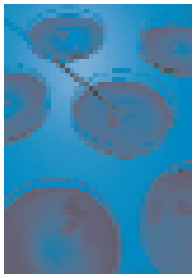
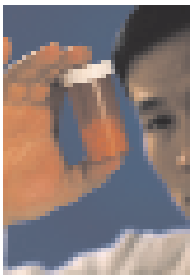
Pharma Futures





The Pharmaceutical Sector

A LONG-TERM VALUE OUTLOOK

DECEMBER 2004

Acknowledgements

This report attempts to capture a rich and complex discussion about the evolution of the pharmaceutical industry over the next ten years, which took place within the Pharma Futures project. As author of the report, I take full responsibility for it, including any mistakes. However, neither the report, nor the project as a whole would have been possible to do without the active engagement and support of many individuals.

The report derives from a scenario planning exercise which was undertaken with great skill by Steve Weber, Erik Smith, Andrew Blau and Lynn Carruthers of Global Business Network.

I would like to thank all members of the Working Group and all external experts for their active participation in the project. In many ways, these people *are* the project. I would also like to thank Cassie Higgs for logistical and research support throughout the project, Helen Wildsmith for her insight and facilitation of the project, Stewart Adkins for his contributions to the report, Helena Vines-Fiestas for her early support and Lawrence Wilkinson and Jonathan Sallett for their participation and contributions to the second workshop. Finally, I would like to thank the funders without whom this project would not have happened and in particular, the Sponsors, who in seeking answers to the question "what does it mean to be an active and responsible owner of a whole sector", have given birth to a project and on-going process for which there are few precedents.

Sophia Tickell
Director
Pharma Futures
Oxford (UK), 2004

Disclaimer

Contents

Acronyms

ARV	Antiretrovirals
PPAR Agonists	Peroxisome Proliferator-Activated Receptors Agonists
BLA	Biologics License Application
BRIC	Brazil, Russia, India and China
CEO	Chief Executive Officer
CVD	Cardiovascular Disease
EPS	Earnings Per Share
FDA	Food and Drug Administration (US)
GDP	Gross Domestic Product
HMO	Health Management Organisation
IPO	Initial Public Offering
IPR	Intellectual Property Rights
NCDs	Non-communicable Diseases
NCE	New Chemical Entity
NGOs	Non-Government Organisations
OECD	Organisation for Economic Cooperation and Development
R&D	Research and Development
TRIPS	Trade-Related Aspects of Intellectual Property Rights
WHO	World Health Organisation

Introduction

This report presents the findings of the Pharma Futures scenario planning project. Pharma Futures was convened in early 2004 by three pension funds; Algemeen Burgerlijk Pensioenfonds (ABP Netherlands), the Ohio Public Employees Retirement System (OPERS, US) and the Universities Superannuation Scheme (USS, UK). As long-term owners of pharmaceutical companies, these and other pension funds have a substantial interest in the continued profitability of a sector that created considerable shareholder value in the 80s and 90s. At the same time they recognise that the industry faces very serious challenges to its business model, not least growing demands for more innovative medicines and for more medicines to be more widely available to people of limited financial means in all markets.

The Sponsors were aware of the limited utility of the traditional tools available to manage risk - namely bottom-up stock-picking or underweighting the sector - especially when they took a portfolio wide and absolute risks/returns perspective. Hence they sponsored this project to facilitate a considered, informed discussion between the industry and its owners about the future of a sector that has such a vital role to play in the development and manufacture of innovative therapies, improving public well-being and so contributing to economic growth.

At the heart of the project is a desire to better align the goals of profitability with society's need for improved access to affordable healthcare, including innovative and life-enhancing prescription drugs. An assumption underpinning this project is that such an alignment is at the heart of any durable business model for the sector.

Pharma Futures brought together fifteen informed private sector stakeholders (pension funds, sell and buy-side analysts, pharmaceutical executives from ethical/branded and generic firms) to review how the sector might develop over the next ten to fifteen years. Their deliberations over a twelve month period were enriched by interviews with thirty external experts and a website discussion forum. The group discussed a range of issues relevant to a successful, long-term pharmaceutical industry including - innovation, adaptive leadership, the emerging markets, access to medicines in developing countries, intellectual property protection, marketing, information and advertising, pricing, societal expectations, government health provision and demographic changes.

The project created an opportunity for participants to do some long-term thinking about the future in a way that is not easy to do in the context of each of their "day jobs". It also allowed them to interact in a collaborative and creative way with people who had very different sorts of expertise about the sector. All participants accepted the project's starting premise: namely that for industry and its investors to act successfully on the challenges facing the sector, some adaptation of the sector's business model will be needed.

This report aims to make a constructive contribution to discussions about the role of this vital industry. The Sponsors hope that in the next phase of the project, this report will be used as a working document for continued discussion amongst the many stakeholders of the industry including: pharmaceutical executives and their consultants, institutional investors, financial analysts, government regulators, purchasers, patients groups, doctors, pharmacists, insurance firms, media and other commentators.

Executive Summary

Pharma Futures was set up in response to the serious challenges facing the pharmaceutical industry including a wave of patent expiries; demographic changes; pressures to reduce health expenditure; corporate pressure to reduce health insurance; calls for price reductions; challenges to intellectual property rights; unmet health needs in developing countries; and media and societal anger at corporate priorities and behaviour. The project addressed the dilemma of how to convince investors of on-going profitability whilst simultaneously meeting growing societal expectations.

Pharma Futures identified a growing imbalance between the short-term benefit that industry provides to shareholders, and the productive research that these shareholders and other stakeholders want from the industry in the long-term. While societal expectations may be changing, institutional investors and other industry commentators continue to have high expectations of pharmaceutical profitability that translate into powerful incentives to the sector to continue with its current business model.

Pharma Futures brought together fifteen informed private sector stakeholders to review the evolution of the sector over the next decade. Their deliberations over a twelve month period were enriched by interviews with thirty external experts and a website discussion forum. The project was able to facilitate creative and problem-solving dialogue between industry practitioners, long-term investors and their analysts, and those who reflect the views of government and societal players.

The Group developed three plausible scenarios about the future of the industry and reviewed the implications of each one for institutional investors, pharmaceutical executives and governments. In addition, the Group identified seven key findings facing the industry and its investors, findings which have relevance across all the scenarios. These are headlined below and fully detailed in the text of this report:

Overall Findings

1. The impacts of emerging markets on the global pharmaceutical industry appear to be significantly underestimated at the present time.
2. If new science does not bring innovative therapies to market quickly the risk of downward valuation of the industry and societal pressure for change are likely to continue.
3. The industry faces a period of transition that requires a step change to more adaptive, flexible and open-minded leadership. This leadership needs to signal to investors the need for change.
4. Any major change to the business model will require a company to embrace the risks and benefits of being the first mover. Investors need to create market-based incentives to reward first-mover behaviour, including reshaping remuneration packages to reward desired behaviour [or] activity.
5. Trust is a key issue for this highly regulated sector and is under serious threat. In addition there is an erosion of investor confidence in the sector's ability to deliver durable shareholder value. All stakeholders need to work to re-establish an equilibrium that acknowledges mutual inter-dependence.
6. Market-based solutions are unlikely to systematically meet the access needs of people in the least developed countries due to extremely low per capita health expenditure. Overseas aid is likely to remain insufficient to meet the need and pressure for access to affordable medicines can be expected to persist. It will be important that relationships with keys stakeholders are well managed.
7. The growth of the patient-consumer lobby is a growing trend that offers long-term benefits in terms of patient empowerment and marketing advantages on one hand, and awareness of therapeutic risks and benefits and calls for increased transparency on the other.

Scenarios

Scenario One: The Producers Scenario

The absence of new drugs continues to cause mounting cost pressures. Efficiencies are sought in marketing, manufacturing and research. Former employees return to the emerging markets of India and China which see a growing concentration of manufacturing and marketing expertise, increased patient demand and government support for research initiatives. Investors see the potential for making money on volume. Western pharmaceutical companies are challenged to deepen existing relationships with emerging country firms. Southern governments become more powerful and successfully insist on technology transfer arrangements and favourable interpretation of IPR agreements. All these changes result in more competition and increased accountability in the global pharmaceuticals market.

Scenario Two: The Patients Scenario

The genotyping of disease propensity advances, but there are no commensurate drug breakthroughs. Individuals assume greater responsibility for their health. Health spending shifts away from drugs and towards diagnosis/prognosis and early treatment intervention. Pharmaceutical companies seek non-conventional sources of medicine, opportunities in emerging markets, herbals, and revisit the existing library for novel indications. Investors signal a willingness to accept greater risks in exchange for potential rewards. Patient groups form an effective, educated lobby with greater awareness of the risks and benefits of therapies and successfully call for increased transparency in clinical trials and post marketing surveillance

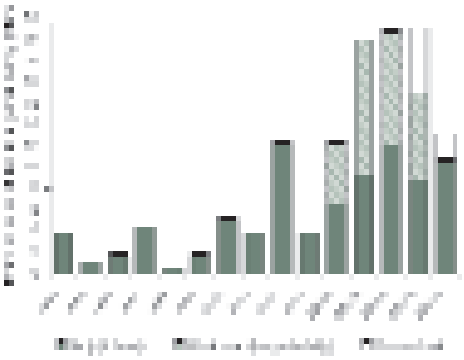
Scenario Three: The Politics & Public Health Scenario

A global flu outbreak causes public outrage about the lack of investment into new antibiotics and vaccines. Governments assume a more active role in directing R&D priorities first for acute and then for chronic diseases. Over time elements of a Social Business Compact become clear, including government commitment to expand access; sophisticated purchasers who negotiate price on value-for-money calculations; higher rewards for innovation in exchange for more secure IPR agreements; patient agreement to a healthy living package as part of insurance and pension plans; pharmaceutical company agreement to less aggressive pricing in exchange for volumes and reward for true innovation.

Rationale for the Project

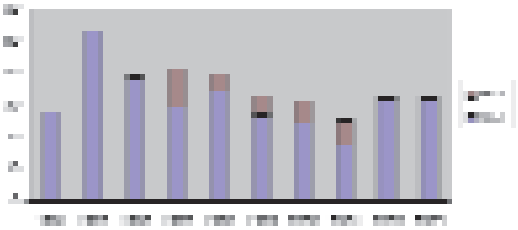
Pharma Futures was set up in response to the serious challenges facing the pharmaceutical industry and, in particular, the dilemma of needing to convince investors of on-going profitability whilst simultaneously meeting growing societal expectations that at least some medicines should be widely available to people on limited incomes in all markets. These challenges include a wave of patent expiries without commensurate compensating new drug approvals (See charts 1 and 2);

Chart 1: Annual Sales of US Brands Facing Potential Generic Competition



Source: US Orange Book; Lehman Brothers estimates

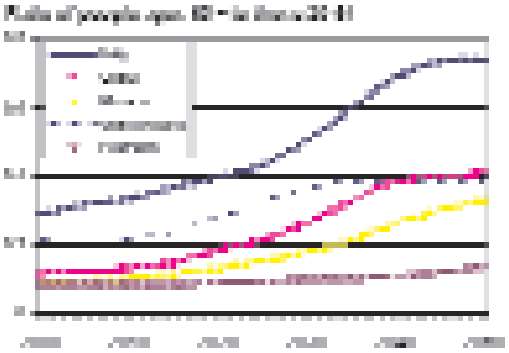
Chart 2: FDA New Drug Approvals



BLA = Biologics License Application
NCE = New Chemical Entity
Source: FDA

demographic changes (see chart 3); pressure on government to reduce health expenditure; corporate pressure to reduce health insurance costs; calls for price reductions, challenges to intellectual property rights; unmet health needs in emerging markets and poor countries; and media and societal anger at corporate priorities and behaviour.

Chart 3: Age-Dependency Ratios for Selected Countries 2000-2050



Source: United Nations, Population Division, World Population Prospects (The 2000 Revision).

Note: China's pattern is unusual because of the country's birth policy. The other four countries represent in broad terms the patterns evolving in the other countries of the world. Pakistan represents the least developed countries. Mexico represents a set of countries in middle stages of development where fertility rates have dropped significantly over the past couple of decades. The United States represents a set of developed countries where fertility rates have not totally caved and where there is some immigration--e.g., Australia, Canada, the United Kingdom and France to lesser degrees. Italy represents a set of developed countries where there is not much immigration and where fertility rates are around or below 1.35.

The project is based on an understanding that existing market structures do not currently provide the right incentives and disincentives for pharmaceutical companies to place adequate priority on meeting a wide range of societal expectations (including responsible marketing, affordable pricing, ethical scientific practices, etc). At the same time institutional investors and perhaps more importantly, sell-side analysts, continue to have high expectations of pharmaceutical profitability. These expectations translate into powerful mechanisms to reward or penalise management and thus help to provide incentives to the sector to continue with its current business model.

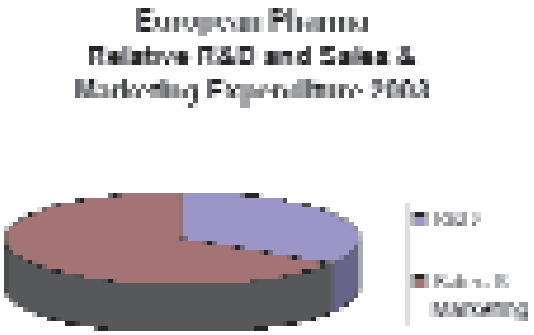
There is therefore a growing imbalance between the short-term benefit that industry

provides to shareholders, and the productive research that these shareholders and other stakeholders want from the industry in the long-term. The result is serious tension for the industry in mature markets. This is exemplified by a range of public initiatives. The Maine Rx legislation in the US mandates the same price discount to uninsured individuals as the largest State purchaser of medicines is able to obtain. In parallel, a growing number of states are permitting re-importation of less expensive drugs from Canada despite the fact that this practice is presently against federal law. Price or reimbursement controls continue to operate in Europe and Japan while similar cost control disciplines are creeping into many US states. Also in the US, private responses are increasingly visible and include concerted effort by large employers and consortia of such organisations (e.g. Business for Affordable Medicines) to cap medicine prices. The recently approved US Medicare drug bill is unlikely to solve the pricing problem. Indeed, some argue it may even make the situation worse, as it offers limited drug coverage, and makes it probable that employers who currently pay for retiree drug coverage will cease to do so. Furthermore, it transfers a growing proportion of the US drugs bill to the government, making price regulation much more likely.

The industry faces internal pressures as well. Innovation faces high failure rates, there is a decreasing scope for obtaining high prices for "me-too" drugs in the face of wider choice from a rapidly growing list of generic alternatives and there are more pressures from regulators leading to more trials and larger patient groups for those trials.

Marketing is under scrutiny for reasons ranging from ethics, legality, reputation and diminishing returns from the traditional "share of voice" marketing strategies. In manufacturing, regulatory requirements are proving difficult to keep up with and companies are being challenged on efficiency grounds. There is also growing concern about the sector's political (and therefore regulatory) influence as a result of its substantial and partisan approach to political donations.

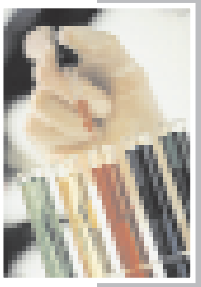
Chart 4: Relative R&D v. Marketing Expenditure

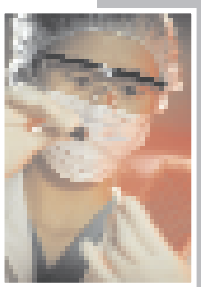


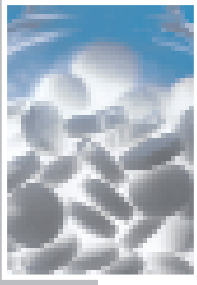
Source: ABN:AMRO

n.b. A proportion of R&D expenditure (possibly between 5-10%) could be phase IV studies which could be classified as Sales and Marketing

In emerging or developing country markets, there has been a high-profile debate about access to ARV treatment for HIV/AIDS. This debate can only intensify as the macro-economic effects of this illness are better understood. And as the incidence of other communicable and non-communicable diseases increases, the debate will involve more companies and become more complex. The situation is likely to be exacerbated by the increase in chronic diseases such as diabetes, cardiovascular disease and hypertension, though the emotiveness of the AIDS debate may be absent. Many recent therapies for the treatment of these diseases are still under patent and in least developed countries and emerging markets are therefore likely to be unaffordable for the majority of the population. Unlike many of those with HIV/AIDS, some of the new "health poor" - particularly those suffering from chronic diseases - will be articulate and empowered middle classes in countries with growing political influence, e.g. Brazil, Russia, India and China (BRICs). Poor infrastructure and lack of delivery mechanisms in poor countries will continue to be a serious problem.







Pharmaceutical companies cannot and should not be expected to provide the solution to chronic under-investment in healthcare resulting from poverty or governmental neglect. Yet, due to popular concern about globalisation, the nature of global communications and high levels of profitability, the sector will inevitably be drawn into the firing line with other stakeholders as the market's failure to meet expressed health needs in poor countries becomes apparent. The sector's involvement, directly or via trade representatives of sympathetic governments, in the debate about generics and patents further exacerbates these risks since it tends to position the sector with some audiences as neither interested in solving the problem or in stepping aside and letting public policy makers and others get on with the challenge. The outcome of these pressures is likely to place unsustainable pressure on an industry that created considerable shareholder value for investors in the 80s and 90s.

The sector has responded assertively to these challenges in the expectation that innovation will be delivered and that this will remove the threats. This holding strategy has worked more or less but it is unclear how long it will continue to do so and what the long-term cost in terms of reputation and ability to adapt will be.

Pharma Futures was created to facilitate a new kind of dialogue where the emphasis is on creative and problem-solving engagement by industry practitioners, long-term investors and their analysts, and those who reflect the views of government and societal players. A solution which excludes any one of these groups is unlikely to lead to a satisfactory resolution to the major problems facing the industry.

Background on Scenarios

Pharma Futures chose to use scenarios as the tool to identify existing trends which, moving on their current course or departing significantly from them, will change the shape of the global pharmaceutical industry between now and 2015.

In recent years strategic planning has undergone a shift from the use of single-point forecasts toward the use of alternative scenarios. In the decade after World War II the global economy grew in a fairly orderly and reliable way. Plans could be made using extrapolations from the past and present. Since the 1960s, however, the global environment has been more turbulent. From the oil shocks of the '70s, through the demise of communism in the '80s, to the deregulation and privatization of many industries in the '90s, to the rise of global terrorism at the turn of the millennium, the future has become progressively less predictable. The methodology known as scenario planning grew in response to these circumstances, and continues to grow in use. Alternative scenarios provide a way of focusing on the future without locking in on any one forecast or "assumed official future" - both of which are likely to be wrong.

Scenarios are alternative environments in which today's decisions may be played out. They are not predictions; nor are they strategies. Instead they are descriptions of different possible futures designed to highlight the risks and opportunities inherent in each one.

To be an effective planning tool, scenarios should be written in the form of absorbing, convincing stories that describe a broad range of alternative futures relevant to an organisation's or industry's success. Thoughtfully constructed, believable plots help decision-makers to become engaged in the scenarios. Through the implications of each unfolding story, stakeholders deepen and cast in new light their understanding of the system under analysis, and thus what they and their organisation need to do in order to manage change.

Scenarios do not claim to be predictions. As a result, they can help overcome anxiety about the lack of hard data regarding the future. The point is *not* to gather evidence for some induction about a most probable future. The point is rather to explore and understand more deeply a number of different possibilities in order to make better reasoned choices among them.

Introduction to the Project Findings

The following scenarios tell three plausible stories about how the pharmaceutical industry might evolve over the next ten years. The stories are not intended to predict the future. Rather they are designed to permit the person telling the story and any subsequent reader, to consider a number of different possibilities in order to make reasoned and informed choices about future actions.

The stories are, nevertheless, built on existing trends, which will be responsible - at least in part - for changes to the global pharmaceutical industry between now and 2015. For this reason, Pharma Futures has outlined possible implications of each scenario for three key stakeholders in the industry: institutional investors, pharmaceutical executives and governments. Through engagement with the set of future stories, the Pharma Futures Working Group also identified implications that are robust across all three scenarios.

The Pharma Futures process began with a close examination of a *status quo* sort of future, one in which the industry manages to "muddle through" tomorrow much as it has today and yesterday. It looked at a range of things that would have to happen, simultaneously, to permit the current business model to continue to operate as it currently does. If looked at individually, it is easy enough to see these trends continuing into the future. However, if considered as a group - along with the assumptions underlying each one - this "muddling through" future collapsed under its own implausibility.

First there would need to be more consolidation to deal with issues of pipeline productivity and revenue pressures. Second, and in spite of accelerating healthcare costs and downward pressure on their budgets, governments would have to be prepared to accept increases in the costs of prescription drugs. Third, more effective marketing would have to provide a counterweight to pricing pressures. Fourth, there would need to be a growth in the availability of and demand for new therapies for chronic and degenerative diseases. Fifth, the introduction of pharmacogenomics, and more highly personalised treatments would need to open up additional disease states to more efficacious (but expensive) treatment. Sixth, developing country demand for access would need to be managed with just enough incremental concessions to keep at bay reference pricing pressures, IP challenges, and other major disruptions to current business practices. And finally, seventh, the expansion of biotechnology resulting in new hybrid products and companies, would need to expand the market overall. While some mix of these eventualities are highly likely, the Working Group did not find it plausible that they would all happen simultaneously, nor even that all would happen.

In addition to the scenarios and a discussion of their implications, the Working Group identified the following cross-cutting themes and trends relevant to all the scenarios and indeed, any likely future:

1. The impacts of emerging markets on the global pharmaceutical industry appear to be significantly underestimated at the present time. These impacts may take many forms. They may offer larger markets than is assumed to be the case; they may generate unexpected models of innovation which could be turned either into an advantage or disadvantage for traditional pharmaceutical companies; and they have the potential to disrupt current trade agreements (see 6 below).

2. The speed and scope of new science in bringing innovative therapies to market will be critical in determining the fortunes of the industry. In the absence of new drugs, the risk of downward valuation of industry is likely to continue and societal pressure for change likely to increase.

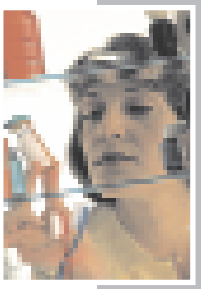
3. The industry faces a period of transition that requires a step change to more adaptive, flexible and open-minded leadership. This leadership needs to signal to investors the need for change. Some of the industry winners of the next decade may not yet be on the radar screen and investors need to find new ways to identify these new winners.

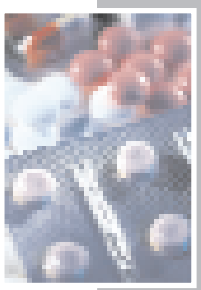
4. Any major change to the business model will require a company to embrace the risks and benefits of being the first mover. At present, financial markets are more likely to punish rather than reward adaptive first mover behaviour. Informed by thought-leaders from within the sector, investors need to develop their own understanding of what constitutes adaptive leadership and create market-based incentives that reward this behaviour.

5. Trust is a key issue for this highly regulated sector and is under serious threat. The lack of trust between many of the stakeholder groups and the industry could lead to balance of power shifts, including in the US from producer to government, impacting industry margins and returns. In addition there is an erosion of investor confidence in the sector's ability to deliver durable shareholder value. As society needs a thriving pharmaceutical industry, all stakeholders need to work to re-establish an equilibrium that acknowledges their inter-dependence.

6. Market-based solutions are unlikely to systematically meet the access needs of people in the least developed countries due to extremely low per capita health expenditure. Continued commitment to overseas development aid is therefore likely to be necessary. Since it seems plausible that aid from Organisation of Economic Cooperation and Development (OECD) countries will remain insufficient to meet the need, increasing pressure for access to affordable medicines can be expected to persist and will inevitably impact on the sector and its shareholders. It will be important that relationships with key stakeholders are well managed.

7. The growth of the patient-consumer lobby is a discernible trend that is likely to become more pronounced. The likely increase in patient co-pays in all markets, combined with more patient information will further contribute to the transformation of patients into more critical consumers. While this offers long-term benefits in terms of patient empowerment and marketing advantages, it is also likely to lead to greater awareness of the risks and benefits of therapies, including an increased understanding of possible harmful side-effects, a greater demand for value for money, and calls for increased transparency on clinical trials and post marketing surveillance.





"PRODUCERS" Scenario

Offices of Global Pharma in Cairo, Egypt, 2015

Dr Evi Redie leans back and rubs his eyes, heavy with exhaustion. The report is finished. He still finds his colleagues' ignorance about his country difficult at times, but now at least - and at last - something is being done about it. Ten years ago concerns about access and pricing in countries like Egypt were still a marginal issue. Now they are fully integrated into the core business. It wasn't altruism that had brought about the change, so much as the agility and aggressive tactics of businesses from across the developing world. He couldn't help feeling the tinge of pride at how the speed of change had left even people in his beloved pharma employer at a loss ...

The Early Years: 2004-2007

The troubles of the pharmaceutical majors continued for the better part of the 2000s. Scientific advances stubbornly failed to deliver beyond phase III trials and accusations of price gouging continued. Corporate profits and stock valuations were volatile, but the overall trend was down. The first of the much anticipated wave of patent expiries on the successful breakthroughs of the late 1980s and early 1990s led to price hikes on the remaining patented drugs. And in turn, this only served to increase public condemnation of the industry. In the absence of new drugs, cost pressures mounted, proving to be too great for some of the medium-sized firms. Employees were laid-off everywhere and some companies went to the auction block. Industry consolidation continued, diminishing the number of pharmaceutical giants.

These events had an interesting impact on marketing. Companies continued to fight to obtain premium prices on patented blockbusters, but the reduced number of these in the portfolio did have the effect of decelerating the marketing arms race that had been building for years. The returns on investment that had been justifiable on a broad portfolio began to look irresponsible when the ratio of sales and marketing to research rose to 3:1. The point of diminishing returns had long since been passed and earnings could only be maintained by cutting marketing costs. Because they were all in the same position, when one firm moved others were obliged to follow. Efficiencies were sought everywhere, in marketing, manufacturing and even amongst scientific staff.

The most significant cost cutting exercise was the shift to more manufacturing in developing countries with established pharmaceutical expertise - in particular India and Singapore. For long-term investments like pharmaceuticals, fixed assets were much cheaper - even considering sunk costs. Savings were made on materials and labour - for both scientific and unskilled staff. Development costs, including clinical trials were also lower, in turn leading to lower regulatory costs - a fact that was to have significant implications later. One company, suddenly waking up to the growth in the number of Hispanic people in the United States, began undertaking extensive (and much cheaper) clinical trials in Mexico.

The other direct impact of cost cutting in the US and Europe, was to encourage a significant number of well trained scientists to return home. Many had come for education in the developed world, and stayed on to work. As companies laid them off the pull of real opportunities in their home countries proved irresistible. America's ever-tighter visa restrictions under its war on terror made the US a much less attractive place anyway and there was little prospect of reversal as the Department of Homeland Security had concluded that no new major attacks meant the strategy was working. Those returning to China most found it easiest to get jobs. In the highly competitive pharmaceuticals market, their experience in OECD countries was viewed as a distinct

advantage. Others went into teaching. A few began to create their own companies, spurred by knowledge that their governments would provide strong support for new initiatives.

By 2007 the debate over stem cell research in America ended - and the scientists lost. Although this was just one important research direction among many the US government's dogged stance against stem-cell research drove much scientific R&D out of the country. The scientists wanted it, the bio-pharma companies needed it, and other parts of the world had no problem using human embryo material to push towards the next big health breakthroughs.

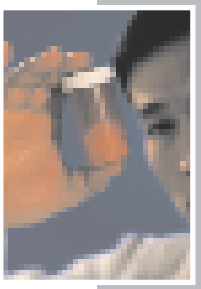
Meanwhile, all over the developed world the cost of healthcare - current and impending-spiralled and added to the incentives to cut costs. In Europe the debates focused on public health systems and the aging of the population, where the dependency ratio of retirees to workers grew ever-more alarming. In the US the political fight was about the ballooning government deficit and prescription drug coverage. Analysts in both places pointed to the costs associated with clinical trials and production and monitoring of use as a noose around the industry's neck. The situation was exacerbated by Europe's decision to impose new regulations on Cox-2 inhibitors and continued pressure for long-term studies on all chronic use drugs and much greater use of trials against best available current medication. Even though various government spokespeople talked about the importance of retaining R&D capacity within existing national borders-typically for reasons of security-the economic realities spoke louder.

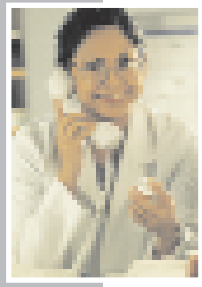
The Middle Years: 2007-2011

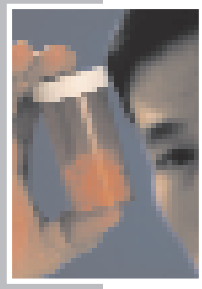
The wave of patent expiries peaked. Coupled with successful cost reductions, the increase in generic competition brought some relief to the pharmaceutical sector, at least in terms of public perception. Earnings continued to be under pressure but tougher questions about new products and deeper concerns about the R&D pipeline remained.

The success of the Beijing Summer Olympics highlighted the arrival of China as a mass market, and it became clear that the country would be a major magnet for growth, particularly in healthcare. Huge numbers of construction workers had poured into Beijing to build the vast stadiums for the Games. The large numbers of migrant labourers on the move woke the Chinese government to the increasing rate of HIV infection among the urban population. In a politically influential move, the Chinese follow-on to the Commission on Macro-Economics and Health was a report on the impact of diabetes and HIV/AIDS on China's economic productivity. Estimates of the previous market valuation of the country's economy at US$2-3 trillion by 2014 were significantly reduced. Until the report was launched the Chinese government had assumed that the country's demographics - an urban population comprised of relatively wealthy and relatively young people - justified the policy of limited State healthcare provision. Once the report was launched and at a time of mass redundancy of State employees with no access to private health insurance, it decided to focus more strongly on drug access.

Prospects for business looked promising. China's spectacular entry into the global economy had been accompanied by increased expectations of healthcare access, particularly among the country's growing urban population that had now reached 450m people. The scientists, doctors and workers who had returned from abroad increased these demands. And they were uniquely placed to understand the domestic market, which was largely concentrated in China's hospitals. Hospital administrators, the main purchasers of medicines, kept their organisations solvent by charging a 50% margin on the drugs







they prescribed. Those scientists and salespeople who had got jobs in both western pharmaceuticals and generics firms were well placed to support the expansion of the money-making premium generics market.

In fact, the Chinese market was just the most powerful example of the extraordinary growth in demand for drugs in middle income developing countries. The large Western pharmaceutical companies did understand the opportunities here. But their hesitancy in developing the most appropriate drugs and pricing models for these settings left most of them on the back foot. Meanwhile, emerging market pharmaceutical production and manufacturing capacity had grown. And not just for domestic production. A production agreement on anti-retrovirals between Brazil, China, India, South Africa and Nigeria, following the Bangkok AIDS meeting in 2004 was extended to other therapies for other diseases.

Developing country governments acted aggressively to promote these developments. Some opened tax-free pharmaceutical production zones, in which taxes were replaced by payment-in-kind of medicines produced there. Others opened tax-free clinical trial zones. China not only enforced the technology transfer provision in the Trade-Related Aspects of Intellectual Property (TRIPS) agreement, but also schooled others on how to do the same. When a Brazilian-Indian consortium applied for a US patent in 2011 on a new anti-retroviral compound, observers started using the phrase "innovative clusters" to describe what was happening outside of Western pharmaceutical companies. The promise of fundamental breakthrough science remained mostly in the West, but it also remained mostly a promise at that point.

The term "innovation" gradually changed. Over time it came to be talked about as something much more incremental, focused on the distinct needs of particular user populations and markets. For example, an Indian company was recognized as the world class leader in the integration of combinations of generic drugs with device-based delivery and monitoring systems, while a Chinese company led the way in "appropriate technology"-based patient compliance systems. Although they differed in terms of funding structure, government role, IPR arrangements, and regional geographic focus, they all shared one thing. They were starting to make real money at what used to be called "the bottom of the pyramid" - or at least part of the way down.

Important philanthropic initiatives continued to meet the needs of some of the world's poorest people. Foundation funding supported a network of Brazilian entrepreneurs, Chinese biochemists and Indian manufacturers focusing on HIV/AIDS drugs. Work on malaria vaccines continued on the back of a guaranteed purchasing agreement of a consortium of developing country governments. The Indian Prime Minister launched an effort in 2010 that brought together western pharmaceutical companies, Indian generics firms and the fast-moving consumer goods industry in a public-private manufacturing and distribution agreement. Despite these efforts, there were large numbers of people, particularly in Sub-Saharan Africa, who still did not present sufficient opportunity for the commercial sector to find attractive and whose needs remained largely unmet.

The End Years: 2011-2015

It was clear by 2014 that what had started as a cost-saving arrangement, led and controlled by leading pharmaceutical companies in the developed world, had radically changed the industry. Local talent, innovative financing and a deep understanding of developing country markets had created a new business model that was both powerful and profitable. It worked well for the emergent firms in developing countries and

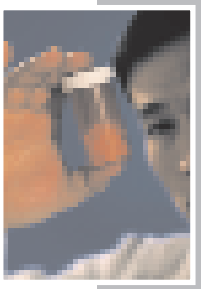
those developed country pharmaceutical majors who had the foresight and willingness to partner successfully with the new consortia.

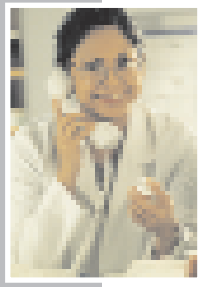
But for these majors it was a hard balance to maintain. The scientific breakthroughs they needed to fast-forward into the next phase of global market leadership kept receding into the future. And in their absence, each year, the negotiated deals became just a little bit more favourable to the erst-while junior partners. By 2015 the balance of power in some of these relationships was really tilting toward the new developing country consortia, and industry observers in the West were telling cautionary tales about what had happened to consumer electronics in the 1980s.

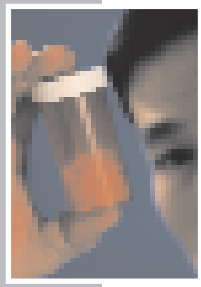
The big difference between consumer electronics and pharmaceuticals was of course, the high degree of government intervention in the pharmaceutical market, governed by strong regulation and now by stringent international trade agreements. The growing market power of these successful consortia and the demand from the expanding developing country middle classes for high-end treatments, led almost inevitably to a revisiting of the TRIPS agreement. The IT industry, faced with problems of its own, no longer felt that this was the best means of defending itself from global piracy and was concentrating its efforts on costly litigation and adaptive means of offering services. Western pharmaceutical firms found themselves increasingly as the sole defender of TRIPS in a World Trade Organisation, which itself had made huge adjustments since the early days when it had disproportionately reflected the interests of wealthy countries. After developing country governments formed a new "G-77" style group to lead a major pushback at the WTO, the second Doha Declaration was born. Facilitated by some high-level regulatory harmonization, Doha II was not an out and out re-writing of the agreement. However, and largely in response to China's stated desire to consolidate its own pharmaceutical industry, the new flexibilities amounted to the same thing. The declaration permitted enough flexibility to continue the wave of innovation already under way and confirmed new technology transfer requirements. It did, however, retain protection for Western pharmaceutical companies past investments-and successes.

All of this set the stage for a much more truly globalised pharmaceutical industry, able to meet the needs of patients in many more markets. As such it began to emerge as the harbinger of the next phase of globalization, effectively replacing IT in that role. People were now excited about the potential for new and more widely distributed R&D centres, and financial analysts wondered which industry would reap these innovation rewards next. The best and brightest of the next generation, particularly in the BRIC countries, aimed to go into biochemistry and pharmacogenomics. Health is ultimately more important and valued than information technology ever was, and also more personal.

This also improved the global public view of what globalization is about. Fifteen years earlier, Thomas Friedman's book, *The Lexus and the Olive Tree* had focused on the benefits of globalisation for the distribution of goods and services. This next phase of globalization became about the health of your parents. Of course none of this would totally remove the public's suspicion of the global pharmaceutical industry or the realisation that there were certain people and countries whose needs were still not met. The regulatory and public policy environment would continue to be tense, requiring companies to demonstrate efficiency, value for money and honesty. What had become clear, though, was that more players in more markets, meeting the needs of more patients was creating healthy competition. And as such, it brought with it checks and balances that increased accountability in a manner that the majority of key stakeholders were satisfied with.







Dr. Evi Redie shuts down the computer. The long hours were still a sign of his personal commitment to his work, but who would have thought that successfully brokering the relationships between pharma companies from across the world would elevate him to Vice-President? Still, there was plenty more work to do tomorrow, and plenty more for days to come.

Implications of Scenario One: The Producers Scenario

Possible Implications for Institutional Investors

1. Investors accept that the traditional pharmaceutical industry will continue to under-perform as investments during the transition phase but also increase their efforts to identify new opportunities and products. Non-traditional sources of innovation become a new target for investment.

2. All links in the investment chain (trustees, asset allocation advisers, fund managers and sell side analysts) place progressively greater emphasis on understanding the economics and logistics of commodity generic markets across different geographies and the ability of the pharmaceutical majors to partner effectively with emerging market producers.

3. Investors actively provide incentives to pharmaceutical executives to make a smooth transition by re-structuring remuneration packages to focus less on maintaining EPS growth per se but rather on R& D productivity and appropriate partnerships. Investors also engage proactively with compan boards on CEO succession planning to ensure senior management is "fit for purpose" given this new environment.

4. Given that the Pharmaceutical Industry is reflective of wider economic and demographic changes, there is a change in the pattern of graduate hiring, with investors looking for graduates and former corporate managers with Chinese and Indian ethnic roots and linguistic skills.

Possible Implications for Pharmaceutical Companies

1. Pharmaceutical executives actively encourage a change in investor perceptions about which markets are important as they begin to see greater patient access to affordable medicines as a market opportunity, rather than a threat. They then progressively adapt business models to realise this opportunity.

2. A new attitude to the trade-off between product volume and access means that trust in industry is re-established and innovative new drugs are able to command high prices commensurate with investment.

3. There is a significant expansion of core competences for top management including:
   - The ability to partner with range of companies and governments to manage expansion into emerging markets, e.g. China. A major determinant of desired joint-venture partners is marketing expertise relevant to local situations.
   - The ability to successfully stratify emerging markets by purchasing power.
   - Aggressive cost-management with regard to marketing.

Possible Implications for Governments

1. There is a progressive widening of regulatory influence from the Food and Drug Administration (FDA) to a tightly linked network of authorities.

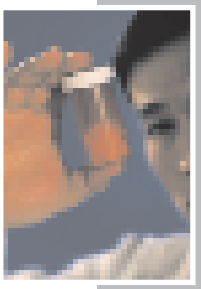
2. OECD Governments consciously frame the public debate as a dynamic tension between the need for cheaper healthcare and the economic benefits derived from a strong domestic pharmaceutical industry.

3. Governments effectively re-negotiate global IPR agreements as a result of pressure from China and other generic producer/consumer nations.

4. Availability of cheaper generic therapies creates headroom for spending to reward innovation and value-added, and on expensive therapies. This puts pressure on all Governments to deliver on health, rather than reinvest the savings elsewhere. This has implications for health expenditure in overall budgets.

5. Emerging market Governments, encouraged by the early successes of these sectors, increase their support for the pharmaceutical sector in producer markets.

6. OECD Governments come under pressure from pharmaceutical companies and non-governmental organisations (NGOs) to increase overseas aid budgets as the potential for access increases. Companies argue for some tying of aid to the products of those firms domiciled in donor countries.



"PATIENTS" Scenario

Madison, Wisconsin, USA, 2015

Felicity is interrupted by the arrival of an email. Glancing up she sees it's from Malini. It must be late in Delhi, she muses. The note is full of news about the Indian Diabetics Group that is proving so successful. Malini is proving an inspirational leader, spurred to the work by the death of her mother from diabetes-related cardiovascular problems. The group has recently had a major success in making new insulin devices widely affordable. Felicity thinks back over the ten years since her own diabetes was diagnosed. At that time she had been obese and mildly depressed. So much had changed since then…

The Early Years: 2004-2007

In 2005 in the world of medicine a glimmer of light shone at the end of the tunnel. After an annus horribilis in 2004, which saw several high profile product failures including the loss of confidence in the Cox-2 inhibitors, the sector began to show signs of life. The pharmaceutical majors, at last, saw a year of tremendous advances in new knowledge of human pathophysiology. The first few pieces of the human disease puzzle seemed to click into place and a trickle grew into a veritable explosion of new information and understanding of people's morbidity and mortality. The media ran constant stories about new breakthroughs in cell biology. For wealthy baby-boomers, watching with anticipation and excitement, dinner party talk moved from stock prices and house prices to the imminence of "personalized medicine" and individual disease propensities.

This increase in personal health knowledge was reinforced by radical healthcare reform. Health costs rose, while budgets remained frozen at best, leading governments everywhere to reform collective healthcare arrangements. In Europe individual patients were faced with increased co-pays. Though the EC continued to resist direct-to-consumer advertising, in most Member States the number of drugs approved for over the counter sales rose considerably. A new awareness about the cost of medicines at the point of sale taught patients much about healthcare and medicines. Eager to reinforce the assumption of greater personal responsibility for health, European Governments moved quickly to revise health budget priorities towards more early interventions: earlier diagnosis, active monitoring and screening of patients. In the US the Government decided to make all patients' medical information and records electronic and transferable by 2014 thus reinforcing people's personalised knowledge.

All this turned out to be good news for those pharmaceutical companies that had specialised in diagnostics - and particularly those which had been able to establish creative partnerships with producers of devices. Together these firms developed and marketed more sophisticated and accurate diagnostics, which of course became increasingly expensive. Though only the wealthy could afford the tests, other people soon began to demand them. And success in diagnostics created other expectations. Everyone expected more - and bigger - therapeutic breakthroughs any time now.

These changes posed big challenges to the insurance industry, particularly in the US. As risks became more precisely known, the economics - and more profoundly - the mindset behind insurance risk pools came under severe challenge. The transfer of risk from pools to individual patients led to a greater intolerance amongst those who knew they were not at risk of particular diseases. Wealthy individuals demanded to take on and manage more of their own personal risk, leaving others to cope as best they could. But these individuals remained in a minority. The insurance industry responded with highly effective advertising campaigns promoting their products

amongst a population newly awakened to health risks, their own liabilities, but still in the main unclear about precisely what risks they ran. US insurance firms expanded into Europe where they were publicly attacked for being unwilling to cover individuals whose genetic tests proved unfavourable. Some insurance firms were bought by mutual funds which began to offer "personal health derivatives". Others re-jigged their financial product to offer customers access to asset pools to pay for unpredictable and catastrophic healthcare costs for illnesses such as cancer.

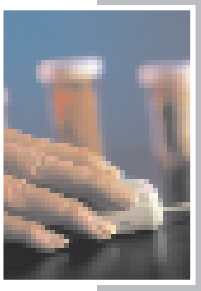
The Middle Years: 2007-2011

Meanwhile, the scientific knowledge-base continued to grow. Alongside the continued hype around genomics and proteomics the understanding about individual disease propensities was becoming more sophisticated. The first people to use - or rather demand - the innovations that did come through were wealthy US citizens. Having tracked the evolution of these scientific discoveries they wanted them translated into new, effective treatments.

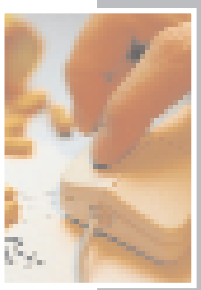
But despite the early promise with a few molecules, the wave never crested and the expected breakthrough products did not materialize. Research scientists in companies large and small were crestfallen. As each layer of the genomic onion was peeled, the only thing it revealed was greater complexity. Despite a few significant advances, most disease pathways proved intractable. Each promising lead led only to another, seemingly endless, labyrinthine and vain pathway. The whisperers in R&D hallways, who for years had questioned whether all the low-hanging fruit had already been picked, began to ask if the high-hanging variety actually existed. A 2007 headline in a scientific journal captured the mood all too well: Depression Gene Discovered, No Treatment in Sight…How Depressing!

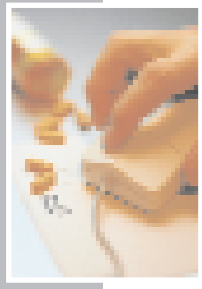
Diagnostics, however, was another story and the impressive developments in this field continued. Individualised knowledge became much more widespread as the impacts of government spending on early interventions were felt by the population at large. The absence of new treatments caused people to focus on the availability and accessibility of existing treatments. Patients with similar disease profiles met up in person and on-line. The discussion and support groups that had existed for years gained in strength and numbers and expanded to cover most major disease categories. The difference was that now people knew whether they belonged to the group before the first symptoms developed. These smart medical mobs created clearing houses, to share the latest on scientific knowledge and emergent diagnostics.

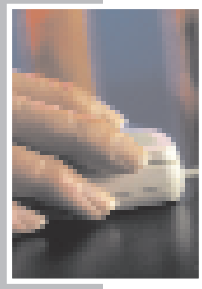
In the process the population consolidated a more sophisticated understanding of healthcare economics and the role of the pharmaceutical industry. Doctors began to notice that their patients were raising educated concerns about possible side-effects associated with the treatments they prescribed. Not only this, but as patients became responsible for an ever higher proportion of medicine costs, they began to ask doctors how to assess whether the drug would work for them prior to purchase. The media was quick to reflect the new zeitgeist with its focus on health and in the UK a major prime time television series about drug efficacy claimed that the ten most commonly prescribed treatments were effective for only fifty per cent of patients.



The public also became much more aware of the workings of clinical trials and the result was a clamour for increased transparency about how such trials were conducted and the incentives structures surrounding them. The strengthening affinity groups meant that companies were in a much better position to recruit the "right" patients in a way that diminished both lead times and costs. As a result, failure rates in Phase III were significantly reduced. But the







patient groups were not passive in their exchanges with companies. They wanted something in return and pushed back hard to obtain better studies of side effects, longer term trials, more post-marketing surveillance and public access to information about its findings. The industry proved unable to resist this trend towards more transparency though it did attempt to control it. Some companies had made their clinical trial data available over the internet as early as 2004. However, it wasn't until 2009 that pressure from patient groups pushed the US Government to combine clinical trail data in a national registry, and to impose compatible reporting standards so data could be shared seamlessly across and between organizations.

This decision by the US Government reflected a change in its positioning towards the industry. The healthcare debate had been growing in importance for years and by now took centre stage in the political arena. The long-term cost implications for the Government of the 2004 Medicare reforms were becoming increasingly apparent and alarming. In Europe too despite extensive healthcare reforms drug costs were still spiralling out of control. Governments began to see the potential bargaining power of a coalition between themselves and the patient groups. But to make the most of the alliance, they too had to make concessions to the newly empowered patient groups and be ready to meet demands for changes in the regulatory environment. The three players, governments, companies and patient groups entered into fierce negotiations about where budgets should be focused. Though the affinity groups were locked in intense competition for scarce government research dollars they did manage to ensure that company savings from more efficient clinical trials were ploughed back into their particular disease.

These patient groups were not only successful at negotiating greater transparency. At the margins, small pockets of people began to address the lack of R&D productivity into their diseases. These *im*patient patients - and particularly those diagnosed as susceptible to terminal disease decided that if drug companies couldn't translate all this knowledge into treatment, then they'd find some way to do it themselves. People on low incomes in the groups were paid by their peers to be the human guinea pigs for untested and unproven treatments. These trials mimicked what had become known as the "Castro Culture" a similar grouping of patients prepared to test treatments for HIV/AIDS in the early years of the AIDS epidemic.

The impact of the emergence of patients as critical consumers had a profound impact on the industry. The lack of new product, combined with a wave of patent expiries had already led to fierce demands to cut costs. The marketing model now also came under pressure as firms fought for diminishing segments of what had been "blockbuster" markets. Greater patient knowledge and much more focused clinical trials meant that blockbuster advertising for share of voice was an increasingly inefficient way to market drugs. It also meant they had to contend with massive rise in competition from increasingly regulated alternative therapy providers. Outraged patient groups pointedly asked big pharma companies, "Why spend all this money on advertising and marketing when you have so little on offer? And what you do have on offer is too expensive for almost everyone? Why don't you put that money into R&D?" Industry observers rang the death knell of the one-size-fits all approach.

The problem was that the markets were too small to support the fixed costs. Everyone aspired to better health, but the reality was an increasing divergence in quality of care, with the well getting weller and sick getting sicker.

The End Years: 2011-2015

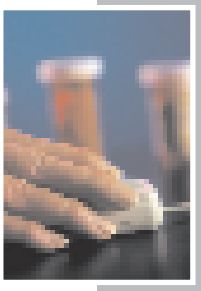
The Western world's pension system crisis, acute in Japan, severe in Europe, and looming in the U.S, put patient power centre stage. With the average OECD percentage of retirees rising to over 50% of the economically active population, there were perilously few workers to support rising numbers of retirees. Many big firms were unable to cope. The closure of occupational pension funds to new employees in the mid-2000s was nothing to the mass default of multinational companies' pension funds in the 2010s. Though some of the more innovative pension funds extended their client base to take on workers in the growth economies of China and India, most did not. More and more retirees in the US were pushed into public sector pension and health insurance plans. In Europe, there was a massive backlash against personal pension provision which was proving almost as limited as that provided by the State. The obvious "bad" news for workers was the compulsion to assume costs themselves. Few believed in the not-so-obvious "good" news that they now had greater personal control. It felt more like a transfer of risk from the State to the individual.

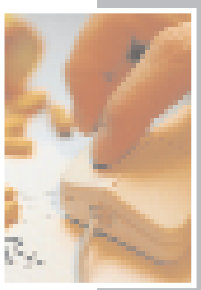
As the patient affinity groups gained steam, governments took a backseat, set some parameters for this new patient power, and left the process of market re-organization to take shape. Patient groups began to flex their political muscle in new ways and became innovative about risk. Some raised money and became de facto venture capitalists spurring specific R&D for their disease. Other groups pre-paid for molecules at early stages of development, effectively front-loading a company's profits to keep that "airplane flying". Still others bought up niche molecules and purchased patents directly. Many financed medical students and PhD researchers through their training in exchange for an agreement to work on a specific disease.

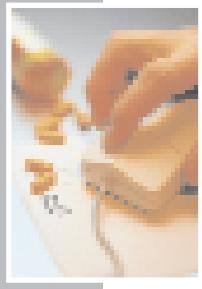
To increase their numbers and their market power, the patient affinity groups reached out internationally. These connections, both through people and broadband, brought a more even distribution of the existing therapeutic regimes and systems, at least for the growing middle classes in developing countries. The baseline state of health for many of these populations improved while the wealthy around the world replaced health as a means of avoiding pain and death with a quality of life ethos. What had been called "lifestyle drugs" in the mid-2000s became known as "quality of life medicines" in the 2010s.

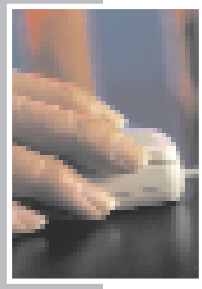
Providing for the wealthy, however, was not sufficient. The growing numbers of uninsured and underinsured brought their own pressures as the market became increasing tiered in both rich and poor countries. Individualised medicine was not working for people on low incomes. They lacked education, access to technology, and the confidence to make it work. In addition, new diagnostics and therapies were unaffordable. While healthy, wealthy patients were able to take advantage of tax free savings for health and pensions, a large proportion of the population with more modest means faced ill health and impoverished retirement prospects. Health therefore remained at the centre of the political stage causing governments to be a less reliable ally for the industry than in the past. Payers across the globe sought out commoditised generics, but this was insufficient to meet everyone's needs. Nevertheless, the more alert investors noticed how two Indian generics firms had managed to yield constant 6-7% returns in the past five years, and began to place their money there.

The challenges to the industry and to government posed by these changes were huge. On the research side, companies sought non-conventional sources of medicine, opportunities in emerging markets, herbals, and revisited the existing library for novel indications. Investors gave out signals that they were prepared to accept greater









risks in exchange for potential rewards, causing a renaissance in the IPO market and in biotech and academic medicines. However, the bigger challenge, arguably, was how to deal with a more organised and articulate consumer lobby arguing that drugs are not all they were cracked up to be, that they are sometimes harmful, and sometimes very harmful. The industry and governments found themselves at a cross-roads. Some found the loss of control intolerable. Others saw the exciting potential to establish creative partnerships with patient organisations. They saw advantages to fostering better expectations amongst an educated public making informed choices. But both companies and governments would have to accept these positive advances were likely to take place in the context of support for more rationing, more scrutiny and much greater accountability to the public.

Felicity shakes her head to snap herself out of the mental replay of the past decade. She must reply to Malini, finish her accounts and outline a new briefing paper called Getting the Balance Right, on lifestyle, prevention and treatment for the forthcoming Congressional hearing. And all this must be done before going to the gym.

Implications of Scenario Two: The Patients Scenario

Possible Implications for Institutional Investors

1. Investors accept that the traditional industry will continue to under-perform as investments, but the increase in overall healthcare expenditure provides investors with new opportunities, e.g. diagnostics, bio-markers and new health promotion ventures.

2. Fund managers seek alternative investments such as emerging market pharmaceuticals and higher risk new product ideas from academia/biotech.

3. Fund managers develop new financial saving products that allow customers access to a pension/life assurance pot to pay for catastrophic healthcare.

4. Investors actively provide incentives to pharmaceutical executives to make a smooth transition by re-structuring remuneration packages to focus less on maintaining EPS growth per se but rather on R&D productivity and appropriate partnerships. Investors also engage proactively with company boards on CEO succession planning to ensure senior management is "fit for purpose" given this new environment.

5. Investors become increasingly alert to political risk associated with growing societal tensions about inequality of access and price this risk into their valuations.

Possible Implications for Pharmaceutical companies

1. Size becomes less important than the firm's negotiation capabilities and ability to target niche markets.

2. As patients become more sophisticated about the economics of pharmaceuticals and become more demanding of value for money, companies shift marketing practice away from 'share of voice' strategies to a focus on better contact with patients.

3. Executives explore business in related healthcare areas, including diagnostics, telemedicine, disease management, surrogate bio markers and devices.

4. A greater proportion of research money is directed into academia with opportunistic ideas and exploration of traditional medicines.

5. Successful Pharmaceutical companies go out of their way to show they are not exacerbating inequality of access issues and seek to divert public disquiet on to governments.

Possible Implications for Governments

1. Governments struggle to manage the societal impact of new knowledge about disease propensity whilst treatments may not be available or affordable.

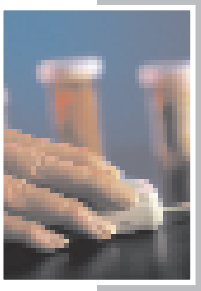
2. Healthcare comes to dominate the domestic political agenda, exacerbated by the growing inequality of access to new treatments. In particular, the unequal distribution of personalised medicines across economic and racial/ethnic groups in the US and other heavily privatised markets is a source of growing tension.

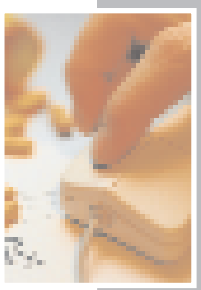
3. Governments shift resources to diagnostics and prognostic monitoring of disease, through diagnostic imaging and screening.

4. Governments change their focus to much earlier interventions in disease management, with surgery, irradiation and device use.

5. Governments deliver sustainable sources of low-cost supply. This may have implications for trade negotiations and current IPR agreements, but equally could depend upon low-cost domestic suppliers.

6. Governments undertake campaigns to promote healthy life style changes.





"POLITICS & PUBLIC HEALTH" Scenario

Ministry of Health, Stockholm Sweden, 2015

Hella Cristianssen looks out onto the snowy roofs of Stockholm thinking of her son, Ingmar. How difficult it is to persuade him away from the computer and out into the snow. She worries about his visible weight gain, especially given the family history of heart disease. How ironic that she is so good at designing successful policies for others, yet finds it so hard to apply them at home. It was surely her days as a hands-on pharmacist that helped her think through how these health providers might play a key role in the new health environment. The change had been incredible, and all in ten short years ...

The Early Years: 2004-2007

Every year public health authorities fought to try and avoid it. In the harsh winter of 2006 they failed and the virulent flu pandemic took hold quickly. No-one was sure where it started, but that ceased to matter as the infection spread rapidly, filling hospitals in London, Mexico City, Washington, Moscow and Delhi. Unlike SARS, and despite the attempts of the authorities, quarantine proved impossible to enforce. Hospital admissions far exceeded capacity to cope as first elderly people and children, and then the population in general, sought treatment for acute respiratory problems.

Then, to the horror of the authorities, it became clear that their worst nightmare was unfolding. Patients already weakened by the flu virus were catching a secondary bacterial infection in the hospital. At first it was only a few cases, but it soon became apparent that resistance to antibiotic treatment for that infection was spreading. In many major cities the death toll rose to the hundreds causing growing panic in the population. Office workers, until then prepared to work in face masks, refused to use public transport or work in an office environment, leading to mass absenteeism and widespread economic disruption. In Russia, the combination of a ferociously harsh winter and collapsing health system led to violent protests outside the Kremlin. Nor were the costs only domestic. International trade was severely disrupted with container ships docked for weeks. Government once again had to massively increase airline subsidies due to loss of business, and major airlines not only went bankrupt again - one finally went out of business. Amid the screaming headlines, the IMF issued a statement predicting that the pandemic would knock 0.5% off American GDP and roughly 0.3% off the global total and expressed concern about structural long-term implications.

The blame game began. Opponents of privatisation in Europe and long-term critics of the pharmaceutical industry, started to vigorously and publicly blame the government. "Why Did You Let It Happen?" by an anonymous whistleblower, said to be a senior industry figure, topped the best seller list for the tenth week in succession. In the face of this intense criticism, governments turned on the drug companies, publicly asking where were the new antibiotics capable of taking on the challenge. A fabled US public affairs programme ran an hour-long special news feature, which revealed how and why one of America's leading pharmaceutical companies had shut down its vaccine subsidiary and scaled back its antibiotic research function. The disgruntled ex-CEO, furious at lengthy public vilification, displayed the analyst report that had effectively closed the company. In it, sell-side analysts strongly criticised the company for continuing to focus on the low margin vaccine and antibiotic side of the business and recommended institutional investors break up the company and so increase the share price. As a result of new corporate governance transparency laws, it was easy for thousands of sick and angry US patients to see which of their State funds had voted for this break-up. A public exposé of why the

system failed by a financial pundit "It's the barrel, not the rotten apple" was followed by widespread debate about systemic problems with the industry's incentive structure and how to encourage innovation and responsible ownership.

The US Government responded by setting up two Congressional inquiries which in turn led to the Congressional appointment of the Disease Prevention Commission, modelled around the 9/11 Commission. In Europe a team of ex-Health Ministers was appointed to an EU Prevention and Treatment Commission. Pan-Asia discussions were kicked off by an unprecedented cooperation between China and Japan.

Across the world, these government appointees called emergency meetings with the pharmaceutical industry about future prevention and cure. Emboldened by the shift in public mood resulting from the shock of the flu epidemic and subsequent bacterial infections, governments began to take a more active role in determining R&D priorities in the anti-infectives market. The EU and US jointly negotiated additional IPR protections that, together with moral suasion, incentivised early production of a new vaccine and antibody. The new antibiotic was brought onto the market with much publicity about the importance of careful use of antibiotics to avoid the development of further resistance. Hospital and community surveillance programmes and new rules on infection control were introduced. Public education campaigns about microbials and the danger of misuse were everywhere. The introduction of a new effective product, alongside these intense campaigns led to an increased public recognition of the benefits of pharmaceutical innovation and a gradual re-establishment of some trust. This was helped in no small part by a spectacular, if short-lived, medical aid programme directed at poorer countries. Then Spring arrived in the northern hemisphere and the pandemic passed its peak. The initiative was conveniently passed to the World Health Organisation which produced a well-researched series on incentives for R&D into new antibiotics.

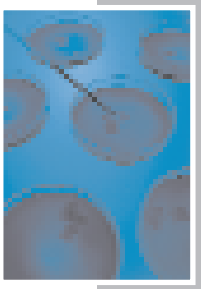
Middle Years 2007-2011

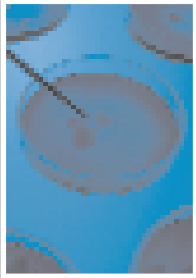
Concerns about acute health problems gradually gave way to a new focus on metabolic diseases which continued to rise steadily across the globe. A prominent medical journal dedicated a whole edition to the rise of metabolic disease and what to do about it.

The rumbling debate about whether public health needs could be met by the industry in its current form was replaced by banner headlines in May 2008, following a high profile article tracking child deaths from obesity-related type-II diabetes and calculating the costs on economic productivity of metabolic disease. Many were surprised at the article's focus on the rise of Syndrome X (insulin resistance syndrome) in children not only in the US, Japan and Europe, but also in Egypt, India, Mexico, Australia, Argentina and South Korea.

The Health Commissioners in the US and Europe were hastily reconvened. These governments had by this time decided that little would be achieved by further vilification of this strategic industry. Moreover, they were mindful that their earlier successful negotiations were achieved when similar public concerns were at their height. The difference between then and now was that previously the problem had been with the production of antibacterial drugs for acute diseases - which posed particular marketing challenges to companies seeking the next blockbuster. The problems they now faced were those of chronic illness.

The WHO Framework Agreement was resurrected but this time by a newly formed Global Super-Commission. Within six months it unveiled two pilot Research and Development co-operation deals between industry and government to generate new





therapies. Drawing upon lessons from Orphan Drug arrangements and what had proved a successful R&D formula by an international health foundation, the pilots provided strong incentives for innovation, including fast track clinical trial arrangements, data sharing collaboration, expanded end markets. In return, governments obtained agreements on expanded access and pricing. The deals also included a new and experimental securitised debt vehicle, designed by the World Bank, which guaranteed that the benefits would be extended to emerging markets, and at highly concessionary rates to the poorest countries. This second round of negotiated R&D agreements was interesting in that it successfully established incentives for both low-margin antibiotics and potentially high margin treatments for metabolic disease.

Once again, the EU used the agreement to kick-start a public health education campaign called Strategic Investments for Strategic Returns. It highlighted how the EU would support the development of new therapies for cardio-vascular disease and paediatric type II diabetes in exchange for more responsible behaviour among patients. A number of health insurance companies in the US linked their product offerings to agreements by their clients to comply with similar lifestyle arrangements.

The financial markets were initially unsure how to respond. The share price of the two leading companies in the agreement fell in the face of critical analyst commentary, despite the efforts of their CEOs to talk up the positive trade-offs in the deal. Likewise, the positive potential of the agreements were imperceptible to the majority of patients and consumers. The vilification of the industry in the US had reached new heights as prices of innovative medicines soared to offset price erosion on "me too" drugs and the number of people with drug coverage plummeted. More than half of the DOW 30 no longer offered retiree drug coverage. There were protests and class actions lawsuits filed, but company managers knew that these people would soon be picked up by the Medicare benefit plan. The number of Americans without health insurance reached 33% of the population in the first half of 2008.

So when, after just five years, the Agreements were successful in bringing two new drugs to market, interest was intense. The markets bucked and share prices soared. One drug, an antibiotic for acute respiratory infection, resistant to the usual products, went into fast track clinical trials, not only in OECD markets, but also in a range of emerging markets and developing countries whose governments had agreed to dedicate a minimum of 4% of GDP to health. The other, a paediatric oral hypoglycaemic agent which used a novel mechanism to promote glucose metabolism, was hailed as a breakthrough for diabetics.

End Years 2011-2014

These advances, though successful, were premised on a degree of global cooperation that proved impossible to sustain. Nevertheless, what the Commission had done was provide a model for the redefinition of the relationship between government authorities and companies. The terms of this new relationship combined greater reward for innovation, improved access and less aggressive pricing agreements. The firms involved in the original deal and therefore with a successful track record under their belt, began to publicly talk about win-win trade-offs and astonishingly money markets remained calm.

The impetus to scale up and to make such negotiations more widespread was most acute in Europe, where the baby-boomer generation was placing unprecedented demands on pension and health systems that did not have the resources to cope. Faced with aging populations and a dearth of young workers, the newly reinvigorated European Commission launched a Europe-wide, referendum on "More Immigration or

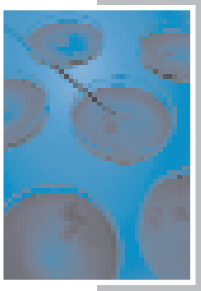
Longer Work". All Member States came back in favour of extending the working life. The EC, newly bullish following its successful negotiations on health with the pharmaceutical industry, began to exercise more assertive leadership about what their populations were required to do on health and retirement care. The retirement age was increased to 72 and the EU, taking a lead from Japan, passed legislation to permit privatised retirement schemes to oblige clients to commit to individual pro-health behaviour including smoking cessation and body mass index control. And they applied this assertiveness to the continued relationship with the pharmaceutical industry, creating the European Institute for Clinical Excellence to establish clear and transparent guidelines by which Member States would monitor value for money and therapeutic outcomes.

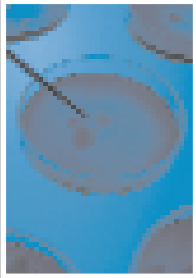
Europe may have been first, but it was not alone. Pricing pressure in the US had led to the consolidation of The Business and State Health Coalition to tackle the challenge of providing adequate health cover to employees and retirees. Its purchasing model was an adaptation of successful experiments in the State of Wisconsin. Each payer set up its own expert pharmacy and therapeutics committee charged with identifying the drugs they required for the population they covered. Then they developed a formulary of what would be offered on the basis of what they could afford, and negotiated price and volume with the drugs firms. To their surprise, HMOs flocked to them for advice about successful negotiation techniques.

The Health Coalition offered price-negotiating seminars that were attended by people responsible for health benefits from a range of industries, HMOs, and increasingly by staff of the US Government's Medicare programme, burdened by the huge numbers of people covered as a result of the Bush Government's health reforms of 2004. Though they attended anonymously, they were recognised and exposed by a wry diary entry in a New York daily paper. Initially, the WHO paid for developing country participants to travel to the US, but soon an in-country outreach programme of training in price negotiation skills and health prevention strategies was set up by the World Bank.

In the face of increasingly sophisticated payers and patients, and a focus on prevention as well as cure, the pharmaceutical industry was encouraged to revise its definition of successful negotiating skills and to compete to offer interesting deals to their customers. Many began to focus new research on the diseases of the elderly, as a concomitant to keep people in work. One firm secured a 20% pricing premium for delivering therapeutic improvement against existing branded therapies for Alzheimer's and osteoarthritis, contingent on the drugs being successfully brought to market and widely accessible. EU Member States in turn agreed to remove the stricture demanding that the price point is fixed at launch, allowing prices to rise post-launch on the basis of new data. The company in response agreed to lower starting prices in exchange for higher sales volume and immediate access.

However, these developments were not all happening in the developed world. Both commercially and politically important changes were taking place elsewhere. In 2015 an unusual mixed delegation of Chinese, Brazilian and Indian Trade and Health Ministers undertook a world tour. As usual, they visited government departments in capitals across the developed world, but this time, they spent more time in corporate headquarters than with their government counterparts. The debate about the efficacy of PPAR agonists had not passed their middle class constituents by. These politically influential people wanted access to the new treatments and they wanted them now. Spurred into action by their desire for political survival and bolstered by earlier successes at the World Trade Organisation, the delegation members offered massive mar-





kets to companies. They promised to do more to support distribution and expanded access. But, they reasoned the diseases of modernity had been acquired before the wealth of modernity, and successfully concluded that something would have to give on prices.

Thus across the globe, elements of Social Business Compact, visible for some time now, became clearly articulated by government leaders who publicly championed a situation in which everyone is better off without anyone being hurt. And it was accepted by business leaders who understood the need for a stable platform on which innovation could flourish. Government began by expanding access in the knowledge that the market place offered the mechanism via which increased volume was delivered. Key to that market mechanism was the existence of much more sophisticated purchasers who negotiated price on the basis of efficacy and a value-for-money calculation that afforded greater premiums to higher innovation and the need for society to maintain vigorous R&D activities. Governments awarded firmer patents in the form of longer period of marketing exclusivity or transferable IPR rights for under-researched diseases with greater security around property rights, and made credible commitment not to impose reference pricing on access in emerging therapeutic markets. Developed nations also invested larger sums in basic scientific research that could fuel bigger breakthroughs and the creation of more personalised medicines, while experimenting with the best means by which that research could be brought to market. Investors had available a new set of investment vehicles for placing long-term bets for long-term returns on long-term problems. Patients agreed a healthy living package as part of insurance and pension plans. Pharmacists began to play a "learned intermediary role" in which all dispensed medicines were accompanied by education and information concerning disease management. And finally and critically, companies agreed to less aggressive pricing in exchange for greater volumes and a tangible reward for true innovation.

Hella stands and stretches. If there was one thing she had learnt it was that lessons are best set by good example. She picks up the phone and calls Ingmar. When he hears of the impending skiing trip the boy shrieks with delight.

Implications of Scenario Three: The Politics and Public Health Scenario

Possible Implications for Institutional Investors

1. Investors accept that the traditional industry will continue to under-perform, but build up weighting again as prospects for R&D agreements between industry and government become apparent.

2. Investors place greater emphasis on generic firms with FDA approved quality standards and necessary standing in lucrative OECD countries, and on those companies successfully playing the volume-price trade off.

3. Investors actively provide incentives to pharmaceutical executives to make a smooth transition by re-structuring remuneration packages to focus less on maintaining EPS growth per se but rather on R&D productivity and appropriate partnerships. Investors also engage proactively with company boards on CEO succession planning to ensure senior management is "fit for purpose" given this new environment.

4. Innovative financing mechanisms for new drug discovery offer new investment opportunities to first-movers.

5. Institutional investors encourage a drug-development friendly regulatory environment.

Possible Implications for Pharmaceutical Companies

1. Firms focus on fewer programmes and fewer products.

2. More consolidation, at first, to ensure pipeline competence in priority diseases. However, market symbiosis also enables smaller companies to have an edge.

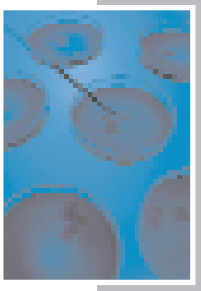
3. Pharmaceutical companies enter into agreements with governments to structure appropriate incentives and transactions in response to health emergencies and potential health emergencies.

4. Leadership ability to manage complex multi-stakeholder relationships and develop and defend new stances on price and marketing on the basis of pharma-economics becomes increasingly critical for corporate success.

Possible Implications for Governments

1. The balance of power between government and pharmaceutical industry shifts to government in order to meet public health needs but with this comes greater pressure on governments to demonstrate that they are able to create market incentives to align industry with government priorities. This includes:
   - Governments become more competent in evaluating a drug on the basis of whether it lowers overall health spend and whether it maintains or improves overall health.
   - In return for high volume sales, government negotiation of industry commitment to affordable pricing, increased and faster availability of cost-effective medicines and greater investment in real innovation.
   - Streamlining regulatory processes to bring new products to market in safe and appropriate way.

2. Governments learn to manage the implications of the cost burden being shifted to consumers. Part of the solution is greater public investment in health prevention, disease management, basic science and stronger incentives for R&D to meet health goals.



Afterword by the Sponsors

No company will feel safe departing from sector norms without the support of its key investors. Individual companies will be able to take a more proactive role if that is the norm for the sector. And the sector as a whole will be best able to respond if a broad group of institutional investors make clear that they understand the challenges and likely ways forward. In turn, these investors cannot act without knowing what key stakeholders - government regulators, purchasers, patients groups, doctors, pharmacists and insurance firms - are willing to accept. The interactions between these groups are also significant. As the Sponsoring pension funds of the Pharma Futures project, we hope that this report therefore contributes to the urgent need for continued and coordinated dialogue. The pharmaceutical sector is too important for investors and stakeholders to do anything else.

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Appendix One - Project Participants

The Pharma Futures Working Group includes:

1. **Stewart Adkins**, Senior Analyst, Pharmaceuticals, Lehman Brothers, UK;

2. **Caroline Dorsa**, Vice President and Treasurer, Merck & Co. Inc., USA;

3. **Martin Eijgenhuijsen**, Senior Portfolio Manager, ABP Investments, The Netherlands;

4. **Shereen El Feki**, Healthcare Correspondent, The Economist, UK;

5. **Lise Kingo**, Executive Vice President, Stakeholder Relations Novo Nordisk, Denmark;

6. **Sarb Klair**, Head of Global Health Care Equity, Citigroup, UK;

7. **Viren Mehta**, Principal, Mehta Partners, USA;

8. **Pankaj Patel**, Chairman, Managing Director & Chief Executive, Zydus Cadila, India;

9. **Cynthia Richson**, Corporate Governance Officer, Ohio Public Employees Retirement System (OPERS), USA;

10. **John Schaetzl**, Vice President, Equity Analyst on Research Coverage of Healthcare, GE Asset Management, USA;

11. **Eloan dos Santos Pinheiros**, Senior Adviser at the Oswaldo Cruz Foundation & ex- Director Farmaguinos, Brazil;

12. **Takashi Shoda**, President and Representative Director, Sankyo Co. Ltd, Japan;

13. **Raj Thamotheram**, Senior Advisor, Universities Superannuation Scheme (USS), UK;

14. **Eric O. Stanchfield**, Secretary, Wisconsin Department of Employee Trust Funds, USA;

15. **Andrew Witty**, President Pharmaceuticals Europe, GSK, UK.

These individuals took part in this project in their personal capacity and organisational affiliations are shown for identification purposes only.

Pharma Futures was directed by Sophia Tickell, with research and logistical support from Cassie Higgs.

Pharma Futures contracted Global Business Network (GBN) to run the scenario planning process: Steve Weber, Erik Smith, Andrew Blau, and Lynn Carruthers. GBN, a member of the Monitor Group, is a global leader in world-class scenario planning and the development of "long view" strategy. *www.gbn.com*

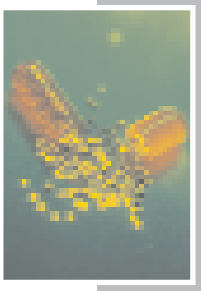
External experts interviewed in the course of the project

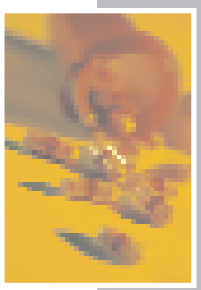
Pharma Futures would like to thank the following specialists who provided detailed input at various stages in the project:

Dr Goran Ando, CEO, Celltech; **Emma Back**, Access to Medicines Team, DfID; **Richard Bumgarner**, Independent Consultant; **Professor Angela Coulter**, Chief Executive, Picker Institute, Europe, **Charles Gardner**, Associate Director for Health Equity, Rockefeller Foundation; **Martha Gyansa Ludderodt**, Program Manager, Ghana National Drugs Program; **Dr William Haddad**, Chairman and CEO, Biogenerics Inc; **Peter Heller**, Deputy Director of the Fiscal Affairs Department, IMF; **Matt James**, Senior Vice-President, Kaiser Family Foundation; **Dr Mohga**

Kamal Smith, Health Policy Adviser, Oxfam; **Dr Richard Laing**, Essential Drugs Project, WHO; **Dr Joel Lexchin**, Department of Family and Community Medicine, University of Toronto; **Lance Lindblom**, Director, Nathan Cummings Foundation; **James Love**, Director , Consumer Project on Technology; **Dr Mary Moran**, LSE; **Jonathan Quick**, President and CEO, Management Sciences for Health; **Professor Alan Sager**, Director School of Public Health, Boston University; **Jonathan Sallett**, Independent Consultant and Visiting Scholar at Berkeley's Institute for International Studies; **Philippa Saunders**, Essential Drugs Project; **Rutai Shao**, Department of Chronic Diseases and Health Promotion, WHO; **Dr Anthony So**, Director, Program on Global Health and Technology Access, Duke University; **Mr Larry Stambaugh**, Chair and CEO Maxim Pharmaceuticals; **Dr Paolo Teixeira**, Head of HIV/AIDS Department, WHO; **Lawrence Wilkinson**, Chairman of Heminge & Condell (H&C); **John Wong**, Senior Vice President Boston Consulting Group, Hong Kong Office; **Roy Widdus**, Director, Initiative for Public-Private Partnerships on Health; and **Ben Yeoh**, Pharmaceuticals Analyst, ABN AMRO.

Pharma Futures would also like to thank those individuals who took part in the web-site discussion forum (see http://www.pharmafutures.org/forum).





Appendix Two - Funding and Governance

Pharma Futures was convened by pension funds; Algemeen Burgerlijk Pensioenfonds (ABP Netherlands), the Ohio Public Employees Retirement System (OPERS, US) and the Universities Superannuation Scheme (USS, UK). These Sponsors were responsible for overall governance of the project.

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A number of other participants in the project made a range of in-kind contributions towards its successful completion.

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Pharma Futures

Pharma Futures is a scenario planning project on the future of the global pharmaceutical industry.

Website: www.pharmafutures.org
E-mail: info@pharmafutures.org

OPERS

ABP Investments

USS