed care organizations since that time, plus the extension of prescription drug benefits to seniors through the Medicare Part D program in 2006, the share of prescription drug expenditures paid by private and public insurance has grown to approximately 80% by 2008 (Kaiser, 2010).

Increased insurance coverage can impact the sales product life cycles of new drug products in contrasting ways. First, increased coverage expands overall demand for prescription drugs co-payments as plan beneficiaries pay lower copayments than retail prices. At the same time, a primary objective of MCOs and PBMs is to actively manage drug benefits to switch individuals to lower cost alternatives. A key strategy has been to encourage generics when they become available for a branded product with the same active ingredient. The growth of generic utilization has been encouraged by PBMs through benefit management techniques such as tiered formularies, prior authorization, step edits, and higher fees to pharmacists for dispensing generics (Grabowski and Mullins, 1997).

The dynamics of generic competition has been studied by a number of economists.⁴ A distinctive pattern of generic competition has been observed. First, commercially significant products have experienced a large number of generic entrants within a short period after patent expiration. Second, there is a strong positive relationship between the number of generic entrants, and the intensity of generic price competition. Third, the more generic entrants, the more rapid the erosion in the brand product market share in units to the generic firms. Fourth, an increasing number of products now have been subject to patent challenges early in their product life cycle as a result of the 180-day exclusivity awarded to the generic firm that is first to file for an ANDA and successfully challenge the product in court.

Generic competition has become the primary cost containment mechanism used by payors to achieve prescription drug expenditure savings in the United States. According to a recent IMS study the savings from generic products in 2009 alone amounted to \$139 billion.⁵ In other developed countries, with price regulation and volume controls on pharmaceuticals, generic utilization has had a lesser presence than the United States. It has played a more significant role in countries that have reference pricing- based reimbursement systems (e.g., Germany) as well as countries that create significant incentives for physicians to prescribe generically (the UK). By contrast, countries like France and Italy, which have stringent price regulation of new product launches and declining prices over time, along with competitive barriers in the pharmacy distribution system, have experienced negligible benefits in savings from generic utilization (Danzon and Chao, 2000).

3.2 *Implication for Innovation Incentives*

How have the Hatch-Waxman (H-W) Act and the growth of generics affected innovation incentives? A second objective of the Act was to preserve innovation incentives by granting patent term extensions to innovators to compensate for part of the patent protection lost in clinical testing and regulatory review. An initial study by the US Congressional Budget Office (1998) found that for R&D returns, the positive effects of the patent extensions present in the bill were outweighed by more rapid loss of sales to generics after patent expiration. In particular, they estimated the present value of net revenues for the representative new drug introductions declined by 12% as a result of the H-W Act over its first decade.

The growth of generics has meant that pharmaceutical firms now realize few sales after generic entry commences (Berndt and Aitken, 2011). While the loss of a molecule's unit sales by brand firms to generics formerly took several years to unfold, it now is typically completed with a year's time. For large-selling products, this often occurs within a few months.

The effective life cycle payback time for innovators has been curtailed. Margaret Kyle and I have investigated the average market exclusivity periods for new molecular entities first experiencing generic competition in the 1995 to 2005 period. Market exclusivity is defined as the period from a new drug's market launch to first entry by a generic competitor. We found that the average exclusivity period for products with \$100 million or more in sales in the year prior to generic entry (the products most exposed to generic competition) was approximately 11 years in length. In addition, Hatch Waxman patent challenges have negatively impacted market exclusivity times over this period (Grabowski and Kyle, 2007).

Patent-related litigation has escalated over time, and there are now many pending lawsuits involving patent challenges as generic firms compete to obtain the 180-day exclusivity period by being the first to file an ANDA (Berndt and Aitken, 2011). The earliest time that an abbreviated application with a patent challenge can be filed under Hatch-Waxman is four years after a new molecular entity is approved. There is a five-year data exclusivity period before generics can enter with an ANDA and there is also a stay on entry of up to 30 months in the case of a patent challenge while litigation is resolved. This rapid rise in early patent challenges by generic firms fosters uncertainty for innovators. In terms of R&D incentives, companies may not pursue promising new therapies with uncertain patent protection. In the case of launched products, new indications may not be pursued until litigation is resolved, but this may occur too late in the product life cycle to earn a positive return.

The situation is very different in the case of biological products. The recently passed law that establishes an abbreviated pathway for biosimilars provides for a 12-year data exclusivity period. In particular, a biosimilar product is not able to enter the market using an abbreviated pathway that relies on the innovators' safety and efficacy data until this 12-year data exclusivity period of the innovator's product has expired. In Europe, a ten -year data exclusivity period has been established for both new chemical entities and biologicals, plus an extra year for a significant new indication.⁶

The appropriate data exclusivity for new chemical entities remains an important issue for further research. The longer data exclusivity for biological entities could further tilt R&D incentives away from new chemical entities, especially given the increased uncertainty associated with early life cycle Hatch-Waxman patent challenges. A recent paper investigates the societal benefits and costs from extending a 12-year data exclusivity time to small molecular drugs (Goldman *et al.*, 2011). Using a simulation model, they found that Americans would benefit over the long term from the resulting increased innovation and longer expected longevity for individuals. However, there are also significant intergenerational distribution effects. In particular, older Americans would experience higher prescription drug costs relative to the benefits from increased innovation, given the lengthy investment times associated with pharmaceuticals.

4. The Economics of Pharmaceutical R&D

4.1 R&D Costs

While increased scientific knowledge and the more “rational” approach to drug discovery have contributed to the discovery of many important new classes of drug introductions, there have not been commensurate gains in terms of cost efficiencies or economies to scale in pharmaceutical R&D. In contrast to many other research-intensive industries like microelectronics and semiconductors, upfront R&D costs have escalated much faster than the rate of inflation.

The growth on real R&D costs for pharmaceuticals reflects a number of factors. Since the passage of the 1962 Amendments, the FDA has continued to strengthen its rules and guidelines.⁷ The average number of patients enrolled in clinical trials has increased significantly with successive cohorts of new drug introductions, rising from approximately 2000 individuals for 1970s introductions to more than 5,000 subjects for 1990s approvals.⁸ Second, the R&D process now typically spans more than a decade and still remains subject to considerable risk and uncertainty. This is reflected by the low probability of success for compounds taken into human clinical trials (historically around 20%) (DiMasi *et al.*, 2003). Third, clinical trials remain a very labor-intensive process. Accordingly, the real costs of recruiting patients and undertaking trials at academic institutions and physician clinics have increased over time, along with the number and complexity of tests administered to clinical trial subjects. Fourth, the drug companies have shifted their focus over time to chronic diseases and more novel classes of drug compounds. This also contributes to higher costs per new drug introduction.

The Center for the Study of Drug Development has undertaken three published studies involving different time periods of the R&D costs per new drug introduction. These studies employ similar methodologies so they can be utilized to consider how average R&D costs have changed over time. In particular, the studies assembled data on the probability of successes at each stage of the clinical development process and combined this with data on the cost to perform the trials at each stage, including the pre-clinical period. All costs were then capitalized at a representative industry cost of capital.

A summary is presented below.

Study	Clinical Trial Period ^a	Average Capitalized Cost (millions of 2000\$)
Hansen (1979)	1963 to mid-1970s	\$138
DiMasi <i>et al.</i> (1991)	1970s to early 1980s	\$467
DiMasi <i>et al.</i> (2003)	1983 to late 1990s	\$802

^aSamples are based on when compounds first began clinical trials

Expressed in constant 2000 dollars, capitalized R&D costs per new drug introduction have grown more than six fold for drug introductions in the late 1990s compared to the 1970s (\$802 million vs. \$138 million). In particular, capitalized costs have grown at a real rate of more than 7% after adjusting for inflation. Out-of-pocket costs have exhibited a similar rate of increase. An analysis of R&D costs has exhibited a similar rate of increase. An analysis undertaken by the FTC economists Adams and Branter (2010) finds similar R&D costs per new drug introduction. They focus on the same time period as that of the DiMasi *et al.* (2003) study, but use different methodology and data sources.

Joe DiMasi and I have also investigated the R&D costs for a data set of biological entities involving both recombinant proteins and monoclonal antibodies (DiMasi and Grabowski, 2007). We found that the R&D costs for a representative new biologic were over \$1 billion in 2006 dollars. Given the upward trend in real R&D costs over time, this estimate for biological entities appears comparable in magnitude to the prior estimates by DiMasi *et al.* (2003) for new chemical entities. However, we found that the underlying R&D cost component differed substantially between new biological and chemical entities. Specifically, biologics experienced higher probabilities of clinical success (30% compared with 21%) but also incurred higher expenditures from the drug discovery and preclinical stages and longer mean clinical development times than new chemical entities.

4.2 Post Approval Risks and Returns

Even after approval, the uncertainties surrounding new drugs do not disappear. When a product moves from a few thousand patients into clinical trials to hundreds of thousands or even millions of patients after approval, new safety risks sometimes become evident that can limit a product's marketability, or in extreme, result in its recall (Grabowski and Wang, 2008). Conversely, new indications developed after a product launch can sometimes be more important than the initial approval indication, and expand its global sales (Berndt *et al.*, 2006).

Competitive risks also add to these uncertainties. Companies are often pursuing similar leads based on new technological opportunities and classes of compounds. Companies whose products are "first-in-class" or "best-in-class" in this competitive race can earn disproportionate returns compared to other introductions in the class. Conversely, the losers in this race may have difficulties covering their R&D investments.

Analyses on the distribution of returns for new drugs that I have performed with John Vernon (1990; 1994) and with John Vernon and Joseph DiMasi (2002) are instructive in this regard. We have examined comprehensive

samples comprising all industry-originated new drug introductions for successive periods in the 1970s, 1980s and 1990s. The distribution of “quasi-rents” – the surplus revenues over costs of production and marketing – is highly skewed. In particular, the top 10% of new drug introductions (the outer “tail” of the distribution) has accounted for 48% to 55% of the overall quasi-rents in these three sample periods. At the same time, only the top three deciles of new drugs have earned enough surplus revenues to cover the average R&D costs of new drug introduction.

Hence, the analysis confirms that a relatively small number of “blockbuster” products have yielded a disproportionate share of industry returns. The R&D process for the last several decades has been driven by a search for innovative products that can achieve blockbuster-level sales. However, given this skewed distribution, even the maintenance of a large, diversified portfolio of R&D projects does not guarantee a relatively stable pattern of new drug approvals for individual firms, and they can experience highly variable outcomes for extended periods.

4.3 R&D Competition as a Rent-Seeking Model

Scherer (2001) has characterized R&D competition in pharmaceuticals as a “virtuous rent-seeking model.” In particular, firms base their investment decisions on the promise of new technological opportunities that create profit potential. Companies compete vigorously to exploit these opportunities, creating new classes of therapies, but in the process dissipating most of the rents. R&D competition with these characteristics can be denoted as a “virtuous” rent-seeking model, given an extensive literature that indicates there are large consumer surpluses and net social benefits from new drug introductions.⁹

The hypothesis that rents are typically dissipated from R&D competition is supported by several different analyses. First, Scherer (2001) has examined trends in R&D expenditures and profit margins over the lengthy period from 1962 to 1996. Analyzing the deviations from trend, he found R&D expenditures and profit margins tend to move in tandem with a .96 rank correlation over this 35-year period. Hence his work suggests that there is an equilibrating mechanism in which marginal R&D expenditures adjust upward or downward to profit perceptions and funding availability. Life cycle-based analyses of the private returns on R&D are also consistent with the rent dissipation model. In particular, average industry returns on R&D investment were generally found to be in line with the industry’s cost of capital for successive sample cohorts of 1970s, 1980s and 1990s new drug introductions (Grabowski *et al.*, 2002). Earlier economic studies of drug industry profitability focusing on company reported data also found that the apparent high observed returns on invested capital for pharmaceuticals in accounting statements largely disappeared when R&D is treated as an investment outlay rather than a current expense.¹⁰

Some have argued that R&D races and rent-seeking behavior are susceptible to wasteful and duplicative R&D. However, given the high degrees of uncertainties that are present in drug R&D, the pursuit of alternative parallel paths to a common goal can be socially beneficial (Scherer, 2010). Furthermore, multiple therapies in the same therapeutic class often have significantly

Figure 1. New drug approvals and R&D spending.

Notes: R&D expenditures are adjusted for inflation; curve is 3-year moving average for NMEs

Source: Tufts CSDD, PhRMA, 2009.

differentiated medical benefits in terms of efficacy or tolerability. Particular drugs, therefore, often can be matched to the demographic characteristics of patients and therapeutic alternatives in a class can be prescribed sequentially when individuals experience issues relating to safety or efficacy. Even in drug classes where products have very similar therapeutic profiles, this can lead to intensive price competition as firms vie to gain access to managed care formularies with discounts and rebates.

4.4 A New Era of Fewer New Drug Introductions?

The pharmaceutical industry has enjoyed relatively robust technological opportunities over the past fifty years with the introduction of many important new classes of drug therapies (DiMasi and Paquette, 2004). The first decade or so after the passage of the 1962 Amendments was an exception to this general result. However, trends in new product introductions since the mid- to late 1990s suggest that the industry may have entered another fallow period, at least with respect to new chemical entities which still account for the majority of new drug approvals.

Figure 1 shows trends in new drug approvals from 1963 through 2008 along with annual industry expenditures based on members of the PhRMA trade association.¹¹ As shown in this figure, new drug approvals peaked in the mid- to late 1990s and have declined to a much lower level of annual introductions. Even allowing for the fact that the timing of 1997 approvals were artificially inflated by the pending law authorizing the renewal of drug user fees, there has been a secular downturn on new drug approvals even though R&D expenditures continue to escalate upward at a fairly rapid rate of real growth.

In addition to the decline in the number of annual new product introductions, there are also fewer products that appear capable of achieving blockbuster levels of sales revenues. (The current industry metric for blockbuster status is \$1 billion or more in global sales.) As a consequence, many of the large pharma firms are facing an R&D pipeline replacement problem, with the sales from new product introductions unable to replace pending losses from generic competition as their leading products face patent expiration and patent challenges.¹²

In response to the industry “shocks” associated with the trend in fewer new drug approvals and more intensified generic competition, the industry has undergone some significant structural changes. First, there has been a series of large-scale horizontal mergers leading to a more consolidated industry structure. At the same time, there has been vertical disintegration associated with more outsourcing at the drug discovery and early development stages through alliances and deals with development stage companies as discussed earlier in section 2.

As for M&A activity in other industry, research to date on horizontal merger activity in pharmaceuticals indicates considerable variation and mixed outcomes. The pharmaceutical industry merger waves have had some success in addressing excess firm capacity and boosting short-term earnings through the rationalization of organization activities. However, there is little evidence to date that they have increased long-term R&D performance and outcomes.¹³

By contrast, the research finding on the effects of industry alliances and vertical-type acquisitions of development-stage companies is more optimistic in nature. As discussed earlier, there is evidence that is consistent with advantages from specialization in different R&D stages. Alliances can increase R&D productivity as reflected in the probabilities of success at different stages of the product life cycle. An analysis that I have undertaken with Margaret Kyle of mergers and acquisitions involving new drug product candidates is consistent with these empirical results on alliances. In particular, we find that R&D boutique firms with only a few products in their pipeline can gain the most from mergers with more experienced firms. This is reflected in higher likelihood of success at later stages of development (Grabowski and Kyle, 2008).

It seems paradoxical that in a time when basic biomedical knowledge is exploding, there are fewer new drugs being approved annually. It remains to be seen whether the downward trend in the Figure 1 represents a long-term stagnation in R&D outputs. On the one hand, many indications historically targeted by industry R&D such as hypertension, GERD, cholesterol reduction, etc., now have very effective drug remedies that are often available at generic prices. At the same time, some of the current areas of R&D focus such as Alzheimer’s Disease and chronic diseases prevalent in an aging population are not as well understood and consequently they are more challenging to design effective drug interventions. Nevertheless, the industry may be in a transition period as it adapts to new technological opportunities associated with an abundance of new biological research discoveries and other scientific advances. There is often a longer lag between these scientific advances and the availability of new medicines than is generally realized.

5. Conclusions

The pharmaceutical industry has had an exemplary record of innovation over the past 50 years, but it still faces many risks and uncertainties as it attempts to create innovative new medicines for indications with high unmet disease burden. The approach to drug innovation has become more knowledge-based, and there is a growing shift toward biopharmaceutical candidates in the R&D pipeline. The structure of the industry has changed from a relatively small number of fully integrated companies to a large networked market for innovation comprising hundreds of development-stage companies as well as a more consolidated group of large pharma firms.

The next 50 years is likely to witness extraordinary change as well. Despite the recent slowdown in new drug approvals, the possibilities presented by personalized medicine, gene-based drug interventions, and other scientific advances are truly exciting. While regulatory conditions and economic factors are likely to continue to become more demanding over time, the path to industry success has always centered around the development of innovative medicines that provide significant medical benefits to patients. I remain optimistic that there will be an innovative drug industry in the future, but it may evolve in ways that cannot be foreseen at the present.

Notes

1. I am indebted to many individuals for sparking my interests on R&D and innovation issues. During my graduate days at Princeton, Dick Quandt and Burt Malkiel ably supervised my PhD work on the "Determinants and Effects of Industrial R&D." Jessie Markham and Mike Scherer provided many helpful ideas and comments that started me on the road to becoming an Industrial Organization economist, along with my classmate and dear friend, Dennis Mueller. Joe Peck and Dick Nelson were very valuable colleagues during my days as an Assistant Professor at Yale, and they contributed to my professional development as an IO economist focused on technological change. I am most indebted to my late colleague, John Vernon, who collaborated with me on dozens of papers involving competition in the pharmaceutical industry. He was an insightful and energetic individual who contributed immensely to my own R&D productivity. Joe DiMasi at The Center for the Study of Drug Development also has been invaluable colleague and co-author over the past two decades.
2. For a recent survey of the literature on alliances, see Grabowski and Kyle (2008).
3. An analysis of the law's key provisions and the regulatory and reimbursement issues associated with its implementation is provided by Grabowski *et al.* (2011b).
4. For a survey of these studies, see Grabowski (2007).
5. This report is discussed in Berndt and Aitken (2011).
6. An analysis of the relationship between data exclusivity time and innovation incentives is provided in Grabowski (2008) and Grabowski *et al.* (2011a).
7. For a survey of academic studies analyzing the effects of the 1962 Amendments on drug innovation and R&D costs as well as the other major regulatory developments over time, see Danzon and Keuffel (2007) and Scherer (2010).
8. For a discussion of this and other factors causing an upward trend in R&D costs, see DiMasi *et al.* (2003).
9. Some representative studies include Cutler and McClellan (2001), Philipson and Jena (2006), Murphy and Topel (2006), and Lichtenburg (2007).
10. For an analysis of the academic literature on R&D costs and returns, see the forthcoming chapter in the *Handbook of Pharmaceuticals* by DiMasi and Grabowski (2011).
11. New drug approvals include both new chemical and biological entities but exclude diagnostics.
12. See Berndt and Aitken (2011) for a discussion of most recent trends involving generic competition and product replacement problems of innovators.

13. Grabowski and Kyle (2008) survey the literature on how mergers and alliances affect innovation outputs.

References

- Adams, Christopher P., and Branter, Van Vu (2010) Spending on new drug development, *Health Economics*, 19, pp. 130–41.
- Arora, Ashish, Gambardella, Alfonso, Magazzini, Laura, and Pammolli, Fabio (2007) A breath of fresh air? Firm types, scale, scope and selection effects in drug development. Unpublished paper. Available from the authors.
- Arrow, Kenneth J. (1983) Innovation in large and small firms, in: J. Ronen (Ed.), *Entrepreneurship* (Lexington, MA: Lexington Books).
- Berndt, Ernst R. (2001) The US pharmaceutical industry: why merger growth in times of cost containment? *Health Affairs*, 20, pp. 100–14.
- Berndt, Ernst R., and Aitken, Murray (2011) Brand loyalty, generic entry and price competition in pharmaceuticals in the quarter century after the 1984 Waxman-Hatch legislation (this volume.).
- Berndt, Ernst R., Cockburn, Iain M., and Grepin, Karen A. (2006) The impact of incremental innovation in biopharmaceuticals, *PharmacoEconomics*, 24, Supp 2, pp. 69–86.
- Cutler, David M., and McClellan, Mark (2001) Is technological change in medicine worth it? *Health Affairs*, 20, pp. 11–5.
- Danzon, Patricia (1997) *Pharmaceutical Price Regulation: National Policies Versus Global Interests* (Washington, DC: AEI Press).
- Danzon, Patricia, and Keuffel, Eric L. (2007) Regulation of the Pharmaceutical-Biotechnology Industry. Available at: www.NBER.org/books_in_progress/econ-reg/index.html
- Danzon, Patricia, and Chao, Li Wei (2000) Does regulation drive out competition in pharmaceutical markets? *Journal of Law and Economics*, 43, pp. 311–57.
- Danzon, Patricia, Nicholson, Sean, and Pereira, Nuno S. (2005) Productivity in pharmaceutical biotechnology R&D: the role of experience and alliances, *Journal of Health Economics*, 24, pp. 317–39.
- DiMasi, Joseph A., and Grabowski, Henry G. (2007) The cost of pharmaceutical R&D: is biotech different? *Managerial and Decision Economics*, 28, pp. 469–79.
- DiMasi, Joseph A., and Grabowski, Henry G. (2011) R&D costs and returns. Forthcoming, in: Danzon Patricia and Nicholson Sean (Eds.), *Handbook of Pharmaceuticals* (New York: Oxford University Press).
- DiMasi, Joseph A., Hansen, Ronald W., Grabowski, Henry G., and Lasagna, Louis C. (1991) The cost of innovation in the pharmaceutical industry, *Journal of Health Economics*, 10, pp. 107–42.
- DiMasi, Joseph A., Hansen, Ronald W., and Grabowski, Henry G. (2003) The price of innovation: new estimates of drug development costs, *Journal of Health Economics*, 22, pp. 151–85.
- DiMasi, Joseph A., and Paquette, Cherie (2004) The economics of follow-on drug research and development: trends in entry rates and the timing of development, *PharmacoEconomics*, 22, Supp 2, pp. 1–14.
- Goldman, Dana P., Lakdawalla, D.N., Malkin, Jessie D., Romley, John, and Philipson, Tomas (2011) The benefits from giving makers of conventional ‘small molecule’ drugs longer exclusivity over clinical trial data, *Health Affairs*, 30, pp. 84–90.
- Grabowski, Henry G. (1968) The determinants of industrial research and development expenditures, *Journal of Political Economy*, 76, pp. 292–306.
- Grabowski, Henry G. (2007) Competition between generic and branded drugs, in: Frank A. Sloan, and Chee-Ruey Heish (Eds.), *Pharmaceutical Innovation: Incentives, Competition and Cost-Benefit Analysis in International Perspective*, pp. 153–73 (Cambridge, MA: Cambridge University Press).
- Grabowski, Henry G. (2008) Follow-on biologics: data exclusivity and the balance between innovation and competition, *Nature Reviews: Drug Discovery*, 7, pp. 479–88.
- Grabowski, Henry G., and Kyle, Margaret K. (2007) Generic competition and market exclusivity periods in pharmaceuticals, *Managerial and Decision Economics*, 28, pp. 491–502.
- Grabowski, Henry G., and Kyle, Margaret K. (2008) Mergers and alliances in pharmaceuticals: effects on innovation and R&D productivity, in: Klaus Gugler, and B. Yurtogiv (Eds.), *The Economics of Corporate Governance and Mergers*, pp. 262–84 (Northampton, MA: Edward Elgar).
- Grabowski, Henry G., Long, Genia, and Mortimer, Richard (2011a) Data exclusivity for biologics, *Nature Reviews: Drug Discovery*, 10, pp. 15–6.
- Grabowski, Henry G., Long, Genia, and Mortimer, Richard (2011b) Implementation of the biosimilar pathway: economic and policy issues, *Seton Hall Law Journal*, 41, pp. 511–57.

- Grabowski, Henry G., and Mullins, Daniel C. (1997) Pharmacy benefit management, cost-effectiveness analysis and drug formulary decision, *Social Science & Medicine*, 45, pp. 535–44.
- Grabowski, Henry G., and Vernon, John M. (1981) The determinants of R&D expenditures, in: Robert B. Helms (Ed.), *Drugs and Health*, pp. 3–20 (Washington, DC: AEI).
- Grabowski, Henry G., and Vernon, John M. (1990) A new look at the returns and risks to pharmaceutical R&D, *Management Science*, 36, pp. 804–21.
- Grabowski, Henry G., and Vernon, John M. (1994) Returns to R&D on new drug introductions in the 1980s, *Journal of Health Economics*, 13(3), pp. 383–406.
- Grabowski, Henry G., Vernon, John M., and DiMasi, Joseph A. (2002) Returns on research and development for 1990s new drug introductions, *PharmacoEconomics*, 20, Supp 3, pp. 11–29.
- Grabowski, Henry G., and Wang, Richard Y. (2008) Do faster reviews affect patient safety? An analysis of the 1992 Prescription Drug User Fee Act, *Journal of Law and Economics*, 51, pp. 377–406.
- Hansen, Ronald W. (1979) The pharmaceutical development process: estimates of current development costs and times and the effects of regulatory changes, in: R.I. Chien (Ed.), *Issues in Pharmaceutical Economics* (Lexington, MA: Lexington Books).
- Henderson, Rebecca, and Cockburn, Iain (1996) Scale, scope, and spillovers: determinants of research productivity in the pharmaceutical industry, *RAND Journal of Economics*, 27, pp. 32–59.
- Higgins, Matthew J., and Rodriguez, Daniel (2006) The outsourcing of R&D through acquisition in the pharmaceutical industry, *Journal of Financial Economics*, 80, pp. 351–83.
- Kaiser Family Foundation (2010) Prescription Drug Trends. Available at: www.kff.org/rxdrugs/upload/3057-08.pdf
- Lichtenberg, Frank R. (2007) The impact of new drug launches on US longevity and medical expenditure, *American Economic Review*, 97, pp. 438–41.
- Mansfield, Edwin (1998) Academic research and industrial innovation: an update of empirical findings, *Research Policy*, 26, pp. 773–6.
- Murphy, Kevin M., and Topel, Robert H. (2006) The value of health and longevity, *Journal of Political Economy*, 114, pp. 871–904.
- Philipson, Tomas J., and Jenna, Anupam B. (2006) Who benefits from new medical technologies? Estimates of consumer and producer surpluses for HIV/AIDS drugs, *Forum for Health Economics and Policy* 9(2) Article 3. Available at: <http://www.bepress.com/fhep/9/2/>
- PhRMA (2008) Medicine in Development Biotechnology, PhRMA, Washington, DC. Available at: <http://www.phrma.org/sites/default/files/4r22/biotech2008.pdf>
- Pisano, Gary P. (2006) *Science Business: The Promise, the Reality and the Future of Biotech* (Cambridge, MA: Harvard Business School Press).
- Robbins-Roth, Cynthia (2000) *From Alchemy to IPO: The Business of Biotechnology* (Cambridge, MA: Perseus Publishing).
- Scherer, F.M. (1999) *New Perspectives on Economic Growth and Technological Innovation* (Washington, DC: The Brookings Institution).
- Scherer, F.M. (2001) The link between gross profitability and pharmaceutical spending, *Health Affairs*, 20, pp. 216–20.
- Scherer, F.M. (2010) Pharmaceutical innovation, in: Bronwyn Hall and Nathan Rosenberg (Eds.), *Handbook of the Economics of Innovation*, Vol. 1, Chapter 2.8 (North-Holland: Elsevier).
- Tusheim, Mark R., Aitken, Murray L., and Berndt, Ernst R. (2010) Characterizing markets for biopharmaceutical innovations: do biologics differ from small molecules? *Forum for Health Economics and Health Policy Research*, 31, Article 4. Available at: www.bepress.com/fhep/13/1/4
- US Congressional Budget Office (1998) How Increased Competition From Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry. Available at: <http://www.cbo.gov>
- Werth, Barry (1994) *The Billion Dollar Molecule* (New York: Simon and Schuster).