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Strategy and structure of the pharmaceutical industry

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ABSTRACT

The case looks at the development of the modern pharmaceutical industry with an emphasis on events in the late 1990s. The various forces affecting the competitive environment around the discovery, development, production, distribution and marketing of prescription and non-prescription drugs are discussed in terms of their origins and recent developments.

INTRODUCTION

During the 1990s news services and other media in both developed and developing countries devoted increasing space to discussing health issues. Healthcare and the rising cost of healthcare treatments were also at the centre of the year 2000 US Presidential campaign because candidates of the main political parties regarded this as a topic of interest not only for retired people but also for the all-important (and ageing) "*baby boomer*" generation. Alongside increasing interest in the industry, pharmaceutical companies engaged in a number of high-worth (and highly publicised) amalgamations while, at the same time, the sector continued to deliver value in most stock markets around the world. How this situation came about and the role of pharmaceutical companies in the debate around healthcare provision are central topics for this case study.

ORIGINS

The origins of the modern pharmaceutical industry can be traced to the late 19th century, when dyestuffs were found to have antiseptic properties. Roche, Ciba-Geigy, and Sandoz all started out as family dyestuff companies based near the Rhine in Basel, Switzerland. Slowly but steadily many chemical companies moved into synthetic pharmaceuticals and eventually became global players. Penicillin was a major discovery for the emergent industry during the 1940s. Throughout that decade and that of the 1950s, research and development (R&D) became firmly established within the sector, with the relative success of specific drugs making or breaking individual companies over time. For example, the use of anti-blood coagulants (i.e. betablockers) to speed up recovery after serious injury were largely discovered by ICI, who formed major franchises out of the treatment of cardiovascular diseases. Companies such as Syntex and Boots established themselves based primarily on the discovery of products to treat swollen muscles with very lenient side-effects (i.e. non-steroidal inflammatory drugs).

The industry expanded rapidly in the 1960s, benefiting from new discoveries with permanent patent protection while the time from discovery to launch took between 3 to 5 years. Regulatory controls on development and marketing were lax and healthcare spending boomed as economies prospered. Around this time a distinctive characteristic emerged for the pharmaceutical industry which marked its development for the following 30 years. This unique feature encompassed the final consumer (i.e. the patient) having little or no say in the choice of drug and treatment. Specialists and general

practitioners were the customers of the pharmaceutical companies because they were ultimately responsible for purchasing decisions. To no surprise pharmaceutical companies' marketing efforts targeted medical practitioners and specialists, building on individual representatives that would alert practitioners of new products through one-to-one sessions at the practitioner's office. This sales approach became known as "*muscle marketing*", and proved to be a successful approach for a fragmented customer base; while increasing the number and spread of sales representatives was an effective way to overcome challenges poised by high mobility of specialists, cramped appointment schedules and general practitioners' geographic exclusivity arrangements.

Since medical practitioners became susceptible to details provided by sales representatives, some newcomers to the industry as well as established providers, found it attractive to devote R&D resources for the development of "*me too*" drugs, copies of a competitor's product. The attractiveness of "*me too*" products for manufacturers was that these drugs traditionally priced at a premium to the existing market on the back of "*muscle marketing*". Doctors would accept a premium price for a new product because it was usually perceived as offering some sort of advantage. For example, the advantage might be a less frequent dosage or the new drug might have a slightly improved side-effect profile. But with regard to its therapeutic outcome, the new product was very similar to the established product with which it was competing.

EVOLUTION

There were two major developments in the 1970s, the first being the introduction of much tighter regulatory controls on clinical trials, greatly increasing time to market and development costs. A second major event was the enactment of legislation allowing the introduction of "*generic*" medicines by setting a fixed period on patent protection. A "*generic*" product is a drug manufactured after patent expiry by another pharmaceutical and usually sold at a cheaper price. Generics are identical in virtually every respect to the branded original and their prices normally are at the bottom of the market. Generics are not developed nor manufactured by the original company and as such, are not backed by the manufacturer's quality control and medical information department. To a lot of medical practitioners that difference was irrelevant, whereas for others the difference was important thus an opportunity to have "*branded generics*" opened up. Branded

generics are generic products which offer a small advantage and which are sold at a price above the lowest-priced generics.

The immediate effect of legislation allowing generic products was that major pharmaceuticals started to develop similar products by investing in similar processes and research agendas. Once patent protection of a well-selling drug was over, other manufacturers would dig into their compound library and start selling "*generic*" alternatives almost immediately. Since the price of generic drugs typically represents only 60% of the price at launch of the branded alternative, legislation provided incentives to reduce the lag time to market, augment price competition for products in top therapeutical segments and lead to an erosion of the branded original's market share. By the end of the decade the combination of lower barriers to manufacturing generic products and more stringent controls on clinical trials was reflected through substantial increases in R&D spending.

During the early 1980s the pharmaceutical industry was unusual, as in many geographic markets there was effectively only one powerful purchaser, the government. In the 1980s, governments around the world began to focus upon pharmaceuticals as a politically easy target in their efforts to control rising healthcare expenditure. At the time there was realisation of changes in the underlying trends at the heart of healthcare provision: patients' expectations were increasing, the cost of healthcare was increasing but, at the same time, the capability of several countries to sustain such spending was not. Many countries introduced some form of price or reimbursement control while industry participants lacked the public or political support to prevent these changes. Take the UK for example. In 1985, the British government introduced its "*black list*", a group of patented drugs that the government would not pay for. Some products that were "*delisted*" from official supply lists or "*blacklisted*" included anti-hypnotics such as valium and some cough syrups. The effect of "*delisting*" had a tremendous differential effect on the industry. Prior to the introduction of the "*black list*" Roche, for one, was in the top ten companies within the pharmaceutical industry but fell to the 40s within the industry when its two major products were "*delisted*".

Despite price controls or claims of increased government intervention, the pharmaceutical industry enjoyed recession-proof growth in demand. Volume business from selected ("*listed*") products during the 1980s resulted in average operating margins in the USA moving from 16% to 24%, gross margins from 63% to 76% and net profit margins from 10% to almost 19%. Increased profitability

resulted from a combination of final consumers still being protected from absorbing a significant share of total costs, together with the effects over R&D platforms and marketing strength from horizontal and vertical integration (more below).

Other key developments in the 1980s were the emergence of biotechnology firms and greater use of computer power. The appearance of small biotechnology start-up companies came about with the assistance of venture capital to exploit the myriad opportunities opened up by molecular biology. This boom was short-lived as genetically-engineered products proved to be even more costly than conventional pharmaceuticals to develop and manufacture. Most start-ups also lacked the finances to cope with the huge risks involved. A few spectacular development failures took the gloss off the sector and investors became more cautious.

However, the introduction of personal computers and more sophisticated information and communication technology equipment during the 1980s had two benefits. The first benefit was the introduction of innovative ways to hold and manage growing numbers of patients' records. The second benefit was allowing for software applications to set a "*formulary*", that is, a list of drugs that encompassed those drugs most often or routinely used by the doctors in a practice, region or group of patients. The computer systems enabled purchasers to print all prescriptions in their generic-form rather than a branded-form. This effectively meant that if an alternative cheaper generic drug was available then the pharmacist could prescribe it and hence save the purchaser money. The result was that the old brand loyalty, which the pharmaceutical industry had spent so much time and money developing, was threatened and could disappear. Furthermore, the viability of large sales forces became increasingly called into question.

Entering the 1990s, public and private finances faced similar challenges. World-wide economic recession reduced cash for provision of healthcare through tax-funded systems such as those in Canada, Italy, Spain and the UK, and the social security supported systems in France, Germany and Japan, as well as the employer/privately funded systems in the US. The ageing population introduced further pressures because the over-65's consume four times as much healthcare support per head as those below 65. An ageing population combined with more expensive high technology solutions and increasing patient expectations created an unsustainable situation: on the one hand, historically under-funded systems (such as those in Spain and the UK) were systematically in deficit

while slow or unable to introduce the latest treatments. On the other, well funded systems were able to afford the latest innovations but, as the experience in the US suggested, lost opportunities to share those benefits with an increasing part of the population.

The year 1993 was a watershed, with the environment filled with talk about healthcare reforms across Europe and in the US. Although many proposals were never put into action, it became evident that governments would no longer tolerate spiralling healthcare costs. Events of 1993 also signalled a global shift in customer behaviour towards healthcare costs in general and pharmaceuticals in particular. In that year, sales in the German pharmaceutical market fell by 11% while the four leading generics manufacturers increased their sales between 10% and 63% per year. Managed competition became the model for healthcare reform, creating a purchaser/provider split which focused attention sharply on achieving "*value for money*".

By the end of the 1990s there were a wide variety of managed competition methods to control public spending on pharmaceuticals, with most countries using a combination of methods (as no country relied on a single approach). Some price control methods have emphasised the supply side, that is, on the manufacturer and the distributor. Supply side methods have included negotiated prices, average prices, reference pricing, lists and other constrains over wholesales and pharmaceuticals. Some methods have emphasised the demand side, the prescriber and the patient. These methods have included patient co-payment, guidelines, fixed budgets, and incentives to prescribe and dispense generic drugs or parallel imports. Other methods such as reimbursement systems affect both demand and supply as volume purchasers negotiate individual drug price levels with manufacturers. Reimbursement systems, therefore, have assisted in controlling prices directly (supply) and may influence demand as they could require the patient to pay a part of the charge.

PRODUCT LIFE CYCLE

The net result of all the factors introduced to manage competition was a more difficult environment for pharmaceutical companies as illustrated below through figure 1 and figure 2. The figures show the aggregate impact of the introduction of price controls and other legislation on the typical pharmaceutical product life-cycle.

Figure 1: *Effects of legislation on ethical drug's product life-cycle*

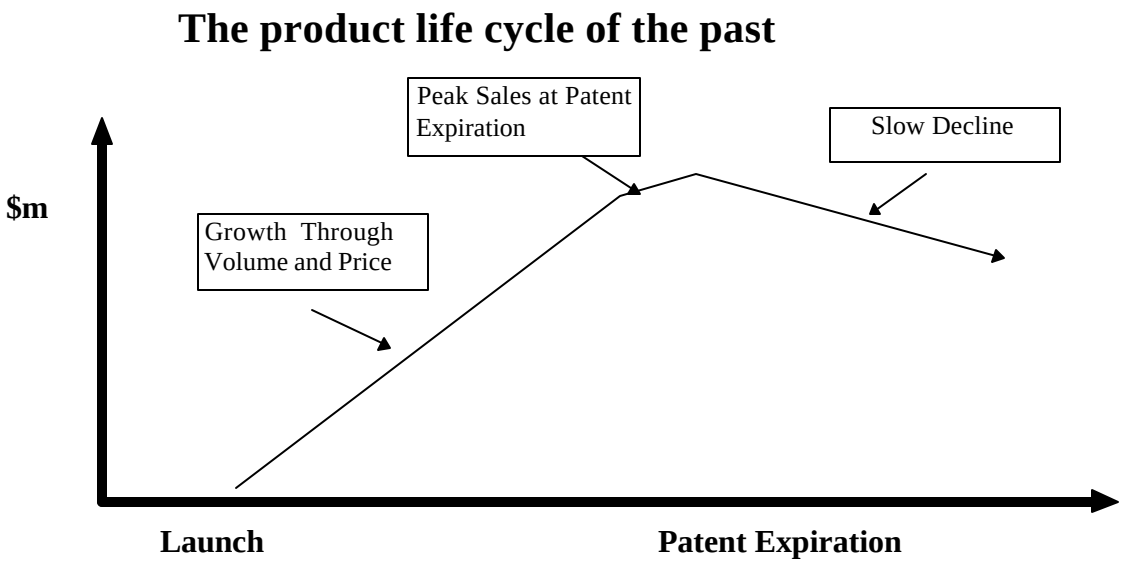
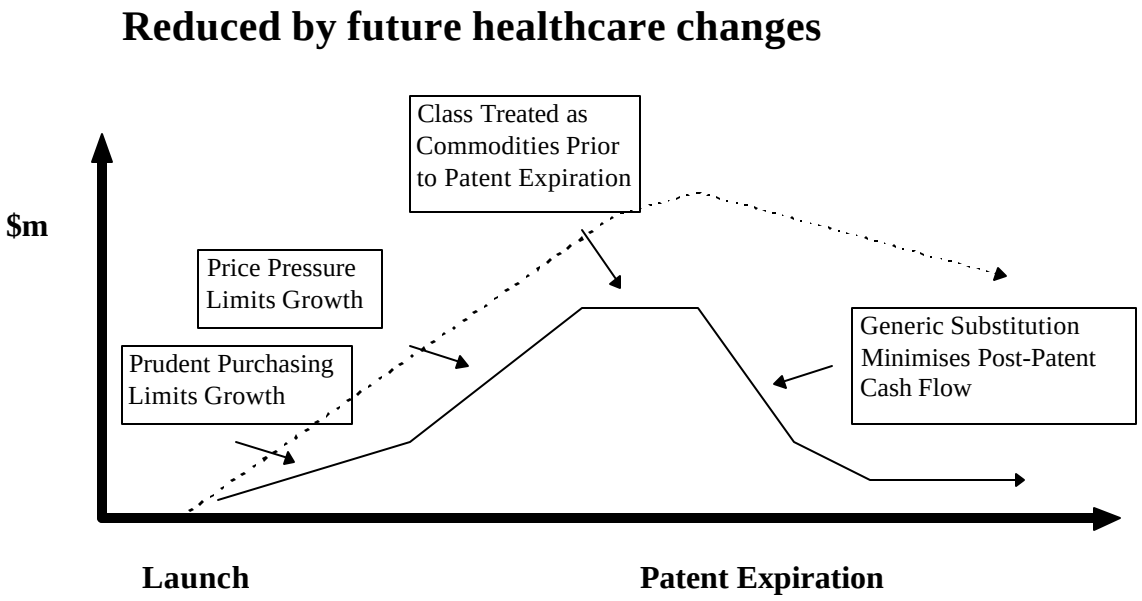


Figure 1 shows how, in the past, growth for drug manufacturers came both through volume and price, with peak sales at patent expiry. The decline in sales after patent expiry took years. Figure 2 shows how the product life cycle pattern shrinks due to external pressures on pharmaceuticals. Prudent purchasing by powerful players limits initial growth and holds down prices. The expiration of the first patent in the same drug class often results in all the members of that drug class being priced as commodities (even before the patents expire). Generic substitution speeds up the decline of sales value with time.

Figure 2: *Effects of legislation on ethical drug's product life-cycle*



Differences between figures 1 and 2 also help to understand why pharmaceutical marketeers have constantly sought ways to extend the product life-cycle. As a product approaches patent expiry, great effort may be invested in switching patients to new improved formulations with longer patent protection. Another strategy for appropriate drugs has been to move them from prescription-only status to over-the-counter (OTC), and encourage patients to recognise and buy a familiar brands. Since OTC drugs are not reimbursed prices may have to fall further, but that fall may be compensated for by increased volume as consumer brand loyalty can then be used as a defence against generic competition.

PARALLEL TRADE

On top of reductions in the product life-cycle, pharmaceuticals have faced the growing importance of distribution. Large distribution companies with pan-European operations emerged as distributors started to source products from the lowest point of supply in Europe through the medium of parallel imports. Parallel imports are products which are available at a cheaper price in lower fixed cost countries. Within Europe the higher-priced markets are Germany, the UK, Sweden and Holland; and the lower-priced markets, Spain, Portugal, France, Italy and Greece. It is from the lower-priced markets that wholesale distributors source parallel imports. Parallel imports grew in strength when pharmaceutical wholesalers began to consolidate internationally with cross-border mergers and acquisitions, and were quick to spot the opportunities to buy in one country and distribute in another. Hence, the creation of the Single European Market led to new problems for the industry because government-introduced controls created significant price differentials between countries. While the Single Market enabled parallel importers to trade ethical drugs, this resulted in minimal benefit to governments or final consumers but a very significant loss in profit for the industry because profit margins went to the parallel importers instead of being ploughed back into R&D.

Institutions such as the European Commission recognised the anomaly created by the enforcement of a free market alongside government price controls and this provided opportunities for pharmaceutical companies to influence European policy. However, there was significant divergence in the goals of the different players in the industry. Some US-based companies argued in favour of complete freedom in pricing pharmaceuticals in Europe, combined with parallel trade. Big European-based companies recognised that national controls on pricing and reimbursement would persist, but wanted a special embargo on parallel trade in pharmaceuticals. Meanwhile, smaller domestic players (who are powerful national lobbyists) simply wanted to continue with existing protective national pricing systems and did not want wholesale change of any sort. The lack of industry consensus, combined with the fundamental paradox at the heart of the problem and the determination of Member States to retain national controls, meant it was unlikely to be any significant change to pharmaceutical regulation in Europe. Furthermore, the enlargement of the European Union (EU) would exacerbate parallel trade as prices in Central and Eastern Europe tend to be low and differentials would worsen if currencies were devalued to ensure compliance with convergence criteria.

Parallel trade was not confined to Europe. It was prevalent in the Far East and could even become a threat in the US given the price differentials with Canada. Parallel trade was a source of concern for managers in ethical drug companies because pharmaceuticals have been subject to strict regulatory controls in virtually all world markets. For example, in the US, the Federal Drug Administration (FDA) requires manufacturers to perform extensive testing to demonstrate safety and efficacy before allowing a new drug to be put on the market. The time taken for the FDA to review a new compound typically requires from 6 to 12 months but this has been a process governed by legislation and therefore, many hurdles have to be jumped before reaching that stage (more below). One could assume that complying with requirements in the US could suffice, but while FDA endorsement could be very helpful, that endorsement in itself has not guaranteed automatic approval in other countries. Regulatory authorities typically wish to ensure that the product is suitable for their population and that the product delivers improved disease outcomes when compared with the standard of care in their country. For example, Japanese authorities firmly believe that people in their country may metabolise the drug differently from Western subjects and insist on separate clinical trials. Pharmaceuticals have thus been forced to develop capabilities to deal with the fact that every regulatory authority is different.

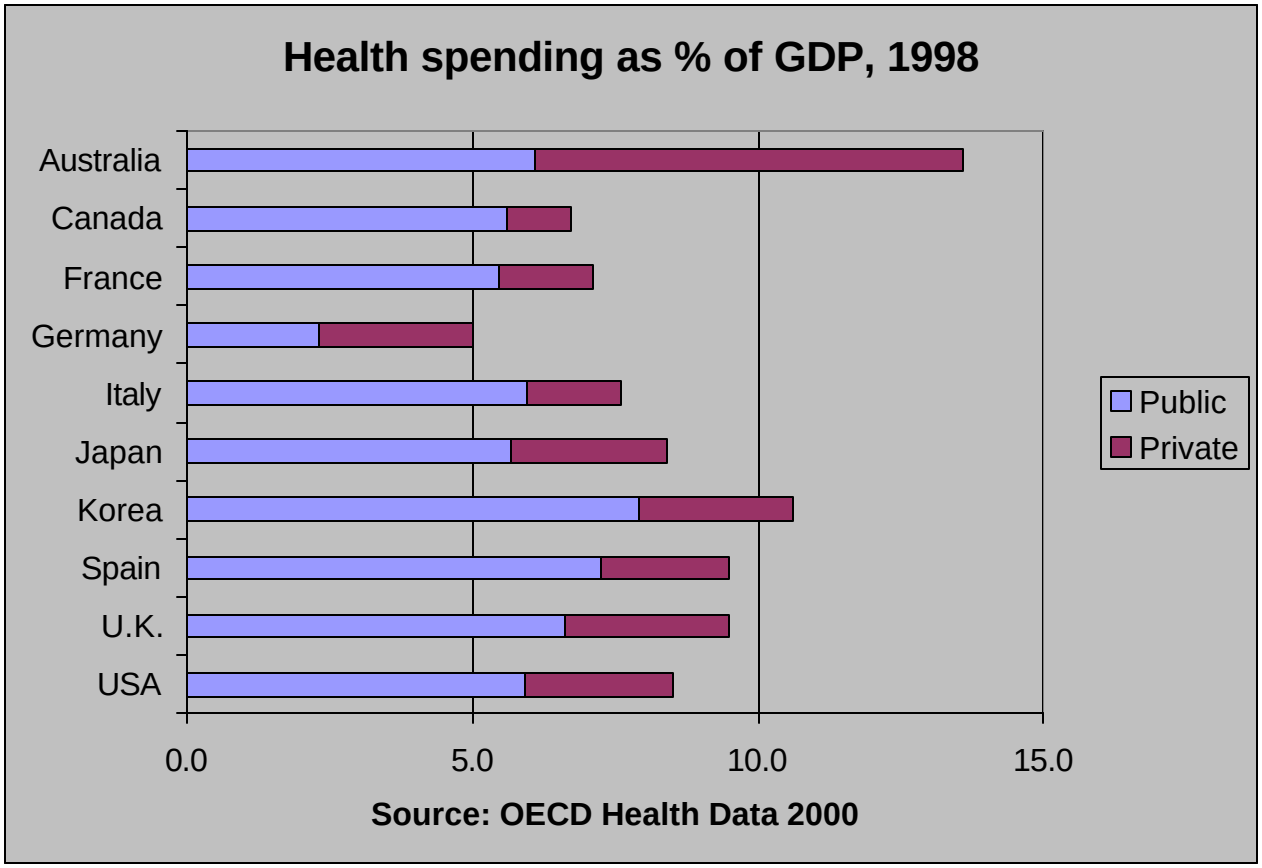
During the 1990s, a positive development for regulation and supervision of pharmaceuticals took place in Europe with the establishment of the European Medicines Evaluation Agency (EMEA) at the same time that European and non-European regulators established the International Conference on Harmonisation (ICH). EMEA is a body expected to enable more rapid approvals across Europe through a system where one country acts as "*rapporteur*" on behalf of the new product, recommending its approval which is then endorsed by the other member states. ICH is a body created by national supervisors from all over the world aiming to co-ordinate international policy and create uniform global standards for drug approval. But at the turn of the Millennium, either one of these bodies had yet to deliver a smoother process for drug approval.

GLOBAL MARKETS

The audited world pharmaceutical market was worth $340 billion dollars in 1999, a growth of 11% over 1998, with projections showing annual global sales growth of 8% over the following five years, which would expand the global pharmaceutical market to $500 billion dollars by 2004. The majority

of sales originated in the "*Triad*" (US, EU and Japan), with nine strategic markets accounting for over 80%, namely US, Japan, France, Germany, UK, Italy, Canada, Brazil and Spain. Of these, the US had grown the fastest since 1995, accounting for 60% of the sales of drugs since then. Furthermore, in 1999 alone the US market grew 16% to $133 billion dollars in sales, so becoming the key market for international companies. See figure 3.

Figure 3: *Health spending as % of GDP, 1998*



There have been two key developments in the US market. First the introduction of managed care, a system in which plan administrators set cost and reimbursement limits on healthcare services. Managed care changed the US environment but the fear that managed care would increase competition and drive down pharmaceutical prices proved somewhat illusory for several reasons: on the one hand, managed care organisations (MCOs) had more important areas of focus than the 10% of expenditure on drugs. They also found it hard to refuse reimbursement retrospectively once the

pharmacist had fulfilled the prescription. On the other, consumers covered by MCOs did not like restrictive drug formularies and offering pharmaceutical choice was therefore a source of differentiation. A second key development in the US market was growth fuelled by direct-to-consumer (DTC) advertising. DTC emerged as pharmaceutical companies began to recognise that patients did take a strong interest in their therapy and were prepared to ask for drugs by name, creating a powerful new *"pull"* strategy. Spending on DTC advertising amounted to $1.8 billion dollars in 1999.

Another interesting example in world markets is Japan, which was the second single biggest market with sales of $51 billion dollars in 1999 and together, Japan and the US, accounted for half the world-wide sales of ethical drugs. As shown in table 1, the US and Japan have also scored highly in the percent of resources spent on healthcare. The Japanese operating environment has historically been very different from that of the US or the EU. This divergence has been observed at all levels, from medical practice, healthcare delivery and funding, to regulatory requirements, higher prices, the lack of generics, distribution, and the accepted approach to sales and marketing. Not surprisingly, the market has been dominated by domestic companies. But due to environmental turbulence during the 1990s, Japanese medical practice begun to shift towards the US model while companies based in the US and the EU began to develop presence through acquisitions.

Emerging markets have also become increasingly important. The pharmaceutical markets in Latin America have proven highly volatile, reflecting underlying economic trends. Nevertheless they have large numbers of wealthy consumers who are able to afford branded pharmaceuticals. In 2000, the Brazilian market was the eighth largest in the world by value, but Mexico was rapidly catching up. Pacific rim countries were also becoming important contributors to the global market. Copy products have traditionally been a significant issue in these markets, where patent protection may be absent or very difficult to police. Another problem associated with foreign companies becoming successful in marketing high-price branded products and then finding themselves affected by parallel imports from as far afield as Belgium. The majority of the population in markets such as India and Africa have different healthcare needs to people in advanced industrialised countries because of the need to improve nutrition, sanitation and health education. Access to effective older products for common infections and diseases has also been a concern. Because the money is not there to provide a return, the research-based pharmaceutical industry has focused little R&D effort on diseases

specific to these markets. The AIDS epidemic in Africa has illustrated how solutions appropriate for advanced economies are unrealistic and inappropriate for developing countries.

Table 1: *Total expenditure on pharmaceuticals & other medical non-durables - % GDP*

	1960	1970	1980	1990	1997	Rank*
Australia	1.0		0.6	0.7	0.9	18
Canada	0.7	0.8	0.6	1.0	1.3	5
France	0.9	1.4	1.2	1.7	2.0	1
Germany		1.0	1.2	1.2	1.3	9
Italy	0.7	0.7	1.0	1.5	1.5	8
Japan			1.4	1.3	1.5	3
Korea				1.2	0.8	25
Spain			1.2	1.2	1.5	13
U.K.		0.7	0.7	0.8	1.1	15
USA	0.8	0.9	0.8	1.1	1.4	2

Source: OECD HEALTH DATA 2000

* = total expenditure per capita in US dollars, 1997

Nevertheless, with their enormous populations, emerging markets do offer significant long-term potential. Many have strengthened patent protection and liberalised equity controls. Pharmaceutical companies have been particularly interested in China, which has one of the most rapidly-growing pharmaceutical markets. While Chinese herbal medicine has remained a core part of healthcare, the use of Western medicines has been increasing dramatically in the booming coastal cities.

At the turn of the Millennium, the US was predicted to continue increasing its world market share, while Japan was expected to decrease and the EU to remain static. The same projections suggested that the most populous countries such as China and India were expected to increase in importance, Mexico was likely to overtake Brazil in Latin America, and Poland to continue growing rapidly in importance. By 2010, non-Triad countries were expected to hold a third of the world market.

THERAPY CLASS

So what has determined the relative importance of market sectors in the pharmaceutical industry and leading companies within those sectors? Although the overall pharmaceutical market appears relatively fragmented, this has disguised the true level of concentration. Since both R&D and commercial franchises break down naturally along therapeutic lines, companies generally choose to compete in a selected range of therapeutic areas. The market leader within a specific area could have a market share as high as 22% (AstraZeneca in Gastroenterology) and a figure around 15% was not uncommon. Typically the top 10 companies hold over 50% of a given therapeutic area. This has emphasised the need for genuine product superiority, since price premiums and/or reimbursement levels awarded by governments are based on perceived innovativeness and superiority, penalising "*me too*" drugs.

Industry intelligence has meant that companies are invariably in a race to market with each new class of drugs. Competition has been waged at the level of drug class and being late to market with an undifferentiated product is a recipe for failure. At the same time and in spite of high concentration levels within specific therapeutic areas, most pharmaceutical companies have been product-led rather than customer-led. This has probably been a consequence of the unpredictability of the R&D process because it has not been easy to develop a product to meet specific customer needs.

Another important source of success has been global reach. As the cost of developing and commercialising a new drug soared to more than $600 million dollars per product, and 80% of products did not recoup their R&D investment, it became imperative to maximise return by launching a product world-wide. Companies which lack marketing presence in key markets have been obliged to make use of licensing deals, which meant sharing profit with another company. Furthermore, a strong global marketing capability has been vital in attracting the best in-licensing candidates and co-marketing deals, thus strengthening the product pipeline. Successful drug launches strongly correlated with product superiority, high prices and high promotional spend. Interestingly, "*satisfied*" markets have not appeared to have been a barrier to success. Drugs can be successful even in the most saturated markets as products offering meaningful incremental improvements are generally more successful than drugs which are first in class. In any event, low product prices are seldom associated with success.

PRODUCT CLASS

The pharmaceutical industry can also be divided into three broad product segments. First, prescription-only medicines (i.e. "*ethical*" drugs) comprise about 80% of the market by value and 50% by volume. A second broad segment is comprised by branded and identical "*generic*" competitors. A third segment are "*over the counter*" medicines (OTCs), which may be purchased without prescription and may also be branded or generic. Each of these three segments has required very different strategic capabilities. Producers of branded prescription drugs require strong R&D combined with sales and marketing infrastructure. Generics companies focus on supply chain management and manufacturing cost leadership in both ethical and OTC sectors. But since OTC's are rarely reimbursed, branded OTC drugs demand direct-to-consumer marketing capability.

The market can also be segmented according to the broad uses to which drugs are put. An important distinction is between "*primary care*" and "*specialist*" products. Primary care products are generally self-administered therapies prescribed by general practitioners, whereas treatment with specialist products is typically initiated in hospitals. Sales volume, marketing spend and skills required differ for the two segments. This as "*primary care*" products require mass marketing while specialist products involve targeted relationship marketing. Therapies for common chronic diseases have been the most lucrative, the biggest sector has been cardiovascular disease, with 5.2% of world audited sales in 2000 and rank third in terms of the number of prescriptions, as cardiovascular disease has remained to be the leading cause of death world wide. The treatments for gastric ulcers, infections, central nervous system disorders, arthritis and asthma have also been important contributors. In contrast, drugs to treat cancer have only made up 1.6% of the world market (in terms of audited sales in 2000) and although with that volume of sales cancer drugs rank number 12 in importance, they hardly were in scene before the late 1990s. Moreover, even in 2000 drugs to treat cancer had negligible volume of prescriptions when compared with top selling products.

Changing trends in audited sales have usually been influenced by demographic patterns and medical advances. But changing trends in the late 1990s, and particularly the rise of new therapeutic classes, have been associated with patients with chronic diseases increasingly well-satisfied with existing treatments. Pharmaceutical companies have thus found themselves forced to pursue research into niche areas which have had a high medical need for new treatments. Up and coming areas have included cancer treatment or so-called "*lifestyle*" conditions such as impotence, obesity and hair

loss. Diseases of the elderly, such as Alzheimer's Disease, have also become important targets for research because drugs aimed at the ageing population have grown in importance to become the two leading therapeutic classes in terms of prescriptions (i.e. product units) in 2000.

MANUFACTURING

One way to segment participants in the markets for prescription pharmaceuticals would consider the type of producer that manufactures the medicine, namely research-based sector, generic manufacturers and biotechnology companies. First, research-based pharmaceutical companies have historically been niche specialists which commercialised in mass volume markets. The typical cost structure at research-based pharmaceutical companies comprised the manufacturing of goods (25%), research and development (12% to 21%), administration (10%), and sales and marketing (25%). Manufacturing at research-based companies historically suffered from low utilisation, high fixed costs and low productivity. Growing costs related to R&D and marketing became an incentive for leading corporations to take steps and restructure manufacturing. Restructuring usually involved rationalising the number of production sites and placing them in strategic locations which offered tax advantages (such as Puerto Rico or the Republic of Ireland). Distribution of drugs to pharmacies and hospitals has been largely performed by specialist wholesalers, although some companies deliver directly. Companies have also made efforts to improve supply chain management and release the value previously trapped in high inventories. However, manufacturing and distribution efficiency at research-based companies has not been comparable with that at manufacturers of generics who have competed on low price and cost leadership. Research-based companies which own OTC and generics businesses generally operate them separately, frequently using another company name. Similarly, those that have acquired biotechnology companies normally leave them to operate fairly autonomously. Other companies in the research-based sector have been increasing grants and joint ventures with research-active universities across the world.

A second type of producer is the generic manufacturer. For them size has also become critical because during the late 1990s there was a collapse of generics prices in the US. As a result, the speed and aggression of generics attacks on branded products increased sharply. The outlook for the sector has been fairly rosy given the increasing number of global brands with patent expiry

looming and markets with untapped generics potential (*e.g.* Italy, Spain, France), with compound annual growth rate of 12% predicted to deliver $30 billion dollars by 2004.

A third type of producer encompasses biotechnology companies, which rely on molecular biology and genetic engineering. Efforts in biotechnology companies opened up vast new areas of medical research but participants were soon to discover that genetically engineered products had far higher production costs than traditional pharmaceuticals, with higher prices limiting applications to low-volume high-need areas. Many biotechnology operations originally planned to integrate and perform all functions from research to sales. However, the very high attrition rate in drug development made integration a high risk strategy. Only three companies have succeeded in achieving this goal namely, Amgen, Biogen and Genzyme. Of these Amgen was the only serious global player as it ranked number 20 in terms of sales during 2000. The remaining leading players (Genentech, Chiron, Genetics Institute) were partly owned by larger firms. Biotechnology companies largely abandoned attempts to market drugs themselves (although they often try to retain US marketing rights) and use the global presence of the research-based pharmaceutical companies to leverage return on R&D investment through licensing and strategic alliances.

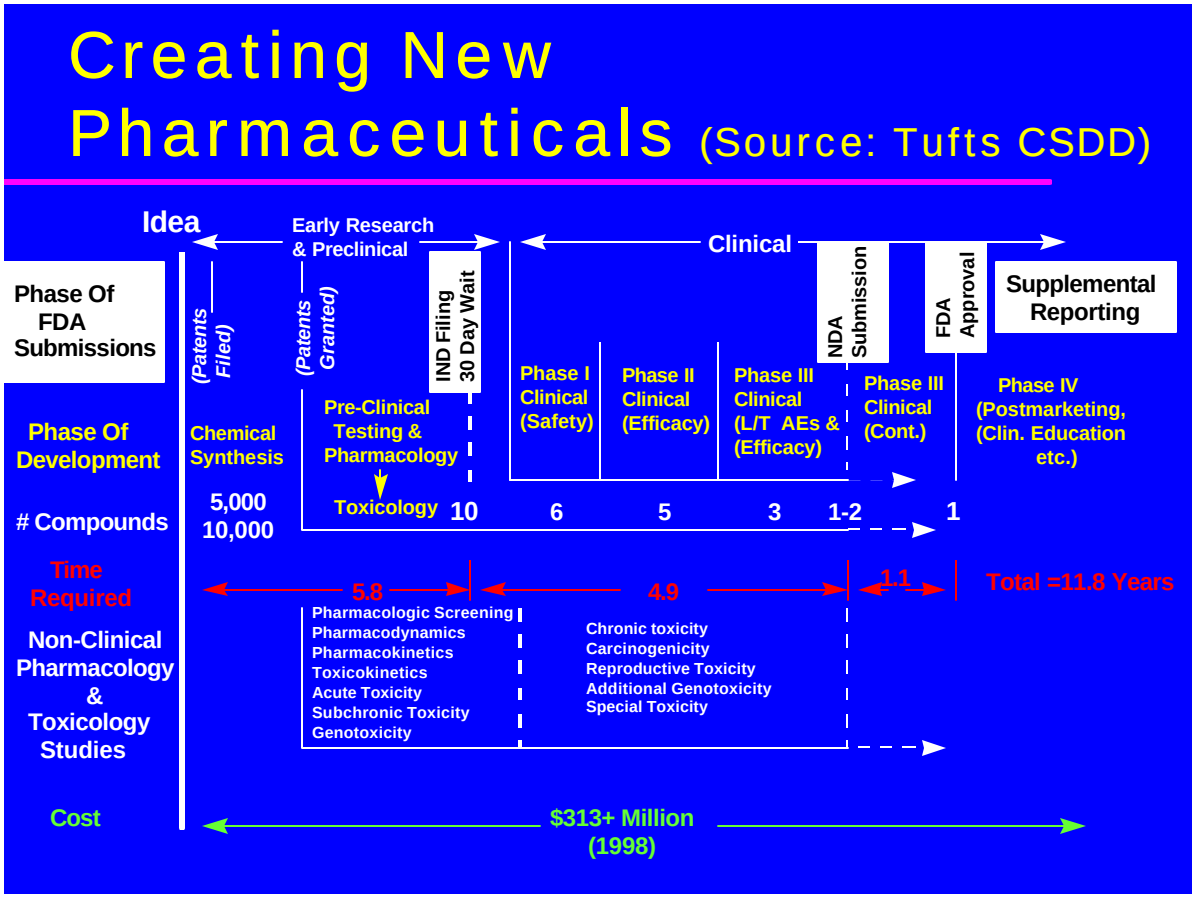
INTERNAL INNOVATION

Managers at research-based manufacturers, generic manufacturers and biotechnology companies have used resources at their disposal to compete and develop competitive advantage by accessing products which are innovative and differentiated; possess the potential for intellectual property protection; can be developed rapidly; and can be marketed successfully. Moves away from the pharmaceutical "*core*" have been made by various firms in the past, the results of which have been mixed at best and usually weakening of earnings as well as stock market performance. Companies with consistently high levels of R&D spending and high productivity resulting from R&D investment have become industry leaders. For this reason, company valuations place as much importance on the R&D "*pipeline*" (i.e. the products in development) as on the currently marketed products. Regarding the "*pipeline*", the pharmaceutical industry differs from most others in its long new product lead times. New product development can be divided into distinct research and development phases. The research phase produces a molecule which has the desired characteristics to be an effective drug for a targeted disease process. Development encompasses all of the

formulation, toxicology and clinical trial work necessary to meet stringent regulatory requirements for marketing approval. As figure 4 shows, time to market from discovery to marketing authorisation typically takes almost 12 years.

Obtaining marketing approval has for some time no longer been the end of the road in many countries as further hurdles must be overcome in demonstrating the value of the new drug to justify its price and/or reimbursement to cost-conscious payers. Development must also consider resources used while manufacturing and commercialising the drug (resources such as those used in market preparation activities). External and internal pressures for the industry have resulted in a shorter, flatter, product life-cycle and a race to market. However, all of the evidence points to lengthening development times and a fall in R&D productivity. For instance, the time taken for drugs to move from laboratory to market increased by nearly 7 years from 1960 to 2000. During that period the time taken for regulatory review remained fairly static and the period before clinical testing rose only slightly. Most of the increase has occurred in the clinical development phase. The average number of trials and the number of patients for each new drug application have increased enormously, that is, from 26 trials involving 1,500 patients in 1980, to more than 65 trials involving over 4,000 patients by 1995. Not surprisingly, a combination of increasing time to market together with easy drug targets (such as simple infections) having been addressed and growing spending on R&D, resulted in the number of new products reaching the market falling. For instance, in 1981, global R&D expenditure was around $5.4 billion dollars while it was estimated to exceed $50 billion dollars in the year 2000. Conversely, 51 new chemical entities (NCE) were introduced in 1980 but only 32 in 1999.

Figure 4: *Creating New Pharmaceuticals*



Given the high attrition rates of NCEs it should be no surprise that "*blockbuster*" or "*megabrand*" drugs have had the potential to determine the fortunes of pharmaceutical companies. GlaxoWellcome's strength was originally derived from Zantac, for the treatment of gastric ulcers, which was superseded by Astra's Losec as the world's best-selling drug for the same indication. To become a blockbuster, a drug must normally be a chronic therapy for a common condition, offer a perceived step-change in efficacy or tolerability and be marketed globally. There has been no official definition, but as suggested in table 2 annual sales should probably exceed $1 billion for a drug to earn this accolade. The table below also shows that one percent or less of available drugs could be considered a blockbuster.

While blockbusters have made immense contributions to company fortunes and provided tremendous returns on R&D investment, they have been few and far between. In 1998, only 40 products achieved over $1 billion sales world-wide, and the average for all drugs has been put at $186 million. Furthermore, over-dependence on a blockbuster can render a company highly vulnerable to generic competition once patent expiry looms and one third of the top 35 molecules

(NCEs) in 2000 faced patent expiry by 2004. In other words, the global exposure to blockbusters in 2000 was nearly $45 billion dollars of which over 60% affected the top eight companies.

Table 2: ***Individual Drug Sales, 1999***

Sales Per Annum	% NCEs Achieving
$1.8bn +	1%
$920m-$1.8bn	1%
$460m-$920m	2%
$180m-$460m	6%
Less than $180m	90%

EXTERNAL INNOVATION

So how have pharmaceutical companies responded to environmental change? The industry has adopted a number of strategic responses to the challenges posed by globalisation and greater R&D scale. Many pharmaceuticals introduced *"disease management"* initiatives. These have involved understanding the goals of the healthcare system in addressing a specific disease area. The pharmaceutical company then aligns itself with the healthcare providers, trying to offer an integrated service which improves eventual disease outcomes, positioning its drugs as one part of the delivery process. The US market saw the brief emergence of an interesting new business model to link pharmaceuticals and healthcare providers while, at the same time, offer the potential to move pharmaceutical companies away from greater R&D scale as critical success factor: Merck acquired a Pharmacy Benefit Manager (PBM) in 1993. Merck's move was deemed interesting because PBMs cover the cost of prescriptions in exchange for insurance premiums, often paid for by employers. After Merck acquired Medco for $6 billion dollars, in 1994 SmithKline Beecham purchased another PBM called DPS, and that same year Eli Lilly purchased PCS. The apparent logic was the conventional strategic rationale for vertical integration. But much to the surprise of managers at pharmaceuticals, barriers were quickly put in place to prevent companies from influencing PBM's formularies and removing competition. While Merck has retained ownership of Medco and has apparently benefited, both SKB and Eli Lilly were unable to create cross-links between their R&D operations and their PBM's databases with the result of costly divestments of the PBMs in 1999.

Another common response has been to conduct pharmacoeconomic evaluations, studies that aim to demonstrate the added value offered by a new drug as a result of improved efficacy, safety, tolerability or ease of use. However, it is very difficult to conduct a health economic study that will be regarded as credible and relevant by the intended audience. The enormous variability in healthcare practice and cost, even within one country, the difficulty of using clinical trial data to model everyday reality, and the fact that industry sponsors most of the research results in most pharmacoeconomic evaluations presumed to be biased. Health economic evaluations, therefore, have added to the costs of introducing and marketing drugs but have rarely made a significant impact on barriers to entry or pricing and reimbursement levels.

ORGANIC GROWTH VERSUS ACQUISITION

Table 3 shows how alongside attempts to vertical integration, the overwhelming industry response to the need for critical mass in R&D and global marketing presence has been a wave of mergers and previously unheard-of hostile acquisitions leading to amalgamation.

Products of mergers in the late 1990s included Novartis, Aventis, AstraZeneca, Pharmacia (with Monsanto), Pfizer (with Warner-Lambert) and the planned marriage of GlaxoWellcome and SmithKline Beecham in 2001. As a result of amalgamation and as table 3 suggests, the leading global players in the pharmaceutical industry have originated from Triad countries and predominantly the US and Europe, as Japanese companies lag behind. American companies have pulled away from European companies in terms of sales growth by benefiting from a strongly growing domestic market. American companies such as Pfizer, Merck, BMS and Johnson & Johnson recorded growth exceeding 15% between 1998 and 1999. At the same time, European-based companies like Novartis, Aventis and Sanofi-Synthelabo languished at around 5% for that period.

Table 3: *Leading Global Pharmaceutical Companies, 1997 and 2000*

(Top world-wide sales, retail market share and major drug mergers in the late 1990s)

1997		2000			
Company	Total Sales, $bn	Company	Total Sales, $bn	Share within Global Retail	Sales Growth (1999 to 2000)
Glaxo Wellcome[1] (UK)	11.6	GlaxoSmithKline[6] (UK)	22.2	7.3%	12.4%
Merck (US)	11.4	Pfizer[5] (US)	20.2	6.7%	12.0%
Novartis[2] (CH)	11.0	Merck (US)	15.5	4.4%	16.0%
Bristol-Myers Squibb (US)	9.3	AstraZeneca[4] (UK/Swe)	14.8	4.6%	4.4%
Johnson & Johnson (US)	8.7	Aventis[3] (Ger/Fra)	13.1	4.4%	15.8%
American Home Products (US)	8.4	Bristol-Myers Squibb (US)	12.0	4.1%	11.0%
Pfizer (US)	8.4	Novartis (CH)	11.6	4.1%	15.3%
Roche (CH)	8.0	Roche (CH)	11.0	3.2%	7.5%
SmithKline Beecham (UK)	7.4	Johnson & Johnson (US)	10.7	3.6%	11.8%
Hoechst (Ger)	7.4	Eli Lilly (US)	9.3	3.1%	8.7%

Notes

Number	Created	Originating Companies	
1	1995	Glaxo (UK)	Wellcome (UK)
2	1996	Sandoz (CH)	Ciba-Geigy (CH)
3	1998	Hoescht (Ger)	Rhône-Poulenc (Fra)
4	1998	Astra (Swe)	Zeneca (UK)
5	2000	Warner-Lambert (US)	Pfizer (US)
6	2000	Glaxo Wellcome (UK)	SmithKline Beecham (UK)

Source: The Economist (21-II-98), Financial Times (6-IV-00) and own estimates.

There has been a strong belief that companies must have critical mass to survive in the long term. Analysis of growth rates provides some support in favour of size, with average growth rates declining with size. However, there have been exceptions to the trend such as US-based Pharmacia and Takeda from Japan, which ranked at 10 in terms of sales volume but grew at over 20% in 1999. Another argument for increasing size to improve R&D productivity has been that productivity rests at least partly on "*technology platforms*"; that is, companies must invest in the development of (expensive) research capabilities if they are to keep up with the industry leaders in terms of time

to market. Managers of many pharmaceuticals, therefore, have considered that the larger the total R&D programme, the greater the number of individual projects that can benefit from the new capability, and the greater the opportunity to amortise these costs.

Table 3 also suggest that merger deals completed between 1999 and 2000 among pharmaceutical companies intensified the pressure on other leading companies to abandon organic growth strategies and consider potential partners. Table 3 shows how companies formed between 1999 and 2000, such as Aventis and the new Pfizer, have overtaken Merck, which followed an organic growth strategy throughout the 1990s and dropped from second to fourth place on a revenue basis. Managers of Merck announced they were maintaining an emphasis on organic growth, but analysts doubted that the company could expand fast enough on its own to compete with GlaxoSmithKline or the new Pfizer. Similar thoughts probably crossed the minds of the management team at American Home Products and Bristol-Myers Squibb, a company that had been confined mainly to healthcare activities but covered a broad scope of products including, for example, OTC products.

According to many industry observers the next big deal could involve Novartis. This company was seen as the potential partner of choice because of a wide range of business that complemented any portfolio of pharmaceutical products. The company also had a large department for the production of generic drugs in Europe. The second partner of choice was Bristol-Myers Squibb whose sales had grown by 9% on average in the second half of the 1990s and was free of patent expirations in early years of the new Millennium. Until the mid-1990s, Bristol Myers Squibb held the number one position in the US market with sales of $8.4 billion dollars in 1998; and third position in the European market, with sales of $2.9 billion dollars in 1998. In fact, the position of Bristol-Myers Squibb as a leading pharmaceutical company was effectively challenged by the round of amalgamations in 1999 and 2000 and as a result, managers could see a need to merge in order to maintain competitive momentum.

In the course of the process of wide spread amalgamation and industry change, European companies have faced tougher challenges than their US rivals. The US has been the world's biggest and fastest-growing market, while Europeans have typically consumed about half the number of pills than people in North America. Perhaps these differences in consumption could explain why only half of Germany's 1,000-plus drug companies had more than 100 workers.

But even as top organic-growth-led companies like Merck were falling in the rankings, few wanted to abandon their strategy. Arguments used by proponents of pharmaceutical firms pursuit of organic growth involved lack of evidence to support scale contributing to greater efficiency. Furthermore, success of biotechnology companies in drug discovery suggested great scale in R&D could actually be a disadvantage as creativity seems to work better in small groups.

Supporters of organic growth have tended to believe that portfolio management can also be problematic in merged companies: cutting too many projects in the search for "*blockbusters*" could result in a much higher level of risk. Cutting too few means under-resourcing potential winners and risks an over-stretched and unfocused organisation. In one analysis, the median number of projects at merged firms fell from 85 in both pre-merger companies to 56 by 3 years post-merger, suggesting that companies which merged during the late 1990s tended to focus on winner products or that merged companies became less productive. Definitive evidence could be years away.

Other supporters of organic growth have claimed that adding more sales power through representatives would bring diminishing returns (particularly in the US) because specialists (as opposed to general practitioner medical doctors) have continued to grow in importance and new distribution channels (such as direct-to-consumer marketing) have also increased in importance. Sales techniques have also been changing because product launches can be implemented by using '*spare capacity*', contracting excess resources from big firms and thus smooth out peaks that could emerged between drug launches and thus, maximising marketing expenditure. The argument effectively evolved around those types of developments plus market segmentation between therapeutic categories allowing medium size companies and drug specialists to mount successful sales efforts.

Yet other proponents of organic growth claimed that marketing success develops from the right skills, resources and competencies rather than from sheer size of the sales force. For them improving internal performance was a superior alternative because big pharmaceuticals have suffered from high employee turnover, talent has seldom been attracted outside the pharmaceutical industry, poor use of technology and sales techniques that have not really changed in 35 years. Moreover, in their opinion, mergers have tended to result in slower growth while big pharmaceuticals look more and more like specialists marketing and development outfits, increasingly subcontracting to academia and biotechnology companies.

But in any event, few could really tell whether amalgamation or organic growth would solve the pharmaceuticals' '*productivity crisis*', the challenge of expanding the revenues in the medium term because of product disappointments which severely undermined the '*pipeline*'. Pharmaceuticals have thus been challenged to sustain high valuation in the stock market once financial disposals finish and before benefits of long term investments (such as those made in genomics) kicked in. However, observers still disagreed whether the amalgamation of pharmaceutical companies could become a race to eliminate bloat and duplication in corporate overheads, sales and marketing. At the same time, regulators have been increasingly concerned that dwindling suppliers in the market place would threaten with dwindling consumer choices.

EMERGING TRENDS

At the end of the 1990s, the sales representative still remained decisive for successful sales and marketing in the pharmaceutical industry. There was a belief that the introduction of managed care meant that the marketing approach based on salespeople providing detailed information to individual prescribers was out-dated, but the challenge was successfully surpassed by the creation of new types of salespeople to liase with MCOs. However, those companies which stuck with the old approach and increased their sales-force size and share of voice, such as Pfizer, found that it paid off.

Nevertheless, it was also true that marketing approaches were shifting. As mentioned above, the ability successfully to market direct to consumers (DTC) was becoming of increasing importance in the US market. The term "*high compression marketing*" (HCM) was coined to describe the approach adopted by leading companies in their efforts to establish new market presence. HCM has involved simultaneous world-wide launches, global branding, and very heavy investment in promotion and share of voice around time of launch. The intention has been to create a rapid take-off curve which will maximise return from the product by creating higher peak year sales earlier in the product life-cycle. A good example was the launch of Celebrex by Searle, a subsididary of Pharmacia, which netted $1 billion sales in the first 9 months.

However, while product-led muscle-marketing seems to be the name of the game in mass pharmaceutical markets, a small number of companies have adopted a very different approach with notable success. These companies build their strategies around specific customer groups, aiming to

satisfy their needs on multiple dimensions. In other words, they develop a franchise. Good examples include Elan Corporation, which has built a profitable niche business by targeting and meeting the needs of the neurology market, and Bristol Myers Squibb, which managed to keep the top position in the specialised cancer market.

Another response to environmental change has been developed by Roche, who claims to be operating a new "*integrated healthcare*" business model. At the core of this model lies a strong diagnostics division which has to create opportunities to use "*diagnostics*" to select patient groups for treatment and thus maximise the impact of information derived from the Human Genome Project (HGP). Genomics is the study of human genes and through a joint multinational effort known as HGP has delivered a complete list, in order, of the chemical "*letters*" making up the DNA in human cells, discovering the location and composition of all human genes. But sequencing the genome does not equal to fully understanding the function of the genes. In order to identify new opportunities for pharmaceutical intervention, it is essential to understand what genes are actually doing. So-called "*functional genomics*" is the next challenge and so develop drugs that interact with "*targets*". For example, enzymes involved in disease processes or the cell-wall of bacteria. The total number of targets discovered up to the year 2000 by the HGP, amounted to well under 1,000. Functional genomics has the potential to increase this by orders of magnitude, offering immense potential for better-targeted, more effective and less toxic therapies.

Furthermore, the HGP provided the sequence for one person's genetic make-up but only the "*plain vanilla*" version of the genome. Variations in genetic make-up (Single Nucleotide Polymorphisms or SNPs) will also be of great interest. Understanding genetic susceptibility to disease could lead to much improved screening tests and earlier intervention (provided that effective therapies are available). Pharmacogenomics involves the use of genetic information to understand why some patients populations benefit more than others from a therapy, or why some populations experience specific side effects. This should allow treatments to be targeted to those who will benefit most (which will appeal to healthcare payers), while pricing policies change to maintain profitability from smaller market segments. In other words, the development of drugs which target specific molecular components of the disease may require patient specific characterisation.

The expectation is that the HGP will provide accurate molecular components if diagnostics provide relevant patient information. Roche identified this opportunity early on and re-positioned itself to take advantage of it. Managers at Roche have had a strong diagnostics division, whose strategic vision was to move from seller of instruments and reagents to a health information provider, offering value through better targeted treatments, convenience and "*peace of mind*". Managers at Roche also recognised the potential impact of surrogate markers on the speed of clinical development. Roche claimed to have developed the only company embracing these principles, having both requisite experience, and all the necessary tools to lead the improvement of disease categorisation as well as lead the shift in healthcare provision offered by genomics and diagnostics. Actually, Roche owned much of the relevant intellectual property with consequent high barriers to entry for other companies who had yet to develop similar capabilities.

Another emerging trend has evolved around the role of direct-to-consumer (DTC) advertising, predominantly on television, will take in pharmaceuticals' marketing mix. As a medium, DTC TV was one of the key drivers behind the strong volume growth of the US pharmaceutical market during the 1990s. Although the EU does not yet allow DTC advertising of pharmaceuticals, consumers with Internet access can obtain information on new products directly. In the year 2000, health was one of the top 2 reasons for people to conduct searches on the Internet with Yahoo.com/Health, Excite.com/Health and AOL.com/Health the three most visited health-related websites. These could be accessed by both US and European consumers while, at the turn of the Millennium, about 71% of US households had Internet access, while in the EU the proportion of adults over 15 with Internet access ranged from 12% in Spain to 65% in Sweden. Internet access had so far largely been determined by the availability of a computer, with penetration rates increasing significantly with the advent of interactive digital television. Moreover, along with a shift of medium from print and TV to the Internet, the late 1990s also observed a noticeable shift in news coverage with the reporting of political events giving way to health related issues.

As the convergence of telephone, information technology and television accelerates, it has been difficult to envisage how a ban on DTC could be maintained. Furthermore, marketing surveys by pharmaceutical companies resulted in nearly half of respondents reporting that they found the Internet better than other sources for health-related information. Thanks to the Internet, consumers could become much better-informed about their health and the available treatment options.

Information on new drug has been reaching consumers *via* company web-sites, independent web-sites and through distribution of press-releases to PR services. Marketing surveys suggested that up to 75% of persons that do search for health-related information on the Internet in the US were likely to discuss that information with their healthcare providers (while the same surveys suggested the number to be 44% on average in the EU). To continue, this trend could increase the level of patient demand for new effective, better-tolerated therapies, particularly in litigious countries such as the US. The increased transparency of information provided by the Internet has not, however, been an unmixed blessing for the pharmaceutical industry. It was also likely to raise awareness of the enormous price differentials that can exist between countries in the same region or trading block for the same product (such as the wide price differential between the US and Canada or between EU countries). As consumers become better-informed, the industry could find it hard to maintain pricing levels. If the very significant barriers to inter-country supply were reduced, consumers could even purchase across borders, using "*intelligent agent*" software to hunt down the best prices.

But in spite of the human genome project (HGP) and the internet, emerging markets and new "*life style*" drugs, the challenge for the future of pharmaceutical companies at the turn of the Millennium, had changed little from 30 years earlier: to discover the right drug for the right dose in the right time. Finding new formulas for value creation will play a major role in this tough challenge, not only by providing new tools and concepts but also by helping to combat criticism as a frenzy of big deals and (for some) frequent changes of focus, proved that most strategies were failing to convince analysts.

DISCLAIMER

This case represents the views of the authors and not necessarily those of AstraZeneca. This case is intended for class discussion and not as an illustration of either good or bad management practice.