

Are the Economics of Pharmaceutical Research and Development Changing?

Productivity, Patents and Political Pressures

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Abstract

Pharmaceutical research and development (R&D) competition in the 1980s and 1990s was characterised by rising R&D expenditures, favourable returns to innovators and the introduction of many new classes of drugs with high social benefits. However, in the past 3 years, the number of new drug introductions has been well below the historical trend, while the cost per new drug continues to increase. In addition to lagging R&D productivity, the industry has been characterised by other economic and policy uncertainties. These include a wave of early patent challenges and growing political pressure to contain pharmaceutical expenditures. This paper examines the consequences of these developments.

The decades of the 1980s and 1990s were marked by rapid progress in the case of pharmaceutical innovation. In particular, these years were characterised by rising research and development (R&D) expenditures and the introduction of many new classes of drugs with correspondingly high social benefits. The first movers and best in class drugs earned high private returns, while overall industry returns were only moderately above the industry's cost of capital.^[1] This has been described as a virtuous pattern of profit-seeking industry behaviour by Scherer in a recent analysis of the determinants of pharmaceutical R&D expenditures.^[2]

Several developments of the last few years have raised questions whether this virtuous pattern of rapidly rising R&D outlays and innovative introductions can be sustained. On a positive note, scientific opportunities remain strong with advances in genomics, proteomics and related bio-

medical sciences. These are currently many new leads and targets for promising medicines. However, the industry is also beset by many economic and policy uncertainties. These concerns include lagging R&D productivity, increasing generic usage and patent challenges and growing political pressures to contain pharmaceutical prices and expenditures.

This paper focuses on some key developments that are influencing the current and future environment for pharmaceutical R&D.

Section 1 examines the issues of R&D productivity and returns. Section 2 addresses the intensifying level of generic competition and patent challenges of major branded products. Section 3 considers the prospects of increased government intervention and more stringent cost-containment measures. Section 4 provides a summary and brief concluding remarks.

1. R&D Productivity and Returns

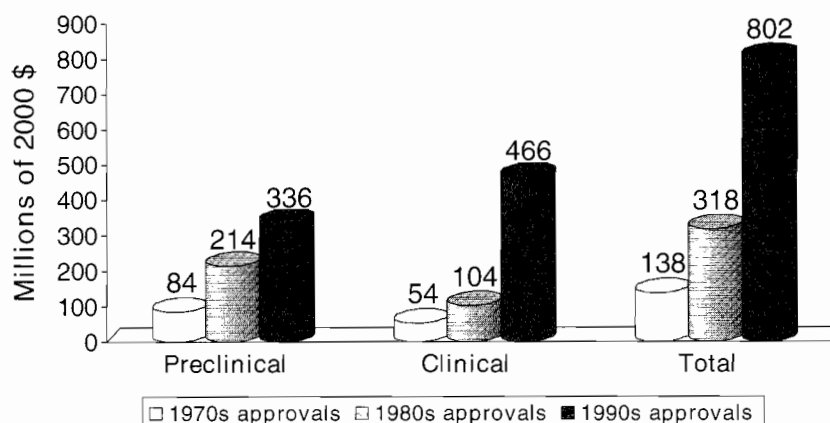
There is evidence from a number of studies that the average R&D cost for a new drug introduction has been growing significantly faster than general inflation. Figure 1 shows the trends in fully allocated capitalized R&D cost per approved US new drug introduction from a recent study by DiMasi, et al.^[3] After adjusting for general inflation, the real cost of a new drug introduction has more than doubled for 1990s introductions compared with 1980s introductions.

The average R&D cost of a new drug introduction for 1990s approvals is \$US802 million, compared with \$US316 million for the 1980s and \$US138 million for the 1970s. These costs are measured in year 2000 dollars and include the costs of failed candidates and pre-clinical expenditures on discovery and lead generation. Figure 1 shows the biggest changes have been in terms of clinical expenditures, which experienced a 3-fold increase for 1990s approvals, relative to the 1980s approvals.

Our study of R&D costs examines various hypotheses on why R&D costs are increasing over time. One of the most significant factors is the increasing number of subjects in clinical trials and the increased complexity (i.e. procedures per patient)

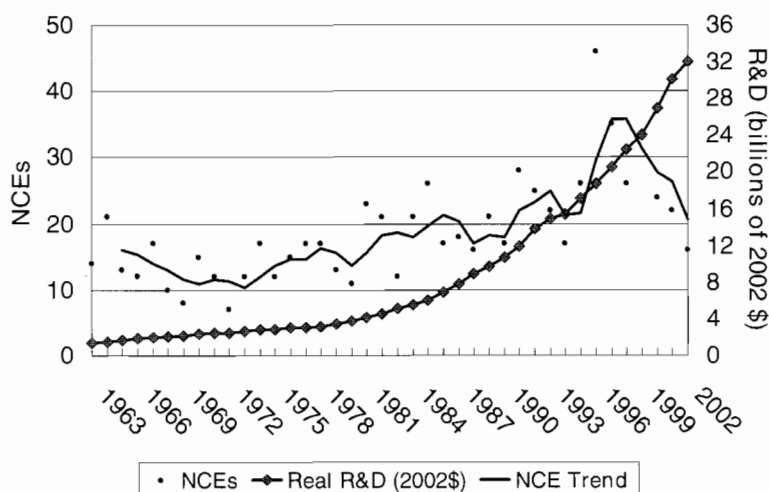
per clinical patient. Other factors include increased costs of patient recruitment, a greater focus on chronic and degenerative disease and more 'head-to-head' studies directed to gaining formulary access and product reimbursement after a drug is approved for marketing by the regulatory authorities.^[3]

Figure 2 shows the aggregate trend in industry R&D expenditures versus new clinical entities (NCE) approvals since 1963. This figure shows that the long-term trend in R&D expenditures has been much steeper than the growth in NCE approvals over time. These aggregate trends are therefore consistent with our findings of higher costs per new drug introduction, based on the representative samples of compounds from three different periods discussed earlier. What is of particular concern about the trends displayed in figure 2 is that the number of new drug introductions since the late 1990s has been significantly below the long-term trend line. The NCE trend line is based on a 3-year moving average. In 1996, there were 46 NCE introductions, but this was an outlier value associated with a catch up in the backlog at the US FDA. Over the period since 1996, the number of NCE introductions has been on a steep downward trend with only 20 NCEs on average having been introduced annually since the year 2000.



Source: DiMasi et al., *J Health Economics* 2003;22(2):151-185

Fig. 1. Trends in Fully Allocated Capitalized Cost per Approved Drug



Source of data: Tufts CSDD Approved NCE Database; PhRMA

Fig. 2. U.S. Pharmaceutical Industry Inflation-Adjusted R&D Expenditures and NCE Approvals, 1963-2002

Of course, one cannot get a full picture of R&D productivity without examining the sales and the therapeutic importance of the new drug introductions in any given period. In my analysis of R&D returns with Vernon and DiMasi, we found that the distribution of R&D returns is highly skewed.¹¹¹ The top decile of new drug introductions have accounted for approximately half of the total cash flows in all of the time cohorts that we have analysed from the 1970s through the 1990s (see figure 3). In this regard, R&D competition in pharmaceuticals has centered around the search for compounds with significant therapeutic benefits and large market potential.

Table I shows the number of NCEs achieving annual global sales of \$US1 billion or more by the fifth year after market launch. This number grew from five in the 1980–4 period to 18 in the 1995–9 period. Moreover, the blockbuster selling drugs in the early 1980s were concentrated in a few therapeutic areas – namely, cardiovascular and gastrointestinal diseases. By the last half of the 1990s, the list of therapeutic areas also included cholesterol, depression, antipsychotics, asthma, diabetes mellitus, cancer, osteoporosis, arthritis, allergies and erectile dysfunction.

Table II shows the list of significant new classes of drugs that were introduced since the beginning of the 1990s. The 1990s, in particular, saw the introduction of innovative categories such as the protease inhibitors (AIDS), taxanes (cancer), atypical antipsychotics (schizophrenia), triptans (migraine) and cyclo-oxygenase-2 inhibitors (arthritis). The top-ranked selling compounds in the 1990s tended to be early entrants or the thera-

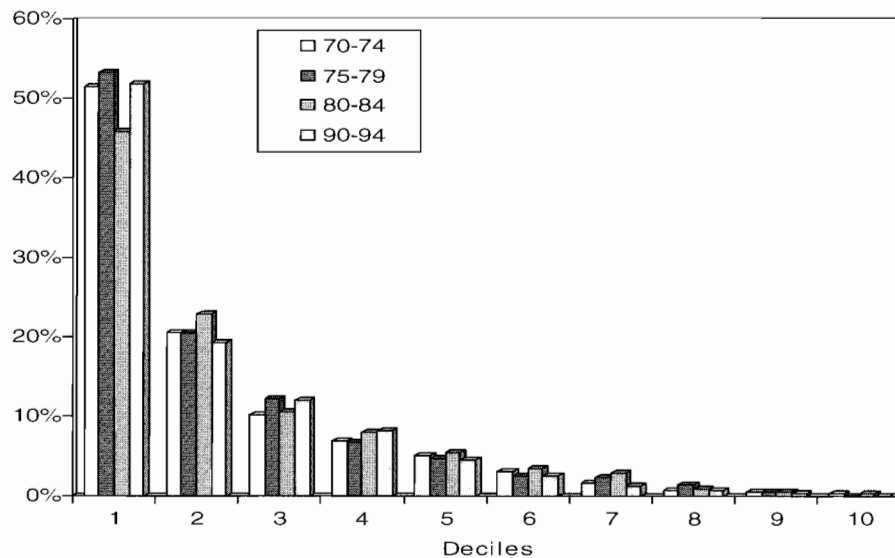
Table I. Number of New Chemical Entities Achieving \$1 Billion Annual Sales^a

Period	NCEs	Medical Indications ^b
1980-84	5	2
1985-89	9	8
1990-94	11	9
1995-99	18	12

a NCEs that achieved annual global sales of \$1 billion (2003\$) by fifth year after launch

b Number of Medical indications for all NCEs - cardiovascular (9), gastrointestinal (5), depression (4), cholesterol (4), anti-infectives (3), arthritis (3), allergies (3), cancer (3), anti-psychoics (2), diabetes (2), migraine (1), asthma (1), osteoporosis (1), anemia (1), erectile dysfunction (1)

Source: authors' calculations based on listings of the top prescription drug products by worldwide sales in the various May issues of MedAd News.



Source: Grabowski et al., *Pharmacoeconomics* 2002; 20(Suppl 3):11-29

Fig 3. Percentage of Total Value by Decile for Four Samples of Drug Approvals

py of choice in these new classes of compounds for important disease indications.

It is difficult to say how the current decade will stack up against this record of innovative activity in the 1980s and 1990s. In particular, we are currently less than half way into the period. It is instructive to note, however, that at a corresponding point in time for the 1990–4 list of new drug introductions, there were 11 drugs ranked in the top 100 drugs in terms of global sales and, similarly, the 1995–9 cohort had ten such drugs.^[4] Only two NCE introductions since 2000 have achieved a

ranking to date among the top 100 drugs categorised by global sales. Clearly, the period since 2000 has been characterised by both fewer total new drug introductions and a dearth of top 100 sales candidates.

The pattern observed in this decade to date may be part of a cycle that will reverse in the later years of this decade. It is instructive to note that during the 1960s and 1970s, economists following the pharmaceutical industry focused on the declining level of new drug introductions and wondered if the industry had entered a mature phase with diminished opportunities for drug innovation.^[5,6] These concerns were allayed in the decades of the 1980s and 1990s.

Looking forward, there are reasons for optimism concerning early stage research opportunities. New discovery technologies have generated an abundance of new disease targets for exploration. Over time, these developments may lead to significant breakthroughs. To the extent that these discoveries also lead to a higher success rate in development, they hold the potential of lower long-run costs as well. At the same time, the transition to a new R&D paradigm has uncertain time-lines and is likely to be characterised by

Table II. Some Important New Drug Classes Introduced During the 1990s

Triptans (migrane)
Taxanes (cancer)
Macrolides (anti-infectives)
Atypical anti-psychotics (schizophrenia)
Protease Inhibitors (AIDS)
Neutrophil Growth Factors (neutropenia)
Cox-2 Inhibitors (arthritis)
SERMs (osteoporosis)

Source: FDA - New Molecular Entities

higher overall costs in the intermediate period.^{17,81} The era of personalised medicines, which many observers envision as the logical outcome of recent technological advances, also poses many challenges for both regulatory officials and pharmaceutical R&D marketing directors.

2. Patents and Generic Competition

The 1984 Hatch-Waxman Act was designed to encourage intensive generic price competition while at the same time preserving sufficient patent exclusivity to facilitate R&D competition and new product introductions. Section I of the act established the Abbreviated New Drug Application (ANDA) process for generic drug entry. Generics need only show in an ANDA submission that their products are bioequivalent to the branded product with the same active ingredient, while relying on the innovators' safety and efficacy data. Section II of the act provides a provision for patent term restoration for branded manufacturers, given that a large portion of the nominal patent term is lost during the clinical trial and US FDA review periods. There is also a 5-year NCE data exclusivity period in the act. This is the minimum period of time before a generic company can enter the market while relying on the innovator's safety and efficacy data through the ANDA process.⁹¹

Since the 1984 act was passed, the generic share of dispensed prescriptions in the US drug market has increased from 19% in 1984 to 51% in 2002.¹⁰⁰ The reduced regulatory requirements for generic products, together with the rapid growth of managed care programmes in the US since the mid-1980s, have been important factors accelerating the rate of generic usage. Managed care organisations have instituted a number of programmes to increase the usage of generic drugs. These include three-tier formularies, maximum allowable cost programmes, higher dispensing fees to pharmacists for dispensing generic drugs and educational programmes targeting physicians that restrict substitution of branded products with generics.¹¹¹

These developments have resulted in a much faster loss in the sales of branded products once generics enter the market. In the initial years after the 1984 act, it generally took 3 or 4 years for generics to capture a dominant share of the market.¹¹² The sales erosion of top-ranked branded products now takes place in a matter of months rather than years. Table III provides information on sales erosion to generics for the three largest oral prescription products experiencing initial generic entry since 2000. These products are: Vasotec[®] (Biovail Pharmaceuticals Inc., Morrisville, NC), Prozac[®] (Eli Lilly & Co., Indianapolis, IN), and Zestril[®]/Prinivil[®] (AstraZeneca Pharm. LP., Wilmington, DE/ Merck & Co., West Point, PA).¹ These products lost more than 75% of the market in the first quarter after initial generic entry.

Table III indicates that these three products enjoyed approximately 14 years of effective patent life, including the patent term extension benefits received through the 1984 act. At the same time, they experienced very intense price competition in the post-patent expiration period that was facilitated by the ANDA process instituted under the act. From the standpoint of the objectives of the 1984 Hatch-Waxman Act, these three products therefore achieved a reasonable balance between the incentive provisions in the act for innovators and imitations.

This balance has been threatened in the case of newer product introductions by a wave of recent patent challenges. The 1984 act includes a provision where generic firms can challenge the validity of the patents that brand manufacturers file with the US FDA. This is called a 'paragraph IV' ANDA filing. In this case, a generic firm asserts that brand name firms' patent(s) are invalid or non-infringed by the generic's product. The first generic firm to

Table III. Generics Erosion for Leading Brands 2000–2002

Product	Launch Date	Generic Entry	Rx's Erosion	
			3 mos	6 mos
Vasotec	Jan. 86	Aug. 00	76%	81%
Zestril/Prinivil	Dec. 87	July 02	88%	94%
Prozac	Jan. 88	Aug. 01	80%	86%

Source: IMS NPA Audit of total Rx's

¹ The use of trade names is for product identification purposes only and does not imply endorsement.

file and prevail under a paragraph IV certification for a particular branded product receives a 180-day marketing exclusivity. However, there is also a 30-month stay on US FDA approval while the patent infringement litigation is in process. The 180-day generic firm exclusivity is triggered by the earliest of: (i) a court's decision that the patent is invalid or non-infringed; or (ii) the marketing of the generic after the 30-month stay has expired.^[13]

Antitrust authorities and legislators have raised concerns that the 30-month stay can be used as an entry barrier by brand manufacturers.^{[13][14]} This can occur if the brand manufacturer lists dubious or frivolous patents late in a product's life cycle to invoke successive 30-month stays for each patent. This practice will be curtailed under a provision in the Medicare prescription drug act that limits each branded product to one 30-month stay. There also have been cases where the generic entrant with first-to-file exclusivity rights and the branded manufacturer enter into agreement whereby the generic firm receives compensation for not entering the market.^[14] This latter practice has been subject to successful antitrust prosecution and class action suits and also is prohibited under the recently passed legislation.

While the potential anticompetitive effects of multiple 30-month stays have received considerable attention by policy-makers, the potential adverse incentives of the 180-day exclusivity provision has received much less attention. In particular, generic firms have focused on a new business model that is built around prospecting in patent challenges. Even if the odds of winning are low, the payoffs to a 180-day exclusivity position in a leading pharmaceutical product are very large. By contrast, the increased price competition in recent years following patent expiration has caused profit margins for generic firms to erode quickly as the number of generic entrants increases. Hence, generic firms are increasingly pursuing a portfolio approach that challenges the patents of a large number of branded products in the hopes of winning a few of these lawsuits. However, this barrage of litigation strains the resources of the legal system and also creates additional uncertainty around the innovators' products. This uncertainty can

Table IV. Major Products with Paragraph IV Challenges Pending in the courts

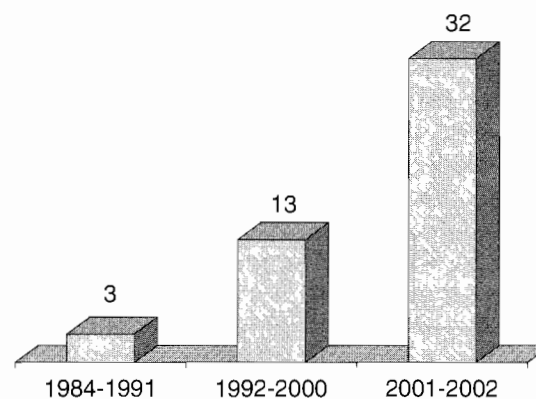
Lipitor	Risperdal
Prilosec	Pravachol
Zyprexa	Fosamax
Zoloft	Oxycontin
Paxil	Effexor
Neurontin	Wellbutrin
Norvasc	Imitrex
Allegra	Cipro

Source: Bear Stearns^[15]

adversely influence R&D decisions for new products as well as R&D for new indications and formulations of existing products.

The strongest form of patent protection in the pharmaceutical industry is a compound patent. These patents may be challenged on grounds of obviousness, prior art or double-patenting. Products with somewhat weaker forms of patent protection, such as those that rely on formulation, treatment-of-use or method-of-use patents are particularly vulnerable to challenge. Table IV provides a partial list of major products that are currently in litigation. At the current time, a large number of the leading selling drug products are subject to paragraph IV challenges. Most of these challenges were filed early in the product's life cycle.

The escalating nature of the phenomenon of patent challenges is depicted in figure 4. This figure shows that the average number of paragraph IV ANDA filings has increased from three per year in the 1984–91 period to 13 per year in 1992–2000, to



Source FTC; Bear Stearns^[13,15]

Fig. 4. Average Number of Paragraph IV ANDA Filings Per Year

32 per year in 2001–2.^[15] In effect, there is now a race among generic firms to be the first firm to file a paragraph IV challenge. This race has been fueled by an increasing propensity to litigate on the part of generic firms, but also could reflect, in some cases, an increased vulnerability of the patent portfolios of innovators (because the branded firms are relying more on method-of-use and formulation patents).^[15]

A key issue that remains open at this time is how the courts will decide the many outstanding cases involving generic patent challenges. The generic firms have recently won some high profile victories at the US District Court level. These include the cases involving the products Paxil (an antidepressant) and Augmentin (an anti-infective). Both cases have appeals pending.

As discussed regarding the Hatch-Waxman Act, there is a 5-year NCE exclusivity period regardless of patent status. The US FDA will accept a paragraph IV ANDA filing 4 years after market launch of the pioneering product. Given one 30-month stay under the new legislation, this would afford branded products a floor of between 5 and 7.5 years of effective exclusivity. This is insufficient time to recoup the R&D costs of the representative new drug, as depicted in figure 1.

Only drugs with sales revenues in the top decile of new introductions would generally earn enough to recoup the mean R&D investment within 7 years. Moreover, this assumes that current exclusivity periods would continue to prevail in other countries. There would be a very adverse impact on drug innovation if effective patent lives in the US were shortened to ≤ 7 years from current levels of 10–14 years. In particular, R&D activities would be expected to severely contract. R&D would be focused on the very largest selling drug candidates as well as those eligible for smaller patient clinical trials and special fast-track status at the US FDA.

The issue of patent strength or type is also relevant from a policy perspective. Many important product introductions, such as the pioneering AIDS product zidovudine, have relied on method-of-use or formulation products because their composition-of-matter patents have already expired. In the case of zidovudine, the product was originally devel-

oped, unsuccessfully, as a cancer remedy, and remained on the shelf for over two decades until its antiviral activity was noted in the intensive hunt for the first AIDS therapy that occurred in the mid-1980s.^[16] It would be an undesirable development if such products were now to be given low priority in the development process because of the possibility that they have uncertain patent protection.

In addition, many firms develop new indications and formulations of their products after the initial product launch. If a product's patent protection is subject to early challenges with uncertain outcomes, this can have a retarding effect on research for new indications and formulations. While a new indication is eligible for a 3-year exclusivity extension under the 1984 act, this is not a meaningful incentive if generics are on the market with an approved labelling for the initial indication. This is because prescriptions by physicians do not specify an indication. Unless the branded product utilises an alternative delivery mechanism, there is no effective way to prevent a less expensive generic from being used for all of the approved indications.^[17]

In most European countries, the patent laws provide a NCE data exclusivity period of 10 years. In the current US environment, in which generic firms are racing to challenge patents validity, a 10-year NCE data exclusivity period would be more consistent with the second major objective of the 1984 act – preserving R&D incentives through sufficient market exclusivity. The R&D costs of generating the original safety and efficacy data to gain US FDA approval now runs into hundreds of million dollars for the representative compound (figure 1). A 10-year NCE data exclusive period would recognise this large R&D expense and curtail the current rush to patent suits very early in the product life cycle. This race contributes to high costs of litigation and can result in a very chilling effect on the decision to undertake R&D development, particularly for products relying on formulation or method-of-use patents such as zidovudine.

3. Political Pressures

In November 2003 the US Congress passed legislation instituting a Medicare prescription drug

benefit. There is uncertainty about how the institution of such a benefit will affect the revenues of prescription drug firms. It will depend, in a considerable part, on how the benefit is administered by pharmacy benefit management firms (PBMs). In the short run, the availability of additional insured individuals should lead to an increase in the overall demand for prescription drugs, but also increased price discounting on prescriptions to elderly beneficiaries. On balance, the gains or losses to pharmaceutical firms in the short run should be modest in nature.^[18] It is the long-run consequences of the program that are subject to great uncertainty.

Pharmaceutical R&D is a lengthy, risky process and is based on the expectations that future market environments will reward successful drug innovation with premium returns. The Medicare drug benefit will have an important effect on these future markets. Moreover, legislators will likely confront strong pressures to expand the program's coverage and deal with strong budgetary pressures. This is precisely the situation affecting most of the state Medicaid programs. It is instructive to examine how they have been responding to these budgetary pressures.

Many states are currently facing their biggest budget deficits in decades. Medicaid, which is a joint federal-state financed program, is the second largest item in most states' budget after education, accounting for about 15% of state general fund spending. Within the Medicaid budget, prescription drug expenditures are small, but have been growing rapidly. The Center for Medicare and Medicaid Services (CMS) projected prescription drug costs for Medicaid programmes will grow by approximately 24% in 2003 to \$US32.5 billion.^[19] Many states have targeted prescription drugs for new cost-containment measures. In this regard, 45 states reportedly plan to implement new controls on prescription drug spending this year. Some of these cost-containment techniques include quantity limits, preferred drug lists and expansion of prior authorisation requirements.^[20]

One of Medicaid key cost-containment tools is preferred drug lists (PDLs). Drugs on the PDL can be dispensed without condition when prescribed. Drugs not on the PDL usually require prior authori-

zation, a process by which prescribing physicians must obtain permission from the Medicaid pharmacy bureaucracy to prescribe a non-preferred drug. Medicaid PDLs utilise prior authorisation to insure adherence, in contrast to the three-tiered formularies used by most health maintenance organisations (HMOs) and preferred provider organisations (PPOs). The latter rely primarily on differential co-pays to influence product selection. For Medicaid, co-payments are nominal, if they exist at all, so this is not a feasible strategy to employ in these programmes.

PDLs tied to prior authorisations can be a much more powerful approach for changing product selection than three-tiered formularies. In a recent analysis Wang et al., examined the introduction of a preferred drug programme in Maine in January 2001.^[21] They focus on the proton pump inhibitors for gastro-oesophageal patients. There was only one preferred drug on the Maine formulary – pantoprazole. The institution of the PDL resulted in a dramatic change in the preferred drug's market share. In Maine there was a 79% increase ex-post compared to 1% to 2% in New Hampshire and Vermont. These latter two control states didn't have a comparable Medicaid restrictive programme for this product class over the time period studied.

Wang et al also found substantial spillovers in the non-Medicaid market. For example, the market share of pantoprazole increased 10% in Maine, among cash prescriptions (vs 3% in the control states) in the period after the Medicaid formulary was implemented. Similarly, it increased 7% in Maine among other third-party prescriptions (vs 1% among the control states).^[21]

Maine is representative of what is happening in many other states in terms of movement to restrictive formularies with prior authorization. Florida and many other states have structured their PDL with a benefit design that requires supplementary rebates in order to be listed on the formulary.^[22] Some states have initiated preferred drug programs that focus on a few leading therapeutic classes (e.g. Minnesota and Oklahoma). Others have adopted comprehensive programmes span-

ning virtually all drugs except for a few exempt categories (e. g. California, Michigan, Florida and Illinois). Many states have such programmes pending with respect to their Medicaid prescription benefits (e.g. Connecticut, Ohio, North Carolina and South Carolina).^[23]

The PDL adopted by Michigan is particularly worth noting. It is based on a reference pricing approach. It is a variant on the approach utilised in several European countries such as Germany, Austria and Denmark.^[24] Under the Michigan Medicaid system, the Pharmacy and Therapeutics (P&T) committee selected at least two preferred drugs in 40 therapeutic categories as 'best in class'. Other therapeutics must match the prices of these chosen therapies to be considered 'preferred', otherwise, prior authorization is necessary. (In Europe, the patient must pay the difference if price is not matched.) Some drug categories such as HIV/AIDS and some mental health drugs are exempt from Michigan's PDL.

A case study analysis of the Michigan Prescription Drug Benefit was undertaken recently by the Kaiser Commission on Medicaid and the Uninsured.^[25] One of the findings was that the preferred drug least appears to be particularly restrictive in some major therapeutic classes such as depression, cardiovascular and diabetes treatments. In the case of the cardiovascular treatments, two popular angiotension receptor antagonists (ARBs) were excluded – valsartan and irbesartan. The ARBs have a better side effect profile than the older ACE inhibitors for which they are substitute therapies, as well as performance benefits and broader therapeutic actions according to recent studies.^[25] In addition, the Kaiser Commission found five of seven leading antidepressant drugs and four of nine leading diabetes drugs were only available through prior authorisation. This is a much more restrictive formulary than the private sector plans operating in Michigan.

While several states including Michigan have claimed significant cost savings from their PDLs, initial evaluations have not examined patient outcomes, spillover costs to other medical services or long-run effects on innovation incentives. One obvious concern is that such restrictive formularies can

produce adverse consequences that offset any immediate cost savings in the prescription drug budgets. Reference pricing schemes in particular can have significant adverse effects on the incentives for R&D drug innovation. The choice of drug clusters or therapeutic categories is critical. If the clusters are chosen very broadly, then a new drug with significant therapeutic advantages may be clustered together with older drugs available at generic prices. When this occurs, it produces especially adverse consequences for future innovation incentives.^[24]

State Medicaid programmes can be viewed as a laboratory that will be closely watched by federal policy-makers. Initially, Congress will rely on PBMs to administer the Medicare prescription drug benefit and the plans will probably resemble other PPO and HMO formularies. The act currently prohibits the Center for Medicare and Medicaid Services from directly negotiating drug prices, but there are currently legislative proposals by Senator Kennedy and others to alter this provision. Over time, Medicare will likely confront similar budgetary shortfalls and pressures to expand the program that the states are now confronting with Medicaid. This could produce a political dynamic toward more stringent measures involving restrictive or closed formularies with prior authorization necessary to obtain non-formulary products. This would also raise the specter of spillover to the managed care market as observed in the Wang et al. study.^[21] A long-term dynamic of this kind would have particularly adverse implications for the economics of pharmaceutical research and development.

4. Summary and Conclusions

The economics of pharmaceutical R&D is subject to many uncertainties as a result of recent industry developments. These uncertainties include lagging R&D productivity, increasing patent challenges by generic firms and growing political pressures to contain pharmaceutical prices and expenditures.

In the case of R&D productivity, the industry has been characterised by waves of innovation followed by periods of adjustment and transition since it emerged as a research-intensive industry in

the middle part of the 20th century. The current period may well represent a transition period, increased investments in new R&D discovery and development paradigms that could eventually produce an upward productivity trend with many significant therapeutic advances. At the same time, some observers expect that the R&D productivity problem will become worse in the short run as the industry transitions into this new era.

Another important concern affecting the economics of the industry is the fact that many leading drugs under patent are being challenged by generic firms early in their market life. Under the 1984 Hatch-Waxman Act, generic firms have strong incentives to be the first to challenge a patent given the 180-day exclusivity provision. Many generic firms have developed a business model that involves prospecting in patent suit challenges, and there is a race by generic firms to be first to file. Congress has recently made some amendments to the 1984 act, but is not addressing this important issue.

Looking forward, a key issue will be how the Medicare Rx drug benefit is implemented. Initially, Congress has structured the Medicare benefit using traditional PBMs and managed care competition to keep costs in check. This is likely to involve three-tiered formularies and other related incentive mechanisms. However, Medicaid programmes recently have become more aggressive in their cost-containment programmes. Many states have adopted preferred drug lists with prior authorisation. Over time, Medicare will likely confront similar budgetary problems to the states' and experience pressures to expand the scope of the programme. A long-term dynamic toward more aggressive cost containment would have particularly adverse consequences for innovation.

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