COMPETITION THROUGH INNOVATION, INNOVATION THROUGH COMPETITION

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CONTENTS

1 EXECUTIVE SUMMARY

Competitive success in the pharmaceutical industry depends on companies bringing new, innovative products to the market. Policy makers face the seemingly conflicting tasks of keeping drug budgets under control, most commonly through price regulation, and maintaining an environment which supports and encourages investments in innovative research and development (R&D).

Assessments of pharmaceutical output reveal that many of the new products approved for sale in the EU resemble ones already on the market. Rather than offer breakthrough innovations, these products, commonly referred to as 'me-toos', offer incremental improvements on existing drugs. Some policy makers and academics propose a formal policy to discourage the development of 'me-toos' with the aim to both cut spending on reimbursing duplicate products and to promote the long term competitiveness of the EU pharmaceutical industry by forcing companies to seek breakthrough innovation. Such a policy might involve setting limits on the number of products approved in any one class or setting a ceiling on the reimbursement prices follower products (i.e., not the first on the market in any one therapeutic category) could earn.

This paper raises questions about the effectiveness of such policies to motivate more innovative research and about the impact on therapeutic advancements of discouraging incremental innovations. Not only is it difficult to define and identify 'true innovation' before products are marketed, 'me-toos' – often more appropriately termed incremental innovations – provide therapeutic and economic value to customers.

The paper is organized into four sections. The first section, drawing on existing literatures on the economics of innovation and innovation in the pharmaceutical industry in particular, examines the difficulties involved in defining and measuring of innovation.

The second section describes the research and innovation processes in the pharmaceutical industry, identifying the factors which influence companies' strategic decisions and the impact that the proposed 'anti-me-too' regulations might have on companies' incentives to innovate. Detailed interviews with managers from the research, portfolio and strategic management, and development departments of major pharmaceutical companies reinforce published work.

The third section demonstrates the innovative continuum in the pharmaceutical industry where new indications and uses may be revealed after marketing. Data from three therapeutic classes are used to substantiate this argument.

Finally the fourth section considers the economic and therapeutic benefits which must be set against the costs of having multiple products in any one therapeutic class.

The material in this report draws attention to three key features of the pharmaceutical industry's innovatory process.

First, companies compete through innovation. Pricing pressures and competition from both patented and generic drugs on the demand side and from scientific discoveries, technological change, and strict regulatory requirements on the supply-side, motivate companies to invest in the R&D of innovative products.

Second, the outcome of this R&D process is highly uncertain. This means that a company does not know whether it will be first on the market when it embarks on a project in a specific therapeutic class. Costs are high in part because of the time it takes to develop a potential idea into a marketable product that meets safety, efficacy and quality requirements, and in part because the probability of failure is high.

In order to offset some of the risks involved in innovative research – research which is intended to produce breakthrough innovations but often results in incremental innovations – companies try to construct balanced portfolios that include some lower cost projects where the probability of success is higher though the expected therapeutic contribution may be lower. The incremental innovations from these projects are what are generally referred to as 'me-toos'.

Third, these incremental innovations should not be written off as wasteful endeavours. They may provide significant incremental improvements over products already on the market. They may also help control drug prices by introducing some price competitive pressures into therapeutic areas. Finally, sales of these drugs may help companies to finance their research programmes.

2 INTRODUCTION

Pharmaceutical companies report that in their dynamic, research and technology intensive industry, competitiveness is synonymous with innovativeness. That is, companies must invest in product research and development (R&D) to stay ahead. To afford this type of strategy, companies seek adequate reimbursement for their time, risk, and investments.

Purchasers (governments, sickness funds, managed care organizations, insurance companies, patients) are concerned about getting value for their money and governments have the additional concern that their own country's industries compete effectively. In contrast to the industry's claims, a fear is intermittently voiced in policy debates that companies, in their pursuit of profits, are not investing in truly innovative medicines (Wastila et. al, 1989; Benzi, 1996)[1]. These industry critics 'contend that profit incentives motivate the multinational pharmaceutical industry to spend too much time, effort and money on 'me-too' research, as well as on research for line extensions of already marketed drugs' (Wastila et al., 1989, 106). These authors define a 'me-too' drug as a substance in the same chemical class and used for the same therapeutic indication as the innovator drug (first in class). The objective of this paper is to analyze the inference of these critics that the incremental improvements of so called 'me-toos' do not add economic and therapeutic value. 'Me-toos' are henceforth referred to as 'incremental innovations' to distinguish them from 'breakthrough innovations'.

According to such criticisms, the prevalence of a 'me-too' R&D strategy would have three serious negative implications:

1. health care purchasers are paying for drugs adding little value; 'me-toos' are poor value for money;

2. companies are distracted from the real social task of serious innovation; a 'me-too' strategy will ultimately threaten these companies' long term competitiveness;

1 According to Wastila et al., (1989) the concern about the 'overabundance of duplicative, noncontributory drugs produced by pharmaceutical firms' published in a report on including prescription drugs in the Medicare program to the US Senate in 1967, popularized the term 'me-too'.

3. justly earned rents to the first entrant in a market are dissipated by the entry of many copies; excessive competition from 'me-toos' might discourage desirable investment in breakthrough innovation.

To motivate companies to invest in higher quality R&D to produce innovative output, some European Parliament members have discussed the possibility of requiring products to meet an innovativeness standard[2]. Repercussions for products failing to meet the standard might be, in the most extreme cases, the refusal of licensing approval by the European Medicines Evaluation Agency (EMEA), or the refusal of reimbursement or, more likely, a reimbursement only at a discount to the leading products in the class within the European Union (EU)[3] (Benzi, 1996; Scientific and Technological Options Assessment for the European Parliament (STOA), 1993). It is hoped that such policies would discourage 'me-too' innovation, while encouraging breakthrough innovation.

Such policies might, however, fail to achieve the intended end, and reduce the level of breakthrough innovation achieved by the pharmaceutical industry, as well as hitting socially useful incremental innovation – what Wells (1988)

2 The original discussion about introducing an innovative standard for products corresponded with the setting up of the EMEA in 1992-93. There was concern that there was insufficient regulation to ensure that companies seeking to exercise an option to use the centralised procedure for gaining approval for their products met minimum innovative standards (Benzi, 1996).

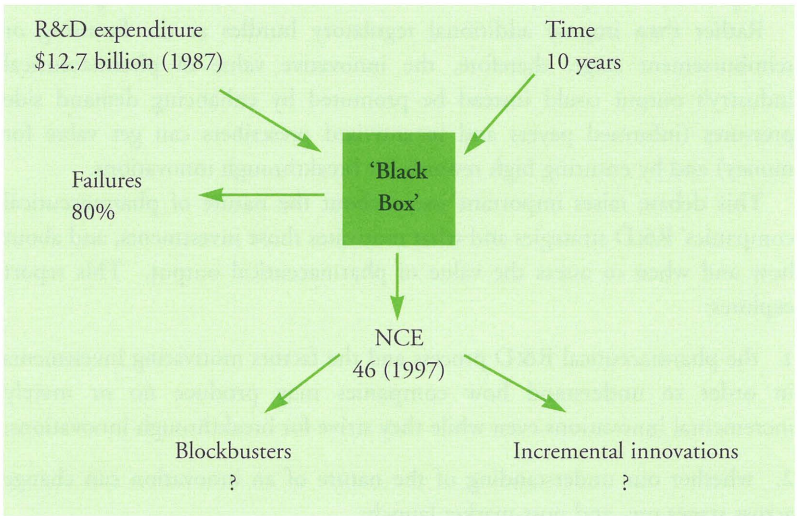
3 Countries such as Canada, Japan, and France use (or are considering using in the French case) innovativeness criteria to determine reimbursement levels. In Canada, for example, there are two pricing categories for new drugs: i. drugs that offer only moderate or no improvement over existing drugs can be priced no higher than those drugs currently on the market; ii. substantial improvement or breakthrough drugs can be priced higher provided they do not exceed the median of the prices of the same drug in the other countries listed in the Patented Medicines Regulations (France, Germany, Italy, Sweden, Switzerland, UK, and US). Once benchmark prices have been established, these drugs are also limited to annual increases in the Consumer Price Index (PMPRB, 1997). A decree for revising the pricing system in France, currently under review, will aim 'to have better prices for innovative products and lower prices for others... Where companies claim higher prices for 'innovative' products, the pricing committee will be looking for evidence that this translates into clear clinical improvements over existing products judged to be similar' (Scrip, 1.7.98, 2). In 1992, in Japan, a new set of product categories and corresponding price premiums were established. Innovative drugs – 'product based on an entirely new concept, judged to offer marked improvements or advancements in pharmaceutical therapeutic health care delivery, and proven to be safe and efficacious' – receive a 20-60% premium. The rest are grouped according to their degree of 'usefulness' with progressively smaller premiums (Ikeda et al., 1996, 547). In practice, the criteria the Japanese government uses to categorize the products are vaguely defined though efforts are being made to make this system more transparent.

referred to as 'innovative chemical extensions'. Pharmaceutical companies argue that the process by which they develop breakthroughs and incremental innovations is one and the same; you cannot tell with any certainty when you are developing a product who will be first to market or who will produce the best product. The discovery and development processes are long and plagued with uncertainties. As a crude illustration of this, assuming the global industry average development time profile of 10-12 years, Diagram 2.1 shows that R&D investments of $12.7 billion worldwide in 1987 corresponded to 46 products obtaining market approval in 1997 (source: CMR International). Given an average failure rate of 80%, this suggests that almost 200 compounds failed to make it through the clinical trial process.

Companies who produce follower products do not necessarily start with a 'non-innovative' strategy. A threat of low reimbursements at the end of the process might therefore discourage, rather than encourage, investment which would have produced fundamental innovations.

There are political and economic arguments against limiting the number of products approved in any one class. From a national competitiveness standpoint, European governments would not want to prevent their own

Diagram 2.1 **The R&D process**



companies from entering a market where the class leader is from outside the EU.

There is also a strong case for incremental innovation. The full therapeutic value of a product is often not known until after it has been marketed to a large patient sample. The first product to market does not always turn out to be the best. Unexpected treatment or disease prevention benefits may emerge when use becomes widespread. This raises questions about the effectiveness of any external 'pre-market' evaluation of innovativeness to weed out 'useless' or 'low value' products.

Incremental innovations may be of considerable value to payers. Some chemically similar follower products may add extra attributes that advance existing therapies. That is, they are 'innovative chemical extensions'. Multiple products in a therapeutic class also promote price competition, potentially bringing down the cost of health care.

Policy makers might respond that in the case of imposing price discounts on follower drugs, they are simply formalizing pricing practices that frequently occur in the market anyway. There is evidence, discussed later in this paper, the producers of follower drugs do tend to introduce them at a price below the leading product. There is, however, a clear difference in the impact on incentives for companies, between a government ordained discount based on external assessments of product value and one that companies decided to offer in response to their perception of the market and the value of their product.

Rather than impose additional regulatory hurdles at the licensing or reimbursement stage, therefore, the innovative value of pharmaceutical industry's output could instead be promoted by enhancing demand side pressures (informed payers and incentivised prescribers can get value for money) and by ensuring high rewards for breakthrough innovations.

This debate raises important issues about the nature of pharmaceutical companies' R&D strategies and what motivates those investments, and about how and when to assess the value of pharmaceutical output. This report explores:

1. the pharmaceutical R&D process and the factors motivating investments in order to understand how companies may produce no or merely incremental innovations even while they strive for breakthrough innovations;

2. whether our understanding of the nature of an innovation can change across stages pre- and post-market launch;

3. the potential therapeutic and economic benefits which need to be set against the apparent redundancy of having multiple products in any one therapeutic class; and

4. whether ex-ante definitions of innovation can be made and are useful for public policy making.

Section 3 presents the range of different definitions and indicators used by various authors and agencies in their attempts to measure pharmaceutical innovation. It is evidently difficult to produce an objective measure. How innovation is defined and measured depends on what the analyst wants to show.

In Section 4 the pharmaceutical R&D process and the factors motivating investments in innovation are explored. Given the time and uncertainty involved in developing a new drug, successful innovation cannot be guaranteed but there are identifiable factors – some endogenous to firm strategy and some exogenous - that set the successful companies apart from the rest. Using information about the decision making process and the factors which encourage innovation, the possible impact of an 'innovation hurdle' on investment decisions is considered.

Sections 5 and 6 look at different aspects of pharmaceutical output. Section 5 presents examples from different therapeutic classes to illustrate the innovation continuum. Many new indications and uses for therapies are only revealed after marketing, as are the relative merits of drugs competing in the same therapeutic class. Evaluating drugs pre-market launch, would risk excluding potentially worthwhile innovations. In Section 6, economic and therapeutic benefits of having multiple products in any one therapeutic class are discussed and set against the possible disadvantages.

The conclusions drawn from this analysis are set out in Section 7.

3 DEFINING AND MEASURING INNOVATION

In this section, the ways that industry experts and academics have defined and measured innovation in the pharmaceutical industry and elsewhere are surveyed. This is done against the background of a renewed focus on competition through innovation amongst policy makers dealing with competitiveness. This represents a shift from the previous emphasis on productivity growth through cost cutting and quality improvements that dominated competitiveness strategies in the 1980s and early 1990s, an era of organizational restructuring captured by concepts such as 'just-in-time' production, 'total-quality-management', and 'team-work'.

For example, participants at the 1998 US Council of Competitiveness Summit – Competing through Innovation – agreed that the 'US economy hinges now more than ever on generating new ideas and translating them into products, processes, and services that command a premium in global markets and support high-wage jobs... Low cost innovation has become as much a part of the competitive picture as low-cost production' (Council on Competitiveness, 1998)[4]. The Department of Trade and Industry (DTI) in the UK as well as the Pharmaceutical Intergroup of the European Parliament have also promoted innovation as the key to competitive success in recent seminars[5] and publications (DTI, 1998).

The pharmaceutical industry is research intensive. It has developed historically through innovation and provides a valuable case study of the dynamics of innovation. Yet innovation is a complex process that is difficult

4 In the industrial organization literature, a lively debate over the importance of innovation and technological change for competitive success has been going on among economists, sociologists and historians for most of this century. Schumpeter is commonly credited as the founder of this literature with his work on innovation as propeller of economic growth. A discussion about what motivates innovation in the pharmaceutical industry is presented in Section 3 of this report. For thorough reviews of literature on innovation and technological change in general see the articles in Stoneman's *Handbook of Economics of Innovation and Technical Change* (1995) by such authors as Cohen, Griliches, and Patel and Pavitt.

5 On October 7, 1998, The European Parliament Pharmaceutical Intergroup hosted a seminar titled 'The Pharmaceutical Innovation: A Challenge for Europe'.

to capture in a narrow static definition or indicator. Views on how 'innovative' a product or process is depends on who the analyst is and their objectives. The best measures in the literature combine scientific and economic indicators; only some of which can be known before market launch.

The DTI defines innovation as 'the successful exploitation of new ideas (product innovation) and new ways of doing things (process innovation). It involves not just the exploitation of new technology, but changes in the whole range of business practices. It implies the willingness to look ahead and think about longer term opportunities and threats' (Treasury and DTI, 1998, 7). In a recent survey of innovation in all European Community industries, innovative products were defined as incrementally improved, radically changed or entirely new products (Kleinknecht, 1996, 3)[6].

Both these broad definitions would include both incremental and breakthrough innovations. Neither sets out to rank the importance of these innovations. The success of one of the DTI's 'new ideas', though not stated explicitly, is presumably determined by the market. An innovative firm is commercially successful and vice versa, in the DTI's view.

From the users' standpoint (be that the patient, the doctor, the hospital), it is not enough for pharmaceutical companies to discover new chemical structures or modify existing ones – difficult tasks in themselves. New pharmaceutical products must contribute to the goals of 'treating diseases that are not currently treatable or to treat these diseases in a more effective manner' (Levy, 1990, 3). Governments and other payers (sickness funds and managed care organizations, for example) under pressure to control costs will also examine whether products with new attributes are cost-effective. From the companies' stand point, new pharmaceutical products must not only contribute therapeutic value but also provide a return on investment.

At issue is how and by whom the therapeutic value or 'innovative' contribution of a new product should be defined and measured. It is difficult to classify varying degrees of innovation from incremental to significant (Patel and Pavitt, 1995). Benzi, a supporter of instituting a new 'innovation' hurdle

6 Studies of innovation in pharmaceuticals tend to focus on product innovations. It should be noted, however, that process innovation through new technologies such as high throughput screening and combinatorial chemistry impact on the way products are researched and developed (Hartwig, 1998, Gambardella, 1995). Research of the human genome is initially impacting on the process of drug discovery, but should ultimately lead to new products as well.

Table 3.1 **Indicators of innovation**

Indicator	*Study*	*Problem*
Patent	H&C, P&P	– different grades of importance, high attrition rates
R&D spend	C&M, S&P	– varying degrees of efficiency in use, high attrition rates
NCEs	C&M, S&P, P&W	– different grades of importance
Global marketing	T, R, B	– no direct correlation between innovation and market success
Number of top selling products	S&P	– no direct correlation between R&D expenditure and the number of top selling products a company achieves
Mix	D&M	– complete data set difficult to construct and maintain
Uniqueness	LB	– the absence of important competitors does not necessarily mean that the drug makes an important therapeutic contribution

Sources:
H&C – Cockburn and Henderson, 1995; Henderson and Cockburn, 1996a, 1996b.
P&P – Patel and Pavitt, 1995.
C&M – Casper and Matraves, 1997.
S&P – Sharp and Patel, 1996.
P&W – Prentis and Walker, 1991.
T – Thomas, 1994a.
R – Redwood, 1993.
B – Barral, 1994.
D&M – Dranove and Meltzer, 1994.
LB – Lehman Brothers, 1997.

to market approval, for example, presents five categories to classify the 'innovativeness' of new drugs.

1. Drugs which show therapeutic efficacy for a disease or a symptom for which there is no active drug available. Examples include HIV, cancer, Alzheimer's Disease.

2. Drugs which show therapeutic efficacy for a disease or a symptom for which an effective drug is already available but whose effect is necessary for a subset of the affected population. Examples include drugs active on patients'

resistance to the reference drug; drugs active with a different mechanism for patients insensitive to the reference drugs.

3. Drugs which are more effective and/or show less serious adverse effects than the reference drug of an equivalent therapeutic effect.

4. Drugs which may be given to special groups of patients with increased efficacy or reduced toxicity.

5. Drugs which are presented in a form which is more practical and/or convenient for the patient. (Benzi, 1996, Annex 1).

The criteria included on the list are similar to those considered by the US Food and Drug Administration (FDA) to prioritize drugs for approval. But in the US, they are not used to exclude drugs from the market. A major problem is that it is often difficult to know for sure if a new drug meets some of these criteria before it is marketed.

Despite the difficulties involved in defining what an innovation is, economists and others analyze innovative performance of nations and companies, using a variety of proxies. These proxies are summarized in Table 3.1. The strengths and weaknesses of these different indicators are discussed in the paragraphs which follow. The complexity of the concept 'innovation' is illustrated by the fact that few authors use the same proxy to measure it.

1. Patents or patents/per R&D spend. Though this type of data is relatively easy to obtain, there are a number of problems with using this as an indicator of final output innovativeness.

A general criticism is that many innovations are not covered by patents, leading innovations to be underestimated by this indicator (Kleinknecht, 1996, 1). This is not such an issue in pharmaceuticals as few companies would initiate clinical trials without first patenting their new idea.

A more serious problem is that, given the high attrition rate, many patents never translate into commercially viable products, so counting patents overestimates the number of products adding value to the market. There is also no guarantee that the winner of the patent race will be the first to launch into the market or even that they will ever turn their potential idea into a marketable product. So, while the owner of the first patent is clearly pursuing an 'innovative' strategy, it may or may not produce any marketable innovations.

Henderson and Cockburn's studies on productivity in pharmaceutical research use the number of patents as their measure for research output. To control for the fact that the significance of individual patents varies widely, they count only 'important patents' – i.e. patents granted in at least two of the three major markets: the United States, Japan, and the EU. As their focus is on the determinants of 'technical success, defined in terms of producing new potentially important compounds, rather than on the ultimate commercial success or failure of new drugs', patents may serve as an appropriate output measure in this case (Cockburn and Henderson, 1995, 512).

Other studies (Patel and Pavitt, 1995; Griliches, 1995) of the usefulness of patents to measure science and technology output find that the present values associated with different patents vary greatly, with the majority of patents having little or no real value, while a small fraction of patents generate really large economic returns. This makes it rather difficult to use patent counts as an index of output for R&D activity except perhaps at a very aggregated level.

2. R&D expenditure and R&D expenditure/sales. R&D expenditure is, at best, a measure of future innovativeness rather than current innovativeness, as there is a lengthy time gap between the investment into research and the production of a new drug (Sharp and Patel, 1996). More likely, it may simply be a measure of revenue allocation and tell little about the innovativeness of a company. Again, given the high attrition rates, there is no guarantee that R&D expenditure will produce marketable products. Some companies will use R&D funds more efficiently than others, so one cannot draw conclusions about whether this comes from strategy or performance using only information about the value of inputs (Kleinknecht, 1996, 2).

Sharp and Patel find a correlation between a company's R&D intensity (R&D/gross output) and the number of new drugs as a percentage of its sales, but not between R&D spend and the number of top selling products (Sharp and Patel, 1996). Thus, the more a company spends, the more products it will put on the market but this does not imply more success in terms of top selling products. This may mean that the incremental R&D spend is generating the sort of low-value innovation that Benzi would like to avoid.

3. Number of new chemical entities (NCEs) and NCEs per R&D spend. Prentis and Walker (1991), for example, define innovation as testing NCEs.

'The decision of a pharmaceutical company to evaluate an NCE in man for the first time represents a major commitment and is therefore used as the definition of innovation' (ibid.). The problem is that not all NCEs are of equal importance. Barral's (1996) analysis of Japanese output provides a good example of this problem. Japanese companies produced 31% of the 290 new molecular entities (NMEs)[7] launched worldwide between 1990 and 1994 (the same number as the US). However, only three of the 90 (3%), fit in the 'most innovative' category according to Barral's definition, i.e., products with a new chemical structure and adding extra therapeutic benefit. 63 of the Japanese products (70%) were considered 'me-toos' by his criteria (products with a known structure and no extra benefit) (Hale, 1996, 55). The point of varying quality between NMEs or NCEs is made by this example, though it should be considered a conservative assessment of Japan's innovativeness. Barral assesses therapeutic value before market launch, though the true value may sometimes not become clear until the drugs are marketed and used by a large sample of patients. This argument is substantiated with examples in Section 5 below.

In an effort to differentiate products according to therapeutic value, some economists have used indicators such as sales performance (an ex-post measure of importance), while others try to assess the scientific contribution of each product.

4. **Global marketing.** To measure a country's innovativeness, Thomas (1994), Redwood (1993), and Barral (1996) look at the per cent of products marketed in seven (Barral) and 12 (Thomas) major pharmaceutical markets. They hypothesize that only significant innovations will be marketed globally. Non-local governments would be less likely to approve incremental innovations, and knowing this, companies would be less likely to invest the money in seeking approval and mass marketing in additional markets.

7 Some authors refer to NCEs and some to NMEs. Exact definitions may vary but for the purposes of this current paper the terms may be treated as approximately equivalent. For example, the Centre for Medicines Research International defines NCEs to exclude biotechnology products and NMEs to include them. The numerical difference between the numbers of NMEs and NCEs by this definition may therefore grow in future if biotechnology products reach the market in greater numbers than hitherto, but the numerical difference in the past would have been relatively small.

Table 3.2 **Innovativeness of pharmaceutical output according to Barral**

1975-1994	*Total NCEs*	*Global*	*International*	*Local*
Percentage in category:*	(1061)	(152)	(273)	(636)
A	10	30	12	5
B	21	35	29	13
C	14	10	14	16
D	55	25	46	66
Percentage that is:	A (109)	B (219)	C (150)	D (583)
Global	42	25	9	6
International	29	36	24	21
Local	29	39	67	73

Barral identifies a correlation between innovativeness and market distribution. The most innovative (A+B) make up only 31% of all NCEs, but 65% of the globally marketed products. On the other hand, 73% of the least innovative products (D) are only marketed locally. Note that Barral considers only pre-market evidence to assess the innovativeness of the specified products.

*Categories are defined as:

A	– new structure, therapeutic benefit
B	– known structure, therapeutic benefit
C	– new structure, no therapeutic benefit
D	– known structure, no therapeutic benefit
Global	– launched in 7 largest pharmaceutical markets
International	– launched in 4-6 of 7 markets
Local	– launched in fewer than 4 of 7 markets
7 markets	– US, Japan, France, Germany, UK, Italy, Switzerland

Source: Barral, 1996.

Barral (1996) finds a correlation between 'innovative' and 'global' products. See Table 3.2. What he terms innovative drugs, categories A and B, make up only one third of all NCEs between 1975 and 1994 but nearly two thirds (65 per cent) of the globally marketed products for the same time period. When the marketing strategies of innovative drugs are considered, we find that 42% of those in category A are marketed globally and an additional 29% are marketed internationally (in four to six of the seven largest pharmaceutical markets). It is surprising that the other 29% are not.

At first sight, Barral's numbers also seem to confirm Benzi's and others'

fears about the quality of pharmaceutical products on the market. 55% of the products launched between 1975 and 1994 are labelled 'me-toos' according to his definition. One must also wonder if the products in category C should be considered innovations given that they apparently add no therapeutic value. Barral does not provide clear definitions for his term 'therapeutic value' and, as was mentioned above, his focus on pre-market attributes may exclude products whose worth is largely revealed post-launch. Furthermore, the advantages that may stem from competition in therapeutic categories such as incremental differences in therapeutic value and reductions in price need to be considered.

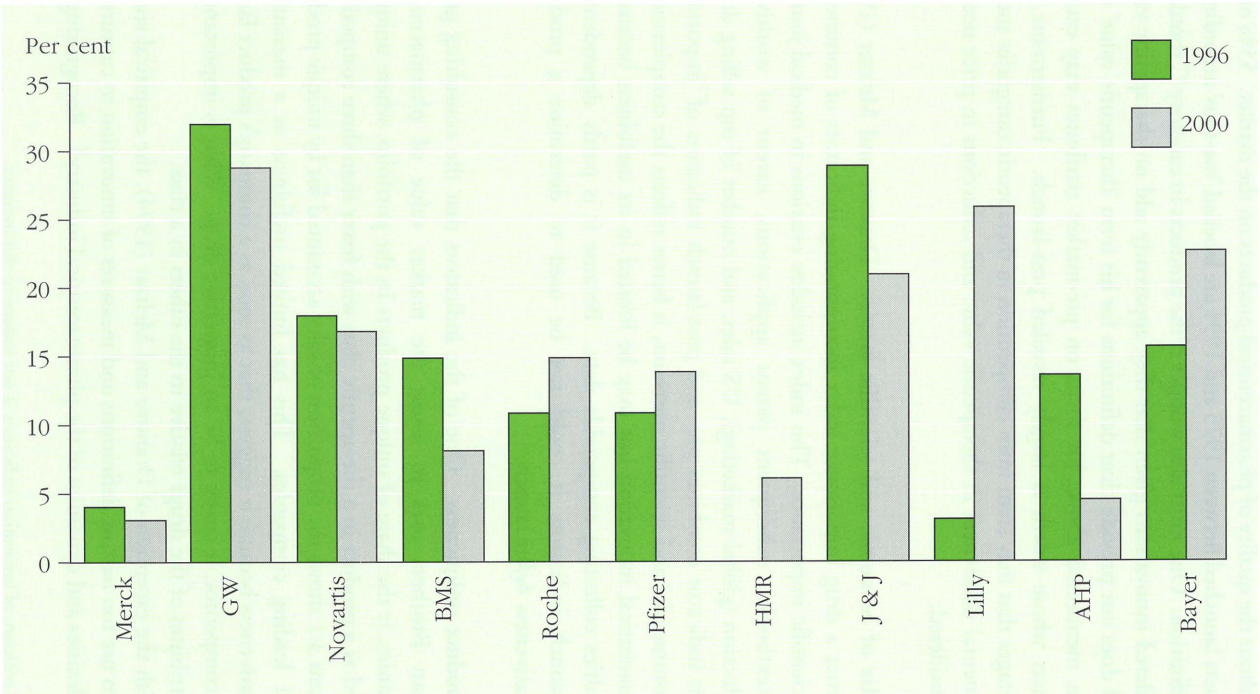
5. **Mix of economic and scientific factors.** Dranove and Meltzer (1994) construct a drug importance index incorporating indicators of commercial and scientific importance. This index includes: citations in medical journals and textbooks, subsequent patent applications, extent of worldwide introduction (global marketing), US sales, and number of top selling drugs. As this indicator combines pre- and post-launch indicators of 'importance' and commercial and scientific measures, it better reflects the complexities of pharmaceutical innovation but may be limited in its usefulness because of difficulties collecting comparable data. Because it is partly dependent on post-launch indicators it could not be used to determine a product's innovativeness *before* launch.

6. **Product uniqueness.** One of the indicators that the consulting group Lehman Brothers uses to assess the market value of pharmaceutical companies, is the share of unique products in the portfolio, where unique is defined as a product in a therapeutic class with fewer than three competitors. Diagram 3.1 shows the proportion of sales accounted for by unique products for 11 leading companies. This has limited usefulness as a measure of innovativeness because it suggests that as soon as a company's product faces a third competitor, it ceases to be an innovative drug. What is important are the attributes of the drugs relative to the others in a class.

With the exception of Dranove and Meltzer (1994), the empirical studies tend to use too narrow definitions and measures of innovation to capture the complexities and dynamics of the pharmaceutical industry[8]. Recognizing the

8 This criticism of innovation indicators is not unique to this industry.

Diagram 3.1 **Innovations – proportion of sales accounted for by unique products at leading companies**



Source: Lehman Brothers, as reproduced by Bayer AG at 'Pharma Research at Bayer' Press Conference, June 15, 1998.

practical barriers to constructing complete indicators, this criticism highlights the importance of including qualitative information that describes the important characteristics of the industry. If the goal of policy makers is to design policies to motivate socially useful innovation in the pharmaceutical industry, then the R&D process must be clearly understood along with the unique factors that affect research productivity, and the way that pharmaceutical companies compete before and after product launch. These issues are addressed in the next sections.

4 FACTORS DRIVING PHARMACEUTICAL INNOVATION

In the first part of this section, a 'typical' R&D process in the pharmaceutical industry is described, and the factors that managers consider in making investment decisions at different stages in the process are discussed. What is important to keep in mind is that many incremental innovations go through the a R&D process similar to products that end up as breakthroughs. In the second part, the factors that account for observed differences in innovative performance are investigated. Finally, in the third part, the impact of introducing a policy with ex-ante exclusion criteria on the decision making processes and on the factors motivating innovation, is considered.

A. Making investment decisions in the R&D process

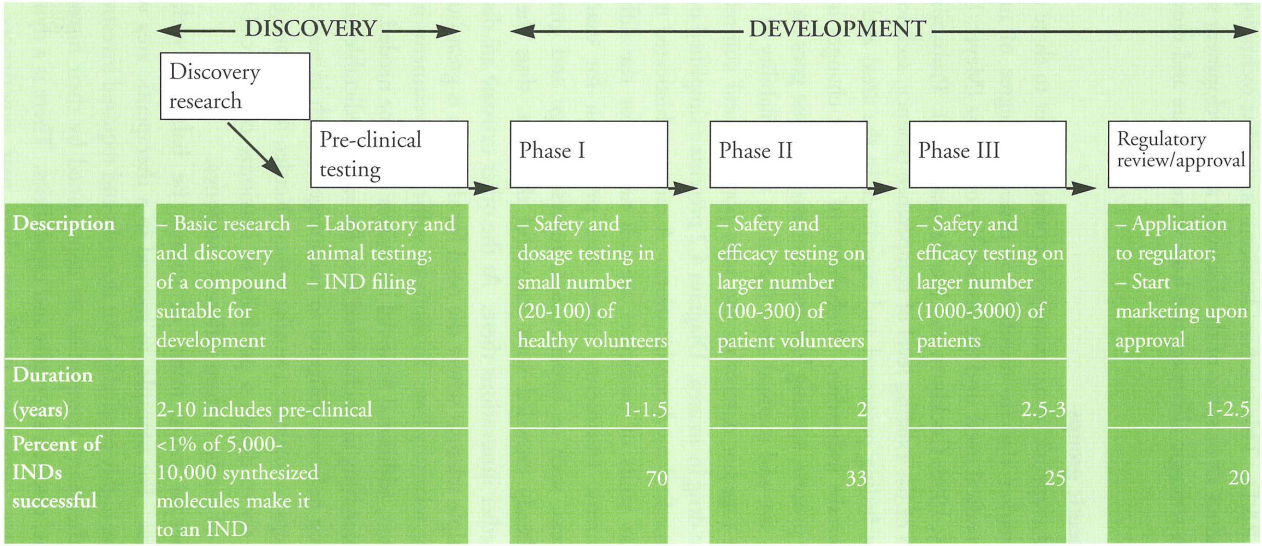
The R&D process in pharmaceuticals is lengthy, risky and expensive. It takes on average 10-12 years to bring a discovered product through pre-clinical and clinical trials to market launch and this process can cost up to $600 million per drug on average (Kettler, 1998). According to some estimates fewer than 1% of the 5,000-10,000 molecules synthesized in the discovery stage will reach the clinical trial stage. DiMasi et al. (1991) estimate that between 20-25% of products entering phase I clinical trials reach the approval stage. Diagram 4.1 shows the life cycle of a typical NCE.

The costly commitments in terms of time and money required to develop a drug mean that the investment decisions that companies make today lock them into development programmes over the medium to long term. The primary goal is to maximize profit over the long run. In designing the R&D strategy, three critical investment decisions have to be made:

- which therapeutic and scientific areas to research in and how much to spend in total and in each broad area of activity;

- which potential candidates to take to pre-clinical testing, exploratory development (Phases I and II of clinical trials) and then large scale clinical trials (Phase III) (where decisions are re-evaluated along the way);

Diagram 4.1 **Life cycle of a NCE from synthesis to market**



Sources: Row 1 – Myers and Howe, 1997, Figure 2; Row 2 – DiMasi et al., 1991; Lehman Brothers, 1997b; PhRMA, 1997; Row 3 – Lehman Brothers, 1997b, 4.
Notes: IND= Investigational new drug. In the UK companies must fill out a Clinical Exemption Certificate (CTX), but there are currently fewer hurdles to initiating clinical trials in the UK than in the US (CMR International).
NDA=New Drug Application – the UK equivalent is the Marketing Authorization Application.
The duration and success rate figures represent typical performance in US companies rather than averages of a specific sample of NCEs.
The diagram uses US data. Because companies in the US face the additional hurdle of filing an IND before they can start clinical trials, the total development time in the US may be longer than in other major markets. According to the Centre for Medicines Research International, the mean development time for a product to reach any global market was 10 years in 1996.

- how to organize R&D. This involves decisions as to what technology to use, whether to conduct all or some of the discovery and development stages in house or through strategic alliances, and how to coordinate and motivate R&D effort.

1. Selecting therapeutic groups

In the selection of therapeutic areas, managers repeatedly refer to three main criteria: expected market size (ie numbers of patients); degree of unmet current and future medical need; and the probability of success (Meyer, 1998; Samuels, 1998; Sully, 1998; Cockburn and Henderson, 1995). Probability of success is a function of the existing level of competence (science, technology, and research base including personnel and experience in the area) and risks associated with a certain indication. Probability of success changes in the course of the R&D process, starting low and increasing as time goes on.

Expected market size and medical need (based on the availability of other existing treatments) together determine the sales potential and commercial value of developing a drug in an area. Diagram 4.2 presents a simplified matrix of market size and medical need combinations. A more sophisticated model would indicate what kinds of medicines are still needed for the different conditions; symptomatic treatments, cures, and prevention for example. Certain research areas, such as hypertension, represent large and growing markets but are already crowded with successful therapies, thus the low medical need for further innovations there. At the other extreme are diseases like AIDS and multiple sclerosis where the need for therapies is great but the number of patients is relatively low. To motivate sufficient investments in this bottom right quadrant, additional financial incentives might be needed, given the added risk of researching in unchartered areas for an unpredictable market. The US' orphan drug policy is designed to encourage research in such areas. The EU is taking steps to institute a similar policy (Kettler, forthcoming). In general, companies try to design a portfolio to maximize commercial value with a combination of products from different categories.

Potential commercial value must, of course, be balanced with the probability of success. For example, to succeed in a therapeutic area where need is great could be highly profitable, but the risks and required investments are also high. Furthermore, companies are constrained by their history of investment decisions, research strengths and capabilities. There is a dynamic learning curve where companies build on their past experiences in a

Diagram 4.2 **Balancing market size and medical need**

Potential patient population	Need for drugs: Low	Need for drugs: Medium	Need for drugs: High
High	*hypertension, NSAID, ulcers,* angina, *common cold*	asthma, bacterial infection, lipid lowering, *MED,* type 2 diabetes	obesity, cancer, osteoporosis, atherosclerosis, *rheumatoid arthritis*
Medium	*contraception*	irritable bowel syndrome, incontinence, epilepsy, migraine	heart failure, chronic bronchitis, stroke, *schizophrenia, Parkinson's,* dementia
Low	emesis	*arrhythmias, diabetes type 1, fungal infection,* herpes	*AIDS, multiple sclerosis,* emphysema, hepatitis

Lehman Brothers assessed medical need for drugs according to the availability of treatments. For example, many people need common cold medications (high potential patient population) but this market is already crowded with drugs (low need for new drugs).
Bayer's research portfolio is highlighted in italics, illustrating this company's attempt to balance market size and medical need in their choice of research areas.

Source: Lehman Brothers, 1997, 14, Meyer, 1998, Figure 2.9E.

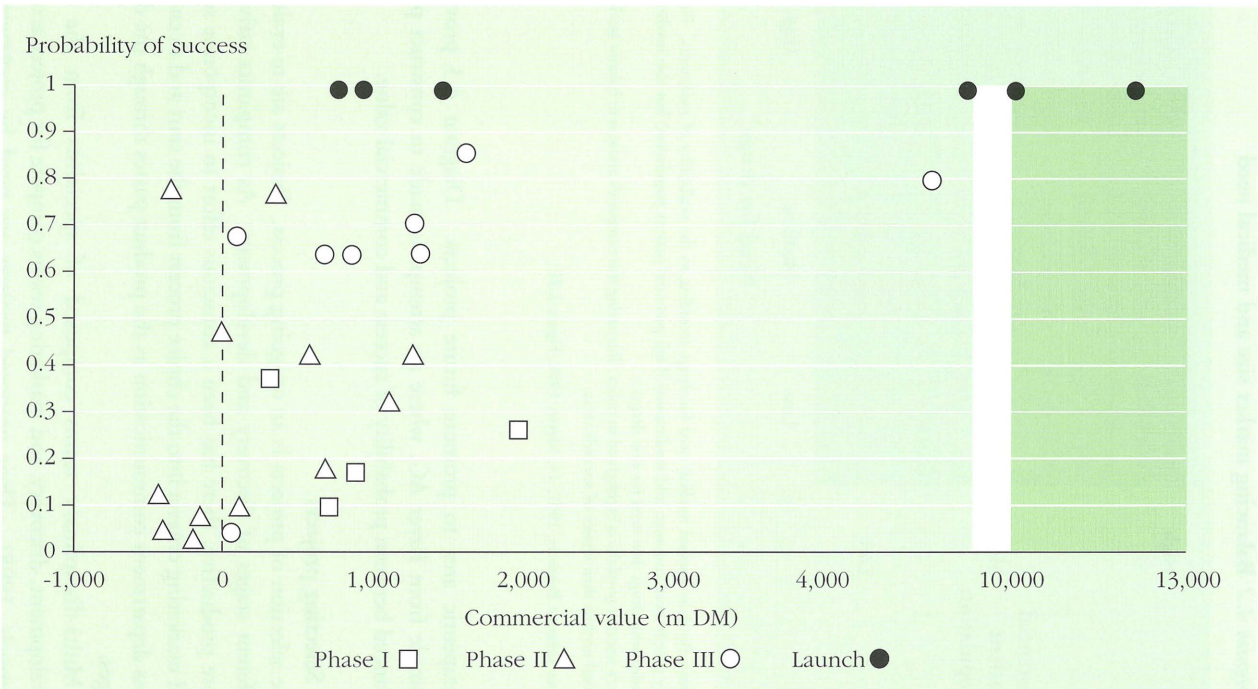
therapeutic area to promote future projects. Diagram 4.3 provides an example from Bayer AG, where an attempt is made to construct portfolio balanced between probability of success and commercial value.

2. Selecting projects

The selection of projects is an on-going process. Projects are re-evaluated at different stages of discovery and development. As companies strive to be more productive, there has been a conscious effort to incorporate scientific and marketing criteria into the choice process from the start and to encourage cross department communication as the product passes through the different stages.

Multi-disciplinary teams composed of specialists from the clinical development, discovery, and marketing teams compete for project acceptance (Samuels, 1998). Their proposed projects are rated by commercial and

Diagram 4.3 **Concentration of attractive segments**
The balance between the probability of success and commercial value is decisive



Source: Bayer AG 'Pharma Research at Bayer' Press Conference, June 15, 1998.

scientific criteria and by the extent to which their product fits within the company's strategic direction. When considering the expected profits of a project just beginning pre-clinical testing, the way the market will look in 10-12 years is what is important. That will be affected by what products are expected to come onto the market before then, how many competitors are already researching in the area, and expectations about potential scientific developments in therapy.

The balance of importance placed on the scientific and commercial criteria changes during the process. 'Early stage projects are driven most heavily by scientific rationale. This remains the case until proof of concept and proof in clinical trials are obtained. Net present value (estimate of future cash flows net of all costs covering the life cycle of the project) becomes increasingly important at the later stages of development. This is the key driver by the time phase III is reached, where the largest costs are incurred' (Sully, 1998, 36). The attention given to outcomes research models and the size of the expected market in the later stages of development represent a change in portfolio strategy. Companies now give more attention to market criteria than in the past when to focus was efficacy and quality requirements.

The balance between the concerns of the marketing and scientific representatives is fragile. In the view of scientists, too much weight given to expected returns too early will result in companies dropping out of projects with good potential to add therapeutic value. Often, the full safety and therapeutic profile will not be known until late in the clinical trial process.

3. Selection of R&D method

Companies must decide whether they will invest in doing the discovery and development stages in house or collaborate with other organisations. Referring back to the balance between the probability of success and potential commercial value, companies may decide that a certain therapeutic area is too important to stay out of but, lacking the required competencies in house and unsure about the long term future of the area, decide to license in a product from somewhere else rather than invest in building up their own discovery and development capabilities. Looked at a different way, collaborative alliances serve as a way for companies to expand their scientific competencies. While they reduce the risk, these alliances also involve sharing the profits, a factor that will be weighed in any company's decision to collaborate.

Companies must also make decisions about investing in new technologies

such as genomics, high throughput screening, and combinatorial chemistry. These involve high fixed costs but have the potential to revolutionize the discovery and targeting process (Morgan Stanley, 1998). Quicker, more accurate screening, for example, has the potential to reduce total discovery costs (Kettler, 1998). These potential cost savings must be balanced against the known initial capital costs. Experience of and access to these technologies will impact on decisions about whether to conduct basic research in-house or license in, or whether to invest in a particular therapeutic area at all. Innovative methods of production will affect companies' abilities to generate innovative products and bring them to market (Henderson, 1994; Hartwig, 1998; Gambardella, 1995).

Some economists have modelled the pharmaceutical R&D process as a race where companies jump at what looks like a profitable opportunity, following a significant new scientific finding, and compete with others (in terms of money invested) to get the first product to market. These race models assume 'winner take all situations' where competition in R&D leads to overinvestment in research. Cockburn and Henderson (1994) have investigated the appropriateness of this model to describe the discovery process.

Their qualitative and quantitative analyses suggest that companies' decisions to invest in a therapeutic area are a function of their own historical investments and competencies. Furthermore, the correlation between different firms' levels of investment within therapeutic areas is weak, i.e., there appear to be no bandwagon effects, once common responses to exogenous shocks (new opportunities arising) are accounted for.

The managers' decision criteria do incorporate the strategic decisions of other companies. Competitor's investment plans affect expected returns and the expected size of the market. But the significance of a company's scientific finding in terms of therapeutic value also weighs into the calculation.

Differences between companies' innovation performance have been observed. Theories to explain these differences suggests that for explicit reasons certain companies can make better decisions and carry them through more productively than others (at certain points in time) and/or that companies produce under conditions more conducive to innovation. In the next section, factors falling into these two categories of innovation 'facilitators' are reviewed.

Continued in Competition through Innovation Kettler Part 2

B. Factors affecting innovation

An extensive literature exists on what factors affect innovative performance. Cohen (1995) raises the question of the degree to which firms' innovative activities and performance are a function of capabilities and the product environment exogenous to the firm and to what degree they are due to differences in the incentives and strategies that comparably capable firms design. For the case of pharmaceuticals, superior performance seems to be linked to both types of influences: conditions that enhance opportunities for innovation, but are outside the firms' direct influence; and firm-specific characteristics that allow for better use of these opportunities. Diagram 4.4 lists the important factors and how some are interlinked[9]. Explanations follow below.

The first set of factors affect the environment in which companies produce. As the characteristics of the market, infrastructure and, to a lesser extent, science and technology, tend to be country specific, they affect companies' decisions about how and where to innovate.

1. Infrastructure

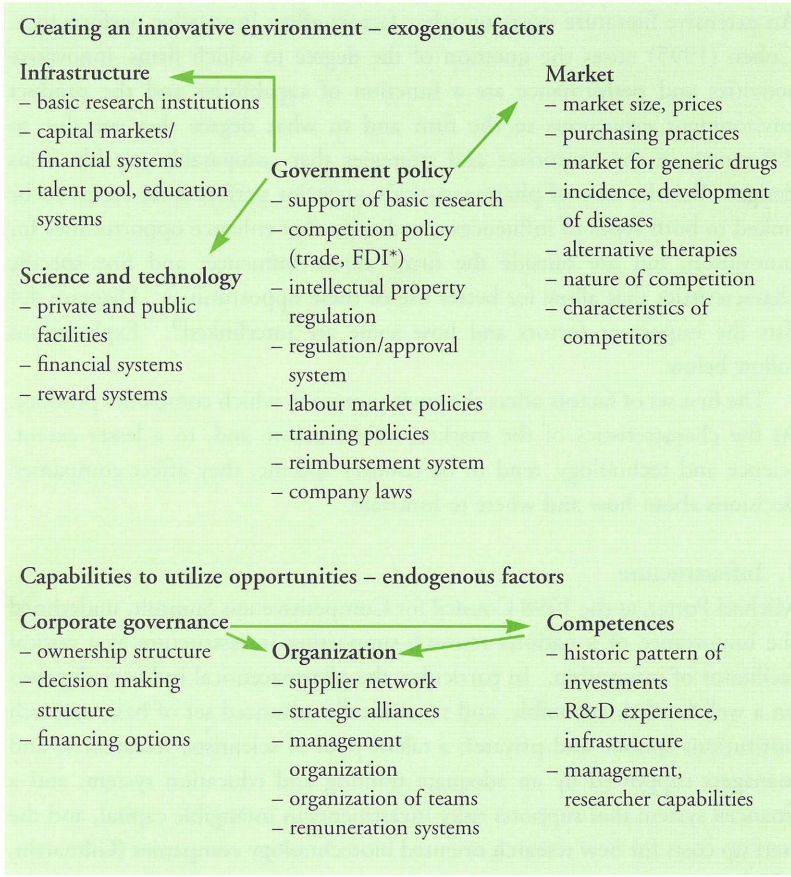
Michael Porter, at the 1998 Council for Competitiveness Summit, underlined the importance of a nation's research-supporting infrastructure as a critical facilitator of innovation. In particular, the pharmaceutical industry depends on a well funded, accessible, and scientifically advanced set of basic research institutions (public and private); a talent pool of scientists, researchers, and managers supported by an adequate training and education system; and a financial system that supports risky investments in intangible capital, and the start up costs for new research oriented biotechnology companies (Gilmartin, 1998).

2. Science and technology

Economists such as Gambardello (1995), Henderson and Cockburn (1996a) have referred to science and technology as a critical driving force of innovative

9 The system of interlinking factors has been simplified to illustrate what motivates innovation and what consequences new government policies might have for that innovation process. In reality, the interactions are more complicated than the diagram suggests. For example, the companies' corporate governance structures are shaped by government shaped by government policies. Company strategy can affect the market. How scientific and technological discoveries affect actual innovations depends on company organization and competences.

Diagram 4.4 **Exogenous and endogenous factors driving innovation**



*FDI – foreign direct investment

opportunities – both products and processes. Recent developments in genomics, for example, create a whole new way to think about developing and targeting treatments. High throughput screening and combinatorial chemistry allow companies to target with greater speed and precision, thousands of new potential targets and molecules. Biotech companies are playing an increasingly important role in furthering technological development in the pharmaceutical industry. As is discussed below, financial

systems must be designed to support small, high risk companies where intangible assets dominate their capital stock.

Afuah (1993) raises the question of whether publicly funded basic research disproportionately benefits local firms. 'It may be the case, for example, that as the scientific community becomes increasingly 'global', publicly funded basic research will benefit all the major pharmaceutical firms. In such a case, the benefits a firm derives from publicly funded basic research may be more a function of its own R&D spending than of its geographic location' (ibid., 12-13).

3. The market

Innovation is demand as well as supply driven (Lazonick, 1991; Kleinknecht, 1996). To motivate companies to develop a new idea into a product, they must expect returns to cover their investments. Expected returns are correlated directly with the size of the market and the users' and payers' ability and willingness to pay higher prices for innovative products. These are, in turn, a function of the nature of the purchasing system and who the primary purchasers are (managed care organizations, insurance companies, governments). Demand for drugs also depends on the existence of alternative therapies. To some extent, companies can also influence demand through marketing.

4. Government policy

Public support of basic research and technology development, education systems, retraining systems can advance infrastructure and the state of science and technology. Government can also set up policies to finance start-up companies. On the demand side, governments are directly involved as purchasers and as regulators of markets. By 'blacklisting' certain therapeutic areas from reimbursement, some governments directly impact companies' investment choices[10]. As controllers of the approval process, governments further influence innovation. How fast or slow and how difficult or easy the process is factors into companies' calculations of expected return from investments in innovation.

10 The NHS in the UK, for example, selects certain products in some therapeutic areas that it will not reimburse. This discourages companies from investing in new innovations in these areas.

A number of studies have investigated the impact of different policies on pharmaceutical innovation. Thomas (1994), for example, directly attributes the UK's superior innovative performance relative to France to the UK's policies. First, in the UK, strict safety and approval regulations are imposed but the price system allows for higher prices, and therefore financial rewards, for innovative products. Second, though the UK government invests relatively less than France in basic medical research, the links between the medical profession and the industry by way of the National Health Service and the profession's focus on science and research created a strong base of research talent and facilities to support the private companies. Finally, British companies have been forced to compete internationally because of the UK's open foreign direct investment (FDI) policy.

Afuah (1993) reviews nine studies of the effects of national public policy on innovation in the pharmaceutical industry. His major findings are a positive impact on innovation from increased local funding for basic research, tight patent protection, strict safety and efficacy laws, and incentives for investment in R&D, and a negative impact on innovation from price controls.

Price regulation is one of the main policy impacting the demand for pharmaceutical products. According to Afuah, Thomas (1993) and Redwood (1993) both attribute an important part of the US's and the UK's innovative and global sales success to their companies' relative freedom to set prices. 'Pricing freedom acts as an incentive for innovation in therapeutic areas where the risk of pioneering failure are at their highest. Pricing regulation also stifles pricing competition' (Afuah, 1993, 9).

The factors considered so far, provide companies with support and opportunities to invest in innovation. Companies' abilities to develop successful strategies are also dependent on their investment and organization decision making and research skills, access to resources, ability to find markets and so on.

5. Corporate governance

Casper and Matraves (1997) investigate how differences in corporate governance systems, specifically ownership structures, the structure of decision making across management, and the relationship between managers and employees affect the development of pharmaceutical innovation in the UK and Germany. They find in their study of biotechnology companies that

the UK firms outperformed their German competitors in terms of developing new competencies in research, marketing and distribution. UK governance and innovation systems were better set up to provide the necessary finance for high risk projects and manager incentives, through remuneration packages, to motivate more rapid response to changing market structures.

6. Organization

How companies organize their production facilities, management, and employees affects the companies' ability to innovate effectively. Henderson (1994a, 1994b) and Henderson and Cockburn (1994) have looked at manager organization and competencies as explanations for R&D productivity, as these things impact on the companies' abilities to respond to changes in technology and the marketing environment. 'The longevity of pharmaceutical companies attests to a unique managerial competency: the ability to foster a high level of specialized knowledge within an organization while preventing that information from becoming embedded in such a way that it permanently fixes the organization in the past, unable to respond to an ever-changing competitive environment' (Henderson, 1994a). According to their work, the best pharmaceutical companies have managed to remake themselves even as the science on which they rely has changed dramatically. Their study has found that the research efforts of the most successful pharmaceutical companies can be as much as 40% more productive than their rivals'. 'This result is substantial enough to suggest that it takes more than hiring the best possible people and giving them funds to be successful. Management plays a crucial role in the innovative process' (Henderson, 1994).

In interviews, pharmaceutical company managers also discussed the importance of organizational changes geared to improve their ability to make good investment decisions, make use of existing technology and research know-how, and produce valuable products in less time. Examples of changes included designing multi-disciplinary teams, incorporating marketing issues early into the decision making process, and making more use of licensing and strategic alliances to broaden the boundaries of their research capacities and capabilities.

7. Competencies

From a static perspective, firms are constrained by a set of competencies – a product of past investment, hiring and training experiences. Then, as in the

case of science and technology discussed above, how companies use these competencies depends on their organization and strategy. From a dynamic perspective, firms can shape their future competencies through their current strategic and organizational decisions.

The next section paragraphs describe how this complex web of interlocking factors affecting innovation might be affected by an approval or reimbursement or pricing policy which attempted to discriminate between products according to how innovatory they are deemed to be.

C. The impact of an ex-ante innovation policy on R&D investments

To manage their risks, given the great uncertainties underlying pharmaceutical R&D, companies create portfolios of projects. According to Grabowski and Vernon (1986), because of the additional investments and uncertainties involved, 'true innovative' products are more risky to develop than incremental innovations. The question is how might companies react to public policies that would artificially restrict the number of so called 'me-toos' allowed in any one therapeutic class or regulate the expected reimbursement for follower products.

Sections A and B described the R&D process and some of the major factors influencing innovation. The following paragraphs discuss how companies might be expected to change their investment behaviour in response to the proposed policies.

- Overall, fewer research projects would be initiated. Many of the lower risk project options (projects in areas where there are already marketed products or where other companies have a head start in developing products) would be eliminated, leaving companies with portfolios of higher risk products. The average proportion of failed to successful products, the risks and consequently the average costs would increase.

- The amount of parallel research going on between companies in any one area would be reduced. This would reduce cross company spill-overs in research and competition with in therapeutic areas.

- From the set of higher risk options, companies may well choose to invest in fewer product areas, concentrating in ones where they believe they have an observable advantage and can expect to be able to push through market-

leading drugs. To better their prospects of being first in class, companies would have to increase their investment in these fewer, higher risk projects, a strategy which would leave them with a less balanced portfolio and a more vulnerable financial situation if a disproportionate number of their projects should fail.

- Looking to try and balance their risk or better their chances of being first in class, companies may look to merge or cooperate with another company with similar or complementary strengths. Especially smaller companies, lacking the finances for in-house innovative projects, might be under increased pressure to merge or drop out of the patented medicines market.

- Alternatively, rather than merge, companies might increase their use of strategic alliances to produce more innovative products.

In sum, the industry might end up with fewer new products and arguably be more concentrated, if not at the aggregate level, then certainly within therapeutic areas.

At first sight, the policy might then seem to have realized its goals of cutting back wasteful investments in duplicative products and reducing the number of companies competing in any one class.

But competition within therapeutic classes has benefits for society. Follower products might offer lower prices – given payers a way to reduce their overall budgets. And up to a point, patients benefit from choice between products.

It remains unclear whether potentially breakthrough innovative projects will also be cut back and what will be the impact of less competition in therapeutic areas. There might be less innovative competition as well as less price competition. Of course, increased concentration may not necessarily be bad. In fact, Gambardella (1995) argues that shifts in technological paradigms over the past two decades have already moved the industry towards more alliances and mergers and fewer, better products, anyway. A 1998 Morgan Stanley Dean Witter industry report confirms Gambardella's point that only large companies will be able to sustain the greater risks and costs of drug development and commercialization created by new technologies.

It is rarely clear at the beginning of a 'race' who will be the first to market[11]. The leading company might change over the course of the

11 It may even not be completely clear in which specific markets their products might eventually prove to have (most) value. See Section 5.

development process as trials reveal more information about the products. Certain companies may delay their programmes and others may drop out all together. A problem with any policy to introduce an innovation threshold is that there is a risk that a therapeutic area would end up with no winners or not enough good therapies because too few companies would be willing to bear the increased risk of commercial failure and so would not undertake the investments.

To discourage competitors in any one development race also risks diminishing valuable spillover effects that exist between different companies' research programmes. Henderson and Cockburn's work on investment behaviour in the discovery phase of R&D identifies a positive correlation between companies' outputs. 'Important patents per discovery dollar are likely to be significantly higher if competitors have recently obtained a number of important patents in the area and far from leading to mining out of opportunities, competitors' research appears to be complementary activity to own R&D. Thus the entry of additional firms into a therapeutic area may enhance welfare' (Henderson and Cockburn, 1996b, 184).

In a second article, they use the history of the discovery of the first ACE inhibitor to demonstrate the way companies forward drug discovery through collaboration and competition (Cockburn and Henderson, 1995). They acknowledge that not all patents are equally important. '(C)orrelation in output across firms may reflect no more than the generation of 'me-too' patents for 'me-too' drugs. Two factors moderate this problem. The first is that so-called 'me-too' drugs may offer important additional therapeutic benefits (See Section 6 below). The second is our finding that output is positively associated with competitive investment as well as competitive output, which suggests that we are capturing the effect of genuine spillovers in knowledge' (Henderson and Cockburn, 1996b, 184).

A third problem with the proposed policy is the outcome of the innovation process in pharmaceuticals is often not just one prize in each therapeutic class. Furthermore, the innovative process does not end at the time of market launch. Empirical evidence suggests that:

- the first product to market does not always turn out to be the best in the class;

- follower products often add therapeutic and economic value to the class of medicines;

- new uses and indications (innovative facets) are often discovered after the product is marketed and used by a large sample of patients, or after new research in related areas is published;
- there are post-market economic and therapeutic benefits to having a number of products in a therapeutic class.

Examples of these four claims are explored in the next two sections.

5 THE INNOVATIVE DYNAMIC AFTER MARKET LAUNCH

In Section 4 the strategic objectives of pharmaceutical companies were discussed. The main commercial goal is to maximize profit over the product's life cycle. This involves reducing the costs in the R&D process and/or increasing the returns while the product is on the market. In this section, examples are used to illustrate the dynamism of the innovative process that does not stop at market launch. 'Once they have entered clinical practice their therapeutic advantages and drawbacks become apparent and this serves to widen yet further the inter-product differences noted from the original viewpoint of structure' (Wells, 1988, 20).

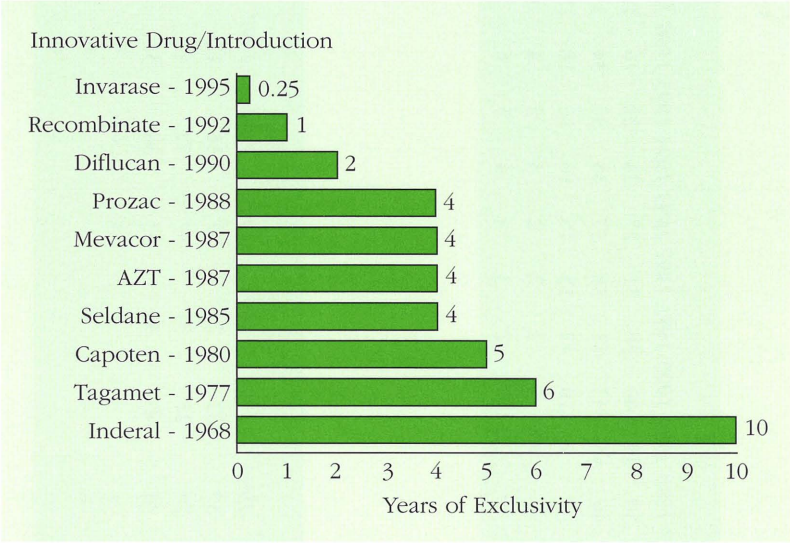
On the one hand, companies have the incentive to conduct further research on their products to develop line extensions or to spawn the development of new products. On the other hand, the amount of testing that can be completed in a pre-market clinical trial is limited and many product attributes, positive and negative, are revealed about product safety and efficacy only after they medicines are marketed. These issues raise questions about the ability of experts to assess the innovativeness of a product before it is launched.

> 'The **evolutionary process** of pharmaceutical development may not be apparent in a snapshot for the collection of drugs available to a given point in time. At the static view point, incremental innovations can be perceived as duplicative, profit driven imitations of successful drugs already in the field, rather than the basis for the next generation of improved pharmaceutical products (as a dynamic viewpoint would suggest).' (Levy, 1990, 37)

A. The first product to market in a specific class is not always the best

The first product to market does not always end up being the most innovative or successful in the class, a fact that should affect strategic investment decisions. On the one hand, according to a report by The Boston Consulting Group (1993), increased competition from generics and lower prices for

Diagram 5.1 **Decreasing exclusivity periods**



Follower drugs:

1996 Norvir	1991 Videx
1993 Kogenate	1989 Hismanal
1992 Sporanox	1985 Vasotec
1992 Zoloft	1983 Zantac
1991 Pravacol	1978 Lopressor

Source: Morgan Stanley Dean Witter, 1998, 18.

prescriptions with the introduction of managed care, increase the pressure on companies to be first in class or face price discounts. They show that on average, the price of new drugs approved between 1991 and 1992, compared with the price of the market leader in the therapeutic category, had an average discount of 14 percent (BCG, 1993, 98)[12]. Lehman Brothers also suggest the importance of being early in class, arguing that additional competitors expose companies to loss of market share and to pressures to discount prices.

On the other hand, revenue studies are actually inconclusive about the advantages of being first to market. As the time between the first and subsequent products in a class seems to be shortening, there is less time to

12 The issue of price competition is returned to in Section 6.

Table 5.1 **Market share development of ACE inhibitors**
(% of world sales)

ACE inhibitor	*Year introduced*	*1980*	*1981*	*1982*	*1983*	*1984*	*1985*	*1986*	*1987*	*1988*	*1989*	*1990*	*1991*	*1992*	*1993*	*1994*	*1995*	*1996*	*1997*
A	1980	100	100	100	100	100	88	68	56	50	44	40	36	31	27	24	22	16	12
B	1985	–	–	–	–	–	12	32	44	46	45	43	41	38	37	35	34	34	33
C	1988	–	–	–	–	–	–	–	–	3	7	10	12	15	15	16	16	18	19
D	1988	–	–	–	–	–	–	–	–	0	0.8	2	2	2	2	3	3	4	4
E	1989	–	–	–	–	–	–	–	–	–	0.3	2	2	3	4	4	5	6	7

Source: Bayer, Market Research, 1998.

Table 5.2 **Market share development of Statins**
(% of world sales)

Statin	*Year introduced*	*1987*	*1988*	*1989*	*1990*	*1991*	*1992*	*1993*	*1994*	*1995*	*1996*	*1997*
A	1987	100	99.7	81	53	47	39	32	29	23	18	12
B	1988	–	0.3	13	25	22	25	28	31	37	42	42
C	1989	–	–	6	22	31	36	40	39	37	34	31
D	1994	–	–	–	–	–	–	–	1	4	6	6
E	1997	–	–	–	–	–	–	–	–	–	–	9
F	1997	–	–	–	–	–	–	–	–	–	–	0

Source: Bayer, Market Research, 1998.

Table 5.3 **Future dynamics in the Statins market**

Projected % of total worldwide (and US) revenues				
	1997	*1998*	*1999*	*2000*
A	14 (18)	8 (11)	6 (7)	4 (5)
B	47 (39)	41 (34)	37 (30)	34 (27)
C	19 (18)	18 (17)	18 (17)	18 (17)
D	6 (8)	6 (7)	5 (6)	5 (6)
E	11 (15)	23 (29)	27 (34)	31 (37)
F	0 (0)	2 (1)	5 (5)	7 (7)
Other	2 (2)	2 (2)	2 (1)	2 (2)

Source: Lehman Brothers, 21.7.97, 27.

reap the benefits of being the market leader and thus the possibility that the second or third product to market ends up being the leader increases, especially if these later products do not have side effects or dosage inconveniences that the first in class may have. Diagram 5.1 shows how the period of exclusivity seems to be decreasing over time. Using UK industry data for 1969-98 period, Towse and Leighton (1998) find a downward trend in average time to first and subsequent follower entrants over the time period.

Market share data by therapeutic class illustrate how follower products can end up as class leaders. Tables 5.1 and 5.2 show the market shares of world sales for the ACE inhibitor and Statin therapeutic classes in the 1980s and 1990s. In the ACE inhibitor market, the second product (B) had the largest market share starting in 1990 but as of 1997 it had lost much of its lead to the third product (C).

In the Statin market the second product to market (B) took over the lead from product (A) but immediately after its entry in 1997, Product E started taking market share from the leader. According to predictions in 1997, this fifth product in class was expected to catch up with the leader by the year 2000 but as of July 1998, it had already taken over the lead in terms of new prescriptions (Scrip, July 1998). See Table 5.3.

The dynamics in the Betablocker market in the 1970s and 1980s were similar. See Table 5.4. Here the first in class rapidly lost market share initially to the second product and then to the fourth product to enter the market.

There is evidence that these follower drugs' strong performances relative to previous market leaders are, at least in part, a function of therapeutic

Table 5.4 **Market share of Betablocker prescriptions**

Beta blocker	*Year introduced*	*1970*	*1971*	*1972*	*1973*	*1974*	*1975*	*1976*	*1977*	*1978*	*1979*	*1980*	*1981*	*1982*	*1983*	*1984*	*1985*	*1986*
A	1965	88	48	34	27	23	33	39	34	31	28	24	23	22	20	18	14	12
B	1970	–	15	18	26	37	50	48	45	40	36	31	26	23	20	17	14	12
C	1970	7	32	43	42	35	8	–	–	–	–	–	–	–	–	–	–	–
D	1976	–	–	–	–	–	–	1	9	13	17	20	23	28	33	41	48	49
E	1977	–	–	–	–	–	–	–	2	3	3	4	5	6	6	5	5	5

Source: Levy, 1990, 26.

improvements. The Statins and ACE inhibitor markets as well as others provide examples.

Using efficacy (LDL, HDL, LDL/HDL, triglyceride levels), safety (adverse effects, tolerability), and compliance (administration frequency) variables to measure performance, Afuah (1992) finds that in the cholesterol market as a whole, each subsequent technological generation has performed better than the previous one and that, within each generation, each member of the family has, on average, improved on the one previous to it. 'The HMG CoA reductase inhibitors (Statins), from the latest technological generation, lead in all the key measurable performance characteristics (decrease in LDL, total plasma cholesterol, LDL/HDL ration, total C/HDL ratio, administration frequency and increase in HDL) except decrease in triglycerides where the fibrates are king. The Statins also have the fewest side effects. Among the Statins, (Product B in Table 5.2) which is a synthetic analogue of (Product A) shows considerable performance improvements over the latter' (Afuah, 1992, 17).

Producers of products E and F in Table 5.2 refer to their products as second generation Statins. A key advantage over the first generation is a higher affinity to the target enzyme which results in lower doses needed in order to achieve the required cholesterol reduction. Lower doses mean fewer side effects and interactions with other drugs. An animal study on Product F showed it to be 100 fold more potent than Product A. 'Vastatins used in therapy are effective in mg doses, while (Product F) offers a new low dose therapy in the mu g range' (Bischoff et al., 1997, 119).

In the ACE inhibitor market, products after A address certain side effect problems (taste disturbances and skin rashes) with a different way of binding zinc. Products B and E are 'prodrugs' that require hydrolysis before they can inhibit ACE. 'This improves absorption and usually delays the onset and prolongs the duration of action' (Wilson, 1997, 2). There are fewer practical differences between ACE inhibitor products, however, than is the case with Statins.

In the protease inhibitor market, three companies, Hoffman-La Roche, Abbott Laboratories, and Merck & Co developed the first three products in class. 'While their products all inhibit the same enzyme (the protease, which is vital to viral replication), were developed at approximately the same time, and might well be considered 'me-too' therapies, they actually have different side effects, levels of bio-availability, and prices. They are an excellent

indicator of why innovation systems that encourage diversity, allow for strategic competition, and facilitate intra-network communication and cooperation are more successful over the long term' (Lamoreaux and Galambos, 1997, 36).

B. Market use reveals new uses

The research and development of a drug does not stop once it receives market approval. 'Post-marketing development can lead to new or better uses of the same product, or there can be reformulation of the active ingredient into a new medicine which either provides advantages for the same indications or allows quite new clinical uses' (Snell, 1986, 33). Companies competing in crowded therapeutic classes such as ACE inhibitors have a particular incentive to continue post-market clinical trials to further differentiate their products from those already on the market. In general, a lot of information about efficacy, safety, and side effects is learned only after the product has been marketed to a large sample of patients. One should consider the question, however, of whether there is not a maximum number of post-market trials beyond which the costs of additional research exceeds the value of subsequent information.

Snell (1986)[13] presents lists of examples for: new uses of drugs in the original therapeutic area achieved by a new formulation (line extensions); substances with pharmacological actions offering clinical potential greater than the indication for which it was first marketed; and discovery of new uses for established medicines observed unexpectedly. See Table 5.5.

The products listed in this table were not necessarily follower drugs, some may have been the first in class. The point of this, albeit slightly dated table, is to illustrate important new uses that became evident after the products were on the market. Some of these new uses were discovered through formal, company directed, post-market trials; others may have come to light following perscribers' observations.

Table 5.6 lists new indications identified for selected Statins and SSRIs. New uses can be found for whole classes of drugs as well as for individual products within classes.

13 Both Wells (1988) and Levy (1990) reproduce these tables.

Table 5.5 **New uses and indications for drugs discovered after market launch**

A New formulations providing improved safety and efficacy or extending the range of indications in the original therapeutic area

Drug	*Original indications*	*New formulation*	*Extended use*
Antibiotics	Parenteral use only	Oral preparations	Bowel preparation; hepatic coma
		Topical forms	Skin, eye, ear infections
		Inhaled use	Cystic fibrosis
Morphine	Pain	Slow-release injection	Prolonged action
		Epidural injection	Regional analgesia
Heparin	i.v. treatment for venous thrombosis	s.c. low-dose	Prophylaxis of postoperative venous thrombosis

B Extension of therapeutic areas of use by application of known pharmacological actions

Drug	*Original indication*	*Later uses*	*Mode of action*
Aspirin	Pain	Prevention of formation of arterial thrombi	Inhibition of platelet aggregation
Danazol	Endometriosis	Hereditary angioedema; benign breast disease, PMS	Modulation of pituitary gonadotorophins
Stanozol	Anabolic steroid	Raynaud's disease; lipodermatosclerosis; cutaneous vasculitis	Fibrinolysis

C Unexpected new therapeutic uses discovered mainly by chance: uncertain or unknown mode of action

Drug	*Original indication*	*Later uses*
Amantidine	Viral disease	Parkinsonism
Antihistamines	Allergies	Sedative; travel sickness
Diuretics	Diuresis	Hypertension; hypercalciuria; suppression of lactation
Imipramine	Insomnia	Depression; nocturnal eneuresis

Source: Snell, 1986, 33, 34, 36.

Table 5.6 **New indications**

Some **Statins:**
(The letters refer to the same Statins as in Table 5.2)

B and C, originally approved for the treatment of high cholesterol have subsequently been approved for three new indications:
1. reduction of death from coronary heart disease (CHD);
2. reduction of risk of myocardial infarction (MI);
3. prevention of stroke and transient ischaemic attack.

B and E also approved for use in patients with elevated triglycerides.

Studies show A significantly reduces the risk of MI or unstable angina in healthy low-risk patients without CHD or raised cholesterol.

Other producers of statins have followed suit and are seeking approval for these new indications as well.

Some **SSRIs:**

SSRIs originally approved for depression have been approved for additional indications:

Fluoxetine – bulimia nervosa, obsessive compulsive disorder (OCD), plans to apply for use in PMS

Paroxetine – OCD, panic attack and awaiting registration in social anxiety disorder

Sertraline – OCD, panic attack, awaiting registration for post-traumatic stress syndrome

Sources: http://www.drugtopics.com, 5.8.98; http://pharminfo.com, 17.7.98.

Established therapeutic classes also develop over time as more/new information and technology become available and/or the diseases evolve or change. In the field of antibiotics, for example, new products have to be developed to respond to resistant strains. In the hypertension market, new research into how the angiotensin system worked led to the discovery of A2 antagonists to block uptake of angiotensin II – a step beyond the process where ACE inhibitors act. While initially considered a new generation and therefore a direct competitor with existing ACE inhibitors, these products have developed into a class of their own. Recent post-market studies suggest that these products could be used in combination for even greater potency.

6 ASSESSING THE THERAPEUTIC AND ECONOMIC BENEFITS OF INCREMENTAL INNOVATIONS

The therapeutic and economic benefits of having multiple products in any one therapeutic class may include:

- incremental improvements to therapeutic classes;
- price competition; releasing health care purchase funds for other purposes;
- risk management for companies;
- revenues to help companies finance further R&D investments by creating 'headroom for innovation'.

1. **Therapeutic improvements from incremental innovations**
   '(T)he symptom-control-cure cycle is the product of incremental increases in the understanding of a disease's mechanisms...New pharmaceuticals may offer incremental improvements that are not breakthroughs in treating a disease, but typically include increases in potency and/or decreases in side effects. In developing these incremental improvements, however, researchers are able to advance both their understanding of the disease mechanism and the technology available to fight it. Incremental improvements eventually lead to treatment breakthroughs and advances along the symptom-control-cure cycle' (Boston Consulting Group, 1993, 41)

As discussed above, incremental innovations often provide valuable improvements to therapeutic classes, responding to specific side effects or dosage problems. The improvements between first and second generation Statins were mentioned in Section 5. Levy (1990) develops further examples from five therapeutic classes – beta-blockers, calcium channel blockers, cephalosporin antibiotics, nonsteroidal anti-inflammatory agents, and sulfonylurea hypoglycemic agents to illustrate therapeutic improvements from new generations of drugs as well as the medical advantages of having choice.

Wastila et al. (1989) provide further evidence of the therapeutic improvements of 'me-toos' over the innovator drug. They show that 50% of the WHO Essential Drug List, a list of drugs deemed by medical experts 'to

be essential and necessary to address minimally the health and medical needs of any developing nation' are 'me-toos' (products with the same chemical structure and used for the same therapeutic indication as the innovator drug). These drugs were selected by way of a benefit/risk ratio – a ratio determined by experts using efficacy, safety, quality, and total treatment cost. Apparently, therefore, these follower drugs had advantages other than price over the first drugs in their respective classes.

2. Price competition

There is some evidence to suggest that the introduction of additional products to a therapeutic class spawns price competition where products are therapeutically similar:

- The Boston Consulting Group (1993) showed that the average discount taken by follower products in the US market relative to the market leaders, was 14% between 1992 and 1993.

- Underlying the Lehman Brothers' estimate of a company's growth, earnings and gross margin potential is the assumption that coming late to a crowded market increases the likelihood that a company will have to take a price discount.

- Towse and Leighton (1998) present price data for the UK market that show a steady reduction over the period 1969-98 in relative prices between follow-up compounds and the market leader at the time the follower compound was introduced to market (for drugs from 19 drug categories). Follower compounds in the mid-1990s typically enter at a price discount to the market leader.

- Green (1998) summarizes Reekie's (1996) study of price behaviour in submarkets across six countries, which shows that in submarkets where rival products were present, new products tended to be launched at a discount, often in excess of 25% and average prices fell in real terms for two thirds of them between 1989 and 1995. 'It is difficult to disentangle the effects of competition from the impact of regulation, but the findings suggest, even in the attenuated form that competition is found in the six countries, that to varying degrees the presence of rival products helps to lower prices' (Green, 1998, 141).

- The US Congressional Budget Office's (CBO) report on drug competition finds that the entry of one or more follower products slowed the rate of

growth of list price increases for breakthrough products and that follower product competitors tended to enter the market with lower prices than the breakthrough drug (CBO, 1998).

Given the evidence that follower products generally entered the market at prices lower than the leader, some might question why companies would then oppose a policy that proposes to formalize such behaviour, that is, discount the reimbursements made available to products deemed to be incremental rather than breakthrough innovations. The critical difference is that in the markets referred to by the empirical evidence it was the companies who decided on the price based on their perception of the market and the relative value of their product. A formal regulation would transfer that decision to an outsider who would first assess the product's innovativeness. As was discussed in Section III, it is difficult to agree on how to define innovation before the products are marketed.

The existence of price competition driven by new entrants should reduce total drug expenditures, although not all incremental innovations will be priced below the market leader; this will depend on the relative effectiveness of the products. The extent to which the potential for incremental innovation to produce savings also depends on the price sensitivity of perscribers.

3. Balancing risk

It has already been mentioned that having some less innovative projects but with a more certain (if modest) expected return helps to balance out the risk in companies' portfolios (Hartwig, 1998; Levy, 1990). Incremental innovations tend to be the lower risk parts of the portfolio because overall they have a better chance of getting to market.

But, as was discussed in Section 4, unexpected set backs or complications during a company's clinical trials of breakthrough products (or unexpectedly rapid progress in their rivals' product development) also means that companies reach the market second or third in a race they hoped to (and invested to) win.

> 'In an environment of restrictive policies, pharmaceutical companies will be confronted with a difficult choice: to continue channeling research investment into incremental advances that may no longer be marketable or to redirect resources and spend even more on radical improvements that are marketable, but have little chance of reaching the market. During the

time of product development, similar products may reach the market, turning a breakthrough prospect into a similar version of another company's drug. If these second or third versions are kept from the market, many pharmaceutical companies may not be able to support continued research. Nobody knows whether innovation could continue in an environment where the risk of failure gets raised higher in this way' (Levy, 1990, 38).

4. Revenue contributions

The sales from follower products can make a valuable contribution to companies' revenue streams by spreading out the returns over time. Companies will not earn more money from the sales of follower products than they would from first in market products, but as the former are more certain, so is some return. This will help support their investments in breakthrough innovations. Wells (1988) found that 'a significant percent of total sales five years and ten years after introduction was attributed to products considered 'innovative chemical extensions' (ICEs). Since pharmaceutical manufacturers finance R&D initiatives out of current revenues, these findings suggest that attempts to restrict the market access of ICE medicines could significantly jeopardize the prospects of innovative advance' (13).

A negative outcome of having incremental innovations vying with breakthrough innovations for market share is that of destructive competition where companies that have committed the funds and the time to develop break through products are denied the necessary years of market exclusivity needed to recover their costs. Evidence presented in Section 5 suggested that years of exclusivity were declining. Morgan Stanley (1998) predicts that new technologies such as combinatorial chemistry which allow companies to modify existing drugs in order to improve therapeutic profile and reduce toxicology, will further reduce years of exclusivity.

Further research is necessary to adequately address this concern but added competitive pressure could also work the other way. In the knowledge that they cannot rely on returns from a few breakthrough products over the long term, companies are motivated to initiate new projects more regularly. However, given the high and increasing R&D costs involved, Gambardella (1995), Gilmartin (1998), and Morgan Stanley Dean Witter (1998) also suggest that only large companies will be able to afford this high investment strategy over the long term.

7 CONCLUSION

The material in this report has drawn attention to three key features of the pharmaceutical industry's innovatory process.

First, companies compete through innovation. Pricing pressures and competition from both patented and generic drugs on the demand side and from scientific discoveries, technological change, and strict regulatory requirements on the supply-side, motivate companies to invest in the R&D of innovative products.

Second, the outcomes of this R&D process is highly uncertain. This means that a company does not know whether it will be first on the market when it embarks on a project in a specific therapeutic class. Costs are high in part because of the time it takes to develop a potential idea into a marketable product that meets safety, efficacy and quality requirements, and in part because the probability of failure is high.

In order to offset some of the risks involved in innovative research, companies try to construct balanced portfolios that include some lower cost projects where the probability of success is higher though the expected therapeutic contribution may be lower. The incremental innovations produced from these projects are often what are generally referred to as 'me-toos'.

Third, incremental innovations should not be written off. They may make significant incremental improvements to products already on the market. They may also help control drug prices by introducing some price competitive pressures into therapeutic areas. Finally, sales of these drugs help companies to finance their research programmes.

With innovation driving the development of medical treatments, a policy objective to provide strong incentives for innovation is a valid one. The findings in this report challenge, however, the likely effectiveness of an ex-ante exclusionary policy, especially when much about the innovativeness of a product may not become known until after the product is marketed. There are other important issues to be considered were such a course to be contemplated, not least whose perspective of usefulness or innovativeness should be taken into account.

Given the importance that companies place on expected return in their

investment decisions – the high risks in R&D mean much of the investment is financed with retained profits (STOA, 1993, 17) – to increase the uncertainty of reward if a company should fail to win first place in an innovative race might end up discouraging rather than encouraging worthwhile R&D investment.

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