

Pharma 2020: The vision Which path will you take?*



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Introduction

Demand for effective medicines is rising, as the population ages, new medical needs emerge and the disease burden of the developing world increasingly resembles that of the developed world. The E7 countries – Brazil, China, India, Indonesia, Mexico, Russia and Turkey – are also becoming much more prosperous, with real gross domestic product (GDP) projected to triple over the next 13 years. By 2020, the E7 could account for as much as one-fifth of global sales.

Yet the biopharmaceutical sector (Pharma) will find it hard to capitalise on these opportunities unless it can change the way in which it functions. Its core problem is lack of productivity in the lab. Several external factors have arguably exacerbated the industry's difficulties, but the inescapable truth is that it now spends far more on research and development (R&D) and produces far fewer new molecules than it did 20 years ago. The shortage of good medicines in the pipeline underlies many of the other challenges Pharma faces, including its increasing expenditure on sales and marketing, deteriorating financial performance and damaged reputation.

At the start of the decade, many people thought that science would come to the industry's rescue and that molecular genetics would reveal numerous new biological targets, but the human genome has proved even more complex than anyone first envisaged. It is no longer the speed at which scientific knowledge is advancing so much as it is the healthcare agenda that is dictating how Pharma evolves.

The first part of our report highlights a number of issues that will have a major bearing on the industry over the next 13 years. The second part covers the changes we believe will best help pharmaceutical companies:

- operate in this new milieu
- realise the potential the future holds; and
- enhance the value they provide shareholders and society alike.

The bottom line:
The global market for medicines is growing, although demand is moving to different therapeutic areas, a shift that global warming could accelerate

A growth market

Demographic, epidemiological and economic shifts are transforming the pharmaceuticals market. The population is growing and aging; new areas of medical need are emerging; and the diseases from which people in developing countries suffer are increasingly like those that trouble people living in the developed world. These changes will generate some huge opportunities for Pharma.

The global population is projected to rise from 6.5 billion in 2005 to 7.6 billion in 2020. It is also aging rapidly; by 2020, about 719.4m people – 9.4% of the world’s inhabitants – will be 65 or more, compared with 477.4m (7.3%) two years ago.¹ Older people typically consume more medicines than younger people; four in five of those aged over 75 take at least one prescription product, while 36% take four or more.² So the grey factor will boost the need for medicines dramatically.

Clinical advances will reinforce this trend. The improvements of the past few decades have already converted some previously terminal illnesses into chronic conditions, thus increasing long-term demand for therapies to manage such diseases. The number of deaths from heart attacks has declined by over 50% in most industrialised countries since the 1960s,³ for example, while five-year survival rates for US patients with cancer (expressed as an average for all sites) have risen from 53% in the mid-1980s to 66% today.⁴

Demand for new anti-infectives is also mounting, with the development of drug-resistant

strains of some existing illnesses. The US Centers for Disease Control and Prevention (CDC) estimates that more than 70% of US hospital infections are resistant to at least one of the antibiotics most commonly used to treat them.⁵ And medical research has exposed problems that were previously unidentified – including risk factors like metabolic syndrome and conditions like chronic fatigue syndrome, which recent evidence suggests is linked to changes in gene expression in the white blood cells.⁶

Meanwhile, new diseases, including mutated forms of old diseases, are surfacing. Urbanisation and greater mobility have contributed to the introduction of new pathogens, some of which spread very fast and are very difficult to treat. SARS moved from Asia to North America and Europe in a matter of days. Similarly, the H5N1 avian flu virus has spread from China and South East Asia to the Middle East. The human cost has been tiny so far, but the impact of an avian flu pandemic could be enormous.

Global warming could also have a major effect on the world’s health. In February 2007, the Intergovernmental Panel on Climate Change (IPCC) reported that the global average temperature had increased by about 0.2°C per decade between 1990 and 2005. The IPCC projects that the average temperature will increase by another 0.2°C per decade for the next two decades, even if the concentration of all greenhouse gases remains constant at year 2000 levels, and that it will “very likely” increase still more, if mankind’s output of greenhouse gases continues to rise.⁷

It is currently impossible to predict the full impact of a change in global weather patterns, or even to be absolutely certain that man-made pollutants are causing the change. But many scientists believe that global warming could bring diseases such as malaria, cholera, diphtheria and dengue fever to more developed regions. Cases of malaria have now been reported in Azerbaijan, Corsica, Georgia and Turkey, where the disease was eradicated after World War II.⁸

Specialists argue that most vector-borne diseases are unlikely to become a major threat in North America or Western Europe, where the climate is cooler and better preventative measures are in place. The greater danger in such regions is an increase in respiratory illnesses like asthma and bronchitis, since higher levels of greenhouse gases are expected to boost the pollen production of ragweed and other common allergens.⁹

But numerous other medical problems could also emerge everywhere, because even a small rise in temperature accelerates the proliferation of many common bacteria. The replication rate of *Salmonella* increases by 1.2% per degree above minus 10°C, for example, while the replication rates of *Campylobacter* (one of the most common causes of gastroenteritis) and *E. coli* increase by 2.2% and 6%, respectively.¹⁰

In short, all these changes are creating new openings for Pharma. Some of them may be in different therapeutic areas. But demand for innovative medicines for old and new conditions alike is growing, not shrinking.

Emerging opportunities

The markets of the developing world are altering even more radically than those of the developed world. At one time, infectious diseases were the biggest killers. This is still true of sub-Saharan Africa and South Asia. But, elsewhere, chronic diseases are now the leading cause of death,¹¹ a pattern that will become even stronger as the population of the developing world gets older, fatter and less physically active.

Two specific instances illustrate just how much the epidemiological profile is shifting. In 2004, an estimated 639m people living in developing countries suffered from hypertension. By 2025, the number is forecast to reach at least one billion – more than twice the projected rate of increase in that same population over the same timeframe.¹² The picture is very similar when it comes to diabetes. The number of people with diabetes in developing countries is expected to rise from 84m in 1995 to 228m in 2025, with India, the Middle East and South East Asia bearing the worst of the burden (see sidebar, **India's insulin dependence**).¹³ Demand for medicines that treat illnesses formerly associated almost exclusively with the developed world is thus expanding in the developing world, at the same time that some countries are becoming increasingly affluent.

The E7 countries look especially attractive. Our economic modelling suggests that the real GDP of the E7 countries will triple from US \$5.1 trillion in 2004 to \$15.7 trillion in 2020, whereas that of the G7 countries will grow by just 40%, from

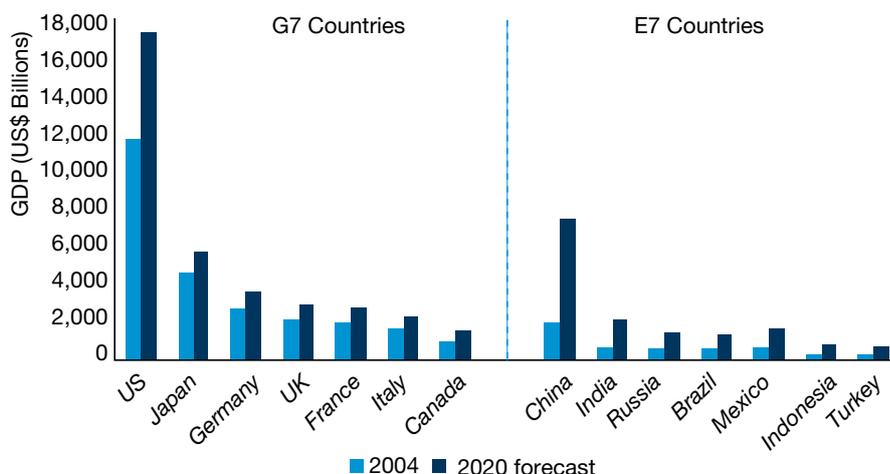
India's insulin dependence

The number of Indians with diabetes is projected to reach 73.5m in 2025. The direct and indirect costs of treating such patients are currently about \$420 per person per year. If these costs remained the same as they are now, India's total bill for diabetes would be about \$30 billion by 2025. But as its economic wealth grows and standards of care improve, treatment costs are likely to rise.

The US spends an average \$10,844 per year on each patient with diabetes. If India's per capita expenditure rose to just one-tenth of this level, the total cost of treating all patients with diabetes would be \$79.7 billion by 2025. The value of prophylaxis in India alone would thus be substantial; preventing 10% of the population from developing diabetes would save nearly \$8 billion a year.

The bottom line:
The diseases of
the developing
world increasingly
resemble those
of the developed
world, and greater
affluence is making
some countries
much more
attractive markets

Figure 1: The E7 economies will treble their real GDP by 2020



Source: PricewaterhouseCoopers Macro Economic Consulting Group
Notes: 2004 estimates based on World Bank World Development Indicators database (except China, which was adjusted for a later large data revision); 2020 projections based on our model

\$25.8 trillion to \$36.1 trillion.¹⁴ Their wealth relative to that of the G7 will rise from 19.7% to 43.4% over the same period (see **Figure 1**).

In 2004, the E7 countries spent 0.94% of their GDP on prescription medicines (although the precise percentage varied from one state to another). They collectively accounted for 8% of the \$518 billion global market.¹⁵ The G7 countries, by contrast, spent 1.31% of their GDP on medicines and accounted for 79% of all sales. So, if all 14 countries continue to spend the same proportion of their GDP on medicines as they do now (and if their GDP grows as we have projected), the global pharmaceuticals market will be worth about \$800 billion in 2020, and the E7 countries will account for about 14% of sales.

However, this is probably too conservative an estimate. The richer countries become, the more they tend to spend on healthcare. The E7 populations are also aging faster than those of the G7; by 2020, 338m of the people living in the E7 countries will be at least 65 years of age, compared with 152.8m of the people living in the G7 countries.¹⁶ But the G7 countries will still be more than twice as wealthy as the E7 countries, and better able to afford the higher healthcare costs associated with an aging population. So it is likely that both the G7 and the E7 countries will spend a larger proportion of their GDP on medicines than they do now. But the rate of growth in the G7 economies will almost certainly be much slower than it is in the E7 economies – and that disparity could eventually make a significant difference.

Suppose, for instance, that the G7 pharmaceutical markets grew by between 5% and 7% a year, while the E7 markets grew by between 10% and 15% a year, for the next 13 years. By 2020, the global pharmaceuticals market would be worth about \$1.3 trillion, with the E7 countries accounting for about 19% of sales. China would be the second or third biggest market in the world, and Turkey and India might well be in the top 10.

One thing is clear from these broad-brush calculations; the financial clout of the E7 countries is improving significantly. The economic, demographic and social changes of the next decade will make them very much more appealing places in which to make and market pharmaceuticals.

Compound crisis

Yet Pharma will not be in a strong position to capitalise on these opportunities, unless it can change the way in which it operates. Its core problem is lack of innovation in making effective new therapies for the world's unmet medical needs. Medicines have helped many individuals enjoy longer, healthier lives. But, as the global population becomes older and more prosperous, people's expectations are rising – and the industry is finding it increasingly difficult to fulfil their hopes.

We predicted that this would happen when we published “Pharma 2005: An Industrial Revolution” in 1998. We argued that the safety, efficacy and cost-effectiveness of new medicines would attract growing scrutiny, and that the

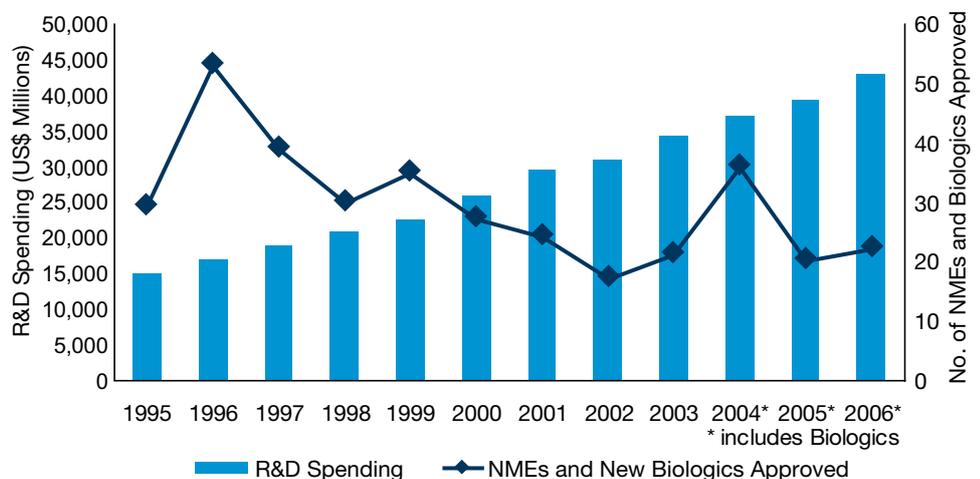
industry's total shareholder returns (TSRs) would plummet, unless it could “industrialise” its R&D.¹⁷ Our forecasts were borne out by 2002, with the publication of “Pharma 2010: The threshold of innovation”. The Pharma 2010 report contended that the industry's best hope of earning higher returns lay in the development of packages of products and services targeted at patients with specific disease subtypes and that, if it was to make such “targeted treatments”, it would have to start by focusing on diseases rather than compounds.¹⁸

However, the human genome has proved more complex and less amenable to mechanistic analysis than many scientists anticipated, when the draft map was completed in 2001. Hence the fact that Pharma

is still struggling to apply the insights it has gleaned from the molecular sciences – genomics, proteomics, metabonomics and the like – to improve its performance.

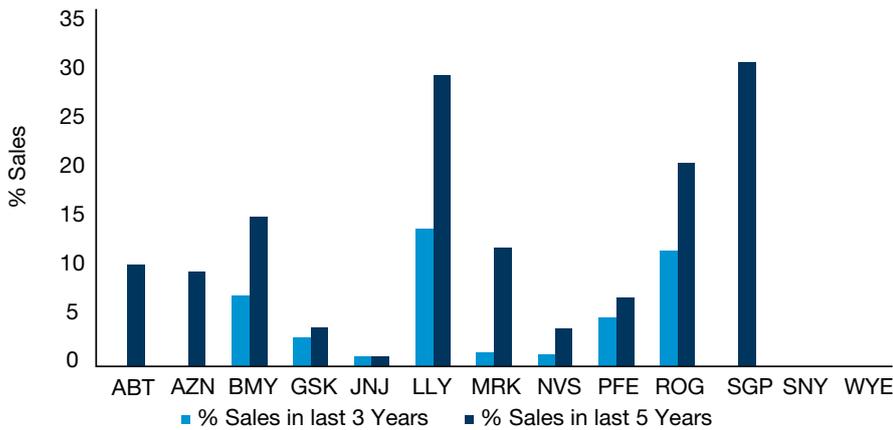
In 2006, North American spending on biopharmaceutical R&D reached a record \$55.2 billion (and the US accounts for about three-quarters of global expenditure in this area). The member companies of the Pharmaceutical Research and Manufacturers of America (PhRMA) spent an estimated \$43 billion, while non-member companies spent another \$12.2 billion.¹⁹ But the US Food and Drug Administration (FDA) approved only 22 new molecular entities (NMEs) and biologics, a far cry from the 53 it approved in 1996 when R&D expenditure was less than half the sum it is now (see **Figure 2**).²⁰

Figure 2: R&D spending has soared but the number of NMEs and biologics approved by the FDA is down



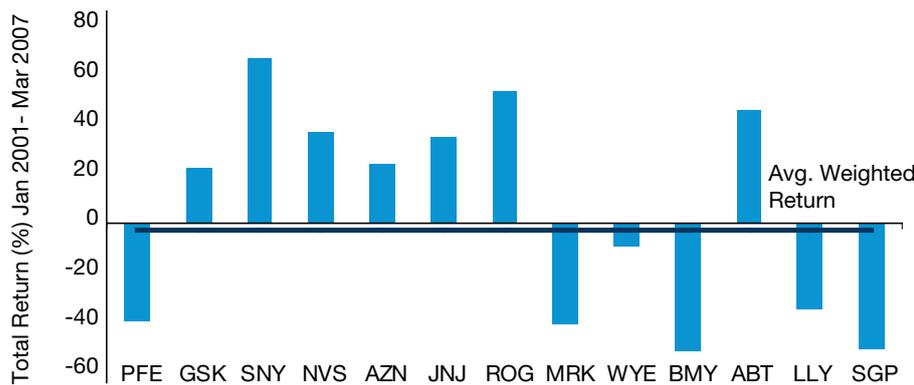
Sources: FDA/CDER Data, PhRMA data, PricewaterhouseCoopers analysis
 Note: Data on R&D spending for non-PhRMA companies are not included here, because they are not available for all 11 years

Figure 3: Only five of the top Pharma companies generate more than 10% of their revenues from products that were launched in the last five years



Sources: IMS Health and PricewaterhouseCoopers analysis

Figure 4: Big Pharma delivered weighted average total shareholder returns of -2.4% per annum between January 2001 and March 2007



Sources: Yahoo!Finance, PricewaterhouseCoopers analysis

Note: Total returns have been calculated for the period January 2, 2001- March 30, 2007, with the exception of Sanofi (now sanofi-aventis) where the total return has been calculated from February 7, 2002. The weighted average return is based on the market capitalisation in 2001

Even allowing for inflation, the industry is investing twice as much in R&D as it was a decade ago to produce two-fifths of the new medicines it then produced.²¹

Moreover, only nine of the new treatments launched in the US in 2006 came from the labs of the 13 companies that comprise the Big Pharma universe,²² a pattern that has changed very little over the past few years. Our analysis shows that, in 2006, only two Big Pharma companies earned more than 10% of their revenues from “major” products that are less than three years old.²³ Worse still, those 38 products generated only \$10 billion of the \$316 billion Big Pharma earned from its entire medicines portfolio.

The situation is little better over a five-year timeframe. In 2006, only five Big Pharma companies earned more than 10% of their revenues from major products launched after 2001, and those 65 products generated sales of only \$30.4 billion (see **Figure 3**). Thus more than 90% of Big Pharma’s total pharmaceutical revenues came from medicines that have been on the market for more than five years. Yet the patents on many of these products are due to expire quite shortly, exposing an estimated \$157 billion worth of sales (measured in 2005 terms) to generic erosion.²⁴

The revenues the industry leaders generate have also come at a very high price. Between 1995 and 2005, the percentage of total corporate spending accounted for by R&D rose from 15% to 17.1%, while the percentage accounted for by sales and general administration rose from 28.7% to 33.1%. Sales and marketing is by far the biggest corporate expense.²⁵

This increasing expenditure on sales and marketing could be seen as yet another sign of the paucity of innovative medicines reaching the market, since it is arguable that products for which there is real demand do not need to be heavily promoted. However, it has generated considerable criticism, too. In a survey of industry stakeholders conducted by the PricewaterhouseCoopers Health Research Institute, 94% of the respondents said that pharmaceutical companies spent too much money on advertising.²⁶

Six US states have now passed “gift laws” requiring all pharmaceutical companies to disclose how much they give doctors, hospitals and pharmacists each year, while another 15 states have similar bills in the offing.²⁷ Several European trade bodies, including the Prescription Medicines Code of Practice Authority of the Association of the British Pharmaceutical

Industry (ABPI), have also launched new codes of practice imposing much tighter rules on the promotion of medicines.²⁸ And, in late 2003, Spain’s Autonomous Regions introduced restrictions on the number of promotional visits sales representatives can make.²⁹

In short, Pharma’s lack of R&D productivity lies at the root of many of the other difficulties it is now experiencing – difficulties that are reflected in its poor financial record over the past few years. Between 1985 and 2000, the industry’s market value increased 85-fold, far outpacing the stock market as a whole.³⁰ But in the six years to March 30, 2007, the FTSE Global Pharmaceuticals Index rose just 1.3%, while the Dow Jones World Index rose by 34.9%. Big Pharma’s TSRs followed the same downward path; between January 2001 and March 2007, it delivered weighted average TSRs of -2.4% a year (see **Figure 4**).

The bottom line:
Pharma must
improve its R&D
productivity, if it is
to meet the world’s
unmet medical
needs and capitalise
on the market
opportunities now
emerging

The bottom line:
The legal framework
in which Pharma
operates must be
altered to promote
innovation and
discourage imitation

External barriers to innovation

Pharma's R&D processes have become so complex – even cumbersome, indeed – that it is hardly surprising its productivity has tumbled. Nevertheless, several political, legal and financial factors have arguably contributed to the problem. Most pharmaceutical companies use internal valuation mechanisms to assess the clinical and commercial potential of the compounds in their pipelines, and select the ones they want to pursue. In other words, like other organisations that are answerable to shareholders, they “follow the money”.

But when they start developing a new medicine, they do not know whether it will be eligible for reimbursement if it reaches the market, unless it addresses a disease for which there is no existing treatment or looks likely to prove much better than any comparable therapies. And, in most countries, they are not allowed to seek guidance from the relevant government agencies.

Many firms therefore try to minimise their risks by “playing it safe”. The Centre for Medicines Research International reports that, in 2004, more than 20% of the money 10 of the largest pharmaceutical companies invested in R&D went on line extensions and other work, as distinct from new development projects. In smaller companies, the percentage was over 40%.³¹

The international laws governing intellectual property rights have compounded this conservatism. At present, all patents last 20 years, regardless of the quality of the intellectual property they protect. But if prophylactics and novel products serving an unmet medical need were granted longer patent lives, while me-too medicines and new formulations were granted shorter patent lives, pharmaceutical companies would have a direct incentive to become more innovative.³²

Determining which therapies were worthy of longer patent lives might sometimes be difficult. If, say, 20 new cancer treatments reached the market within a few months of each other, it might be hard to decide which were the most deserving – let alone who should make that judgement. But, given the typical product lifecycle, we estimate that an extra five years of patent life would increase the cash flows from a truly innovative medicine by between 50% and 100%, depending on how vulnerable it is to generic erosion.³³

That, in turn, would furnish governments with much stronger grounds for arguing that the prices of such products should be reduced and thus brought within reach of many more patients, since the industry would have a longer period in which to recover its investment. Indeed, there may even be a case for extending the patent lives of groundbreaking vaccines like Gardasil to 50 years or more, on the understanding that they are priced at levels which are universally affordable.

Mixed signals

The political and legal framework in which Pharma operates has thus deterred it from taking some of the risks that are required to produce genuinely innovative new therapies. Its communications with the capital markets may have muddied the waters still further. The preliminary results of some research we recently conducted show that there are significant variations in the value the top city analysts accord R&D pipelines, and that most analysts focus mainly on the quality of the molecules in Phase III. Two major changes during the past decade help to explain why.

In the mid-1990s, the leading pharmaceutical companies announced plans to launch two or

three NMEs a year. Most companies subsequently acknowledged that these aspirations were completely unattainable. But, in repeatedly altering the targets they then set themselves, they have failed to give the investment community a clear idea of what to expect. Attrition rates in Phase II have also deteriorated significantly over the same period.³⁴ The variations in the value different analysts place on pipelines are entirely understandable in light of these conflicting signals, as is their reluctance to attribute any value to molecules whose fate still remains extremely doubtful.

However, in sending the capital markets such mixed messages, Pharma has also made life harder for itself. It is more difficult to determine how best to increase a company's

value when its pipeline is valued differently by different analysts. And it is more tempting to maximise the number of candidate molecules in Phase III, even though it would be better to weed some of them out at an earlier and cheaper stage of development.

These are by no means the only problems. Analysts also look for evidence of sustainable returns. But most pharmaceutical companies' revenues are becoming much more cyclical, as the billion-dollar blockbusters in their portfolios come off patent and they struggle to develop new medicines that can replace this income. Research by investment management firm AXA Framlington shows the scale of the challenge (see **Table 1**).

Table 1: The leading pharmaceutical companies will lose between 14% and 41% of their existing revenues as a result of patent expiries

Company		2010		2011		2012	Share of Revenues (%)
AstraZeneca	Arimidex	(\$2.2bn)*	Seroquel	(\$4.7bn)	Symbicort	(\$3.7bn)	38**
BMS			US Plavix	(\$4.8bn)	Abilify	(\$2.1bn)	30
			Avapro	(\$1.3bn)			
GSK	Advair	(\$3.8bn)			Avandia	(\$2.5bn)	23
Eli Lilly			Zyprexa	(\$4.8bn)			22
Merck	Cozaar/ Hyzaar	(\$3.2bn)			Singulair	(\$4.5bn)	22
Novartis	Femara	(\$1.1bn)			Diovan	(\$6.0bn)	14
Pfizer	Aricept	(\$800m)	Lipitor	(\$12.1bn)	Viagra	(\$1.7bn)	41
			Xalatan	(\$1.6bn)	Detrol	(\$860m)	
					Geodon	(\$1.1bn)	
sanofi-aventis	Taxotere	(\$2bn)	US Plavix	(\$3.8bn)	Lovenox	(\$3.1bn)	34
			Avapro	(\$2.1bn)			

Source: AXA Framlington

Notes: * Estimate of global sales in 12 months prior to patent signing

** Value of products losing patent protection as a percentage of total company sales over next five years

The bottom line: The investment model used by the capital markets does not work very well for an industry that works to timelines of 10 years or more, and is unlikely to do so unless Pharma “re-sets” market expectations

Many pharmaceutical companies face a serious dilemma, then. For the past 20 years, they have “sold” themselves on their ability to develop blockbusters, but they now have to alter their story without forfeiting the confidence of the capital markets. They also have to meet short-term earnings targets (from quarterly reporting or other, more subtle pressures) that may be at odds with their long-term aspirations – and they have to do these things at a time when competition for funding is getting more intense, thanks to the revival of interest in the biotech sector.

In the US, where the sector is relatively mature, the cycles of investment in Pharma and biotech have converged. But, elsewhere, there is still a major disjunction between the two. So, if the biotech sector’s charms grow over the next couple of years, as some investors predict, Pharma could find itself out in the cold.

The bill for every ill

The same features that will ensure Pharma’s market continues to expand have also exposed the limitations of the current approach to healthcare funding: namely, that most of the world’s pharmaceutical spending goes on the treatment of disease rather than its prevention. This is partly because some diseases are so complex that scientific understanding of their pathology is still very limited, and developing cures or prophylactics for such illnesses is therefore extremely difficult. In addition, the risks associated with preventing disease in healthy people are quite different from those associated with treating people who are already sick.

However, most countries invest much less in public health than they do in other forms of healthcare; the OECD average is just 2.9% of total health expenditure.³⁵ In effect, society’s spending priorities are back-to-front. A specific example shows the full extent of the bias. Gardasil, Merck’s breakthrough vaccine for cervical cancer, sells for just \$360 in the US, compared with an average annual wholesale price of \$19,289 for Betaseron, \$22,875 for Rebif and \$28,400 for Tysabri, all products that modify the symptoms of multiple sclerosis but cannot cure or prevent it.³⁶

As the global population grows and ages, and demand for better healthcare management increases, this emphasis on treatment rather than prevention will become increasingly unsustainable. Older

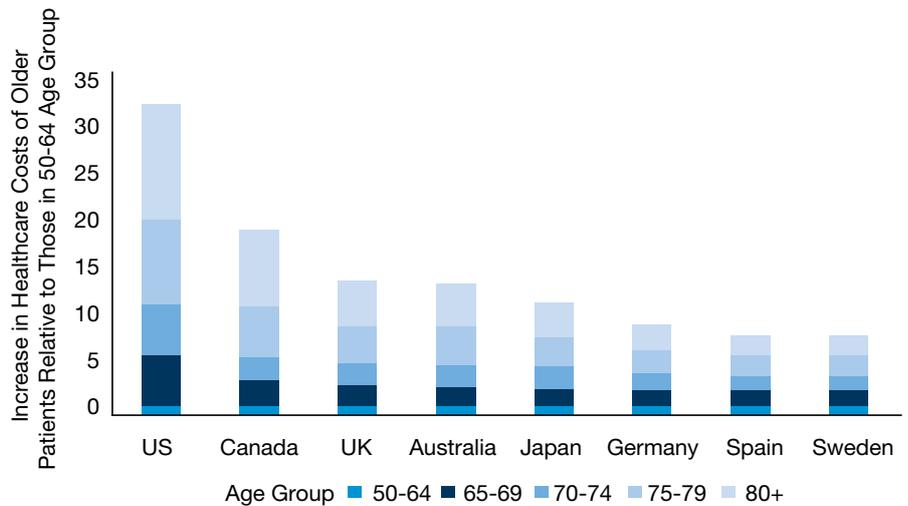
people consume more healthcare than young people everywhere, although there are some huge national discrepancies. In Spain and Sweden, for example, the average level of healthcare spending on patients aged 80 or older is twice as much as it is on patients aged 50-64; in the US, by contrast, it is 11.5 times more (see **Figure 5**). We estimate that, by 2020, the OECD countries, excluding the US, will spend 16% of their GDP on healthcare, while the US will spend a huge 21%. In all, they will spend \$10 trillion on healthcare (see **Figure 6**).³⁷

So, governments everywhere will have to reverse their approach. They will have to devote a much larger proportion of their healthcare expenditure to preventative measures, and reward the development of vaccines and cures more highly than they do palliative medicines. Without such a change of strategy, no country will be able to fund the healthcare needs of its inhabitants by 2020.

The aging of the population, together with dietary changes and more sedentary lifestyles, will also increase the burden of chronic disease. The World Health Organisation (WHO) estimates that 60% of all the deaths that took place in 2005 could be attributed to chronic conditions, and predicts that the number of deaths from chronic diseases will increase by 17% over the next 10 years.³⁸

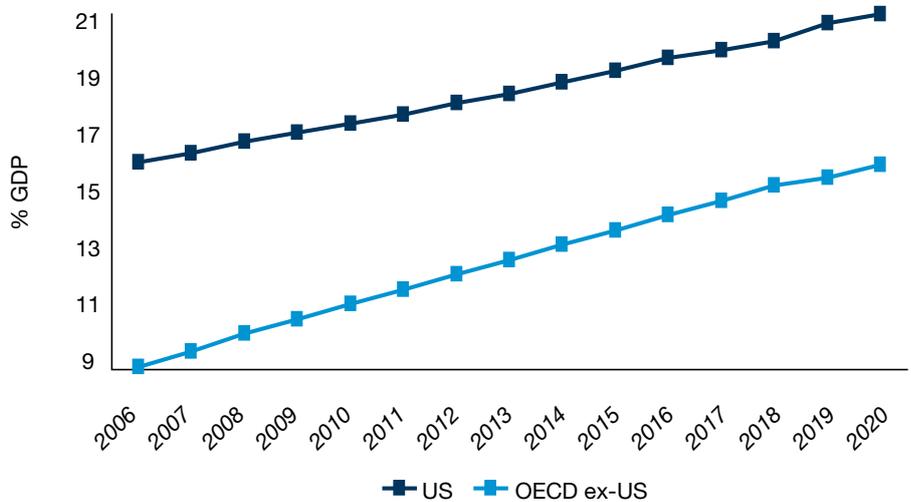
The toll is highest in developing countries, which account for 80% of all mortalities from chronic diseases and where the onset of disease is

Figure 5: Older people consume more healthcare than younger people do



Source: Laurence Kotlikoff & Christian Hagist, "Who's Going Broke?" National Bureau of Economic Research, Working Paper No. 11833, December 2005
 Note: Ratio of average spending on individuals in each age group in each country relative to an individual aged 50-64 in the same country. Numbers rounded

Figure 6: Health expenditure as a percentage of GDP is increasing rapidly in the OECD countries



Source: PricewaterhouseCoopers Health Research Institute

The bottom line: Pharma will have to participate in the debate on healthcare funding and demonstrate the value of its products or risk coming under huge pressure to cut the prices of many mass-market medicines

often much earlier than it is in the developed world. In the US, for example, only 12% of deaths from cardiovascular disease (CVD) occur in working-age people, compared with 28% in Brazil, 35% in India and 41% in South Africa.³⁹

But the developed world is also paying dearly. One recent study puts the cost of CVD in the European Union (EU) alone at about €169 billion (\$226.1 billion) a year.⁴⁰ And though the developed countries have been very successful in pushing some chronic diseases up the age ladder, increasing longevity will force more people to work longer. Most of these changes – like the raising of the retirement age in Belgium and the UK – will take place after 2020. However, the overall direction is clear; a bigger percentage of the population of the developed world will still be working at the point at which chronic diseases kick in.

These trends have several implications for Pharma. As healthcare rises up the political agenda, the industry will have to engage in the debate on how it is funded and play its part in helping to control costs. The social and economic value of good medicines for chronic diseases will rise with the extension of working life around the globe – and many such medicines already exist, as falling mortality and morbidity rates in the developed world demonstrate. But there will simply not be enough money in the pot to cover the world's future healthcare needs, unless Pharma can cut its operating costs and margins on these products.

Washington blues

The extent of the problem with healthcare funding is particularly apparent in the US, Pharma's biggest and most profitable market. As an article recently published in *The New York Times* put it: "What is the most pressing problem facing the [US] economy? A good case can be made for the developing healthcare crisis."⁴¹ The impact on the automotive manufacturing industry has already been well documented. In 2006, General Motors and Ford spent about \$5.9 billion and \$2.9 billion, respectively, on healthcare – a bill that adds more than \$1,380 to the cost of producing each car.⁴²

In fact, administrative costs are responsible for between 20% and 31% of US healthcare spending.⁴³ Hospital spending accounts for nearly 33% of all expenditure, and prescription products for just 10.1%.⁴⁴ But governments often focus on the prices of medicines because they are a relatively easy target, and many people believe the medicines bill is much higher than it really is. In a survey conducted by the PricewaterhouseCoopers Health Research Institute, 97% of consumers estimated that prescription medicines accounted for at least 15% of overall US healthcare costs, while 63% put the figure between 40% and 79%.⁴⁵

Moreover, with the Democrats now in the ascendant on Capitol Hill, Pharma could find itself much more exposed. Two measures, in particular, are worth discussing in further detail: the proposal to introduce a national health insurance scheme; and the bill to give the federal government the

power to negotiate medicine prices for Medicare Part D, the medicine benefit programme for the elderly.

Some 16% of the 300m people living in the US currently have no medical cover, and the Democrats are keen to redress the situation by introducing a universal health system. However, such a move would be very expensive. In 2005, the US spent almost \$2 trillion on healthcare, about \$50-60 billion of which went on providing medical treatment for the indigent. It is extremely difficult to calculate the additional cost of covering the uninsured population as a whole, but one study suggests that it could be between \$125 billion and \$150 billion a year, depending on the particular model that is used.⁴⁶

Some public-policy researchers argue that the cost of restricting access to healthcare for the uninsured, measured in terms of shorter lives and poorer productivity, could be as much as \$130 billion a year, and that the introduction of a federal healthcare programme for the uninsured would ultimately be revenue-neutral.⁴⁷ But even if this proved true, the initial investment would be many billions of dollars, and the government would find it difficult to raise such a sum. The introduction of a national health system in the US would thus increase the number of people who had access to modern medicines, but it might also result in more widespread use of treatment protocols, generics and over-the-counter (OTC) medications, making life more difficult for research-based pharmaceutical companies.

The Democrats' proposed changes to Medicare Part D could have an

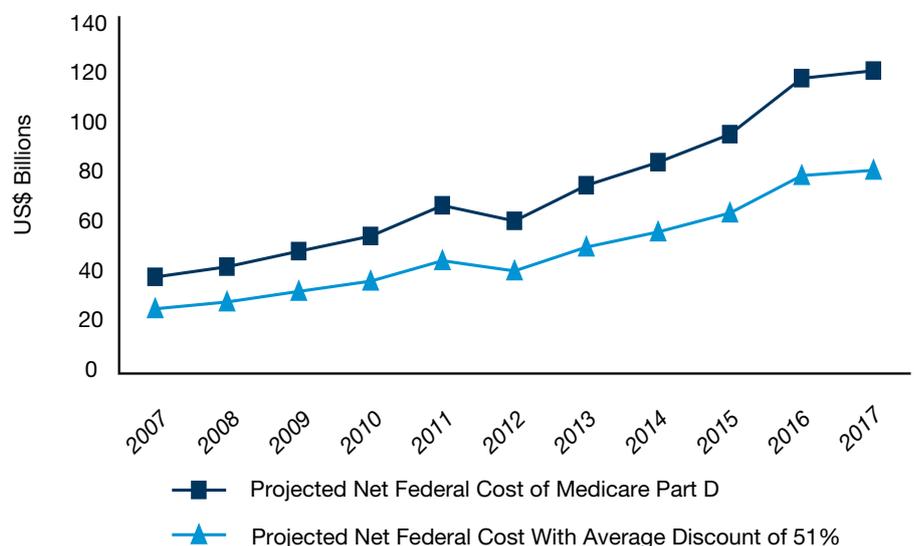
even bigger financial impact on the industry, if they are ever translated into practice. In January 2007, the House of Representatives approved a bill requiring the government to negotiate Medicare prescription drug prices, rather than having each plan provider deal directly with manufacturers, as is now the case.⁴⁸ President Bush has said that he will veto the Medicare Prescription Drug Price Negotiation Act if it passes the Senate.⁴⁹ And, even if the Act does become law, it makes no provision for altering a government programme that is administered by third parties. But the Democrats argue that negotiating medicine prices centrally could produce substantial savings. So what sort of sums might be involved?

The net federal cost of Medicare part D is currently projected at \$794 billion for the period 2007-2017.⁵⁰ The US Department of Health and

Human Services estimates that the average level of discounts and rebates in 2006 was about 27%.⁵¹ But research by the Congressional Budget Office shows that average discounts for the six federal programmes which negotiate prices directly with manufacturers range from 51% to 59%.⁵² If the government were to secure similar discounts for Medicare Part D, its net expenditure on medicines under the programme would therefore fall from \$794 billion to \$532.9 billion – a total saving of \$261.1 billion – by 2017 (see **Figure 7**).

In practice, it is doubtful that the US government would introduce quite such draconian price controls. Critics claim that the programme administered by the Department of Veteran Affairs offers a relatively narrow range of treatment options in many classes of therapies, and that patients and physicians accustomed

Figure 7: If the US government negotiated drug prices for Medicare Part D directly, Pharma's revenues could drop



Source: PricewaterhouseCoopers

The bottom line:
Pharma cannot rely on the US market to bail it out. Nor can it assume that it will always be able to charge a lot more for its products in some markets than in others

to a much wider range of choices under private health plans would be unlikely to accept such restrictions.⁵³ Nevertheless, it is clear which way the wind is blowing – and, if the Democrats have their way, Pharma will come under huge pressure to cut its prices.

Moreover, if price controls are introduced, their impact will not be confined to Medicare Part D. By January 2010, the US government will pay for 37% of all prescription drug expenditure under Medicare and Medicaid. Employers will pay for another 39% under private insurance programmes.⁵⁴ Given the extent to which rising healthcare costs have already impaired the competitiveness of US industry, it seems reasonable to assume that any price controls the government adopted would soon spill over into the private sector.

So Pharma cannot continue to rely on the US to bail it out of its current difficulties. Indeed, it may ultimately be unable to count on differential pricing in any market whatever. The Internet has already eroded geographical variations in the prices of consumer electronics, for example, and the European Commission recently threatened to fine Apple for charging higher prices to download music in some European countries than in others.⁵⁵ Buying medicines on the Internet is currently much more dangerous, of course, unless the supplier is a reputable company with an established track record. But, by 2020, the problem of counterfeiting should be largely resolved, thanks

to electronic pedigrees, DNA labelling and the like. A growing number of governments are also using prices in other countries to benchmark the prices they pay. There may thus come a time when many medicines command a regional or even global price.

Blurring healthcare boundaries

Changes in the way healthcare is delivered will arguably play an even bigger role in shaping the industry's future. The primary-care sector is expanding and becoming more regimented, as general practitioners perform more minor surgical procedures and healthcare payers increasingly mandate the treatment protocols they must follow, including the drugs they can prescribe. Conversely, the secondary-care sector is contracting, as clinical advances render previously terminal diseases chronic; healthcare providers like Clinovia in the UK, and Gentiva in the US, deliver secondary care at home; and hospitals focus on the specialist care that cannot be supplied anywhere else.

The self-medication sector is also growing, as more and more products that would once have been available only on prescription are sold in OTC formats. Most medicines that acquire OTC status are used for non-chronic conditions which are relatively easy to self-diagnose and have little potential to cause harm, if abused. But, in May 2004, the UK Medicines and Healthcare products Regulatory

Agency (MHRA) broke with this convention by reclassifying simvastatin 10mg as an OTC medicine.⁵⁶

Meanwhile, Australia's Therapeutic Goods Administration approved the weight-management therapy Orlistat for OTC use in October 2003.⁵⁷ The FDA followed suit in February 2007,⁵⁸ and Boots, the British pharmacy chain, introduced a trial scheme to sell Viagra over the counter only a few days afterwards.⁵⁹ The definitions of primary and secondary care are thus blurring, as some forms of care that were traditionally delivered by secondary-care providers are transferred to a primary-care setting, and some forms of primary care are transferred to the patient (see **Figure 8**).

This trend is particularly pronounced in the UK, but it is taking place in other countries, too. In the US, for example, some large discount stores and pharmacy chains have

set up retail medicine outlets staffed by nurse practitioners who provide basic medical care, including writing prescriptions.⁶⁰ An increasing number of surgical procedures are performed in ambulatory surgery centres rather than hospitals. And the FDA has said that it hopes to boost the number of medicines it switches to OTC status by 50% a year.⁶¹ The American Pharmacists Association is also advocating the introduction of a "behind-the-counter" option such as already exists in some European countries and the FDA has endorsed the idea, although any such move would require congressional approval.⁶²

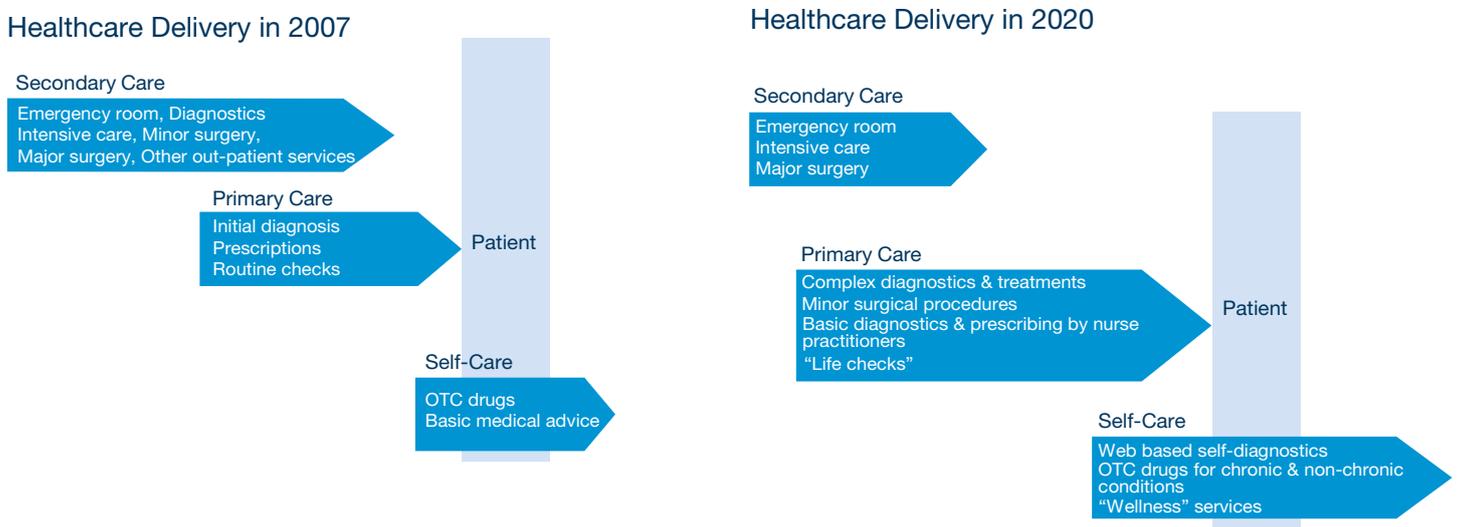
A better understanding of the taxonomy of disease, together with better diagnostic tools and monitoring devices, will provide the means with which to bring healthcare delivery even closer to the patient. By 2020, it is quite

conceivable that patients will be able to use web-based receiving algorithms to establish whether they have a condition that will sort itself out without recourse to prescription drugs. This would eliminate a substantial number of consultations, since self-limiting diseases are thought to account for about 85% of all visits to primary-care physicians.⁶³ Any patient who needed additional diagnostic tests or treatments would then see a nurse practitioner, and would only be referred to a doctor if his or her case were more complex or required surgical intervention.

These changes in the healthcare system have obvious benefits for healthcare payers; healthcare is cheaper, the more it is planned and the closer it is delivered to the patient's home. But they have huge ramifications for Pharma as well.

First, as treatment protocols replace individual prescribing decisions and

Figure 8: The provision of healthcare is moving closer to the patient



Source: PricewaterhouseCoopers

The bottom line: Pharma's target audience is changing, as healthcare policy-makers and payers increasingly control the prescribing decision

technology improves the ability to diagnose conditions, the decision-making authority is gradually moving from doctors to healthcare policy-makers and payers. However, the criteria policy-makers and payers use for adopting new medicines are different from those physicians use; payers typically focus on risk and cost-effectiveness,⁶⁴ whereas doctors put safety and efficacy before cost.⁶⁵

Second, the sales and marketing model on which the industry has historically relied is becoming increasingly obsolete. There is little point in sending out a large sales force to influence primary-care practitioners who do not choose which medicines they prescribe.

Lastly, with the erosion of the conventional boundaries between self-care, primary care and secondary care, the needs of patients are shifting. Where treatment is migrating from the doctor to ancillary staff or self-care, for example, patients will require more comprehensive information about the medicines they take, more advice and more surveillance. Where treatment is migrating from the hospital to the primary-care sector, they will require new services such as home delivery.

Thus Pharma should be focusing on the provision of a full range of products and services spanning the healthcare spectrum, and using different channels to distribute different kinds of products and services. In fact, some companies are already beginning to use different distribution channels in the US – a trend we shall discuss in more detail further on.

Pay-for-performance

The provision of healthcare is not all that is changing; so is the way in which it is measured. Several countries have set up agencies specifically to compare the safety and efficacy of different forms of intervention and promote the use of evidence-based medicine. The US Agency for Healthcare Research and Quality is one such body, as is the UK Centre for Health Technology Evaluation – a division of the National Institute for Clinical Health and Effectiveness (NICE) – although the latter also considers economic performance.

The Australian Pharmaceutical Benefits Advisory Committee, New Zealand Pharmaceutical Management Agency and Finnish Office for Health Care Technology Assessment (to name just a few) also conduct pharmacoeconomic evaluations of new medicines, devices and procedures. But there is as yet no systematic process for measuring cost-benefit ratios, and the volume of outcomes data these agencies can analyse is still relatively small – a restriction that will end during the next decade with the widespread adoption of electronic medical records (EMRs).

The US aims to develop a national health information network by 2014.⁶⁶ The EU has also called for every member state to create an EMR,⁶⁷ and several countries have already made considerable headway. Denmark now has a comprehensive health data network,⁶⁸ while the British system is expected to be operational by 2012, despite the many problems that have dogged

it.⁶⁹ Thus, by 2020, some countries will have between six and eight years' worth of longitudinal data. This may not be enough to assess the impact of treatments for diseases that progress quite slowly, but it will certainly be sufficient to evaluate the clinical and economic performance of many therapies.

The effect on Pharma is likely to be two-fold. First, healthcare policy-makers and payers will use outcomes data to determine best practice. They will include medicines that are particularly safe, efficacious and cost-effective in their treatment protocols, and exclude those that are not – as recently happened in the UK, when NICE ruled that Aricept, Exelon and Reminyl should only be prescribed for people with moderate to severe symptoms of Alzheimer's disease because they “did not make enough of a difference” to justify the cost of giving them to patients in earlier stages of the disease.⁷⁰

It is impossible to predict just how many medicines will fail to pass muster. But in one recent analysis of 45 frequently cited studies claiming that certain treatments worked, nearly a third of the original findings proved wrong.⁷¹ If this were true of all the medicines on the market, and the industry were still reliant on blockbusters in 2020, the impact would be punitive; Big Pharma had 273 major products with average sales of \$963m apiece in 2006, suggesting that the fate of about 85 medicines with aggregate revenues of about \$82 billion (in today's terms) would be in question.

That said, the failure rate itself might not be so high. Extensive outcomes

data would expose those instances in which a medicine works well for one patient population and not for others. And if the industry succeeds in changing its approach to R&D, and launching many more drugs with individually smaller revenues, it would also be spreading its risk to a much greater extent.

Second, the price any therapy can command will be based on its performance, not what the manufacturer thinks it should fetch. This is essentially what the UK Office of Fair Trading proposed in its recent review of the British medicines pricing scheme. It recommended that the current “profit cap and price cut” scheme be replaced with a value-based pricing system in which the prices of products are set by comparing their clinical value with that of other treatments for the same condition.⁷²

When a new therapy is launched, the manufacturer will also be expected to assume a much greater share of the financial risk. At least one such deal already exists; in September 2006, GlaxoSmithKline struck an agreement with two European governments under which the prices of two new medicines will be increased or reduced, once enough data are available to judge their true efficacy and cost-effectiveness.⁷³ In future, such risk-sharing arrangements will be commonplace.

The remit of healthcare payers is growing, then. They are not just negotiating prices, they are starting to stipulate best medical practice – and access to extensive amounts of outcomes data will give them much more ammunition. By 2020, Pharma

The bottom line:
Pharma will have to prove to healthcare payers increasingly interested in establishing best medical practice that its products really work and provide value for money

will have to prove that its products really work, provide value for money and are better than alternative forms of intervention. It will have to charge much lower prices for new therapies or formulations offering only minor improvements on treatments that already exist, and even when it is marketing medicines that represent a genuine breakthrough, it will have to be much more flexible in its approach to pricing such therapies. Lastly, it will have to build very much better relationships with the agencies that perform the health technology assessments on which many healthcare payers will rely, since it currently has very little input into such evaluations.

Medicines for different markets

The changing global epidemiological profile has yet other implications. We have already discussed the extent to which demand for medicines for chronic diseases is spreading to the developing world. But differences in ethnic origin, diet and environmental factors have produced marked variations in the nature and incidence of the disease subtypes from which these populations suffer (see **Table 2**). Ethnic origins likewise play a large part in determining how people respond to particular therapies.

The rate at which the E7 populations are aging – and thus likely to suffer from the diseases of aging – also varies substantially. By 2020, 15.2% of the Russian population will be 65 or older, compared with just 7% of those living in India.⁷⁴ And the level

of affluence differs considerably both among and within countries. Mexico's per capita gross national income (measured in international dollars) is over 10 times higher than India's, for example, while the wealthiest 20% of the Brazilian population enjoy incomes that are over 30 times higher than those of the poorest 20% (see **Table 3**).

In short, the markets of the developing world possess very different clinical and economic attributes – and these are by no means the only features that separate them. They vary in their use of traditional medicines, the robustness of their laws governing the protection of intellectual property, their healthcare infrastructure and so forth. Any company that wants to serve these markets successfully will therefore have to devise strategies that are tailored to their individual needs.

Table 2: There are marked variations in the incidence of the disease subtypes from which the E7 populations suffer

Cancer site	Brazil	China	India	Indonesia	Mexico	Russia	Turkey
Oesophagus	6.4	26.2	5.5	0.4	1.4	8.4	1.7
Stomach	15.5	39.9	4.2	2.5	9.0	44.4	9.6
Colon & rectum	11.0	13.3	3.6	8.9	5.6	32.7	7.4
Liver	2.6	37.9	1.7	8.4	3.3	5.6	2.1
Pancreas	3.1	3.8	1.1	1.4	3.1	9.5	2.0
Larynx	6.5	1.5	4.5	1.5	3.6	9.8	6.4
Lung	15.8	40.7	6.6	14.2	11.2	80.4	37.3
Skin melanoma	2.1	0.2	0.3	0.3	1.0	3.0	0.8
Prostate	37.1	1.5	3.1	4.7	19.2	15.6	6.1
Testis	1.5	0.5	0.6	0.9	3.3	2.2	1.4
Kidney etc.	2.6	2.0	0.9	1.4	3.7	12.6	1.7
Bladder	6.6	3.6	2.3	2.9	3.8	15.3	8.6
Leukaemia	5.2	5.7	2.8	3.8	5.6	8.6	5.1

Source: International Agency for Research on Cancer, Globocan 2002 database
 Note: Crude rate of cancer in males in the E7 countries (incidence per 100,000 people)

Table 3: The level of affluence varies substantially both among and within the E7 countries

Country	Per Capita GNI (PPP\$)	Percentage Share of Income or Consumption	
		Lowest 20%	Highest 20%
Brazil	3,000	2.6	62.1
China	1,500	4.7	50.0
India	630	8.9	43.3
Indonesia	1,130	8.4	43.3
Mexico	6,930	4.3	55.1
Russia	3,410	6.1	46.6
Turkey	3,750	5.3	49.7

Source: World Bank Development Indicators 2006

Healthy habits and fab jobs

A growing number of governments in both developed and developing countries are also trying to shift the focus from the treatment of disease to its prevention. At least 18 countries have already introduced nationwide bans on smoking in enclosed public places, as have a number of US states.⁷⁵

Fat is an FTO issue

Researchers at the Peninsula Medical School and Oxford University recently found evidence that people with two copies of a particular variant of the FTO gene have a 70% higher risk of obesity than those with none, and weigh an average 3kg more. Those with one copy of the variant (which differs from the other allele by a single mutation in the DNA sequence) have a 30% higher risk of being obese. They estimate that half of all white Europeans carry one copy of the variant, and one in six has two copies. The team hopes that further research to understand the gene may help unravel the basic biology of obesity and pave the way for the development of medicines that can prevent it.

Similarly, some countries are waging war against the world's spreading waistlines, although recent research suggests that genes play a major role, too (see sidebar, **Fat is an FTO issue**).⁷⁶ Australia, the US and Chile have all launched national anti-obesity initiatives, for example,⁷⁷ while Europe's health ministers recently approved the world's first charter to fight fat.⁷⁸ The Chinese government is battling the juvenile bulge by requiring students to exercise or play sports for an hour a day at school.⁷⁹ And, in 2006, the British government announced plans to introduce "Life Checks", as well as providing more support services for keeping physically and mentally well.⁸⁰

Most of these initiatives are far too small to make a fundamental difference to mankind's health, despite all the political grandstanding that accompanies them. The amount of money governments invest in such measures is still just a fraction of the sums they spend on healthcare as a whole. Nevertheless, they are indicative of the direction in which the world is slowly moving.

The bottom line:
The markets of the developing world are heterogeneous, and Pharma must understand their specific needs

The bottom line: The increasing emphasis on prevention of disease will provide Pharma with new business opportunities

Social and economic pressures are gradually causing a sea-change in attitudes towards healthcare.

Fears about bio-terrorism and a flu pandemic have also kick-started a new wave of public investment in vaccines, while philanthropic institutions like the Bill & Melinda Gates Foundation are funding research into vaccines for malaria and other tropical diseases.⁸¹ And the success of Gardasil has demonstrated that it is possible to make a profit from such products. The US, German, French, Italian and Austrian health authorities have recommended that every girl be vaccinated with Gardasil,⁸² and the US public programme to vaccinate all minors will generate at least \$2 billion of sales alone.⁸³

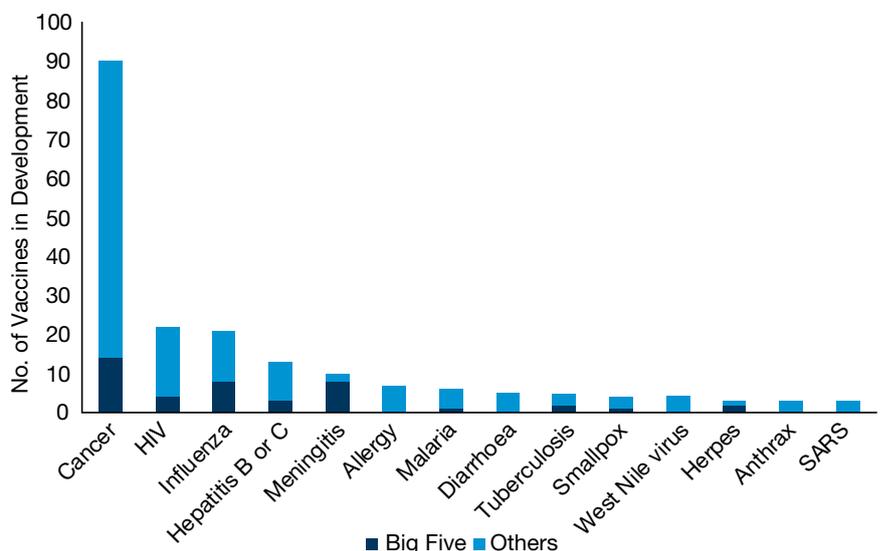
The vaccines sector is growing rapidly, then; there are now 245 pure vaccines and 11 combination vaccines in clinical development,⁸⁴ and some industry experts estimate that the market could be worth as much as \$42 billion by 2015.⁸⁵ Five

major players – GlaxoSmithKline, Merck, sanofi-aventis, Wyeth and Novartis (via its acquisition of Chiron) – have traditionally dominated the field, but a number of smaller pharmaceutical companies have also entered the fray.

Moreover, the range of indications they are researching is surprisingly varied. It includes vaccines for cocaine addiction, diabetes, hypertension, Alzheimer’s disease, psoriasis, food allergies, rheumatoid arthritis and nicotine withdrawal. But oncology is by far the most significant new therapeutic area; according to IMS, there are 90 therapeutic (as distinct from prophylactic) vaccines for cancer in the pipeline, and more than two-thirds of them are in late-stage development (see **Figure 9**).⁸⁶

However, conventional vaccines are very different from other therapies in several respects. They usually require very large safety and efficacy trials using healthy volunteers; long-term surveillance to ensure

Figure 9: Many of the new vaccines in the pipeline depart from the conventional vaccines model



Source: IMS KnowledgeLink, January 2007

the persistence of the antibodies they induce; and strict control of live materials in the manufacturing process (although new technologies are emerging, which should help to stabilise production).

More importantly still, any therapy aimed at the healthy carries a higher risk than one that treats the sick. This is not an insuperable obstacle, but it does suggest that Pharma may have to assume some sort of underwriting role. It could, for example, guarantee to cover the medical costs of any patient unfortunate enough to develop a disease against which he or she has been inoculated, where the patient has shown signs of a positive immune response after vaccination and the normal period of immunity still applies, in much the same way that insurance companies provide cover against accidents and thefts.

The global shift in attitudes towards healthcare, and increasing emphasis on prevention, offers Pharma a number of new prospects, then – although governments will have to invest very much more, if they are serious about trying to forestall disease. It will enable the industry to enter the realm of health management, with wellness programmes that supplement what governments and employers provide. It will also boost demand for vaccines. This could ultimately generate totally new business opportunities in the health insurance sector, although Pharma currently lacks any such experience.

Sticking to the rules

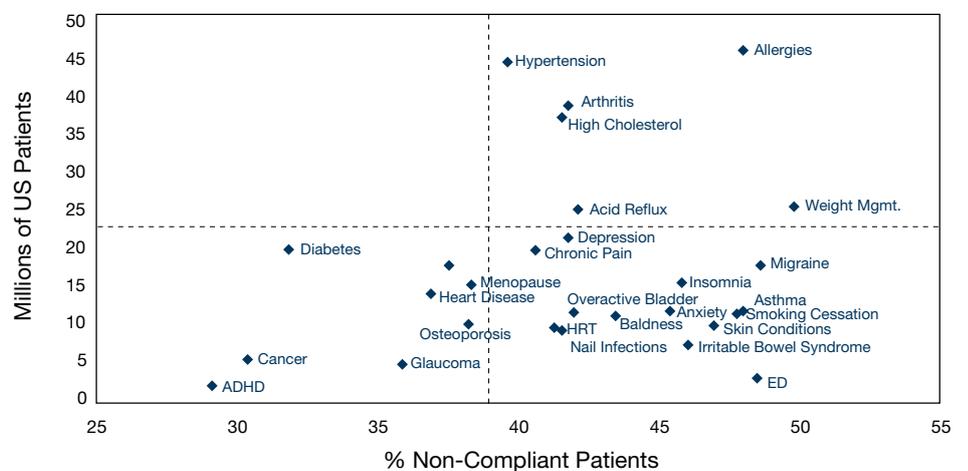
In fact, two of the key elements of disease management will soon be in place. As we have already indicated, better patient monitoring and outcomes data will change the way in which medicines are prescribed and paid for, but they could also be used to improve compliance. This would put an end to the future of those “me-too” products that only garner sales because a first-line treatment seems to have failed when, in reality, the patient has not taken the medication properly. However, it could also provide a substantial increase in sales of some therapies that really work.

In a perfect world, all patients would adhere to their treatment regimens. But the world is far from perfect. The FDA and National Council on Patient

Information and Education report that 14% to 21% of US patients never fill their original prescriptions; 60% cannot identify their own medications; and 12% to 20% use other people’s therapies.⁸⁷ Even patients who do not commit such flagrant abuses often compromise the effectiveness of the therapies they take by consuming them at irregular intervals or failing to complete the course, while some people with chronic diseases stop taking their medications altogether (see **Figure 10**).

The problem is not confined to patients with relatively minor illnesses; it applies equally to patients who suffer from life-threatening conditions. In a survey recently conducted by Cancer Research UK’s Psychosocial Oncology Group, for example, 72 of 131 women who had

Figure 10: Non-compliance is a major problem in people with minor and serious illnesses alike



Source: Manhattan Research, 2004

Table 4: Reducing non-compliance rates could dramatically increase sales of some drugs

Year	No. of Patients at Start of Year	Patient Attrition from Non-Compliance	Sales Lost through Non-Compliance (US\$ bn)	New Patients	New Sales (US\$ bn)	No. of Patients at Year End	Total Revenues (US\$ bn)	Cost of Compliance Programme (US\$ bn)
0						1,000,000	3.00	
1	1,000,000	222,222	0.67	333,333	1	1,111,111	3.33	0.317
2	1,111,111	246,914	0.74	333,333	1	1,197,530	3.59	0.347
3	1,197,530	266,118	0.80	333,333	1	1,264,745	3.79	0.371

Source: PricewaterhouseCoopers

Note: We have calculated compliance costs based on the number of patients at the start of the year and half the additional increase in the number of patients at the end of the year

been diagnosed with breast cancer at least two years previously said that they sometimes failed to take their treatments.⁸⁸ More than half of all renal transplant recipients are also thought to be non-compliant, even though they depend on immunosuppressive medications to survive.⁸⁹

The impact of non-compliance on healthcare costs is horrendously high. In the US alone, it has been put at anything between \$77 billion and \$300 billion a year.⁹⁰ (The figures vary, depending on whether they cover direct costs like wasted medications, re-testing and acute or emergency care that would otherwise have been unnecessary, or include indirect costs like lost productivity.)

No comparable financial data are available for other regions, although the problem seems equally widespread. WHO reports that adherence to long-term therapies for chronic illnesses in developed countries averages 50%. In developing countries, the rates are even lower.⁹¹

Compliance rates for short-term medicines like antibiotics are not much better. In one recent survey, 22% of the respondents said that they had omitted doses or failed to complete their last course of antibiotics, and the non-compliance rate exceeded 30% in some countries.⁹² Yet improper use of antibiotics can create disease-resistant bacterial mutations, and antibiotic resistance is now a major public health concern.

Seen from Pharma's perspective, non-compliance thus represents a huge opportunity to maximise the value of its products. Indeed, Datamonitor estimates that better compliance could generate more than \$30 billion a year in additional sales.⁹³

A simple illustration shows how the sums stack up. Data from the Medicines Monitoring Unit at the University of Dundee indicate that only one-third of patients are fully compliant with their prescriptions, another third are partially non-compliant and the remaining third are totally non-compliant.⁹⁴

Suppose, then, that a medicine for a chronic condition costs \$3,000 a year; generates revenues of \$3 billion a year; and has an annual patient turnover of 33%. In other words, it generates \$1 billion a year from new sales and loses another \$1 billion worth of sales through non-compliance, so its revenues are stable at \$3 billion a year.

What happens if, with better monitoring and mnemonic devices, the manufacturer can reduce attrition rates by 33% a year while continuing to generate an extra \$1 billion a year from new sales? As **Table 4** shows, its revenues will rise from \$3 billion to \$3.8 billion between the first and third year, generating an additional \$1.7 billion in sales over the entire period. The total cost of a compliance programme (at about \$300 per patient per year) would come to just over \$1 billion,⁹⁵ so it would see an additional profit of \$700m over three years – a prize well worth having.

More importantly still, compliance monitoring offers Pharma a means

Driving the healthcare bill down

Analysis of healthcare expenditure in the US shows that 5% of the population account for 49% of the total bill. Conversely, 50% account for just 3%. The five most costly conditions are heart disease, cancer, trauma, mental disorders and pulmonary conditions; they collectively account for 32.7% of overall healthcare expenditure. So it makes good sense to focus on funding support services for patients with these diseases first.

But big savings can also be achieved by helping people with chronic diseases. In a study of more than 137,000 US patients with diabetes, high cholesterol, hypertension or congestive heart failure, Medco Health Solutions measured the impact of compliance on healthcare costs. For each additional dollar spent on prescription treatments, the cost of caring for patients with diabetes was reduced by \$7, that of caring for patients with high cholesterol was reduced by \$5.10 and that of caring for patients with high blood pressure by \$3.98.

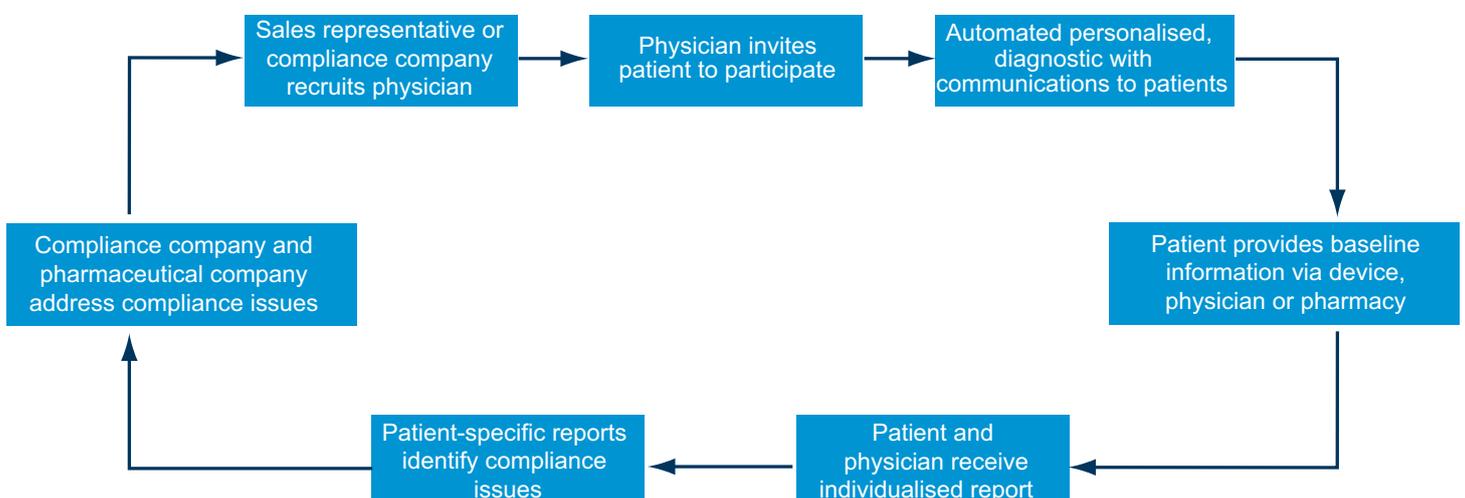
of expanding into healthcare, improving outcomes and reducing overall healthcare costs (see sidebar, **Driving the healthcare bill down**).⁹⁶ The industry has already begun to make this transition in the US, where some companies have been funding specialty pharmacies providing clinical support for patients with serious illnesses for more than a decade. However, most countries currently lack such an infrastructure.

One obvious solution to this dilemma, for conditions that fall outside the realm of specialty pharmacies and in countries where such channels do not exist, is the use of an intermediary to provide a personalised monitoring service. It is already possible, for example, to use behavioural algorithms to predict which patients are most likely to violate their medical regimens and design monitoring plans suited to their individual needs. A growing

number of electronic devices such as mnemonic bottle tops are also reaching the market and, thanks to modern communication technologies like email, short message services and automated voice calls, it is becoming increasingly easy to reach people wherever they are (see **Figure 11**).

Several firms already offer limited compliance services. But we believe that, by 2020, personalised monitoring will be a standard feature of the packages many pharmaceutical companies provide. That, in turn, will have a bearing on how they develop new medicines, since they will be required to test both the compounds themselves and the compliance programmes that are used to support them. It has even bigger implications for their supply chains, which will have to manage the mechanics of contracting and delivering these services to multiple customers.

Figure 11: How compliance programmes work



Source: PricewaterhouseCoopers

The bottom line: Pharma needs to help patients and payers with compliance. But will a jaundiced public trust the industry to provide advice and monitoring services?

Nevertheless, the provision of support services for patients with specific diseases will enable the industry to target its products more effectively and boost its revenues. Handled responsibly, it might also create an opportunity to build stronger relationships with patients and improve its image in the healthcare community.

What's in a name?

Billy Tauzin, PhRMA's president and chief executive, recently summed up Pharma's reputation, when he noted: "There is one great problem that seriously challenges the ability of America's research-based pharmaceutical companies to continue doing what they do better than any other entity on the globe: research and develop new cures and treatments. In a word, it is 'trust'."⁹⁷

The problem is especially acute in the US, where respondents in the latest Harris Interactive poll ranked Pharma thirteenth out of 17 industries for honesty, behind life insurance companies and carmakers.⁹⁸ Research conducted by PricewaterhouseCoopers shows that many US consumers believe pharmaceutical companies do not focus primarily on health needs when setting their research agendas, that they are too aggressive in promoting products for unapproved uses and that they cannot adequately monitor the safety of medicines that are already on the market.⁹⁹ An increasing

number of Americans also resent paying higher prices for medicines than people in other parts of the world, although they sometimes massively overestimate the real size of the nation's pharmaceuticals bill.

However, Pharma is under fire in other countries, too. In a recent survey of EU stakeholders, including Members of the European Parliament, respondents said that the industry was "too profit-driven", "too faceless" and did not participate sufficiently in the healthcare debate.¹⁰⁰ Pharma's poor reputation has also spread to the developing world, where prices have long been a sore topic and there is now growing concern about the recruitment of trial patients who are allegedly unable to look after their own interests.¹⁰¹ In short, the industry has numerous issues, fair or otherwise, to resolve before it can recover its good name (see **Table 5**).

This tarnished reputation has serious implications for Pharma's future wellbeing. It will limit the industry's influence on the political agenda at a time when healthcare is rising to the forefront of government concerns, and impair the credibility of its claims for its products. It will impede access to the outcomes data companies will need to make effective new therapies and move from making pills to helping patients manage the illnesses from which they suffer. And it will restrict Pharma's ability to recruit the bright young scientists who can help it develop those medicines.

Table 5: Pharma has numerous stakeholder challenges to resolve before it can recover its good name

Drug Safety	Understating the adverse reactions associated with a drug	Exaggerating the dangers involved in importing drugs	Failing to monitor the safety of marketed drugs adequately
Clinical Trials	Failing to disclose the full results of clinical trials	Making improper financial arrangements with trial sites	Manipulating trial data to maximise sales
Drug Prices	Charging prices that are perceived as too high	Ignoring social responsibilities in pricing for the developing world	Spending excessively to protect patents
Sales Practices	Promoting products for off-label indications	Providing physicians with financial incentives to prescribe products or write favourable articles about them	Inventing new lifestyle diseases
Investor Relations	Over-managing price/earnings and earnings per share ratios	Remunerating senior management exorbitantly	Ignoring negative publicity
Innovation	Spending R&D funds to develop “me-too” drugs	Spending too much on sales & marketing, and diverting funds from R&D	Developing drugs on the basis of sales potential rather than medical need

Source: PricewaterhouseCoopers

The bottom line:
Unless Pharma improves its reputation, its political, commercial and clinical credibility will be eroded, with serious implications for its future success

The need for a dynamic new approach

Pharma is at a pivotal point in its evolution. The dearth of good new compounds in its pipeline is central to all its other problems, including its rising sales and marketing expenditure, poor financial performance and battered reputation. Moreover, though global demand for medicines is growing, as demographic, economic and epidemiological trends reshape the marketplace, soaring healthcare costs will force Pharma to engage in the dialogue on healthcare funding and work much harder for its dollars. Clinical advances and financial constraints are already changing the way in which healthcare is delivered and will soon change the way in which it is measured. The political climate is likewise becoming much more aggressive – and no politician will stand up for an industry that does not win votes.

These trends will ultimately apply everywhere. The US is struggling to foot a healthcare bill that touches \$2 trillion and cannot continue to

generate the bulk of the industry's profits. And though the E7 countries look increasingly promising, they cannot afford to match the prices the developed world has historically paid.

Thus Pharma's traditional strategy of placing big bets on a few molecules, marketing them heavily to primary-care physicians and turning them into blockbusters will no longer suffice. J.P. Garnier, chief executive of GlaxoSmithKline, admitted as much in February 2007, when he noted: "This is a business model where you are guaranteed to lose your entire book of business every 10 to 12 years." The "first reflex" for many companies is to merge and that buys them "a little time" to deal with patent expiries, but fundamental changes will ultimately be necessary, he concluded.¹⁰²

Some of these changes will depend on the nature of the products and services different companies offer, since there can be no one solution to the needs of an industry as complex as Pharma. The choices

each organisation makes will have a bearing on the structure it adopts, alliances it forges, culture it espouses and people it employs. But some common themes are likely to emerge.

We believe that Pharma will have to use new technologies to improve its understanding of disease, reduce its R&D costs significantly and spread its bets to increase its productivity in the lab. It will also have to work more closely with governments, regulators and the healthcare community to make the medicines patients really need, test them as quickly and effectively as possible, and provide a more holistic healthcare service. Lastly, it will have to tailor its sales, marketing and pricing strategies to new audiences and markets; show that its products are worth the money that is spent on them; and rebuild its reputation by adhering to the highest ethical standards. We shall discuss some of the changes we believe will be required in more detail in this next section of our report.

Degrees of change

The number of doctorates awarded in the natural sciences and engineering has levelled off or declined in the US, UK and Germany since the late 1990s. Conversely, it has been rising steadily in Asia. The US still leads the way; it accounted for 22.5% of the 50,644 doctorates that were awarded in the physical and biological sciences in 2002 (the most recent year for which global data are available). The EU accounted for 37.2% and Asia for 18%. However, foreign students earned 32.3% of the doctoral degrees in the physical or biological sciences that were awarded in the US; 28.5% of those that were awarded in the UK, and 15.7% of those that were awarded in Germany. Many of these foreign students returned to their countries of origin, once they graduated.

The scientific literature published outside the established scientific centres of the US, EU and Japan is likewise growing rapidly. Between 1988 and 2003, the number of published articles rose from 466,000 to 699,000. The US share fell from 38% to 30% over this period, while the EU share rose from 28.9% to 31.5%. China's output rose by a huge 530% and that of the Asia-8 (South Korea, India, Indonesia, Malaysia, the Philippines, Singapore, Taiwan and Thailand) by 235%, boosting their combined share of the world total from less than 4% in 1988 to 10% in 2003.

Access to basic research

Pharma will have to begin by expanding the pool in which it fishes for basic research. It has traditionally scoured the scientific literature to get leads or bought them in from academic institutions and niche biotech companies, but this approach is becoming increasingly unviable.

Most of the Western universities in which scientific research is performed are under huge pressure

to commercialise their findings. Between 2000 and 2004, for example, there was a 70% increase in the number of patents the leading US research institutions filed (although the number of patents they were granted remained broadly the same).¹⁰³ British universities are also getting much smarter about the value of their research. There was a three-fold increase in the number of licences and options they executed, and a two-fold increase in the gross income they generated from intellectual property, over the same period.¹⁰⁴ So, where basic research is available, it is generally costing the industry considerably more.

The same is true in the biotech sector. Between 2000 and 2005, the average cost of an early-stage compound increased by a factor of eight, and the competition for assets is now so intense that valuations have started to overtake the figures recorded for Phase III deals just a few years ago. Many biotech companies are also securing more favourable rights, in the form of co-promotion arrangements or other options, suggesting that they are keen to make the transition from pure R&D to commercialisation.¹⁰⁵

Much of the scientific research performed in the West is becoming prohibitively expensive, then, but the research base itself is also shifting east – and Pharma is not in a strong position to exploit these new sources of knowledge (see sidebar, **Degrees of change**).¹⁰⁶ Most of the industry leaders are trying to establish a foothold in Asia. Wyeth has, for example, opened a joint early development centre with Peking Union Medical College Hospital in Beijing;¹⁰⁷ Roche has set up a research base at Zhangjiang

Hi-Tech Park in Shanghai;¹⁰⁸ and AstraZeneca is planning to do likewise.¹⁰⁹ Meanwhile, Novartis is building an \$83m R&D centre in Suzhou, near Shanghai; and GlaxoSmithKline is contemplating a move to China, too.¹¹⁰

Similarly, Eli Lilly, Novartis and GlaxoSmithKline have all set up research centres in Singapore.¹¹¹ Novartis has also just embarked on a new clinical research venture in Indonesia.¹¹² AstraZeneca has opened a process R&D laboratory in Bangalore.¹¹³ And GlaxoSmithKline plans to set up a global drug development support centre in Mumbai with Indian software firm Tata Consultancy Services.¹¹⁴ But these investments are tiny, compared with the amount Big Pharma is spending on R&D in the West.

Moreover, although the majority of multinationals are keen to expand their presence in Asia, relatively few are focusing on research. In a survey recently conducted by PricewaterhouseCoopers, only 8% of respondents said they were interested in doing more research in Asia, whereas 50% wanted to increase their sales and marketing activities, and 25% to increase their manufacturing activities, in the region.¹¹⁵

This may prove a rather short-sighted approach. If Pharma is to get access to the basic research it needs, it will either have to establish a much stronger footprint in Asia or forge close links with the most reputable centres of scientific excellence in the area. That, in turn, means it will have to overcome barriers of language and culture. And, as experience in the IT sector shows, following the herd can prove a costly mistake. Many parts of India are now short of the very

resources that prompted numerous companies to flock there in the first place, so it is essential to choose the right location.

Pharmaceutical research

But even if Pharma can get access to good basic research, it will still need to transform the way in which it performs R&D. At present, many companies concentrate on investigating new molecules before they have created a clear picture of the pathology of the diseases they are trying to address and the physiological responses those diseases cause. This is too narrow a focus at such an early stage in the research process, and helps to explain why attrition rates in development are so high.

We believe that, by 2020, the most successful companies will be those that focus on building a much better understanding of the pathophysiology of disease.¹¹⁶ They will study the disease variability arising from multifactorial aetiology, the underlying disease mechanisms, targets that are amenable to therapeutic intervention and what markers could be used to distinguish between patients with similar clinical symptoms but distinct biological conditions.

Scientists currently use public-domain information on disease epidemiology, pathways, mechanisms and targets to formulate hypotheses about the likelihood of being able to alter the course of disease via pharmacological intervention. They then use internally generated data derived from *in vitro* cellular models or *in vivo* animal studies to achieve limited validation

of a specific target and, when they have established a certain degree of non-clinical “confidence in rationale” (CIR), they begin high throughput screening to find a molecule that can interact with the target protein.

Once they have identified a series of leads, they initiate a full programme of lead optimisation and experiments to test the physical and toxicological properties of a given molecule, but it is only after several more years have elapsed that the molecule is ready for studies in man. Even then, early clinical studies do not test the central hypothesis that the target has any pathophysiological link to the disease being investigated; they focus on establishing what the human body does to the molecule. It is not until Phase II (some five to seven years after the first high throughput screen against the target) that the CIR is truly tested – and this is the point at which most compounds fail, although some fail at an even later stage in development (see sidebar, **Molecular fallout**).¹¹⁷

The key to reducing the time and costs involved in researching new molecules is to test the hypotheses underpinning them in man as early as it is safe and practicable to do so, and to invest far more in creating a more holistic understanding of disease pathophysiology and epidemiology before embarking on expensive development programmes. Today, it is clear that the real source of intellectual capital is a robust understanding of disease, and that the research process should no longer be limited to a specific therapeutic area, disease mechanism, target or biological pathway.

Recent research indicates, for example, that there are eight different disease mechanisms underlying Type 2 diabetes.¹¹⁸ In order to develop a treatment for patients with Type 2 diabetes, it is therefore necessary to understand the “context” of the disease, including:

- The nature and incidence of the various disease subtypes
- Whether all eight mechanisms are amenable to therapeutic intervention
- The relevant targets for therapeutic intervention
- The feasibility of developing biomarkers to identify which patients suffer from which disease subtypes
- The safety characteristics of different potential therapies; and
- The commercial viability of those therapies.

Once it has acquired an in-depth understanding of the pathophysiology of disease, a company can develop a probe molecule and biomarkers for early testing of the CIR in humans.

Molecular fallout

In one recent analysis of 73 molecules that failed in Phase III, 50% of the compounds that failed did so because they could not be proved effective. Compounds with novel mechanisms of action failed more than twice as often as those using established ones. Such studies show that the industry is sinking large sums of money in developing molecules whose pharmacological impact it does not comprehend in sufficient detail beforehand.

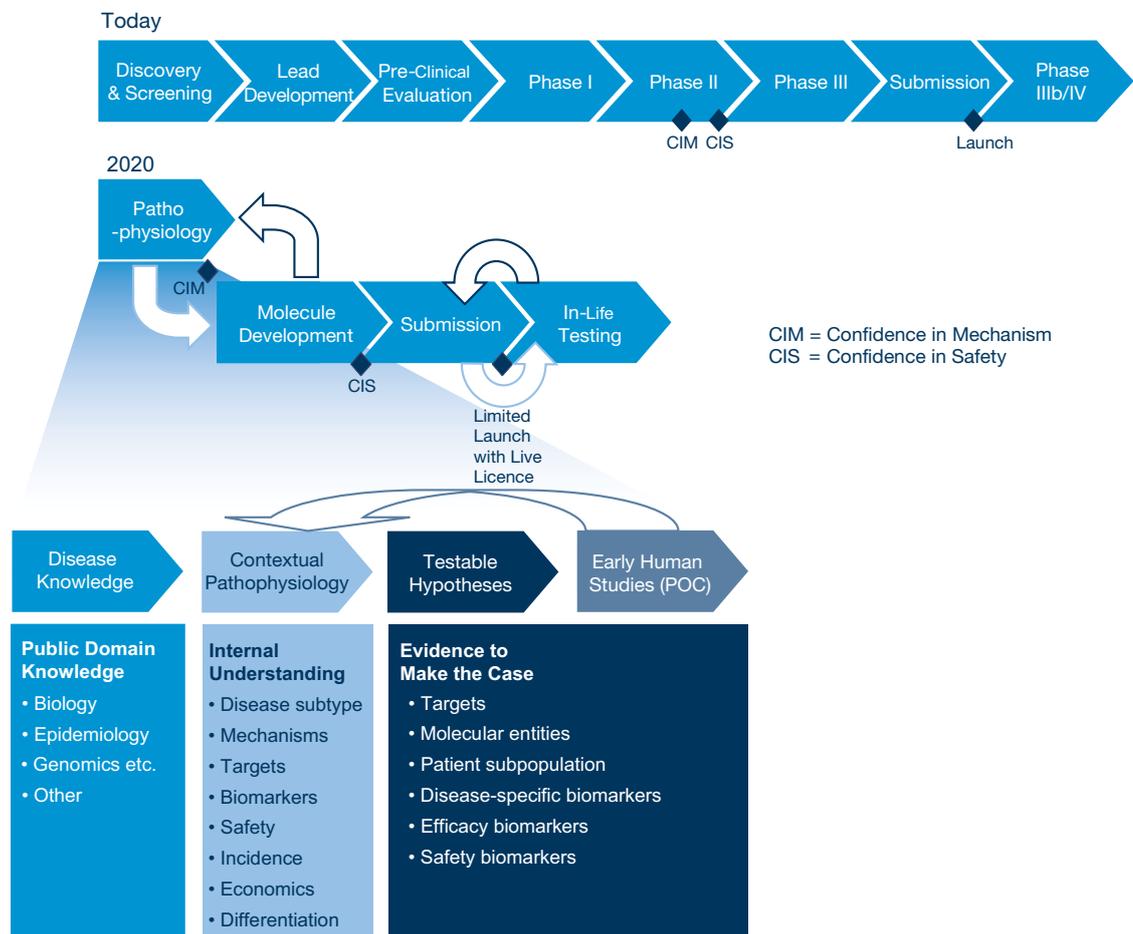
This will generate a steady, iterative increase in its knowledge about the relationship between molecular intervention and disease pathophysiology, as well as enabling it to create a more precise and sensitive set of biomarkers for determining disease subtypes, patient subpopulations, safety and efficacy. When it is confident that the mechanism of action in the probe molecule works as intended (based on iterative testing in man), it can move the molecule into “development” (see **Figure 12**).

Some biotech firms and specialised research organisations already use this approach to accelerate their research, establish the commercial viability of their molecules and reduce attrition rates – with obvious benefits. Big Pharma typically takes about 40 months and \$25m to establish proof of concept. Conversely, Chorus, the independent drug development unit set up by Eli Lilly, took just 12 months and \$2.7m to show that an anticoagulant with a novel mechanism of action worked in 74 patients.¹¹⁹

We suggest that Pharma should emulate such pioneers, and that acquiring a much deeper knowledge of the pathophysiology of disease should become an early part of the research process. Such an approach would alter the balance of risk dramatically by enabling the industry to pursue many more leads than it can currently afford and develop them with a much greater probability of success.

Some of the new technologies now emerging will also help it to integrate the insights derived from the

Figure 12: In the R&D process of the future, a pharmaceutical company will only develop a molecule when it is confident that the mechanism of action works



molecular sciences with other kinds of knowledge. Semantic webs will, for example, enable scientists to move seamlessly from one database to another, analyse disparate forms of data spanning multiple disciplines and organisations, and connect genomic, proteomic and metabonomic data with clinical data. They will also facilitate the mining and re-use of data from previous research projects and clinical studies to generate testable new hypotheses.¹²⁰

The W3C Technology and Society domain has already developed a prototype development dashboard – the BioDASH – which connects information about biological targets and compounds with data on the molecular biology of specific diseases.¹²¹ Several big pharmaceutical companies have also been conducting pilot studies, and some industry experts predict that use of semantic technologies could be widespread within the next five years.

Common data standards will clearly be necessary to support such technologies. But the Clinical Data Interchange Standards Consortium (CDISC) has already developed several data standards, and there are others in the pipeline. They include various labelling standards; the HL7 “family” of standards for discharge summaries, summary patient records and medical claim attachments; and the Digital Imaging and Communications in Medicine (DICOM) standard for transmitting medical images.¹²²

Other, more remarkable advances – such as machine-learning systems – are also on the horizon. “Autonomous experimentation”, as it is sometimes called, will ultimately allow Pharma to use

artificial intelligence techniques to carry out the entire cycle of scientific experimentation, including the origination of hypotheses to explain observations, the devising of experiments to test these hypotheses and the physical implementation of the experiments using laboratory robots (see sidebar, **The road to robot scientists**).¹²³

However, crucial though such new technologies will be in facilitating biopharmaceutical research, they cannot redress the cultural obstacles Pharma faces – and these are an even bigger roadblock. The corporate cultures and kinds of people the largest pharmaceutical companies employ often preclude them from being very innovative. Some companies are still wedded to the blockbuster model of R&D, and restrict their research agendas accordingly. But even those that have abandoned the blind pursuit of blockbusters generally have very complex decision-making processes. They also reward research scientists for delivering candidate molecules to the clinic (most of which seem to come through just before the year-end) rather than for acquiring sufficient insight to determine whether those molecules are viable or not.

It is therefore quite possible that new entities may emerge to fill the gap. By 2020, for example, specialist organisations focusing exclusively on biological pathways and proofs of mechanism may sell their research, just as biotech firms now sell promising molecules. Indeed, given the cultural and organisational challenges the industry must tackle, it may be questionable whether pharmaceutical companies are even the right place in which to perform such work.

The road to robot scientists

Adam, the “robot scientist” designed by scientists at the University of Aberystwyth, Wales, is one example of autonomous experimentation. The robot conducted a series of simple experiments on different strains of yeast, each of which had a gene missing. The data it generated were analysed using a closed-loop machine-learning system to create hypotheses, identify the most likely ones and decide which additional experiments should be performed. The information was then fed back to the robot, which completed the necessary tasks. The robot’s performance proved significantly cheaper and better than random experimentation.

Pharmaceutical development

The development process, like the research process, needs to undergo major changes to reduce the time and costs associated with bringing new medicines to market. As Dr Scott Gottlieb, the FDA’s Deputy Commissioner for Medical and Scientific Affairs, recently noted, the highly empirical, statistical method that currently predominates is inflexible; it restricts innovation and results in “overly large” trials that yield information “about how large populations with the same or similar conditions are likely to respond to a treatment. But doctors don’t treat populations, they treat individual patients.”¹²⁴

Of course doctors still lack many of the diagnostic tools and medicines they need to treat patients individually because “stratified medicine”¹²⁵ depends on the ability to identify the patients who are most likely to respond to a particular

therapy – and without a sufficient understanding of the multifactorial causes of disease it is impossible to devise a means of distinguishing between patients with different disease subtypes. However, this is where clinical biomarkers have already begun to revolutionise clinical development and medical practice alike.

As the authors of an excellent article on the subject explain, developing biomarkers to stratify patients with related but distinct conditions will enable Pharma to make different treatments for different patient subpopulations, test them only in patients who suffer from those conditions, and thus reduce both the number and size of the trials required to prove efficacy. It will also help to cut endpoint observation times when a clinical biomarker is an accepted surrogate for a longer-term endpoint such as survival. In all, the authors estimate, better use of safety and efficacy biomarkers could halve development costs.¹²⁶

Moreover, targeted treatments have a very different economical model from that of conventional medicines. Clearly, the potential number of patients any one such treatment can serve is smaller than the number for whom a mass-market therapy can be prescribed. But targeted treatments, by definition,

offer superior clinical results for the patient subpopulations whose distinct conditions they address, so they can generally command premium prices and are more rapidly adopted. The biomarkers themselves also provide additional opportunities for creating value, and using biomarkers to monitor patients' progress can improve long-term compliance.

Combining biomarkers and medicines will thus help Pharma to make safer, more effective therapies more economically. In-silico testing will likewise improve its ability to predict the safety and efficacy of new medicines in different patient populations. US life sciences company Entelos is one of several firms leading the way in the virtual domain; Entelos has created mathematical models of various diseases, including CVD, asthma, obesity, diabetes and rheumatoid arthritis, which it is using to acquire a better understanding of disease, identify targets and test potential medications.¹²⁷

Lastly, “pervasive healthcare” – the use of remote devices to monitor patients on a real-time basis wherever they are – will allow the industry to test new medicines outside a clinical setting. Pervasive computing is still in its infancy, and the infrastructure required to support

it has yet to be fully developed. But, by 2020, robust portable monitoring devices and the wireless networks across which the data they collect can be sent will both be in place (see below, **Anytime, anywhere healthcare**).¹²⁸ Together with EMRs, “smart cards” containing details of patients' individual health records (much as store cards track their shopping habits) and semantic technologies to link different kinds of data, pervasive healthcare will create a day-to-day environment that equates with the controlled environment in which clinical trials are conducted today.

All these changes will facilitate the refinement of the development process. A company will begin by defining the minimum amount and kind of information it needs to secure approval for “in-life testing” of a new medicine.¹²⁹ It will then perform a series of small, highly targeted clinical studies, using simulation, modelling and other technologies, to ensure that it understands the efficacy and safety of the product concerned, before submitting the data to the relevant regulatory agency – thereby rendering the traditional four-phase approach to clinical development redundant.

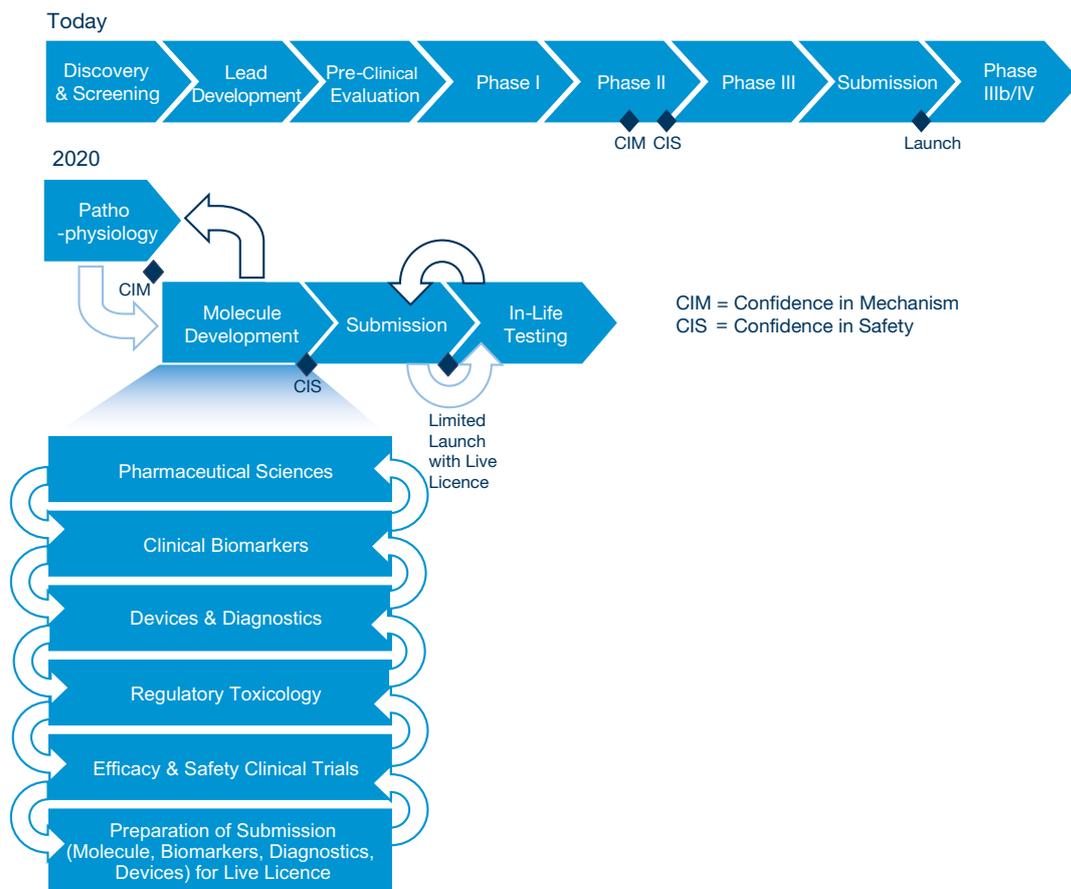
If the regulator is satisfied with the evidence, it will issue a “live

Anytime, anywhere healthcare

By 2020, wearable or embedded devices will be used to monitor patients wherever they are. Some of these devices will function on a constant basis, while others will take intermittent measurements. The surrogate markers they track will determine which mode is most suitable; a device that monitors the heart rate in a patient with a history of cardiac events must be constant, for example, whereas a device that monitors lipid levels in the bloodstream of a patient who has high cholesterol need only be intermittent.

The data a given patient generates will be transmitted to a hub at his or her medical centre, where they will be electronically filtered using intelligent algorithms. If the data fall outside certain predetermined parameters, the patient will be contacted via an automated voice messaging system and asked to come to the medical centre. If the patient does not respond, and the data suggest that he or she has had an acute episode, the system will automatically contact the medical centre with a request for immediate assistance.

Figure 13: The development process of the future will be much more refined



Source: PricewaterhouseCoopers

licence” permitting the company to market the medicine on a very restricted basis. The company will thereafter conduct in-life testing of that medicine in a small population of patients (many of whom will be referred via specialist centres or patient advocacy groups). With each substantive increase in evidence of the medicine’s safety and effectiveness, the regulator will extend the licence to cover a larger number of patients, a different patient population or multiple indications (see **Figure 13**).

This process has several advantages. It will reduce clinical development costs still further and allow pharmaceutical companies to recoup some of their costs more quickly, thereby enabling them to charge lower prices for new therapies. It will facilitate testing for polypharmacy in wider populations. And it will align the bench and the bedside more closely. Indeed, it might ultimately culminate in the complete integration of clinical trials with clinical practice, as is already starting to happen in the treatment of cancer. So, for example, a patient

who suffered from diabetes and lived in Paris would be automatically given the opportunity to enrol in clinical trials in the area at the same time as receiving treatment. In effect, clinical trial participation would become part of normal care.

Regulation

Clearly, some of the reforms we have outlined depend on the willingness of the regulators, as well as the political and legislative changes required to alter any

regulatory regime. However, the European Medicines Agency (EMA) and FDA have already shown that they are ready to grant conditional marketing approvals for some therapies, subject to certain obligations, including the completion of in-life testing. The EMA authorised the use of conditional approvals for orphan drugs and therapies for life-threatening conditions in April 2006 under Regulation EC 507/2006,¹³⁰ and the FDA is piloting the concept under the Prescription Drug User Fee Act (PDUFA) III.¹³¹

By 2020, we believe that all medicines which receive approval will be approved on a real-time basis, with live licences contingent on the performance of extensive in-life testing, including trials in specific patient subpopulations, and a predetermined schedule for reviewing each set of results. If in-life testing confirms that a medicine is safe and effective, the company

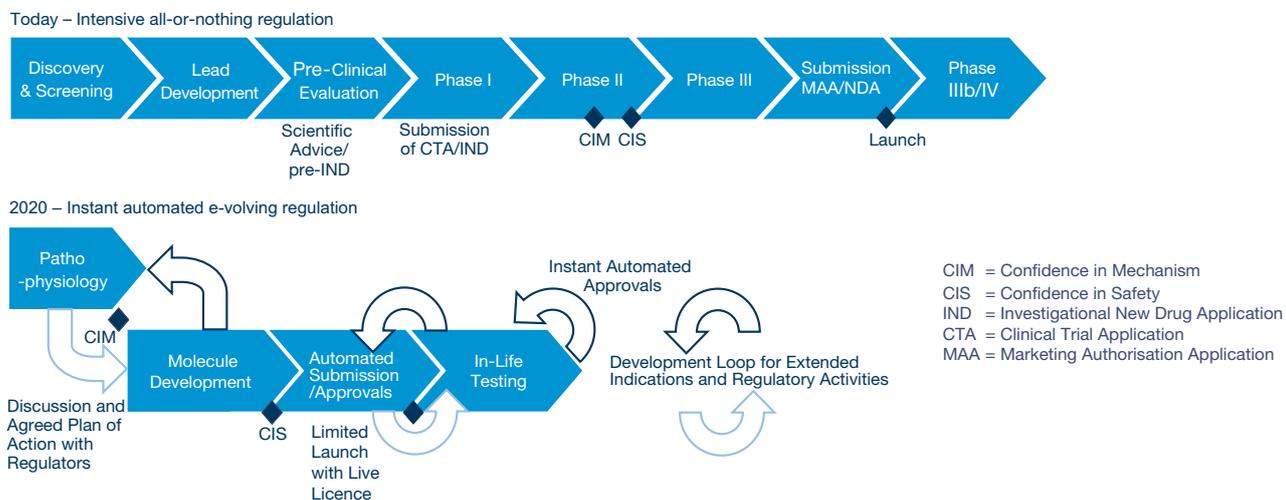
making it will be granted an extended licence or special permit – such as the paediatric use marketing authorisations (PUMAs) which are already used in Europe – so it will have an incentive to conduct further studies. In other words, every medicine on the market will have a prearranged, fully automated pathway throughout its lifecycle, and its development will be a continuous process rather than ending when it is approved (see **Figure 14**).

But, as the legislation governing new medicines and the way in which they are licensed becomes more complex, the regulators will insist on greater collaboration and expect to be consulted on a regular basis from a much earlier point in development. The FDA has already signalled its determination to become more involved in the development process with its Critical Path Initiative, which aims to create a new generation of predictive tools for improving

safety and efficacy.¹³² Similarly, one of the goals of the EMA's Road Map to 2010 is to facilitate the formation of "an adequate product development toolkit, able to address the bottlenecks during the development of innovative medicines".¹³³ The European Commission and European Federation of Pharmaceutical Industries and Associations (EFPIA) have now set up the Innovative Medicines Initiative, a pan-European collaboration to produce new drug development tools.¹³⁴

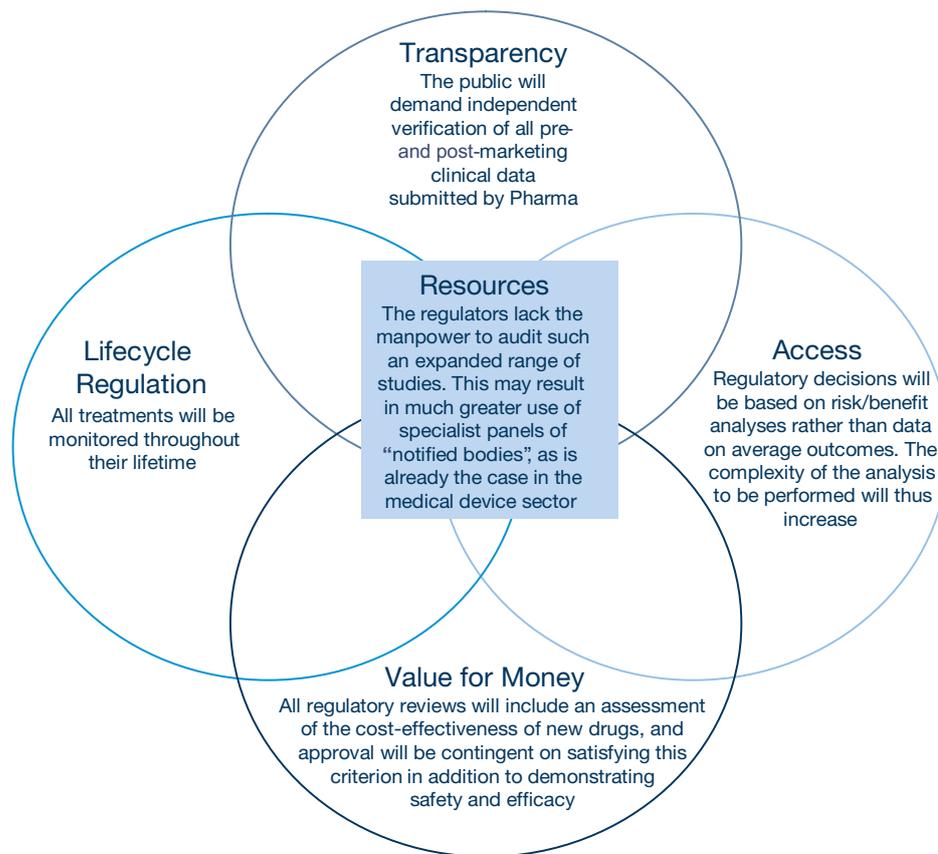
The criteria for approval will also become more challenging and more specific. The regulators are increasingly looking for evidence that new medicines are not just safe and effective, but better than any comparable existing therapies. The EMA often requires "comparator studies" where an alternative pharmacological treatment is available,¹³⁵ and the FDA recently

Figure 14: In 2020, R&D and regulation will be fully integrated and continuous



Source: PricewaterhouseCoopers

Figure 15: New auditing bodies and processes will be required



Source: PricewaterhouseCoopers

hinted that it would only approve prescription painkillers which filled an unmet medical need for patients who have no other “relatively safer” alternatives.¹³⁶

Several agencies are simultaneously beginning to develop more sensitive detection systems and a more sophisticated attitude to risk management. The EMEA has, for example, launched a new European Risk Management Strategy which requires that all pharmaceutical companies provide detailed information not only on what they

know, but also on what they do *not* know, about the risks associated with any medicines or manufacturing processes they submit for approval. They may then be required to develop risk minimisation plans.¹³⁷ And one US expert has called for a new risk assessment framework that takes individual variations into account (see sidebar, **Getting personal**).¹³⁸

These changes in the burden of proof will be accompanied by demands for greater transparency. Pharmaceutical companies will, for example, be required to disclose

Getting Personal

In his new book *Overdose*, American scholar Richard A. Epstein argues that, in focusing on the average response to a medicine when they are assessing its safety and efficacy, the regulators overvalue risk, ignore individual differences and needlessly deprive patients of valuable treatments. He suggests that the regulators should begin by asking: Is there is a significant fraction of cases in which the compound under review outperforms the placebo? If the mean response is well below that of the placebo and the variance in individual responses is small, the answer is likely to be no. But if the variance in individual responses is substantial, they should ask a second question: What do we know about individual variations?

If there is very little such knowledge, the product should be banned. But if a prescribing physician can make an intelligent estimate of where a patient lies within the spectrum of individual variations (through genomic profiling or other sources of information), the drug should be approved. In other words, part of the regulatory burden should be shifted downstream to the doctor, thereby enabling patients to receive treatments that work for them, even where they do not work for other patient cohorts.

all data from all clinical studies and in-life testing, regardless of whether they are favourable – with punitive treatment of any firm that breaches this rule. They will have to submit all product information electronically; supply data on all adverse events to a website managed by an independent intermediary, to which all prescribing doctors will be given access; and cope with additional scrutiny, in the form of third-party auditing of all their functions from R&D to sales and marketing (see **Figure 15**).

The EMEA already maintains a database of all clinical trials conducted within the EU, which interested parties can easily access. EudraCT, as the system is known, is rapidly becoming much more comprehensive in what it covers and may ultimately provide the basis for a global platform that ensures the transparency of all trial data.¹³⁹ Similarly, the MHRA has expanded Sentinel, the paperless system it launched in 2002, to cover licence submissions and product safety reporting,¹⁴⁰ and the other EU regulators are likely to follow in its footsteps.

The FDA is also investigating ways in which to create an entirely paperless submission process and build an electronic exchange for sharing clinical research information.¹⁴¹ And Dr Mark McClellan, a former FDA commissioner, recently called for the creation of a database linking US public and private healthcare payer claims systems to improve monitoring for adverse drug events. He argued that such a database would make it possible to target in-life studies more accurately, collect information about safety signals more effectively and better assess usage patterns.¹⁴²

In future, many agencies will share such safety and efficacy data to create a broader picture of how different medicines perform. Indeed, by 2020, such data may even be managed in one global database to which every regulator has access. Several national and regional regulators have already begun to collaborate. In September 2004, for example, the FDA and EMEA launched the Joint Scientific

Advice programme, a forum for working together to provide companies with input during the development process and thus avoid the unnecessary replication of trials or use of diverse testing methodologies.¹⁴³

But with the globalisation of R&D and the markets, as well as the transfer of a growing amount of pharmaceutical manufacturing to the developing world, the regulators of the E7 countries will become increasingly important, too. The member countries of the Association of Southeast Asian Nations (ASEAN) have already revolutionised the regulatory systems of the Pacific Rim with a framework designed specifically for their patient universe. They are now building a common set of technical application forms for pharmaceutical registration, Good Manufacturing Practice (GMP) inspection and labelling.¹⁴⁴

The logical conclusion to such cooperation is, of course, the development of a single global agency charged with regulating pharmaceuticals everywhere – although this is unlikely, if for no other reason than national pride. Nevertheless, by 2020, there may well be one global regulatory system administered by national or federal agencies responsible for ensuring that new treatments meet the needs of the patient populations within their respective domains. The initial investment required to create the supporting technological infrastructure might be substantial, but such a system would help to reduce the spiralling costs of regulatory compliance.

The supply chain

Globalisation will also have a profound impact on the pharmaceutical supply chain. As a growing amount of R&D migrates to Asia, the industry will have to manage resources that are much more widely dispersed. Similarly, as the markets of the developing world get bigger, more affluent and better able to afford a wider range of medicines, and as greater mobility increases the potential for pandemics, it will have to build a supply chain that is much more globalised, scalable and secure.

Globalisation will almost certainly exacerbate the incidence of parallel trading and counterfeiting. About €4.2 billion (\$5.7 billion) worth of medicines (at ex-factory prices) are already reimported every year in Europe alone.¹⁴⁵ Counterfeiting is likewise on the rise; the FDA estimates that 10% of all medicines sold worldwide are counterfeit, and the problem is much worse in developing countries. Over half the anti-malarial treatments sold in Africa are thought to be fakes.¹⁴⁶

The geographical expansion of the supply chain will thus make it much more difficult to manage, as will several other changes already starting to take place. The number of products companies make will increase, as they spread their bets and some of those bets start to pay off. The nature of the products they make will become more diverse, with the advent of combination therapies, diagnostics, biomarkers and treatments targeted at patients with specific disease subtypes. And the technologies they use to manufacture some of these new therapies will become much more complex.

Biologics are particularly hard to manufacture and transport, because they are more fragile than small molecules and more susceptible to impurities in the manufacturing process. But many of the new medicines reaching the market will also use novel delivery technologies like controlled-release implants and magnetically targeted carriers. These technologies are far more complicated than the inhalants, transdermal patches and drug-coated stents that predominate today. So the manufacturing process will have to become much more flexible, with different manufacturing routes for different kinds of products.

It will also have to become much more robust. The FDA's cGMPs for the 21st Century initiative calls for the design of effective and efficient manufacturing processes to assure product quality and performance; product specifications based on a mechanistic understanding of how different formulations and processes affect product performance; and continuous real-time assurance of quality.¹⁴⁷ Several US states have also passed product pedigree laws, and many others are contemplating such legislation.¹⁴⁸ These laws will ultimately apply to every contractor in the worldwide supply chain, including active pharmaceutical ingredient manufacturers.

In short, Pharma will have to learn how to manufacture an increasingly diverse range of products in an increasingly challenging environment, drawing on resources that are much more geographically scattered – and it will have to do so just as manufacturing costs come under much greater pressure. The pharmaceutical supply chain is currently geared to the production of

blockbusters for large populations. But, as these medicines come off patent, the economies of scale they generate will diminish. However, the industry is already suffering from overcapacity, with utilisation rates of less than 50% at some plants. Many companies will therefore have to sell off their manufacturing assets or find new ways of exploiting them.

So what will the manufacturing process of the future look like? We believe that, by 2020, some therapies will be “assembled to order” rather than “made to forecast”, using lean manufacturing techniques learned from the automotive sector. New technologies will also play a much bigger role. Simulation and data analysis tools will accelerate the transfer from development to full-scale manufacturing. Process tomography and high-frequency camera systems will provide a better understanding of flow patterns. And integrated sensors will continuously monitor the performance and quality parameters of each manufacturing process on a real-time basis, thereby ensuring the quality of the medicines that are made and generating the data needed to optimise production.

However, since many pharmaceutical companies lack the skills required to manage turnkey operations and perform specialist manufacturing, they may decide to outsource most of their production to contract manufacturers. That, in turn, will require much greater collaboration. Instead of treating such firms as “toll manufacturers”, they will need to treat them as strategic partners for the duration of the product lifecycle. They will also need to work closely with their customers, vendors and logistics service providers, to create supply chains that

can be rapidly reconfigured as market conditions alter.

The distribution process will undergo equally major changes. The industry has traditionally relied on wholesalers to distribute its products, but the proliferation of inexpensive overnight courier services has made it feasible to ship medicines directly to pharmacies, thereby enabling many companies to reduce their inventory, control product “leakage” more effectively and lower their delivery costs.

The channels Pharma uses to reach the market are also beginning to fragment, as a growing number of companies fund the provision of support services tailored to the needs of patients taking specific therapies. In the US, for example, some firms now offer drug dispensing packages that include patient education, monitoring and counselling, drug administration training, nutritional advice, cognitive-and-motor-skill tracking and the like.

By 2020, most pharmaceutical companies will use this model not just for distributing speciality medicines but also for distributing an increasingly wide range of treatments for common diseases, and thereby creating a more intimate relationship with patients. The role of the conventional “middle man” will thus decline, although some wholesalers may decide to expand their remit by providing support services. However, the supply chain will be responsible for commissioning those services and ensuring that they are delivered to standards that meet the manufacturer's specifications – a transition that will ultimately enable it to become a means of revenue generation and competitive

Automated dispensing

By 2020, the fulfilment of prescriptions for most primary-care medications will be fully automated. The doctor will write a prescription, check the reimbursement criteria and download the scrip to the patient's smart health card or email account, depending on the preferences of the individual patient. The patient will then forward the scrip to an online pharmacy, which will check his or her identity, using a web-based biometric device, and mail the medication to the specified address. Alternatively, the patient will visit the local shopping centre and insert his or her smart card in a vending machine which will automatically authenticate his or her identity and dispense the medication.

differentiation, rather than a cost-centre.

The way in which medicines are dispensed will also evolve. Targeted treatments and other secondary-care medications will be dispatched directly to patients or their healthcare providers, while simple primary-care medications are dispensed electronically (see sidebar, **Automated dispensing**). That, in turn, will reduce costs and release the retail pharmacists who previously dispensed such medicines to perform more value-adding activities such as patient counselling and monitoring.

Moreover, all medicines will be tracked, using technologies like DNA labelling and "smart dust". Both technologies are still very immature, but they have potential applications in combating counterfeiting. DNA labelling could provide a way of fingerprinting proteins and identifying where they have been

manufactured, if the problems with selecting a DNA fraction that does not affect a protein's performance can be overcome. Smart dust – minuscule motes capable of finding and connecting with other motes, creating a network and communicating data across the network – could be used to track the position of all the products covered by any given network in real time, and transmit information about vibrations, temperature and light.

Sales and marketing

While the supply chain expands to accommodate a wider range of medicines and markets, the sales and marketing process will become more concentrated. Pharmaceutical companies will focus most of their efforts on the policy-makers and payers who increasingly determine which medicines are prescribed (see **Figure 16**). Moreover, some of these authorities will compare notes. In September 2006, the European Commission launched the "Pharmaceutical Forum", which aims, among other things, to share information on the relative effectiveness of comparable medicines and pricing and reimbursement.¹⁴⁹ By 2020, a single pan-European agency could replace national bodies like NICE.

The stakes will get steadily higher, then, and the success with which pharmaceutical companies can make such "big ticket" sales will depend on their ability to differentiate their medicines from those of their rivals, demonstrate value for money and contribute to the overall improvement of human health. Many firms will therefore

seek to enhance their offerings by funding the provision of services like compliance monitoring, home delivery and disease management.

These changes in the marketplace will gradually render the traditional model for selling medicines defunct. Pharmaceutical companies will replace their large sales teams with key account managers and specialist advisers capable of managing the tender process. There will be far fewer sales people in markets that are currently saturated with sales staff, like the US – although growing demand will increase the need for key account managers and specialists in developing economies.

Some companies may even band together to sell "bundles" of medicines, including branded treatments, generics and OTC products, for specific patient segments. So, for example, a bundle of medicines targeted at patients with CVD might include a statin, ACE inhibitor, diuretic, Omega 3 oil, anti-platelet drug and aspirin. The financial services industry already operates in this fashion, with "tied" financial advisers who can in certain circumstances market products from other providers. But whether or not different pharmaceutical companies decide to join forces, the consolidation of the sales and marketing process should enable the industry to reduce its costs and redeploy the money it saves in further R&D or the provision of new value-adding services.

Patients will also play a bigger part in the sales and marketing equation, as they foot an increasing share of their own healthcare costs. The link between what they spend and the

healthcare they receive will become progressively clearer, and some patients may be willing to pay more for health plans that offer them access to a wider range of therapies.

Many pharmaceutical companies will therefore invest more effort in reaching patients, and the growing emphasis on promoting wellness rather than managing illness will provide them with new opportunities for doing so – opportunities that are seen as more palatable than direct-to-consumer advertising, which has generated some bad media coverage. Healthcare payers will increasingly reward patients with healthy habits and penalise those with unhealthy ones. Pharma can play a major role in helping patients by providing products and services that encourage healthy behaviour.

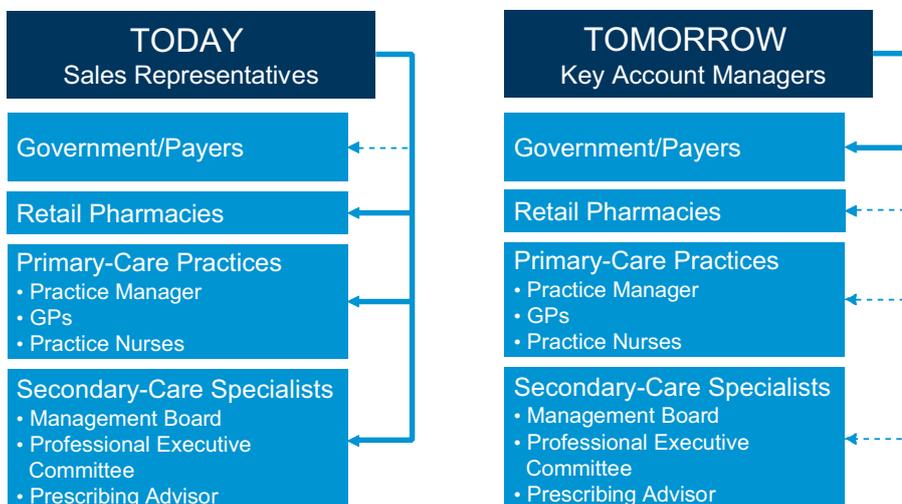
It can also offer support in the form of much better and more comprehensive product literature.

With the de-skilling of many elements of primary care and the transfer of a growing number of medicines (some of them quite potent) to OTC status, patients will need clear, accurate and unbiased information about the treatments they take and how best to manage their conditions, if they have a chronic disease. Again, Pharma can make a valuable contribution by providing access to such information either on paper or online. And, in moving closer to patients, it can begin to rebuild the esteem in which it was formerly held.

The sales and marketing process will thus undergo some profound alterations. The pricing process will change even more fundamentally. We have already talked about how, with widespread outcomes monitoring, the price any medicine can command will be based on its performance. The advent of live

licences conditional on further in-life testing will also have a huge impact. The industry will almost certainly be expected to price such therapies on a sliding scale, with price rises tied to the extension of the licence and quota of patients for whom a treatment can be prescribed. If it is to demonstrate the true value of its products, it will have to help healthcare providers distinguish responders from non-responders and improve compliance rates among the former while prescribing other treatments for the latter.

Figure 16: Pharmaceutical companies will focus most of their marketing efforts on the policy-makers and payers who determine which medicines are prescribed



Source: PricewaterhouseCoopers

Conclusion

By 2020, the context in which Pharma operates will be very different from that which prevails today. And one of the recurring motifs in all the shifts we have described is globalisation: the globalisation of the markets, as demand for medicine rises in the developing world; the globalisation of R&D, as a growing share of R&D migrates to Asia; the globalisation of the regulations governing the development of new medicines, as national and federal agencies collaborate; and the globalisation of information, as healthcare payers share data on the clinical and financial performance of medicines.

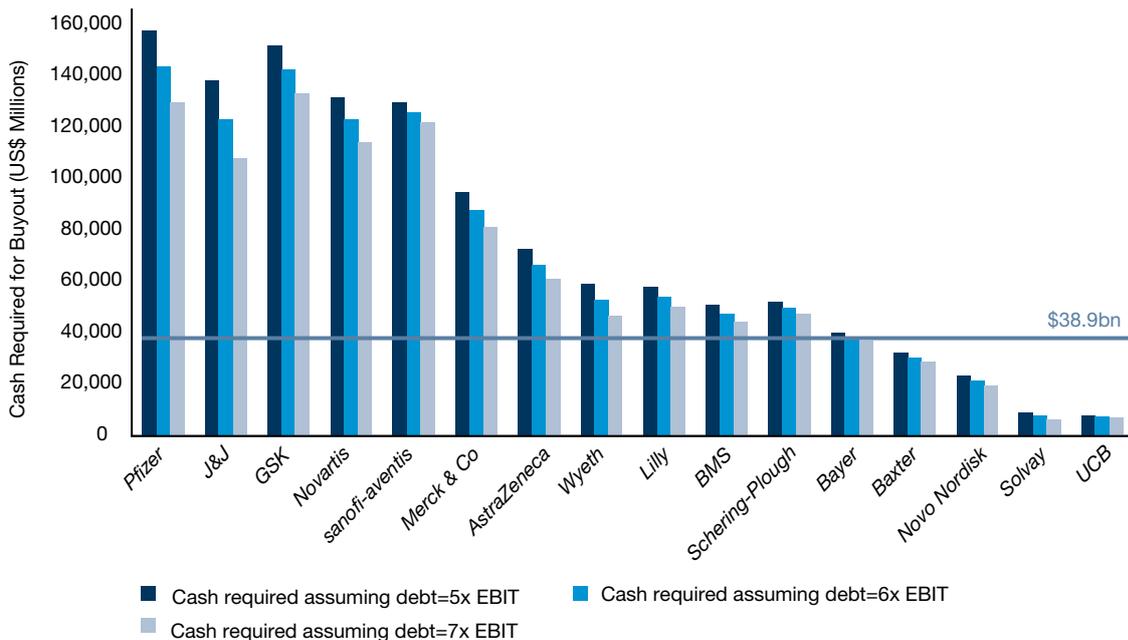
Globalisation will increase the risks Pharma faces; if a product fails in one market, for example, it may well fail in all. But it will also create opportunities for considerable savings. Global IT platforms, process standardisation and data standards, global regulatory requirements and global marketing efforts will enable the industry to eliminate inefficiencies and reduce its costs.

If Pharma is to thrive in this new environment, though, it will have to make sweeping changes throughout the value chain. Moreover, the incumbent management will have to move fast. The disintegration of

the traditional way of making and selling medicines could fuel another round of mergers and acquisitions very different in nature from those that took place a few years ago. One large company could buy another, for example, and strip it of all but the assets it wants. Private equity houses and hedge funds could also play a significant role in reshaping the sector.

Private equity firms have shown relatively little interest in Pharma to date. This is partly because they typically like to invest in companies with tangible assets and steady cash flows, whereas

Figure 17: How much cash would a private equity consortium have to pay to buy one of the leading pharmaceutical companies?



Source: PricewaterhouseCoopers

Note: The UK Financial Services Authority recently reported that the average debt to earnings ratio for the five largest transactions in the 12 months to June 2006 was 6.41. We have therefore calculated the cash required to complete a leveraged buyout of a leading pharmaceutical company assuming debt multiples of between five and seven times earnings before interest and tax (EBIT)

research-based pharmaceutical operations have intellectual assets and increasingly cyclical cash flows, and partly because their high market capitalisations have kept all but the smallest pharmaceutical companies off the radar screen.

However, a number of funds have been dipping their toes in the water. In January 2005, for example, a consortium of private equity investors bought speciality pharmaceuticals company Warner Chilcott for \$3.1 billion.¹⁵⁰ Similarly, in December 2006, Nycomed (which is owned by Nordic Capital and CSFB Alternative Capital) acquired Altana's pharmaceuticals division for €4.8 billion (\$6.5 billion).¹⁵¹ And several private equity firms are thought to have put in bids when Roche put its OTC business on the block in mid-2004, although Bayer eventually prevailed.¹⁵²

Clearly, the sums involved in such transactions are tiny compared with the cash that would be needed to buy a major pharmaceutical concern, but the private equity industry is rapidly getting larger and hungrier. In December 2006, David Rubenstein, co-founder of The Carlyle Group, predicted that there would be a \$100 billion deal within two years.¹⁵³ Two months later, Blackstone pulled off the biggest ever leveraged buyout with the \$38.9 billion acquisition of Equity Office Properties Trust.¹⁵⁴

On this showing, at least one of the 13 companies in the Big Pharma universe is already within reach of

the chief consortia, although giants like Pfizer, Johnson & Johnson and GlaxoSmithKline are still far too massive to touch (see **Figure 17**).¹⁵⁵ We therefore think it is very likely that one or more leading pharmaceutical companies will fall into the private equity industry's hands within the next 13 years – and private equity houses do not flinch when it comes to radical restructuring.

Yet in some respects it does not matter who holds the reins, for Pharma cannot do everything itself. It cannot train a new generation of research scientists unless there are scientists to train. Nor can it make the medicines people need without society's support – and we are dishonest if we pretend otherwise. We cannot expect charities and individual philanthropists to fund the research that is required to develop new therapies.

Several relatively small changes would make a considerable difference. Investing in school science labs and specialist teachers, and giving science a more prominent place on the school curriculum, would encourage more pupils to study the sciences at university, thus creating a larger pool of researchers on whom the industry could call. Altering the patent laws to recognise the value of long-term research, rewarding the development of vaccines and cures more generously, and demonstrating a genuine commitment to the prevention of disease would likewise

help to put the industry on a firmer footing in its efforts to decode the molecular basis of disease – surely one of the biggest and most worthwhile intellectual challenges the world faces.

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