THE GLOBAL PHARMACEUTICAL INDUSTRY

Sarah Holland* and Bernardo Bátiz-Lazo**

*The case looks at the development of the **ethical** pharmaceutical industry. The various forces affecting the discovery, development, production, distribution and marketing of prescription drugs are discussed in terms of their origins and recent developments. Readers are then invited to consider trends for the future.*

In late 2003, Britain's *Guardian* newspaper commented that, on the face of it, the global pharmaceutical industry "looks like the epitome of a modern, mature industry that has found a comfortable way to make profits by the billion: it's global, hi-tech, and has the ultimate customer, the healthcare budgets of the world's richest countries."[1] Manufacturers of pharmaceuticals certainly did not appear to be in industry with a looming crisis, yet, declared the newspaper, that was the alarming conclusion of a research report by analysts at investment bank Dresdner Kleinwort Wasserstein. The analysts argued that the world's largest drugs companies were operating a business model that was unsustainable and "rapidly running out of steam". The treatment they prescribed was further industry consolidation. This case explores some of the trends affecting the "***ethical***" (research-based) sector of the industry and invites readers to prepare their own analysis and prescription.

[Insert Box 1 around here]

INDUSTRY EVOLUTION

As described in Box 1, the pharmaceutical industry is characterised by a highly risky and lengthy R&D process, intense competition for ***intellectual property***, stringent government regulation and powerful purchaser pressures. How has this unusual picture come about?

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, which moved into synthetic pharmaceuticals and eventually became global players. Penicillin was a major discovery for the emergent industry, and during the 1940s and 1950s R&D became firmly established within the sector. The industry expanded rapidly in the 1960s, benefiting from significant new discoveries with permanent patent protection. Regulatory controls on clinical development and marketing were light and healthcare spending boomed as economies prospered.

The pharmaceutical market developed some unusual characteristics. Decision-making was in the hands of medical practitioners whereas patients (the final consumers) and payers (governments or insurance companies) had little knowledge or influence. As a result, medical practitioners were insensitive to price but susceptible to the sales efforts of individual representatives. This enabled numerous "me too"

This case was prepared by Sarah Holland (Manchester Business School) and Bernardo Bátiz Lazo (London South Bank University). It is intended for class discussion rather than as an illustration of either good or bad management practice. Comments from Christopher Berry, Simon Ling, Stella Richter, Justin Boag and MBA graduates of the Open University are gratefully acknowledged.

drugs to achieve satisfactory returns on investment. Imitating a known drug reduced R&D risk considerably, while the marketplace was open to products offering minor advantages such as a more convenient dosage form or fewer side effects, but with much the same therapeutic outcome.

There were two important developments in the 1970s. Firstly, the Thalidomide tragedy (where an anti-emetic given for morning sickness caused birth defects) led to much tighter regulatory controls on clinical trials, greatly increasing development costs. Secondly, enactment of legislation to set a fixed period on patent protection (typically 20 years from initial filing as a research discovery) led to the appearance of "***generic***" medicines. Generics have exactly the same active ingredients as the original brand, and compete on price. The impact of generic entry is illustrated by Bristol Myers Squibb's brand Glucophage, a treatment for diabetes, which generated US sales of $2.1bn in 2001. Following loss of the patent in January 2002, brand sales plunged to $69m for the first quarter. The introduction of generics, however, was very beneficial for society: valuable medicines became extremely cheap. Indeed, health economists have estimated that the social returns from pharmaceutical R&D exceed that appropriated by firms by at least 50 to 100 per cent.

Generics legislation had a major impact on the industry, providing incentives for innovation and a race to market. The time during which R&D costs could be recouped was drastically curtailed, putting upward pressure on prices. There was also greater emphasis on encouraging medical practitioners to remember drugs by brand name. By the end of the 1970s generic entrants and more stringent controls on clinical trials had led to substantial increases in R&D spending.

The pharmaceutical industry is unusual in that in many countries it is subject to a "monopsony" - there is 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, although drugs typically accounted for less than a tenth of that expenditure. Many countries introduced some form of price or reimbursement control and price increases began to be outlawed. The industry lacked the public or political support to resist these changes.

Entering the 1990s, worldwide economic recession reduced cash for provision of healthcare through tax-funded systems (Canada, Italy, Spain and UK); social security supported systems (France, Germany and Japan), as well as employer/privately-funded systems (US). It was recognised that healthcare had none of the normal checks and balances of a free market to match supply and demand. Payers would no longer tolerate spiralling healthcare costs and created incentives for decision-makers to gain better value for money. In Germany in 1993, overall pharmaceutical sales fell by 11 per cent while the four leading generics manufacturers increased their sales between 10 and 63 per cent. Pressure was put on the industry to deliver genuine product innovation rather than "*me too*" drugs.

A new type of player had appeared in the 1980s- small biotechnology start-ups backed by venture capital to exploit the myriad opportunities opened up by molecular biology and genetic engineering. By

[1] *The Guardian*, September 12, 2003.

2003 there were more than 600 publicly traded ***biotechs*** worldwide. However, biologicals were more complex to produce than traditional pharmaceuticals, causing a global shortage in production capacity. This drove up prices and often limited biotech applications to low-volume, high-need areas. Although sales doubled in the 5 years to 2002, at $27 billion biologicals contributed only 7 per cent of global market value. Many biotechs originally planned to integrate and perform all functions from research to sales. However and as noted by Kenneth I. Kaitin, director of the prestigious Tufts Center for the Study of Drug Development, the very high attrition rate in drug development made the creation of integrated sales and research platforms a hazardous strategy:

"Business as usual is no longer an option when it comes to developing new prescription drugs. Pharmaceutical and biopharmaceutical companies are spending more on R&D than ever before, yet the number of new drug approvals has declined steadily. As a result, many drug firms are focusing on ways to improve the efficiency and productivity of their R&D programs."[2]

Most biotechs lacked the finances to cope with the huge risks involved in an integrated sales and research platform and by 2003 only three companies had achieved this goal namely, Amgen, Biogen and Genzyme. Moreover, only 40 out of 1,466 biotech companies in the US were trading profitably. Amgen was the only serious global player, ranking number 17 in terms of sales during 2002. The other leading biotechs (Genentech, Chiron, Genetics Institute) were partly owned by larger firms. Biotechs had thus largely abandoned attempts to market drugs themselves (although they often sought to retain US marketing rights) and instead used the global reach of the research-based multinationals to leverage return on R&D through out-licensing and strategic alliances. As stock market funding dried up[3], the sector began to consolidate to marry revenue streams with promising pipelines. In the UK, for instance, British Biotech merged with drug company Vernalis, while Celltech acquired Oxford Glycoscience.

INDUSTRY SECTORS

At the turn of the millennium, prescription-only or *"**ethical**"* drugs comprised about 80 per cent of the global pharmaceutical market by value and 50 per cent by volume. Ethical products divide into conventional pharmaceuticals and more complex "biological" agents and vaccines. The remainder were "***over the counter***" medicines (***OTC***s), which may be purchased without prescription. Both ethical and OTC medicines may be branded or "generic".

The typical cost structure at ethical pharmaceutical companies comprises manufacturing of goods (25 per cent), research and development (12 to 21 per cent), administration (10 per cent), and sales and marketing (25 per cent). The key strategic capabilities at these companies are R&D and sales and marketing, and manufacturing historically suffered from low utilisation, high fixed costs and low productivity. Growing pressure on margins became an incentive to restructure manufacturing, rationalising the number of production sites and placing them in strategic locations offering tax

[2] *Business Wire*, January 6, 2004.
[3] US stockmarket flotations of biotechs fell from 40 in 2000 to only 4 in 2001-2.

advantages (*e.g.* Puerto Rico, Republic of Ireland). Companies also improved supply chain management to release the value trapped in high inventories.

However, manufacturing and distribution efficiency at research-based companies was not comparable with that of generics manufacturers who competed on price. During the late 1990s, there was a collapse of generics prices in the US and a shakeout to determine cost leadership. In this environment economies of scale proved decisive and the sector underwent consolidation. As a result the speed and aggression of generic attacks on branded products increased sharply. By 2002 generics captured 65 to 80 per cent of new prescriptions within 5 weeks of patent expiry on major drugs and overall accounted for nearly a third of market volume. Given the number of major global brands with patent expiries looming and markets with untapped potential (e.g. Italy, Spain, France, Japan), plus US legislation to prevent delays to market entry, the outlook for the generic sector was rosy. In 2002, nine of the top 10 fastest growing pharmaceutical companies were generics manufacturers and predicted compound annual growth rate of 12 per cent was forecast to deliver $30 billion dollars in sales in 2004.

Thus there are four broad types of industry player: ethical, OTC, generic and biotech. Each requires very different strategic capabilities. Producers of branded prescription drugs require strong R&D and global sales and marketing infrastructure. Branded OTC drugs demand direct-to-consumer marketing capability. Generics companies focus on supply chain management and manufacturing cost leadership. Biotechs must create and defend ***intellectual property*** in specialised research fields. Because of the different attributes and cost structures involved, multinationals which own OTC and generics businesses generally operate them separately, frequently using another company name. Similarly, those that have acquired biotechs normally leave them to operate fairly autonomously.

BUSINESS ENVIRONMENT

As key economies stagnated in 2002, challenges in funding healthcare advances remained. Ageing populations created further pressures, since the "over-65s" consume four times as much healthcare per head as those below 65. This combined with more expensive high technology solutions and increasing patient expectations created an unsustainable situation. On the one hand, universal coverage systems (such as those in Spain and the UK) were slow or unable to introduce the latest treatments. On the other, insurance-funded systems (such as that in the US) were able to afford the latest innovations but were unable to share those benefits with an increasing part of the population. In 2002 the number of US citizens without health insurance rose by 5.7 per cent to 43.6 million, the biggest single annual increase in a decade.

In response to these pressures, payers used a wide variety of methods to control spending on pharmaceuticals (see Exhibit 1). Some put the emphasis on the supply side - the manufacturer and distributor. Some emphasised the demand side - the prescriber and the patient. Other methods affected both. No country relied on a single approach. Types of control reflected deep-rooted cultural differences with supply-side measures were favoured by more centralised, less market-oriented

economies. The choice of strategy was also affected by the importance or otherwise of the national pharmaceutical industry as a contributor to GDP, balance of trade and employment.

Exhibit 1: Methods used to control pharmaceutical spending

Controls on suppliers	Mixed effect	Controls to influence demand
Negotiated prices	Partial reimbursement at price negotiated with manufacturer	Patient co-payments
Average pricing		Treatment guidelines
Reference pricing		Indicative or fixed budgets
Positive and negative lists	Generic substitution	Incentives to prescribe or dispense generics or parallel imports
Constraints on wholesalers and pharmacists		Transfer from prescription-only to OTC

In countries with supply-side controls, negotiating price or reimbursement approval could take as long as six months or a year.. In countries with demand-side controls, there were similar delays in achieving market penetration, because of the need to negotiate product inclusion in formularies, or endorsement by bodies such as the ***National Institute for Clinical Excellence*** (***NICE***) in the UK.

Generics posed a particular threat. Several important markets (Japan, France, Spain, Italy) featured low volume use of generics – no more than 6 per cent. However, generics were being actively encouraged in all EU markets and rapid penetration was anticipated. Computer systems enabled prescriptions to be printed in their generic rather than branded form, enabling the pharmacist to supply the cheapest generic drug. Brand loyalty was no longer a safeguard following patent expiry.

Pharmaceutical spending controls were designed to reward genuine advances. Price premiums and/or reimbursement levels were based on perceived innovativeness and superiority, penalising "me too" drugs. As a result, there was a race to market with each new drug class, since only the first to market would benefit. Competition was waged most fiercely at the level of drug class and being late to market with an undifferentiated product was a recipe for failure.

The industry adopted a number of strategic responses to these challenges. Many pharmaceutical companies introduced ***"disease management" initiatives***. Another common response was to conduct pharmacoeconomic evaluations, studies that aimed to demonstrate the added value offered by a new drug as a result of improved efficacy, safety, tolerability or ease of use.

Government price controls created another challenge for the industry in the form of "parallel trade". The principle of free movement of goods across the Single European Market meant that distributors were free to source drugs in the cheapest markets (Spain, Portugal, France, Italy and Greece) and ship them to high price markets (Germany, the UK, Sweden and the Netherlands), pocketing the difference. There was minimal benefit to governments or consumers, but a significant loss for the industry. Instead of being ploughed back into R&D, this profit went to the parallel importers. Parallel imports were exacerbated when pharmaceutical wholesalers consolidated internationally through cross-border mergers and acquisitions, making it even easier to buy in one country and distribute in another. By 2002, parallel imports had gained 17 per cent of the UK, 7 per cent of the German market and were

estimated to account for 3.5 billion euro of revenues a year across the EU. Furthermore, the enlargement of the European Union was expected to exacerbate parallel trade, as prices in Central and Eastern Europe tended to be low.

Parallel trade was not confined to Europe. It was prevalent in the Far East and there was even a latent problem in the crucial US market given the price differentials with Canada. Canada had one of the toughest environments worldwide for the industry, with stringent and inflexible pricing and reimbursement criteria. In contrast, the US had no formal price controls and price increases were customary. Over time, this led to a wide disparity in prices (best-selling cholesterol-lowering drug Lipitor was $3.20 per pill in the US in 2003, compared with just $1.89 in Canada) that exposed the industry to sensationalist newspaper headlines such as "Canada's Rx drugs pouring into USA"[4]. Cross-border trade was driven by the rapid rise in medication cost, the 25 per cent of US seniors with no drug coverage, the economic slowdown, the ease of long-distance commerce over the Internet and increased awareness of price disparities. By 2003, state governors and Congress representatives were proposing to institutionalise and promote imports, despite opposition from the FDA and the Justice Department. Storefront import pharmacies and drug-sale parties in care homes were appearing all over the US and grass-roots activism was rife. The real threat to the industry was not the actual level of imports ($800m in 2002), but the risk posed to free pricing in the US from the public backlash. FDA commissioner Mark McClellan declared that there was an impending global crisis. The situation where US citizens bore the lion's share of the global cost of pharmaceutical R&D appeared unsustainable. Either US prices would fall, damaging R&D investment, or other wealthy countries, such as Germany and Canada, needed to shoulder a fair share of the burden. But with domestic pharmaceutical industries in decline, there was scant incentive for other governments to change their practices.

[Insert Box 2 around here]

KEY MARKETS

The majority of global pharmaceutical sales originate in the "Triad" (US, EU and Japan), with ten key countries accounting for over 80 per cent of the global market. The US has been by far the largest pharmaceutical market by volume and value ($192 billion in 2002 - half of global sales), with the strongest growth among key markets, contributing 65 per cent of global market growth. In 2002, the US accounted for a staggering 70 per cent of blockbuster sales, compared with only 4 per cent from Japan and 12 per cent from the EU. Projecting out to 2007, the US was predicted to increase its share of the global market, while the shares of Japan and the EU would decline. Non-Triad countries were expected to retain around 11 per cent share between them. Overall, the world market was set to become even more US-centric, leaving the industry heavily exposed to fluctuations in that market.

Following regulatory changes in 1997, pharmaceutical companies were permitted to market directly to US consumers. ***Direct-to-consumer*** (***DTC***) advertising transformed the marketplace and fuelled rapid

sales growth. However, the US operating environment was getting tougher. Managed care, in which plan administrators set cost and reimbursement limits on healthcare services, was also changing market dynamics. In 1990, 63 per cent of prescriptions were paid in cash by patients but by 2001, 73 per cent were paid by managed care plans. As companies' cost for providing drug benefits to employees increased 19 to 20 percent annually, MCOs began to encourage the use of generics through schemes where the consumer paid less if a generic was prescribed and extra for newer drugs. Furthermore, powerful bulk purchasers, such as the Veterans Administration with 6.9 million members, were able to extract prices even lower than those in Canada, so that average US prices paid were actually significantly lower than headline figures in the popular press suggested.

Japan has traditionally been the second largest market for pharmaceuticals, with sales of $47 billion in 2002. The Japanese operating environment has historically been very different from that of the US or the EU. This divergence occurred 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, relatively small domestic companies dominated the market. The Japanese pharmaceutical industry experienced significant environmental turbulence in the 1990s. Following a number of scandals, the system controlling clinical trials and regulatory approvals underwent a major modernisation programme, and many domestic companies were ill equipped to operate to the new standards. The economic recession caused tax revenues to fall, while the cost of treating the world's most rapidly ageing population was rising. This resulted in unprecedented price cuts, changes to healthcare funding and the introduction of stringent price controls. The upshot was very low pharmaceutical market growth of only 1 per cent in 2002.

Europe makes up the third part of the Triad, with the top five markets (Germany, France, Italy, UK, Spain) predicted to continue contributing around three quarters of EU sales out to 2007. European markets each have their own unique operating environments but they are generally characterised by strong payer pressures and consequently lower prices than the US or Japan. Combined with slowing economies, these pressures constrained EU market growth to 8 per cent in 2002. Expansion of the EU, however, provided opportunities for growth, especially in Poland and central Europe, but also brought new challenges from generics and low-priced parallel imports.

Although growth prospects for emerging markets were considered modest in 2003, their enormous populations and high levels of unmet need offered significant long-term potential. Many had strengthened patent protection and liberalised equity controls. The pharmaceutical markets in Latin America had proved highly volatile, reflecting underlying economic trends. Nevertheless they had large numbers of wealthy consumers who were able to afford branded drugs.

Pacific rim countries were becoming more important. Copy products were traditionally a significant issue in these markets, where patent protection was absent or very difficult to police. Pharmaceutical companies focused particularly on China, which had one of the fastest growing pharmaceutical

[4] *USA Today*, October 7, 2003.

markets. While Chinese herbal medicine remained a core part of healthcare, the use of Western medicines was on the increase, especially in booming coastal cities such as Shanghai.

Although least developed countries were not in a position to offer a significant market opportunity, they did present the industry with important strategic choices in the area of corporate social responsibility which had global ramifications. This is discussed further below.

INNOVATION

Ethical pharmaceutical companies establish competitive advantage by developing products that are innovative and differentiated, patentable, can be developed rapidly; and marketed globally. Moves away from the pharmaceutical "core" have been made by various firms in the past, the results of which were mixed at best and usually weakened earnings and stock market performance. Companies with consistently high levels of R&D spending and productivity became industry leaders. For this reason, stock market valuations place as much importance on the R&D "pipeline" (i.e. the products in development) as on the currently marketed products.

Basic research is vitally important to probe into the causes of disease and identify new potential targets for pharmaceutical intervention. As well as conducting in-house research, many companies sponsored academic research, although it was becoming much more difficult and expensive to secure intellectual property rights from academia. Companies also sought research alliances with biotechs and ***genomics*** companies (see Box 3).

[Insert Box 3 around here]

The holy grail of pharmaceutical R&D is the "***blockbuster***". Like "killer applications" in the software market, blockbuster drugs are genuine advances that achieve rapid, deep market penetration. Because of their superlative market performance, blockbusters often determine the fortunes of individual companies. Glaxo went from being a small player at the beginning of the 1980's to the world number one, with a presence in 50 countries, on the strength of a single drug - Zantac for stomach ulcers. A blockbuster drug is typically a long-term therapy for a common disease that offers a substantial perceived improvement in efficacy or tolerability and is marketed globally. Annual sales must normally exceed $1 billion for a drug to earn this accolade.

While blockbusters made immense contributions to company fortunes and provided tremendous returns on R&D investment, they were few and far between. In 1998, only 40 products achieved over $1 billion sales worldwide, while the average for all drugs was put at $186 million. However, blockbusters rapidly increased in importance and by 2002 this number had tripled. Seeking a blockbuster was clearly a high risk R&D strategy, but was fast becoming the only game in town, exposing an already high-stakes industry to even greater levels of risk. The 1995 industry pipeline had 450 drugs with average estimated peak year sales of $260 million, while the 2001 pipeline had 209 with average estimated sales of $634 million. However, over-dependence on blockbuster sales rendered companies highly

vulnerable to generic competition at patent expiry. Between 2003 and 2008, twenty blockbuster drugs were due to lose patent protection. By 2002 global exposure to generics was already around $40 billion of which over 60 per cent affected the top eight pharmaceutical companies. So even if the risky R&D pipeline delivered a blockbuster, blockbusters vastly exacerbated the volatility of the corporate sales line.

Unfortunately for the industry, development times were lengthening and R&D productivity was arguably in decline. The time taken for drugs to move from laboratory to market increased by nearly seven years from 1960 to 2000. Most of this increase occurred in the clinical development phase. The average number of trials and the number of patients for each new drug application increased enormously, from 26 trials involving 1,500 patients in 1980, to more than 65 trials involving over 4,000 patients by 1995. This resulted from more stringent regulatory hurdles, the need to produce evidence to convince payers, and the desire to maximise return by launching with a broad platform of promotional claims. As a consequence clinical trials became, by far, the most expensive element of the development process.

As clinical trials became ever more complex and costly, there was a sharp rise in R&D expenditure. The average fully capitalised resource cost (including research on abandoned drugs) to develop a new drug was estimated to be $1.4 billion in 2003. The corresponding figure in 1987 was $231 million and would have grown to under $500 million by 2003 at the pace of general inflation. R&D spending by the major corporations reached $35 billion in 2001, double the figure for 1997 and nearly triple the 1992 investment. But despite increasing average R&D spend from 11 to 12 per cent of annual sales to 16 or even 17 per cent, pharmaceutical companies had not much more to show for it. The launch of 24 genuinely new drugs in 2001 in the US was considered poor and the 2002 figure dropped further to 17, the lowest for 20 years. The European Medicines Evaluation Agency received only 31 applications, down from 58 in 2001. While this could have been a natural consequence of blockbuster focus, half of the applications were for treatment of diseases with a limited commercial market.

Pharmaceutical companies endeavoured to be both creative and efficient. Some argued that the secret of successful R&D lay in organisational competencies such as team working, knowledge management and close relationships with opinion leaders. Others emphasised "lean and flexible" operations and outsourcing of all but core competencies. Some large companies attempted to rekindle innovation and productivity by reorganising their R&D so as to create smaller and more nimble units - like internal biotech companies. Others sought external innovation, entering alliances where technology was emerging, and only acquiring in-house capability once the technology was proven. For example, Aventis prided itself on managing a complex web of alliances with more than 300 universities and biotechs. In such companies, the management of alliances itself became a key competency. Not surprisingly, biotechs were contributing an increasing share of the industry's new products - a record 35 per cent in 2001.

The organisational infrastructure required to deliver a new drug application had become large and complex. However, because of high attrition in new drug development, company pipelines could often be "lumpy": a company might have no products in Phase III, and then shortly afterwards find it had several promising candidates. Many companies concluded that maintaining a high fixed-cost clinical development capacity did not make sense. Instead, they out-sourced some clinical development to ***Contract Research Organisations*** (***CROs***). Typically it would cost more to conduct a trial *via* a CRO, but capacity could be switched on or off at will.

As the needs of patients with common chronic diseases became increasingly well satisfied by existing treatments, companies sought new research arenas. Some chose to pursue areas of high unmet need, such as cancer and Alzheimer's disease. Others focused on so-called "lifestyle" conditions such as impotence, obesity and hair loss. It was not surprising that with drug targets becoming more challenging, increasing time to market and tougher regulatory hurdles, fewer new products reached the market.

Some questioned whether the levels of R&D investment could be sustained. For example, in 2002 there were 340 cancer drugs in development. With pressures on payers growing it seemed improbable that such enormous aggregate R&D investment could ever be recouped. Overall the industry arguably faced substantial R&D overcapacity. Financially-tight biotech firms offered acquisition opportunities for cash-rich pharmaceutical firms. For instance, in 2003 Novartis acquired a 51 per cent stake in Idenix, a biotech that had been forced to abandon plans to float. Licensing deals also provided an important source of promising new products. Two-thirds of the industry's total pipeline resided in small companies with 67 per cent available for licensing. Alliances, however, required some sacrifice of sales margins and late stage deals (*i.e.* those where the product was close to reaching the market) were rare, costly and competitive.

SALES & MARKETING

Sales and marketing capability became an increasingly important source of competitive advantage. A company that developed a strong global franchise with its customers could maximise return on its in-house products and was in a good position to attract the best in-licensing candidates. In fact Bristol-Myers Squibb built the world's leading cancer business based entirely on in-licensed compounds.

The traditional focus of drug marketing was the personal "***detail***" in which a sales representative (rep) discussed the merits of a drug in a face-to-face meeting with a doctor and often handed over free samples. Pharmaceutical promotion was subject to industry self-regulation. For example, in the UK, sales reps had to pass an examination testing medical knowledge within two years of going on the road. For new drugs, government regulatory agencies examined the proposed brand name, to avoid potential dangerous confusion with other drug names, often checked that promotional claims were consistent with the data, and might even comment on proposed visual images and branding.

Payer efforts to influence prescribing in the 1990s gave rise to a belief that large sales-forces were becoming obsolete and could be replaced by small numbers of specialist payer liaison salespeople. However, companies that also continued to increase their conventional sales-force size and resulting "share of voice", such as Pfizer, found that it paid off handsomely. Experience taught firms that the more sales reps they deployed, the higher their sales. As a result the number in the US almost tripled from 1995 to 2002, reaching around 90,000, while the number of doctors rose only 20 per cent to 850,000. However, doctors had less time to see sales reps with the average call lasting less than 5 minutes. More reps selling fewer drugs resulted in returns from every dollar invested in marketing falling from $22 in sales in 1998 to $17 by 2001. Although cutting sales-force numbers would have made sense overall, firms were caught in a classic "prisoners dilemma"- no one was willing to call off the arms race.

Given the resulting squeeze on margins, maximising sales-force effectiveness became crucial. Pharmaceutical companies became more sophisticated in the tools they gave reps and in the targeting of their selling efforts. Novel communication channels such as e-detailing, where the doctor heard a presentation over a computer link, suited busy doctors' schedules and saved costs.

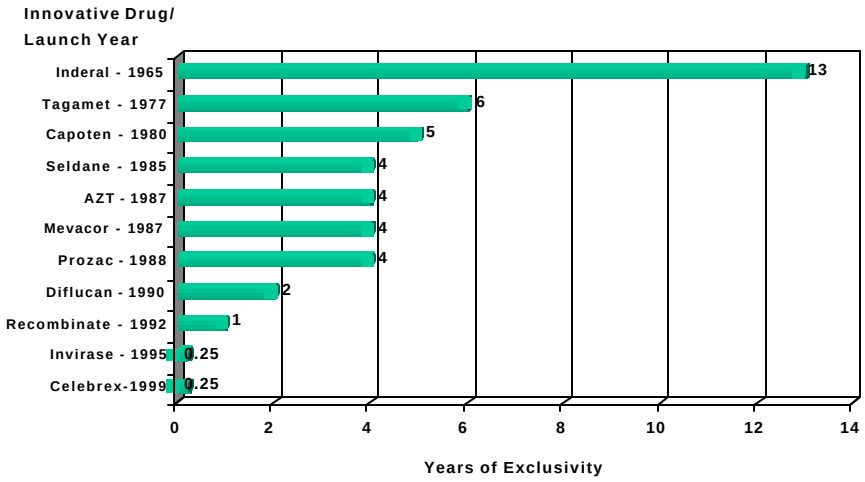
There were important differences in the marketing of "primary care" and "specialist" products. Office-based practitioners generally prescribed primary care products, whereas treatment with specialist products was typically initiated in hospitals. Sales volume, marketing spend and skills required differed for the two segments. Product-led muscle marketing was the name of the game in the primary care sector, while specialist products involved targeted relationship marketing. A small number of companies built their strategies around under-served specialised customer groups, aiming to satisfy their needs on multiple dimensions. In other words, they developed a franchise. An example was Elan Corporation, which built a profitable niche business by targeting the needs of the neurology market. However, most pharmaceutical companies were product-led rather than customer-led, probably as a consequence of the unpredictability of the R&D process.

In 2002, firms spent nearly $9.4 billion on marketing in the US. A key factor that drove up costs was the growth in DTC advertising, where spending reached $2.7 billion by 2002. Companies recognised that well-informed patients were prepared to ask for drugs by name, creating a powerful new "pull" strategy. DTC could be very costly because of the vast target audience and expensive television advertising. It also required new marketing skills – both Pfizer and Novartis employed consumer marketers to smarten up their DTC promotion and branding. DTC also rendered drug advertising much more visible and risked creating a backlash against the industry. For instance, some medical practitioners found themselves correcting misinformation or misconceptions.

Successful drug launches correlated strongly with product superiority, high prices and high promotional spend. An interesting trend began to emerge where drugs that were second to market were more successful than the original pathfinder drug. Evidently, it proved relatively easy to identify flaws in the first drug and deliver a follow-up positioned as "best in class" or targeted at specific sub-

populations. Exhibit 4 illustrates that the period of ***market exclusivity*** for first in class drugs was also shrinking fast.

Exhibit 2: Number of years of *market exclusivity* enjoyed by selected drugs, 1965-1999



The term "high compression marketing" was coined to describe the approach adopted by leading companies to launch global brands. This involved simultaneous worldwide launches, global branding, and very heavy investment in promotion and share of voice around time of launch. High compression marketing aimed to create a rapid take-off curve that would maximise return from the product by creating higher peak year sales earlier in the product lifecycle. A good example was the launch of Celebrex in 1999, which netted $1 billion sales in the first 9 months. Truly global branding was vital, with consistent brand name, messages, and visuals used around the world for maximum impact. Blockbusters launched between 1998 and 2003 typically reached $2 billion in sales within 3.5 years, at least twice as fast as historical norms.

In addition to seeking an earlier, higher sales peak, marketers in pharmaceutical companies also aimed to extend the product life cycle. As a product approached patent expiry, effort might be invested in switching patients to new improved formulations with longer patent protection. Another strategy involved moving drugs from prescription-only status to OTC. The aim here was to encourage patients to recognise and buy a familiar brand. Consumer brand loyalty could then be used as a defence against generic competition.

[Insert Box 4 around here]

CORPORATE SOCIAL RESPONSIBILITY

During the 20th century average life expectancy in developed countries increased by over 20 years. A significant part of this improvement can be attributed to pharmaceutical innovation. Few other industries can claim to have done as much for the well being of mankind. So how did an industry that has delivered such enormous benefits acquire such a tarnished image and become an easy target for unpredictable government intervention?

One problem is that the market for pharmaceutical innovation has the characteristics of what economists describe as a "public good" – *i.e.* expensive to produce but inexpensive to reproduce. The manufacturing cost of drugs is usually tiny compared with the amortised cost of R&D that led to the discovery. Setting prices that attempt to recoup R&D therefore looks like corporate greed in comparison with the very low prices that can be charged by generic manufacturers. Similar issues are faced by the software, film and music industries. However, unlike those, there is also something inherently distasteful to some people about making a profit from addressing unmet medical need - they would prefer pharmaceutical companies to have a social mission. Most of these same people will have pensions partly invested in pharmaceutical shares, on which they expect a healthy return. So the pharmaceutical industry needs to be very good at explaining the nature of its business and balancing societal and shareholder expectations.

Some companies in the industry acted in ways that damaged its overall reputation. The short-term result may have been greater profit, but the long-term consequence was a steady increase in government regulation and intervention. We have seen how clinical trials were subjected to tighter controls, but marketing practices attracted the most criticism, even being described as "legalised bribery". Sales details in particular were under increasing scrutiny. In Italy in 2003, 40 GlaxoSmithKline staff and 30 doctors were under investigation for *comparaggio* – the prescribing of drugs in exchange for gifts such as computers and lavish trips. Many EU countries restricted the value of such gifts and voluntary industry codes of conduct were increasingly augmented with formal regulation.

Similar problems also emerged in the US: for instance, TAP Pharmaceuticals was fined $875m by the US Department of Justice for giving doctors free samples on the understanding that they would then bill the federal government. Pharmaceutical firms paid over $2 billion between 2000 and 2003 in cases brought by the US Justice Department, principally for pricing and marketing crimes.

The industry also faced growing condemnation of its response to the enormous unmet need in developing countries. The industry was criticized for oligopolistic behaviour, the use of patents and trademarks to protect proprietary technology and control particular markets, the high social cost of numerous parallel programmes of R & D aimed at questionable innovations, enormously expensive and sometimes misleading marketing practices, and other policies such as transfer pricing. The image was

of an industry prepared to break its own ethical rules when not properly policed on the fringes of the global economy. A best-selling novel[5] was even based on the bizarre premise that a Swiss pharmaceutical firm would choose to launch an unproven drug in Africa before the rest of the world, would deliberately test it on pregnant African women and then hide undesirable side-effects and deaths.

An investigation by the United Nations Centre on Transnational Corporations in the 1980s found evidence for questionable industry practices[6]. Twenty years later campaigning organisations such as Health Action International claimed those practices were still rife and that the types of drugs consumed did not correspond with the real health needs of developing countries. In Thailand, consumption of antibiotics was seven times higher than necessary, while drugs to combat tuberculosis, malaria and leprosy were under-used. Ineffective products such as tonics, vitamins and cough syrups were firms' best sellers in developing countries, some even containing addictive components. The resources could have been better directed at life-saving treatments, and marketing pressure was assigned part of the blame. The marketing of unsafe drugs that had been withdrawn in Western markets was a particularly depressing finding. Dangerous products were among the best sellers in Argentina and Brazil and had increased the incidence of fatal childhood anaemia in Colombia.

Lacking adequate sanitation, nutrition and primary health care facilities for much of their population, developing countries relied on pharmaceuticals as the first line of defence against a wide range of infectious and parasitic diseases. Although for many diseases affecting millions of people, effective drugs and vaccines already existed, often their cost was beyond the means of the people who needed them. It was argued that leading pharmaceutical companies could make a significant contribution such as reallocation of R&D efforts in favour of major tropical diseases, the sale of low-priced essential drugs and technology transfer. According to a report by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), some global firms were rising to the challenge.[7] IFPMA claimed that humanitarian efforts by the industry made a very significant contribution. In sheer size, spending by pharmaceutical companies rivalled that of the World Health Organisation (WHO), and programmes benefited tens of millions of people in over a hundred countries. The IFPMA detailed numerous examples, such as Pfizer's commitment to provide its antifungal medicine Diflucan free of charge and without time limits to people in the least developed countries living with HIV/AIDS and with cryptococcal meningitis and/or oesophageal candidiasis.

Questions around the purpose and ethics of the global pharmaceutical industry gained a high public profile as disputes over access to modern antiretroviral therapies for AIDS patients reached crisis point and threatened to jeopardise broader world trade agreements. AIDS was killing 3 to 4 million people annually, 2.3 million of them in Africa. The humanitarian efforts of major corporations were inadequate in the face of this immense need and according to campaigners, often came with unacceptable strings attached. Countries began taking matters into their own hands. Brazil halved the

[5] John Le Carre, *The Constant Gardener*, Hodder and Stoughton, London, 2001.
[6] United Nations Centre on Transnational Corporations (UNCTC), *Transnational Corporations in the Pharmaceutical Industry of Developing Countries*, UNCTC, New York, 1984.

number of people dying of AIDS by providing patented anti-retroviral drugs to 150,000 people free of charge. It either made cheap, generic versions of the drugs itself, or obtained them cheaply from the patent-holder by threatening to do so. However, multinationals worried that supplying drugs free or at very low prices would flood higher priced markets with parallel imports. When the South African government proposed legislation to allow generic imports, a coalition of 39 firms took legal action. Given the tragic AIDS epidemic and the saintly figure of Nelson Mandela, this wasn't one of the best examples of corporate public relations.

Between 2002 and 2003 the CEO of GlaxoSmithKline (GSK), Jean Paul Garnier, helped negotiate the industry out of the South African court case and established clear principles of operation for GSK. The company would supply critical drugs to poor countries on a no-loss, no-profit basis. As for investing in research into "not-for-profit" diseases, Garnier declared:

"We'll go after it. It's just that we've got to be street smart about the funding... There's plenty of money .. to fund those initiatives and we've never been turned down. I talk to Bill Gates all the time".[8]

By early 2003 other companies were under pressure to follow GSK's example. A group of powerful investors stated publicly that the industry risked becoming the "new tobacco" unless it cleaned up its act. Firms were accused of failing to prioritise cures for diseases prevalent in poor countries while concentrating on lucrative "lifestyle cures" for prosperous ones. The group, with combined investments totalling $940bn, said if the industry did not shape up its reputation would be destroyed and future profits put at risk. "The statement came from a concern about the impact on shareholder value in the long term," commented one industry analyst.[9]

At the Doha trade talks in 2001, ministers stated that patents could be broken in cases of national emergency, such as AIDS or tuberculosis epidemics. Intellectual property rights should not prevent efforts to "promote access to medicines for all". However, while this enabled countries to copy patented drugs, it did not grant the right to export them, leaving most poor nations no better off. Eventually, in 2003, a deal was struck whereby these nations could import from manufacturing countries such as Brazil or India. The industry negotiated safeguards so that generic drugs would be labelled, packaged, shaped or embossed differently from the patented original, and importation could only be "in good faith to protect public health" and not in order to "pursue industrial or commercial-policy objectives". However, corporations feared a broader threat to the hard-won intellectual property at the heart of their business model. Garnier portrayed the battle as an "economic war" in which unscrupulous generics companies were using AIDS as a "Trojan horse" to undermine the patent system. His concern was that those companies sought to pirate hard-won pharmaceutical discoveries and supply them to countries such as China and India, accounting for around 80% of the world's population. "If the patents go away in those countries it's the end of the pharmaceutical industry as we

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[7] *Building Healthier Societies Through Partnerships*, IFPMA, August 2003.
[8] *The Guardian*, February 18, 2003.
[9] *BBC News*, March 24, 2003.

know it."[10] The agreement valiantly attempted to balance the interests of the global industry with the public-health needs of the world's poor, but it remained to be seen whether it offered a workable solution.

STRATEGIC RESPONSES

While the pharmaceutical market remained relatively fragmented, with very large numbers of domestic and regional players, it was consolidating at the global level. No company held more than a 7.5 per cent market share in 2002, but Pfizer's acquisition of Pharmacia took this over 10 per cent in 2003. The top 10 players accounted for nearly half of global pharmaceutical sales and significantly only 2 blockbuster drugs were held outside the top 20 corporations. A strong trend was for previously diversified conglomerates to divest their non-healthcare businesses (*e.g*. agrochemicals), to focus purely on high-margin pharmaceuticals.

Although the overall market appeared fragmented, this disguised the true level of concentration. Since both R&D and commercial franchises divided naturally along therapeutic lines, competition was fought at the level of therapeutic area and most intensely within specific product classes. The market leader within a franchise might hold a share as high as 28 per cent (AstraZeneca in Gastroenterology & Metabolism in 2002) and 20 per cent was not uncommon. The more successful companies led key franchises and competed in product classes that were large, fast-growing or had high unmet need. In 2002, the top 10 classes grew at 37 per cent compared with overall market growth of 8 per cent.

There was a strong belief that companies needed critical mass in R&D and global marketing presence in order to compete effectively. However, there were notable exceptions such as Sanofi-Synthelabo from France, and US-based Amgen, which ranked at 17 in terms of sales but grew at over 20 per cent in 2002.

The position of Hank McKinnell, CEO of Pfizer, was typical of the view amongst management of global pharmaceutical company towards the issue of size and amalgamations. He rejected the notion that big drug acquisitions were short-term financial bandages for research woes and stated that:

"Pfizer's strategy, including the $60bn acquisition of Pharmacia [in 2003] and that of Warner-Lambert two years before, recognised the need to hedge the risk of failure in research… such deals have covered Pfizer from exposure, while rivals claiming 'smaller is better', with good research growth, have often stumbled over lack of strong resources. I suspect if we had not [gone ahead and merge], we'd be like the other list of names."[11]

Exhibit 4 shows how the industry response to the need for critical mass had been a wave of mergers and previously unheard-of hostile acquisitions leading to amalgamation.

[10] *The Guardian*, February 18, 2003.
[11] *Financial Times*, August 23, 2002.

Exhibit 3: *Leading Global Pharmaceutical Companies, 1997 and 2002*

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

1997		2002			
Company	Total Sales, $bn	Company	Total Sales, $bn	Share within Global Retail	Sales Growth (2001 to 2002)
Glaxo Wellcome[1] (UK)	11.6	Pfizer[5] (US)	29.5	7.3%	11.4%
Merck (US)	11.4	GlaxoSmithKline[6] (UK)	27.9	7.0%	7.0%
Novartis[2] (CH)	11.0	Merck (US)	20.0	5.0%	6.6%
Bristol-Myers Squibb (US)	9.3	Johnson & Johnson (US)	18.6	4.6%	16.1%
Johnson & Johnson (US)	8.7	AstraZeneca[4] (UK/Swe)	18.1	4.5%	8.6%
American Home Products (US)	8.4	Novartis (CH)	16.6	4.1%	12.8%
Pfizer (US)	8.4	Aventis[3] (Ger/Fra)	14.3	3.6%	10.0%
Roche (CH)	8.0	Bristol-Myers Squibb (US)	14.3	3.6%	-7.4%
SmithKline Beecham (UK)	7.4	Roche (CH)	12.5	3.1%	6.5%
Hoechst (Ger)	7.4	Pharmacia (US)[7]	12.2	3.0%	8.1%

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)
7	2000	Monsanto (US)	Pharmacia (US)

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

Mergers had resulted in the formation of Novartis, Aventis, AstraZeneca and GlaxoSmithKline, while Pfizer acquired Warner-Lambert and then Pharmacia. Exhibit 4 shows how Pfizer overtook Merck, which followed an organic growth strategy throughout the 1990s. Leading companies were under pressure to consider further mergers after Pfizer's acquisition of Pharmacia. Eliminating duplicated costs remained one sure-fire way to keep profits relatively healthy. But there was little conclusive evidence that mergers had actually enhanced revenue or R&D productivity. There was a noticeable polarisation in corporate performance, with companies either outperforming or under performing - there was no longer a safe middle ground. Successful mergers were based on strategic purpose and fit, rather than exacerbating weaknesses, and managing the process effectively had itself become a strategic capability.

A key rationale for mergers and acquisitions was to combine a company with a strong pipeline but weak sales and marketing with its converse. For example, the acquisition of Warner-Lambert gave Pfizer full marketing rights to the cholesterol-lowering agent Lipitor, which Pfizer then built into the world's best-selling drug.

Another argument for increasing size was to improve R&D productivity, since it rested at least partly on “technology platforms”. Companies had to invest in expensive new capabilities (such as such as

High Throughput Screening) to keep pace with the industry leaders in speed to market. The larger the total R&D programme, the greater the number of individual projects that could benefit from the new capability, and amortise these costs. Pfizer's acquisition of Pharmacia gave the new entity an R&D budget of nearly $7 billion, 50 per cent greater than its nearest rival.

Others argued that mergers actually reduced R&D productivity: more management layers resulted in greater bureaucracy, less freedom to innovate and a reduced research output. The success of biotechs in drug discovery suggested creativity was greater in small R&D organisations. Portfolio management could also be problematic in merged companies. Cutting too many projects in the search for blockbusters could exacerbate risk. Cutting too few meant under-resourcing potential winners and risked 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 three years post-merger. Companies were either removing duplication and focusing on winners or becoming less productive. Definitive evidence was years away.

Another argument for increasing size was to invest in larger sales-forces to secure greater "share of voice" and to acquire global reach. Pfizer's acquisition of Pharmacia took the new entity from No.4 in Europe and No.3 in Japan to No.1 across the Triad. Companies which lacked presence in key markets were obliged to make use of licensing deals, sharing the profit with another company. A strong global marketing capability was also vital in attracting the best in-licensing candidates and co-marketing deals, to strengthen the product pipeline. Supporters of organic growth claimed that marketing success came from combining the right skills, resources and competencies rather than sheer sales force size, pointing to the success of smaller "franchise" players.

Some advocates of further industry consolidation emphasised that its purpose should be to create dominance in just a few therapeutic franchises, with non-core activities being sold of, making these huge corporations more manageable, and focusing R&D and sales and marketing efforts. Others proposed that the R&D and commercial functions could operate autonomously. The commercial organisation would develop a product portfolio based on therapeutic franchises, using clearly defined business relationships with external R&D partners. In turn, this would free in-house R&D to discover and to develop innovations beyond the commercial portfolio strategy.

There were, however, other possible strategic responses to the environmental changes facing the industry. Different business models had been explored in the past. In reaction to the growth of managed care in the US, Merck acquired a ***Pharmacy Benefit Manager***[12] (***PBM***) called Medco for $6 billion in 1993, followed in 1994 by SmithKline Beecham (SKB) who purchased DPS and Eli Lilly who purchased PCS. The apparent logic was the conventional strategic rationale for vertical integration - gaining control of distribution channels. However, barriers were quickly put in place to prevent companies from influencing PBM formularies to displace competitors. While Merck retained

[12] ***PBM***s act as intermediaries between manufacturers and MCOs.

ownership of Medco and apparently benefited, both SKB and Eli Lilly were forced into costly divestments.

An intriguing response to environmental change was adopted by managers at Roche, who positioned themselves as operating a new "integrated healthcare" business model. Roche had a strong diagnostics division, owned much of the relevant intellectual property, and Roche's managers portrayed it as a complex business with consequent high barriers to entry. Their strategic vision was to move from seller of instruments and reagents to a health information provider, offering value through better targeting of treatments, convenience and "peace of mind". Roche claimed to be the only company embracing these principles, having both requisite experience, and all the necessary tools to lead the paradigm shift in healthcare offered by genomics and diagnostics.

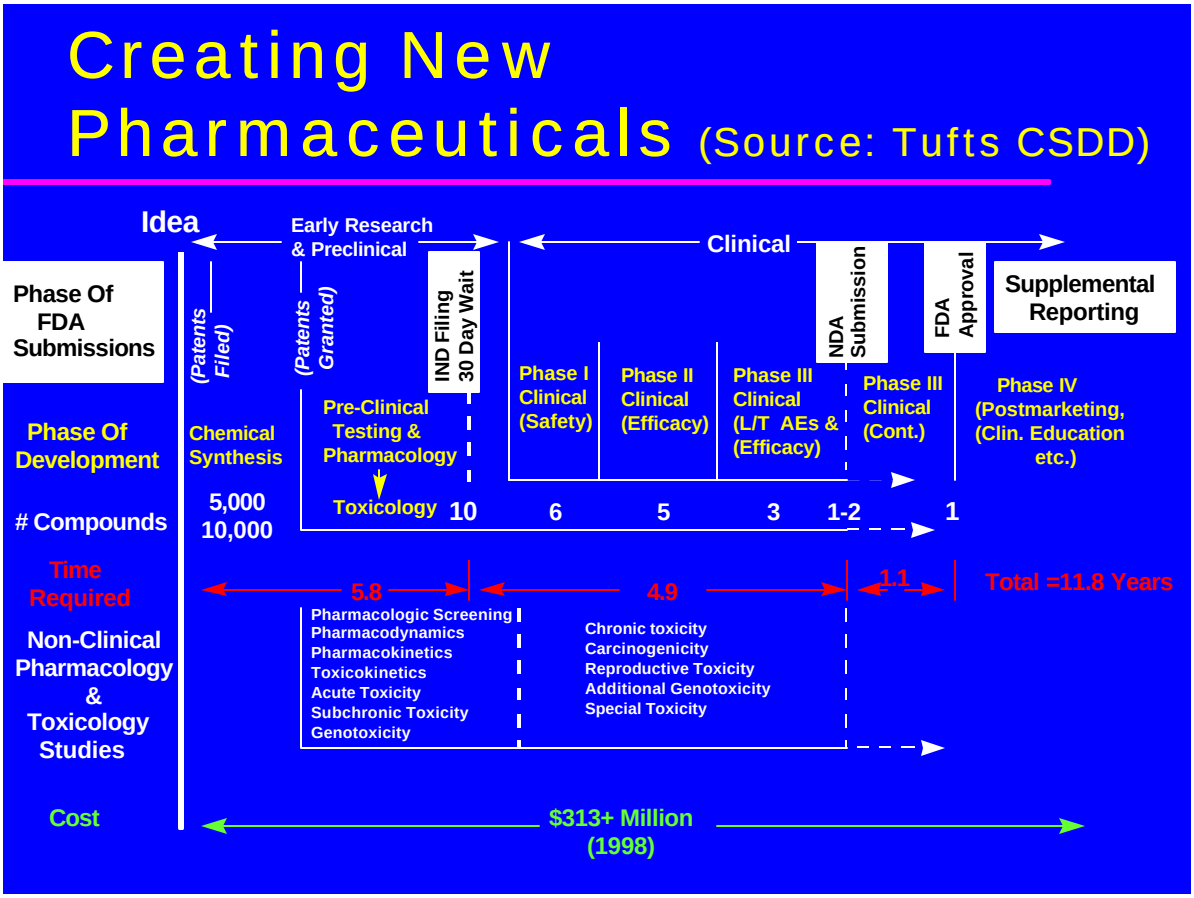
SUMMARY

Many large pharmaceuticals companies are facing their toughest outlook in a decade. The industry has made a tremendous contribution to human well being, yet is vilified in the media and targeted by governments in their efforts to curb spiralling healthcare costs. R&D costs have risen sharply, while the product life cycle has shortened. Product approval, pricing and promotion are subject to increasingly onerous regulation, yet free trade allows wholesalers to extract a large chunk of value from the chain without adding anything back. Companies must balance shareholder return against the huge unmet need of developing nations. Exciting opportunities do still exist – more educated consumers, advances in genomics, regulatory harmonisation and of course unmet medical need. Industry consolidation is driven by the dominant belief that size is what counts, although a few players prefer to build focused franchises or offer integrated healthcare solutions. Ultimately, meaningful innovation is what matters most, but it is not clear that a business formula based on inventing and selling blockbuster drugs can continue to sustain double-digit growth rates.

BOX 1: THE DRUG DEVELOPMENT PROCESS

The pharmaceutical industry has long new product lead times, with period from discovery to marketing authorisation typically taking almost 12 years (Exhibit 1). New product development can be divided into distinct research and development phases. The research phase produces a ***new chemical entity*** (***NCE***) with 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.

Exhibit 1: *Creating New Pharmaceuticals*



During all of these phases "attrition" occurs, as promising agents fail particular hurdles, so most R&D projects never result in a marketed drug. Of those that do, 80 per cent fail to recoup their R&D investment. The cost of developing and commercialising a new drug is now estimated at $500-$800 million dollars. When the costs of all the projects that do not reach fruition are considered, it becomes clear that pharmaceutical R&D is a very high stakes game.

Given the enormous risks and considerable investment involved, it is not surprising that pharmaceutical companies compete fiercely to establish and retain ***intellectual property*** rights. Only by securing a patent that can be defended against imitators can the value of all this R&D be recouped. The patent clock starts from the moment that a promising agent is identified in pre-clinical tests and its chemical

structure and synthesis filed with patent offices worldwide. Once the patent application is made public, other companies are likely to try to create improved, patentable versions. Where genuine discoveries or inventions are made, patents can also be obtained for manufacturing method and even mode of administration. All of these supplementary applications can extend patent life and the earnings period for a new drug.

Pre-clinical development involves testing new agents against the target - for example, lowering cholesterol - to select the most promising leads. After further tweaking, these best candidates are evaluated in animal disease models to find the one with the best trade-off between efficacy and tolerability. Finally the lead agent is put through a battery of toxicology tests in animals and if successful put forward for clinical development in humans. Clinical development is usually divided into three phases. Phase I trials determine whether the product is safe to use in humans. Phase II trials aim to select dose and demonstrate efficacy. Phase III trials are conducted versus the best current treatment, with the goal of proving superiority. Typically only 1 in 10 molecule survives from Phase I to launch, with late failures (Phase III) being more costly.

The industry is subjected to rigorous regulatory scrutiny. Government agencies such as the ***Food and Drug Administration*** (***FDA***) in the USA thoroughly examine all of the data to support the purity, stability, safety, efficacy and tolerability of a new agent. The time taken is governed by legislation and is at least six months. Every regulatory authority is different and while FDA endorsement is very helpful it does not guarantee approval in other countries. Companies must address varied geographic requirements as regulatory authorities wish to ensure that the product is suitable for their population - for example, some Japanese people may metabolise the drug differently from Western subjects - and delivers improved health outcomes when compared with the standard of care in their country. Obtaining marketing approval is no longer 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.

BOX 2: GLOBALISATION

A number of factors contributed to the globalisation of the pharmaceutical industry. Chief among these was the international convergence of medical science and practice under the influence of modern communications technology and increased travel and information exchange. Well-funded US universities and hospitals generally led their fields, while conferences and specialist seminars in the US were the most prestigious platforms to learn about new discoveries. This may account for the fact that drugs first launched in the US gain far greater global market share and achieve twice the sales of those first launched elsewhere.

Regulatory processes were also undergoing international harmonisation. In Europe the European Medicines Evaluation Agency (EMEA) was established to enable more rapid regulatory approvals across Europe through the "centralised" procedure, which granted regulatory approval in all Member States simultaneously. The creation of EMEA offered great benefits in terms of reduced costs and accelerated time to market for pharmaceutical companies, but also increased risk as more was at stake on one decision. There was also a move towards global harmonisation of standards for drug approval through the International Conference on Harmonisation (ICH).

Further evidence of globalisation could be found in the tripling of the number of blockbuster brands between 1998 and 2003. There were also clear signs that leading corporations were "globalising". Most had a presence in all significant markets, with overall sales reflecting the market size of each country. Production sites had a global mandate and were selected by worldwide screening. R&D was sourced from best place worldwide regardless of location, and that often meant the US. In 1990, the industry spent EUR 8 billion on research in Europe and EUR 5.3 billion in the US. By 2001, the US was receiving EUR 26.4 billion of spending compared with EUR 18. billion in Europe. GlaxoSmithKline, Europe's biggest drugs company, was being run from Philadelphia, while Novartis, the second largest, announced it was moving its research headquarters to Boston.

In 2003, the leading global industry players all originated from Triad countries - predominantly the US and Europe, as Japanese companies lagged behind. The strong US market enabled US companies to grow faster than their competitors and provided a springboard in achieving global ambitions. Pfizer, Merck and Johnson & Johnson recorded 2002 growth at or above 15 per cent, while Novartis and Roche languished at around 7 per cent. US companies even outdid their rivals in the EU market – of the seven top 20 companies that achieved double-digit growth in 2002, five were US firms. Multinationals from the US and EU also developed presence in Japan through acquisitions and in 2003 occupied 4 of the top 10 positions, where they were significantly outperforming domestic firms.

BOX 3: GENOMICS

(could illustrate with a technical image of a micro-array)

Genomics is the study of human genes and through a joint multinational effort known as the Human Genome Project (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 did not equate to fully understanding the function of the genes. It was essential to understand what genes were actually doing - so-called "proteomics", in order to identify new targets for pharmaceutical intervention. The total number of drug targets discovered up to the year 2000 amounted to well under 1,000. Proteomics had the potential to increase this by orders of magnitude, offering immense promise in the search for more effective and less toxic therapies.

The HGP provided only the "plain vanilla" version of the genome, reflecting one individual's genetic make-up. Variations in genetic make-up (Single Nucleotide Polymorphisms or SNPs) were also of great interest. Understanding genetic susceptibility to disease could deliver improved screening tests and earlier intervention. Furthermore, "pharmacogenetics" exploited genetic knowledge to understand why some patient populations benefited more than others from a therapy, or why some experienced specific side effects. A senior R&D executive at GlaxoSmithKline explained that 90% of drugs only work in 30-50% of people, and claimed that "by eliminating the people that we predict will be non-responders we'll be able to do smaller, faster and cheaper drug trials."[13] As a consequence, "we will have better and better targeted drugs, better and fewer side effects" enthused a CEO.[14] This was likely to appeal to payers.

Some commentators predicted a dramatic increase in productivity at the early stage of research, and argued that while output would dip in the short term because of increased costs, it would soon take off again. Others believed that the HGP had led to irrational investor exuberance in 1999-2000 and driven biotech valuations to an unsustainable peak

[13] Allen Roses of GSK, quoted by the *BBC News*, December 8 2003.
[14] Matthew Emmens, CEO of Shire Pharmaceuticals, quoted in *The Guardian*, November 15, 2003.

BOX 4: CONSUMERS AND THE NET

Increasingly vocal, well-informed and demanding consumers seemed inevitable. As the convergence of telephone, information technology and television accelerated, it was difficult to envisage how a ban on DTC in the EU could be maintained. Patients with Internet access could obtain information on new products directly themselves. It was easy for non-US citizens to access US websites, and information on new drugs reached consumers via both company and independent web sites and through distribution of press releases to PR services. Health was one of the top two reasons for people to conduct searches on the Internet. In the US, up to 75 per cent of those that searched for health-related information were likely to discuss that information with their healthcare providers (44 per cent on average in the EU).

This trend was likely to increase 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 was not, however, an unmixed blessing for the industry. It also raised awareness of price differentials that might exist between brands and for the same brand between countries. This posed a further challenge to pricing levels. Consumers were even beginning to purchase across borders, but with no guarantee that the drugs they received had been stored and shipped correctly and were not adulterated, contaminated, or counterfeit. The US FDA estimated that fake drugs accounted for over 10% of the global medicine market, generating annual sales of more than $32 billion, with fake Viagra being an internet best-seller. More worrying, it was easy to purchase addictive painkillers and other potentially harmful drugs over the Internet, and rogue websites even offered miracle cures for cancer and AIDS. The pace of change was outstripping the capabilities and powers of regulators.