PharmaFutures

The PharmaFutures series was created in 2003 to allow institutional investors to hold a sustained dialogue with senior pharmaceutical managers on how they are seeing and responding to challenges in the external operating environment. The dialogues aim to highlight the importance of societal expectations in shaping pharma’s ability to generate long-term value. At its heart, this requires a business model that delivers health outcomes as the primary driver of sustainable shareholder value. PharmaFutures seeks to achieve this end by encouraging frank, open and constructive exchanges between people who hold widely differing views and by building trust and collaboration between them.

PharmaFutures dialogues are structured around a Working Group, formed of senior pharmaceutical executives, institutional investors and health system representatives from within the different markets. Their face-to-face deliberations are enhanced by inputs from a group of senior expert practitioners with years of experience of working in pharmaceutical companies, reimbursement, and health system policy and administration (see PharmaFutures Participants), and by extensive desktop research.

This report concludes the fifth PharmaFutures dialogue, which ran from 2011 to 2013 and focused on the changing reimbursement landscape. It summarises the global implications of trends in Europe, the emerging markets and the US. It builds on the conclusions of three regional studies, Perspectives from Europe, June 2012, Perspectives from the Emerging Markets, December 2012, and Cost and Choice in the US Market, April 2013. All are available on the Meteos website, www.meteos.co.uk/pharmafutures.
Executive Summary

This report examines worldwide health reforms and their implications for pharmaceutical reimbursement. The reforms are transforming health systems globally by introducing new measures of accountability for evaluating and delivering health outcomes and ways to improve and measure productivity. They are attempting to contain rising healthcare costs and applying increasingly sophisticated use of complex data to measure the impact of health interventions. In some places, greater importance is being placed on the role of the patient in understanding clinical effectiveness in the real world and determining value. These reforms are changing perceptions of what offers value to health systems and as such they are highly relevant to pharma.

The reforms coincide with early indications of an upturn in pharmaceutical R&D productivity. The combination of promising research and health reform offers a real opportunity to develop a more agile and cost-effective system for drug discovery, development, licensing and usage. The goal is to achieve greater understanding of what works, for whom, and at what stage in the disease pathway.

To achieve this goal, today’s binary decision-making at the point of regulatory approval and price setting will need to be replaced by iterative, dynamic decision-making that adapts as evidence is accrued, and value determined over time. Collaboration along three key decision points in today’s pharmaceutical development could make a huge difference. First, collaboration is required during the process of building evidence for a drug, when it is important to work out how to combine the safety and efficacy data generated in randomised controlled trials with evidence of clinical effectiveness in the real world. Second, today’s zero-sum approach to authorisation could be replaced with a model of adaptive licensing sufficiently robust to guarantee safety and efficacy on approval, at the same time as being sufficiently flexible to allow for iterative evidence-building over time. Third, pricing models could be adjusted away from today’s fixed price point to ones that reflect changing perceptions of the absolute and relative value of a medicine based on evidence accrued as it is used in clinical practice.

Achieving these changes will not be easy. Strong leadership to encourage collaboration, build mutual understanding and build trust will be essential. Enlightened executives across the system will need to champion and endorse new ways of working in order to overcome the practical and cultural challenges involved in change. They will need to require their personnel from all parts of the system to collaborate on new approaches to value definition; to enter negotiations with a better understanding of the constraints and pressures faced by their counterparts across the table; and to overcome mistrust by encouraging people to recognise positive change where it is taking place and to take action on those behaviours that continue to create mistrust.

The pharma industry can only fully engage with these changes in its business environment if it has the support of its investors. Companies cannot predict what their returns will be, but they can explain the investment case for undertaking adaptive licensing or risk-sharing price deals in ways that resonate with investors. This includes the potential for earlier cash flows, less regulatory risk and less reimbursement risk.

Health systems, pharma and their stakeholders face a strategic choice. To ensure that evidence-based decision-making is embraced as an opportunity to agree the true value of pharmaceuticals – with all the implications this has for transparency, pricing and collaboration on outcomes. Or to perpetuate a problematic zero-sum approach to value definition which encourages mistrust and antagonism.

Replacing today’s model of drug development and reimbursement with a new systemic approach would reduce the risk and cost of bringing a medicine to market and increase the likelihood that the medicine will improve productivity and patient outcomes. This result is a value proposition that works for all.
These changes are profoundly important to the pharma industry. When *PharmaFutures* began in 2003 investors’ overriding concern was low R&D productivity. After waves of innovation in the 1970s-90s which produced new classes of medicines to treat cardiovascular conditions, diabetes, CNS, and stomach ulcers, there was a significant slowdown from the mid-1990s.

Ten years ago the majority of investors were gloomy about pipeline prospects, a fact reflected in their valuations. R&D productivity was low, and because neither companies nor investors were willing to forego the margins and earnings growth that they had enjoyed in the previous decades, a number of behaviours designed to uphold these margins were triggered. The definition of innovation was creatively extended and ruthlessly enforced, sales force reps sought ever more sophisticated ways of accessing and persuading prescribers, and in the US in particular, prices jumped higher and higher. In the process, the social contract between industry and society became increasingly frayed and many wondered if industry’s primary purpose of discovering and developing medicines to treat unmet need had been lost.

There are now early indications of a recovery in R&D. In 2012 the FDA approved 39 new drugs, the highest level since 1996, and this came after a previously good year in 2011. Many of the new drugs were for different cancers or for conditions that were hard to treat or relatively rare, such as Hep C and Cystic Fibrosis. Approvals also included a new treatment for TB (where existing treatments face the increasingly serious threat of multidrug resistance) and a new anti-clotting drug. The interest in unmet need is also evident in current pipelines, with continued investment in therapies for auto-immune diseases, such as rheumatoid arthritis and multiple sclerosis, specific cancers, and rare diseases. There are more drugs in development today than for some years, some of which are potentially first in class, though the challenge to bring them successfully through Phase III remains.

The market into which these new treatments will be sold is remarkably different to the one that existed when their development began. Health reforms across the world are altering the relationship between the providers of goods and services and the health systems they serve. The ability of the system to link inputs to outcomes has been massively improved by the advent of new data capabilities which allow for the integration of enormous data sets. Health reform also aspires to increase patient engagement and introduces structural reforms to integrate care around the patient. These changes are leading to new payment models, new measures of accountability, and more stringent demands for value as a condition of reimbursement. In the process, the relationship between the pharmaceutical industry and health systems has changed from binary decision points (a yes/no for approval, a yes/no for reimbursement) to multiple interactions, over time, along the value chain. These interactions need to be dynamic, iterative and negotiated. This amounts to a “reset” of the
industry’s relationship with society.

This is a huge opportunity. The combination of promising new treatments and adjustments to the system offer a chance to use the new desire for evidence to get medicines to patients who need them; to improve compliance for better health outcomes; and to do so in a way that helps those managing health systems to improve productivity and manage cost concerns. The PharmaFutures interviews and discussions identified appetite from within health systems and industry for new types of collaboration at key decision points in drug development and usage to achieve these goals. These included opportunities to cooperate over evidence collection, during licensing and reimbursement and at many points post-approval.

The uptake of this opportunity is not a foregone conclusion. Considerable mistrust exists between parties. Health professionals and payers have criticised industry over marketing practices; manipulation of trial data; the basis for pricing and inappropriate lobbying. Pharma, in turn, has accused governments of arbitrary price cuts; moving the goal posts when it comes to evidence; unmanageable data requirements; procurement policies that do not adequately recognise the benefits of investment in health or the savings pharma offers to the system; and delaying tactics. Finally, both sides share a concern that regulatory systems have not kept pace with the changing environment. As health reforms begin to bite, these tensions may intensify.

The industry and key stakeholders face a strategic choice: to respect the constraints one another faces and to collaborate to develop a model that meets the needs of different stakeholders, or to remain focused on short-term financial imperatives – of the capital markets and of health budgets – with all the damage that such an approach can wreak. There is much at stake – most notably the health and wellbeing of the patients that both sides are there to serve.
Section One: Regional Perspectives

The dialogue explored reimbursement trends in Europe, the emerging markets and the US. The key findings from each are summarised below.

Europe

Europe’s health systems are under intense pressure, as they cope with the fall-out from Europe’s deep and prolonged recession at the same time as managing the long-term trend of rising chronic disease in an ageing population. This recession has taken a huge toll on the health sector. Although the commitment to universal health coverage remains, austerity measures have led many countries to cut health budgets, sometimes drastically. This has meant closures of health facilities (e.g. in Greece), reductions in hospital beds (e.g. in Italy), and cuts to mental health services (in the Netherlands and Portugal). Co-pays, cost-sharing and user charges have been increased or introduced in Portugal, Italy, Russia, Denmark and the Netherlands, across a range of services including emergency services and specialist consultations. Although the full impact of these measures will take time to understand, there is already evidence from Greece of both intense human suffering and worrying signs of a rise in infectious disease.

With health budgets under such extraordinary pressure, it is unsurprising that drug prices too have come under intense scrutiny. Health technology assessment is now used across Europe to evaluate both clinical and cost effectiveness of medicines. Specialty medicines and orphan drugs are under particular scrutiny due to their extremely high prices – the latter sometimes costing well over €100,000 a year per person. Many health systems have consequently introduced price cuts and called for discounts on pharmaceutical products. The Dutch health minister, for example, recently argued for the prices of drugs for two rare genetic disorders to be cut to “acceptable levels.”

Price cuts and discounts have had a big impact on pharmaceuticals. The industry calculates that in 2010 and 2011 price cuts and discounts in Greece, Ireland, Italy, Portugal, Spain accounted for more than 8% of annual pharma turnover there. A particular challenge is the growing impact of price changes in one country on others throughout Europe (and beyond) through the practice of reference pricing. Industry argues that a 10% drop in prices in Greece could lead to a €299m hit in that country, and a much bigger potential €799m impact if this price fall is referenced in other European markets.

The dilemma for pharma is how to manage a stagnating European market, at the same time as acknowledging that health need does not always translate into ability and willingness to pay for products. Europe’s top 5 markets (UK, France, Germany, Spain and Italy), which until recently could be relied upon for 3.8% annual sales growth, could see this figure fall to -1% to 2% over the next four years. And a Europe that accounts for just 18% of global pharma spend by 2016 could be of less strategic importance than the emerging markets, anticipated to account for 30% by that year, or the US which is forecast to hold up at 31% of the total. Though the commercially obvious choice might be to focus elsewhere,
the ethical and reputational fallout of withdrawing medicines from people in need could be huge, while governments run the risk that European patients are no longer at the forefront of considerations about new medicine development.

Payers and governments for their part face the dilemma of how to improve health outcomes and keep long-term health reforms on track (such as more patient-centred care, more care in the community) while budgets are squeezed. Many agree that pharma can and should play a useful role in helping health systems improve outcomes and productivity, as well as contribute to the knowledge economy and labour productivity. However, the fragmentation of the European market – where governments retain responsibility for most healthcare decisions; the intensity of the demands of health reform; and the antagonism generated by differences on pricing, makes negotiating these complex issues highly problematic. The challenge to pharma and Europe’s governments, nationally and collectively through the European Commission, is to work to ensure that pharmaceutical products get to those who need them, and that Europe remains sufficiently attractive for the industry to remain invested there.

**Emerging Markets**

In strong contrast to Europe, the emerging economies offer significant growth potential, with pharma spending set to double by 2016 (adding $150bn-165bn over five years). There are several drivers of this growth. The first and most striking is the commitment to universal health care reform, which is leading to a huge expansion of basic coverage across many countries, including China, Thailand, Rwanda, South Africa, Mexico and Brazil. Second, these markets are characterised by strong economic and population growth, both of which are likely to increase the demand for health care. Of particular relevance is the increasing purchasing power of the growing middle classes, with much of the growth from 1.8bn people to 3.2bn by 2020 coming from Asia. The third driver of emerging markets pharmaceutical growth is epidemiological: the dramatic increase in the incidence of chronic diseases in many middle and low-income countries. Diabetes, for instance, is reaching epidemic proportions in some countries, with prevalence in China estimated at just under 10% (over 90m people) and accounting for some 13% of China’s healthcare budget (or $25bn).

All these factors significantly increase demand for healthcare, and pharmaceuticals in particular. Medicines often play a highly significant healthcare role in emerging markets where health services and infrastructure are under-resourced compared with high-income countries. In the absence of these services people turn to medicines as a major source of healthcare, a fact that makes their availability, affordability and quality highly relevant.

From pharma’s perspective, the growth potential is clearly there, but realising it will not be straightforward. One reason for this is that societal expectations about the role of the industry in facilitating access to medicines in low and middle-income countries remain high. This is illustrated by a number of disputes in many countries over the price of oncology treatment, and by the issuing of compulsory licenses in India, Indonesia and Thailand.

At the same time, as in other markets, the industry is having to navigate a reimbursement landscape in a state of flux. Governments are increasingly assuming responsibility (directly or indirectly) for the purchase and provision of medicines used in publicly-funded health systems. The result is a range of measures by governments to influence drug pricing, from nascent cost-effectiveness through to reference pricing and control of mark-ups.

There are other challenges as well. Pharma’s ability to sell its drugs can also be constrained by weak infrastructure, poor distribution, and poor quality control and monitoring.

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Commerically, these markets require a different business model to that of industrialised markets with strong health infrastructure and third party payers. Due to the high numbers of people living on incomes significantly lower than those in industrialised markets, and high out of pocket expenditure, they are likely to require a price/volume trade-off. Branded generics are likely to continue to be important, particularly in key Asian markets, but the bulk of new demand is more likely to be for non-premium priced generics. This presents uncertainties about how innovation will be paid for and what the impact on margins will be of moving to a volume business model. The situation is further complicated by the fact that global pharma finds itself increasingly coming up against competition from domestic companies, benefitting, in some places, from government support in industrial and procurement policies.

Despite these challenges, the industry is much more optimistic about emerging markets than it is about Europe. They are growing rather than stagnating, and appear to offer both an obvious commercial opportunity but also the more strategic opportunity of engaging with governments and other stakeholders as a partner in new approaches to healthcare. Longer-term, this engagement could result in business models that might serve as templates for other markets, and partnerships that could accelerate the global search for better R&D. Success of this nature is, however, likely to be dependent on industry playing an active role in increasing access to medicines for poorer patients.

**The US**

The US healthcare market is in upheaval as providers, payers and patients absorb the implications of the landmark US health reform. The Patient Protection and Affordable Care Act (ACA) aims to expand health coverage to over 30m Americans at the same time as addressing spiralling health costs (health expenditure in the US is roughly 18% of GDP, way above other industrialised countries) and improving management of chronic diseases (where outcomes in the US are poor compared to the OECD averages).

In the process, the reform is radically reshaping US healthcare through the introduction of new institutions and incentives. These include the creation of insurance exchanges, where people can go to buy a basic insurance package, and an increase in the number of Accountable Care Organisation (ACOs) – umbrella groupings of health providers incentivised to streamline services, improve patient care and save money.

Quite how the health reform will play out is uncertain, due to the highly fragmented and complex nature of the US system, and the politicised nature of healthcare debates. The only consistent bet most market analysts are prepared to place is that the landscape will be highly unpredictable for the next few years or even decade. This is partly because recent reforms do not change the underpinning free-market and consumer-led characteristics of US healthcare. Although the role of the state in healthcare will increase, the private sector – insurers and providers in particular – are bolstered by the reforms. Historically, these private players have led the field in seeking cost-effectiveness from pharma, actively managing generic substitution and using formularies to channel patients towards particular drugs. More recently private providers and payers (increasingly consolidated) have been investing in technology they hope will allow them to generate, analyse and integrate clinical and claims data to determine comparative effectiveness and measure health outcomes. As in Europe, rising costs of healthcare has led to more of the cost being transferred from insurers to patients, a trend that is leading to changes in patient behaviours. They too are seeking the best possible value for money, and as costs of co-pays and co-insurance rise, some people are proving willing to accept a more limited choice of medicines in exchange for lower costs.

The US market is still pharma’s most important market by some margin and therefore how these moving parts unfold is of huge importance to the industry.
The US market is still pharma’s most important market by some margin, both in terms of size and profitability, and therefore how these moving parts unfold is an issue of huge importance for the industry. In the short to medium term, the consensus is still for a relatively healthy outlook. IMS data forecasts compound annual growth of 1-4% through to 2016, and within that, continued strong growth for branded medicines – though this does not include discounts and rebates.  

However, in the longer term the reconfiguration of payers, patients and providers could lead to a different outcome. A number of uncertainties could contribute to this change. The first concerns how the health reform plays out. Will the exchanges take hold, and will those elements of the ACA designed to contain costs be retained? If they do, what impact will the massive expansion of Medicaid (the health programme for people on lower incomes) have on traditional employer-sponsored healthcare? Could it lead to a reduction in the quality of insurance offerings overall, and if so, what impact will this have on the breadth of pharmaceutical offerings and the price of medicines? If the costs – of Medicare (the health programme for the over 65s) in particular – are not controlled, will cost effectiveness eventually be permitted in publically subsidised programmes? Finally, are the high and growing prices for specialty medicines and biologics sustainable? Until now, payers have been shielded from the pain of price rises in these medicines because of a relatively large number of patent expiries, enabling the swift and broad take-up of generics. Although 2012 saw a small generics-driven dip in US drug sales, many experts believe there will be a growing pushback from payers. As patent expiries wane, the growing share of overall drug spend accounted for by specialty medicines is likely to become more visible and more controversial.

As in Europe and the emerging markets, the pharma industry faces strategic choices. The US pharmaceutical market continues to grow, but the changes in healthcare raise doubts about the sustainability of this growth and mean that the industry is becoming much more accountable for its role in health outcomes. How it collaborates with those in the health system determining what will be valued and why is likely to influence its long-term fortunes in this highly significant market.
Section Two: Common Characteristics of Systems in Flux

Despite wide variations in cultural, economic and social underpinnings, there is surprising consistency in how different public and private actors in health systems are seeking to address the underlying challenge of managing health costs that have been rising faster than GDP growth rates (see Fig 1). Even where budgets are increasing, health systems are seeking to improve value for money. To do this, policymakers are focusing on a set of inter-related measures: emphasising the links between health investment and the outcomes it delivers; restructuring systems to increase efficiency and reduce waste; using data to monitor and measure progress against these aims; and finally, seeking greater involvement of patients in determining value.

Health Outcomes

The objective of government health reform the world over is to improve both patient and population health outcomes. For the US and many emerging markets, a core component of this is the extension of basic healthcare provision to citizens without cover. In other developed markets, the principal challenge is to achieve better quality of life, less morbidity and longer life expectancy for the growing number of people living with chronic disease. Both health professionals and service providers, including pharma, are being held more accountable for these goals as policymakers, particularly in the US and Europe, evaluate the outcomes of health services in new ways.

This has increased the focus on measures such as hospital readmissions and on clinical outcomes that may differ from the endpoints used in clinical trials. Cancer treatment is a case in point. There has been an increasing tendency for clinical trials to use “progression-free survival” as an important endpoint. Yet some experts have questioned how accurately such an endpoint correlates to the primary

Figure 1:
International Comparison of Total Expenditures on Health as a Percentage of GDP, 1980-2008

measure used by patients and payers: overall survival and quality of life. In diabetes, research has also focused on how to correlate surrogate measures of metabolic control – such as HbA1c which feature in clinical trials – with the endpoints that patients and their doctors worry about – such as cardiovascular disease and microvascular complications, like retinopathy.

Performance data across hospitals and across specialties, such as surgery, is also becoming more widely available. At the same time policymakers and providers are attempting to assess how well therapies do when they are delivered in the real world and not just in the artificial context of clinical trials. In addition, the perspective of patients is gaining more influence through the use of patient-reported outcomes in both the UK and the US.

The challenge for pharma is to articulate the role its products play in delivering better outcomes that health systems want and will pay for. The task is made harder by the fact that key stakeholders think about value, health outcomes and cost effectiveness in different ways. In this complex new world, pharma will have a bigger stake than ever before in the rational use of medicines and in the measuring of real world effectiveness. How it contributes to this and works with patients, providers and payers is a strategic question.

Comparative Effectiveness and HTAs

The increasing use of health technology assessment (HTA) is part of the trend towards seeking improved productivity: to ensure the system is getting more “bang for its buck” in health terms. All European markets now use some form of comparative and/or cost-effectiveness to define whether innovation offers sufficient clinical benefit and/or value for money. Recent changes in France, Germany and the UK could place even more onus on pharma to demonstrate the novelty and added benefit of its products compared with existing therapies. France is introducing a new way of assessing additional clinical benefit (ITR). Germany’s pricing reform (AMNOG) rates the added clinical benefit of drugs relative to strict comparators – an issue which has generated some controversy.

Unlike Europe, America’s publicly funded health programmes (CMS) are specifically prohibited from using drug price controls and cost-effectiveness measures, although the ACA has introduced the Independent Payment Advisory Board (IPAB) designed to contain rising Medicare costs. It is in the private sector, however, that many see the most significant cost containment measures, including increasing use of comparative effectiveness research (CER) which aims, as many HTAs do, to assess the effectiveness of new therapies against existing alternatives. In addition, evidence-based guidance and drug pathways are now used by many of the larger US providers. Mindful of the perverse incentives built into the fee-for-service model, many in the US are shifting towards payment models, such as capitation and bundled payments.

Health technology assessment requires institutional capabilities. In many emerging markets, where health systems are only recently being established, these capabilities are consequently only now being developed. Nevertheless, there is clear appetite to develop this capacity in Asia and Latin America in particular and some predict that as institutional capacity is strengthened, it is only a question of time before HTAs become widespread.
The move towards evidence-based decision-making should provide greater predictability as to what health systems value and will be prepared to pay for, both of which are desirable outcomes for pharma. However, two significant challenges accompany these processes. First, evidence-based decision-making has not, as yet, eliminated the introduction of apparently arbitrary price cuts or other sudden interventions driven by political expediency. Second, there has been very little standardisation of data requirements, with multiple health systems requiring different information from companies. If these data requirements are not rationalised, they are likely to prove unsustainable in the long run.

Cost Containment and Downward Pricing Pressures

Healthcare expenditure has generally been rising above GDP growth, leading many governments to seek to contain these costs. Healthcare expenditure has generally been rising above GDP growth, leading many governments to seek to contain these costs. Pharmaceutical price increases have been particularly high, with rising prices of high profile biologics and specialty medicines of particular concern, as they are increasing much faster than other medicines. In the US, for example, they rose by 17% in 2011, compared to an overall pharmaceutical price increase of 2.7%. Globally, the $86bn orphan drug market has grown 10% a year, twice as fast as the overall sales from pharma companies, though the rate is expected to slow dramatically going forwards. European governments have tended to focus on pharma prices as they struggle to keep budgets under control in a context of austerity. Some measures, such as cross-border referencing have created more push back than others: for instance, Germany’s decision to include poorer and crisis-hit countries such as Greece, Portugal and the Czech Republic as potential references for German drug prices. But pricing is only half the equation. Some experts have pointed out that other important levers, such as drug utilisation remain under-used across the region – citing especially the market share and take-up of generics compared with the US.

In emerging markets, other means of cost containment include regulation or the monitoring of mark-ups along the supply chain (such as in Russia, Indonesia and South Africa). China too is changing rules on the mark-up on medicines, which until now have been a key source of revenue for health practitioners and health services. In other places, including Brazil and India, indirect pressure on prices has been exerted by stimulating generic competition and through the introduction of compulsory licenses.

As outlined above, some people believe that the US market – still the largest pharma market by some margin – could remain immune to these pressures. They consider the commitment to patient choice and the lobbying power of the industry to be a strong buffer against price shocks. However, in November 2012 the decision of New York’s Memorial Sloan-Kettering Cancer Center not to recommend a particular cancer therapy for use in the hospital on cost grounds was seen by some as a harbinger of greater resistance to the price rises of specialty medicines. Specialty oncology prices in particular, and the likelihood of increased patient co-pays, are both cited as potential triggers to sustained downward pricing pressures in the US.

The introduction or increase in co-pays is another form of cost containment, as seen across Europe and the US, as insurers and governments seek to shift more of the drug costs onto individuals.

RISING PRICES OF HIGH PROFILE BIOLOGICS AND SPECIALTY MEDICINES ARE OF PARTICULAR CONCERN, AS THEY ARE INCREASING MUCH FASTER THAN OTHER MEDICINES.
A key enabler of these changes has been the increasingly sophisticated use of large and complex data sets, from multiple sources. This remains in its early stages, it is now – at least theoretically – possible to aggregate and analyse vast amounts of claims data to provide an indication of drug utilisation. The ambition of early initiatives, such as the recent agreement between the Mayo Clinic and UnitedHealth in the United States, is to integrate this data with the relevant clinical data, which would provide insights into patient outcomes. If successful, these changes offer the prospect of revolutionising definitions of value by accelerating new approaches to comparative effectiveness. Elsewhere too, providers, HTAs, patients and companies are increasingly interested in how medicines are performing once in the marketplace. There are growing

“Big Data”

A key enabler of these changes has been the increasingly sophisticated use of large and complex data sets, from multiple sources. The efforts to rationalise and streamline costs and to evaluate outcomes have been made possible by dramatic advances in technology. Although...
requirements for companies to continue post-marketing evaluation as a condition of approval and more sophisticated management of data is playing a crucial role in making this possible (see Fig 2).

It is worth noting that this type of data management in healthcare is still in its infancy and raises a number of questions that will need to be resolved before it is widely used. It poses legal challenges about data protection and patient confidentiality. It raises practical challenges about how to go about delisting or narrowing the target population of a drug if it is proved to be of limited value for the majority, but works for some. The task of integrating such complex sets of data is difficult and time-consuming, and remains an imperfect science. It is also expensive, raising questions about who will pay for the data that will be needed to evaluate performance. The most pressing question, however, arises because having more data does not, of itself, lead to clearer answers about the effectiveness of drugs. The core challenge is to ask the right questions when analysing and interpreting the data, in order to obtain increasingly robust evidence of value.

**A New Patient Voice**

The final characteristic of health reform is the increasing importance of the patient voice in determining value. This may be expressed through the introduction of formal measures within the health system such as the use of Patient Reported Outcomes in the UK and the US. In other instances, it might be the creation of new institutional capabilities, such as the US’s Patient-Centered Outcomes Research Institute (PCORI). The patient voice can also influence through “grass-roots” groups – such as PatientsLikeMe or disease specific organisations, like Lymphoma and Leukaemia (LL&C) or the Cystic Fibrosis Society, which have been involved as funders of research. These new expressions of patient demand present opportunities – by providing a new way of understanding clinical effectiveness in the real world, for example – and challenges of how to integrate this new source of data with existing surveillance data gathered by health systems. In the US, for example, where patients pay a proportion of drug costs through the system of co-pays, the patient perspective is likely to become more significant as insurers off-load more of the cost of medicines onto patients.

As with data management, this growing trend towards more active patient involvement in healthcare has not reached its full potential. At present, it is more visible in markets, such as the US, where patients contribute to health costs, but seems set to become more widespread, driven by growing price sensitivity and the need for more effective, patient-directed management of chronic diseases.

These new expressions of patient demand present opportunities to improve understanding clinical effectiveness in the real world.
Section Three: The Opportunity

The combination of promising research and health reform offers a real opportunity to develop a more agile and cost-effective system for drug discovery, development, licensing and usage. The goal is greater understanding of what works, for whom, and at what stage in the disease pathway – boosted in some cases by the use of diagnostics to target certain types of therapies. The result could be better disease management, better patient outcomes and a more efficient system.

Improved collaboration would allow the drug development process to move from one of binary decision-making at the point of regulatory approval and price-setting, to one that is characterised by iterative, dynamic decisions that are adapted as evidence is accrued, and value determined over time. To achieve this, changes in approaches and behaviour at three key decision-points in today’s pharmaceutical development could make a huge difference. Although not an exhaustive description of commercial and clinical decision-points, rethinking how pharma, regulators, payers, patients and health system representatives interact during clinical development, at the point of market authorisation and during pricing negotiations could significantly enhance the rational functioning of the system.

1. Clinical Development: Beyond the RCT

The Challenge

Randomised Controlled Trials (RCTs) are the lynchpin of today’s model of drug development, considered to be the most reliable way possible to determine the effect that a drug has on a disease as well as its safety. Despite these strengths, there is a growing body of opinion arguing that RCTs are necessary, but insufficient, because they cannot assess the effect a drug will have in real clinical settings as distinct from the idealised conditions of a trial. The challenge is to combine different types of data that are asking different types of questions (RCT data and observational data) into a coherent measure of the value of a drug. More sophisticated data management will help with some of this. But the more fundamental task is for relevant stakeholders to reach a scientific consensus on the standards for evidence that should be used to assess the real-world impact of drugs on health.

The Opportunity

To combine safety and efficacy data with evidence of clinical effectiveness in the real world to determine the value of a medicine.

Green Shoots: New Approaches to RCTs

“Pragmatic trials”: these are randomised trials that are embedded in routine clinical care – e.g. offered by GPs in the UK – to assess relative effectiveness of a drug that is already in use, or a drug that has yet to be licenced.

Inclusion criteria: this involves relaxing inclusion criteria so that RCTs more accurately reflect the type of patients who might use the drug in clinical practice.

Shorter Phase III: whereby regulators approve drugs for rare diseases on basis of reduced number of RCTs. Experts also argue for making greater use of biomarkers and diagnostics in smaller, targeted, groups of patients in Phase II studies.
2. Licensing: The Challenge of a Zero-Sum Approach to Authorisation

The Challenge
The point at which a drug is licensed is vested with huge significance. After years – and sometimes decades – of research and hundreds of millions of dollars of investment, the regulator makes a decision about whether a drug will be authorised for use. As with RCTs, this focus on a single decision point is increasingly perceived as inadequate given increasingly sophisticated data collection and management. Specifically, it is not sufficiently flexible to reflect the findings of additional evidence, whether positive or negative, as it accrues in the real world. Other concerns about today’s licensing regime include a criticism that it is not agile enough to respond to some urgent unmet needs, such as the need for new antimicrobials or treatments for neurodegenerative diseases, despite FDA and EMA initiatives to expedite promising treatments through Accelerated Approval or Conditional Marketing Authorisation. Likewise, the risk appetite of the regulator may not be matched by the risk appetite of patients – particularly in the area of rare diseases, where patient risk appetite may be higher.

The Opportunity
To create a model of adaptive licensing sufficiently robust to guarantee safety and efficacy on approval as well as being sufficiently flexible to allow for iterative evidence-building, over time.

Green Shoots: New Approaches to Authorisation
There are many proposals for how to take adaptive licensing forward. These include:

- **EMA’s Road Map to 2015**, which “staggers” approval from patients that respond well to include other patients as real world data builds.
- **MIT New Drug Development Paradigms**, which is working together with Singapore Health Sciences Authority in a new multi-stakeholder group to work on the design and impact of adaptive licensing on a number of therapeutic areas.
- **Green Park Collaborative**, which is a multi-stakeholder forum to develop methodological standards for studies that demonstrate real-world effectiveness of drugs.

Figure 3:
Performance-based Risk Sharing Arrangements

![Performance-based Risk Sharing Arrangements](chart)


1. Described by Eichler et al. as “a prospectively planned, flexible approach to regulation of drugs and biologics...”
3. Pricing: The Challenge of a Fixed Price Point

The Challenge
Although the process of defining how much will be paid for a medicine varies the world over, many pricing decisions are fairly inflexible: intense negotiations culminate in a pricing decision that is then fixed for a period of time. Companies seek the highest possible price for a medicine knowing that it cannot later be adjusted upwards if the drug proves more effective, and bearing in mind that whatever price is achieved will be noted in other markets. Payers for their part seek the lowest, often referencing low prices in other countries, arguing that this price will not fall further, even if the drug disappoints. These winner-takes-all price negotiations are frequently antagonistic, contribute to mistrust between parties, and are insufficiently flexible to reflect changing perceptions of a drug’s value once it is in use in the real world.

There is widespread acknowledgement among pharma and payers that the use of real world, observational data presents an opportunity to rethink how the value of medicines is measured and rewarded. There are two main areas of uncertainty that make coming to agreed definitions of value and translating them into a price a complicated process. First, there is uncertainty on outcomes and response to treatment: will the anticipated links between surrogate endpoints and actual clinical endpoints, for instance, play out as expected in the real world? Second, there is uncertainty over who will benefit and how these sub-populations can be identified. Addressing the challenges of clinical development and adaptive licensing (as outlined above) could help answer these questions.

The Opportunity
To create pricing models that reflect changing perceptions of the absolute and relative value of a medicine based on evidence accrued as it is used in clinical practice.

Green Shoots: Flexible Pricing
There are many attempts to introduce more flexibility into current pricing models so that the price paid reflects the fact that the cost effectiveness of a drug is not known from the outset (See Fig.3). Attempts to design such new models include:

Risk-sharing deals on outcomes: Pharma agrees upfront to share some risk (linking payments to performance, or refunding costs to payer) if certain disease-specific outcomes are not met.

Risk-sharing deals on evidence: Payers agree to reimburse a new drug under certain conditions: e.g. patients must be enrolled in a study so that more data can be collected.

Value-based pricing: These are new pricing models aimed at applying broader set of criteria to all medicines pricing (severity of a condition, degree of innovation, wider economic/social impact e.g. on patients’ carers). The UK currently plans to introduce value-based pricing in 2014.
Section Four: Recommendations

Today’s linear system of decision-making on drug development and use needs to evolve into a cyclical process, with decisions at each stage building on each other and feeding back to improve the next round of decisions. It needs to build on the findings of the many initiatives and experiments outlined in the previous section and to acknowledge that the solutions to the challenges posed at each stage lie in weaving them together into a whole.

Recommendations to Pharma and Health System Stakeholders

We make the following recommendations to help achieve this goal, with details on how they might be implemented:
**Recommendation 1:**
**Agree Mechanisms to Identify and Assess Value**

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<thead>
<tr>
<th>Step</th>
<th>Description</th>
<th>Who needs to be involved?</th>
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<tbody>
<tr>
<td>1.</td>
<td>Signal priority therapeutic areas early and clearly.</td>
<td>Health systems ✔ Pharma ✔ Regulator ✔ HTA ✔ Payer ✔ Clinician ✔ Patient ✔</td>
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<tr>
<td>2.</td>
<td>Agree criteria to be used to determine value of drug (effectiveness/innovation/economic value/unmet need).</td>
<td>Health systems ✔ Pharma ✔ Regulator ✔ HTA ✔ Payer ✔ Clinician ✔ Patient ✔</td>
</tr>
<tr>
<td>3.</td>
<td>Agree which clinical endpoints are relevant proxies for improved patient health and wellbeing.</td>
<td>Health systems ✔ Pharma ✔ Regulator ✔ HTA ✔ Payer ✔ Clinician ✔ Patient ✔</td>
</tr>
<tr>
<td>4.</td>
<td>Introduce tools to make value assessment work (best practice dissemination, guidelines and on-going monitoring).</td>
<td>Health systems ✔ Pharma ✔ Regulator ✔ HTA ✔ Payer ✔ Clinician ✔ Patient ✔</td>
</tr>
<tr>
<td>5.</td>
<td>Negotiate and agree standards for the collection and analysis of real world data. To include data quality, statistical methodologies and adjustment for confounders.</td>
<td>Health systems ✔ Pharma ✔ Regulator ✔ HTA ✔ Payer ✔ Clinician ✔ Patient ✔</td>
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<td>6.</td>
<td>Agree how potential conflicts between RCTs and observational data will be resolved.</td>
<td>Health systems ✔ Pharma ✔ Regulator ✔ HTA ✔ Payer ✔ Clinician ✔ Patient ✔</td>
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**Recommendation 2:**
**Coordinate Pre and Post Launch Decision-Making**

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<tr>
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<tr>
<td>1.</td>
<td>Early involvement of payers and HTAs in the regulatory process, particularly on accelerated approvals/conditional marketing authorisation and design of trials (choice of comparators).</td>
<td>Health systems ✔ Pharma ✔ Regulator ✔ HTA ✔ Payer ✔ Clinician ✔ Patient ✔</td>
</tr>
<tr>
<td>2.</td>
<td>Greater coordination between regulators on types of adaptive licensing.</td>
<td>Health systems ✔ Pharma ✔ Regulator ✔ HTA ✔ Payer ✔ Clinician ✔ Patient ✔</td>
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**Recommendation 3:**
**Improve Data Management**

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<tbody>
<tr>
<td>1.</td>
<td>Agree a system for data transparency (for RCT and observational data) that is scientifically credible but preserves commercial and patient confidentiality.</td>
<td>Health systems ✔ Pharma ✔ Regulator ✔ HTA ✔ Payer ✔ Clinician ✔ Patient ✔</td>
</tr>
<tr>
<td>2.</td>
<td>Conduct relevant observational data (incentives and monitoring to be put in place).</td>
<td>Health systems ✔ Pharma ✔ Regulator ✔ HTA ✔ Payer ✔ Clinician ✔ Patient ✔</td>
</tr>
<tr>
<td>3.</td>
<td>Enroll Patients in Electronic Registries.</td>
<td>Health systems ✔ Pharma ✔ Regulator ✔ HTA ✔ Payer ✔ Clinician ✔ Patient ✔</td>
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<td>4.</td>
<td>Agree standardised (or workable levels of agreement for) electronic health records.</td>
<td>Health systems ✔ Pharma ✔ Regulator ✔ HTA ✔ Payer ✔ Clinician ✔ Patient ✔</td>
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<td>5.</td>
<td>Integrate different data sets (clinical, health service utilisation, claims) across health systems (primary care and hospitals).</td>
<td>Health systems ✔ Pharma ✔ Regulator ✔ HTA ✔ Payer ✔ Clinician ✔ Patient ✔</td>
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**Recommendation 4:**
**Establish New Pricing Parameters**

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<th>Description</th>
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<tbody>
<tr>
<td>1.</td>
<td>Agree the methodology used to incorporate long-term value into pricing, including how and when price adjustments would be determined (and type of evidence needed to justify these adjustments).</td>
<td>Health systems ✔ Pharma ✔ Regulator ✔ HTA ✔ Payer ✔ Clinician ✔ Patient ✔</td>
</tr>
<tr>
<td>2.</td>
<td>Commitment to price rises as well as cuts if data proven.</td>
<td>Health systems ✔ Pharma ✔ Regulator ✔ HTA ✔ Payer ✔ Clinician ✔ Patient ✔</td>
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<tr>
<td>3.</td>
<td>Agree how to tackle more difficult elements of flexible pricing (e.g. how to account for the long lead times for evidence gathering which may exceed patent life).</td>
<td>Health systems ✔ Pharma ✔ Regulator ✔ HTA ✔ Payer ✔ Clinician ✔ Patient ✔</td>
</tr>
</tbody>
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**Notes:**
- Health System refers to provider networks in the US (both privately and publicly funded) and institutions such as NHS Confederation in the UK.
- Payer refers to consolidated institutions that pool risk on behalf of individuals (such as large private insurers, social health insurance or systems funded through general taxes).
Section Five: Conclusions

*PharmaFutures* concludes that there is a genuine convergence of interest between pharma, patients and health systems. There is an opportunity to develop a systemic, evidence-based approach to collaboration. Over time, this could reduce the risk of bringing a medicine to market and improve understanding of how the medicine could improve productivity and patient outcomes. To achieve this end, certain prerequisites will have to be met.

**The Importance of Leadership**

Leadership from different stakeholder groups will be essential. Reframing the relationship between pharma and health systems will not be easy, and not everyone is convinced that it is either possible or desirable. Strong leadership will therefore be needed to encourage collaboration, build mutual understanding and build trust. Enlightened executives across the system will need to champion and endorse new ways of working in order to overcome the practical and cultural challenges involved in change.

**Collaboration on Value Definition**

Leadership will be needed to bring together industry, regulators, HTAs, payers, patients, journals and clinicians to forge a new, systemic approach to evaluate and define how pharmaceuticals represent value to changing health systems. This is primarily a question of agreeing how data will be managed in future, scaling up and weaving together the results of the many different initiatives and experiments being undertaken today. Over time it is should be possible to identify what is working best, and carefully and deliberately patch together a mosaic of best practice.

As seen in this report, the conditions now exist to move beyond today’s siloed approach and it is already possible to envisage what this would look like. Although it is highly unlikely that RCTs will lose their status as the gold standard in determining efficacy and safety, it is entirely plausible for regulators and pharma companies to agree on what would be required for observational studies in the real world to complement their findings. It is inconceivable that either EMA or the FDA would forgo their independence or temper safety considerations with cost effectiveness concerns, but very reasonable to ask them to coordinate their thinking and practice on adaptive licensing and managed entry. It is unlikely that health technology assessment bodies and health insurers across the world will agree a single common methodology to determine pricing decisions, but it is entirely feasible to ask for a degree of cross-border agreement on what clinical evidence is acceptable, how assessment should be undertaken and what is clinically effective. And finally, though it is difficult to imagine how health systems or providers could coordinate their thinking on the value a medicine offers to their particular system, it is easy enough to imagine that they might share approaches and methodologies.

**Enhance Mutual Understanding**

The pressures on all players are real. The best way to ensure on-going collaboration is for agreements to be based on mutually beneficial outcomes that meet the institutional needs of all interested parties. Health systems urgently need to deliver increased productivity and better outcomes while managing unprecedented demand and intense cost pressure. And they have to do so in a highly politicised environment. Health
reform is hugely disruptive and politically sensitive, and time for innovative approaches can be hard to find. In addition, while many in health systems are seeking greater integration, they still tend to be siloed and lack system coherence. Pharma, in turn, has to manage the tail end of a period of low R&D productivity before new products come onto the market and in the process it has to satisfy investors who compare pharma stocks with other asset classes. This, and the widely held desire to maintain today’s pricing model for as long as possible, is leading to antagonistic exchanges with payers. And there is no industry-wide consensus on how to respond to these challenges.

Leaders will need to require their personnel in all parts of the system to enter negotiations with a better understanding of the constraints and pressures faced by their counterparts across the table. With this improved mutual understanding, demands are likely to be more realistic and sustainable, and respect is likely to be forthcoming.

**Address the Trust Deficit**

Mistrust between the industry and health systems representatives remains a serious problem. Health professionals and payers have criticised industry over its marketing practices; the perceived selective publication of trial data by companies and journals; pricing, particularly of specialty products; and inappropriate lobbying. Pharma, in turn, is frustrated by unpredictable government approaches to pricing, particularly reference pricing. It accuses governments of moving the goal posts and of making unmanageable and uncoordinated demands for data and is frustrated at the on-going inability of the system to recognise in full the potential savings pharma could offer. Some mistrust is caused by historic behaviours and needs to be recognised as such. But mistrust also continues to grow. Leadership to encourage people to recognise positive change where it is taking place, to take action on those behaviours that are creating mistrust today and to model new behaviours, is the final prerequisite for success.

**Investor Understanding**

The pharma industry can only fully engage with these changes in its business environment if it has the support of its investors. Shareholders in pharma – as other sectors – are looking for income and the returns that will come from wise capital allocation. Companies cannot predict what their returns will be, but they can explain the investment case for undertaking adaptive licensing or risk-sharing price deals in ways that resonate with investors. This includes the potential for earlier cash flows, less regulatory risk and less reimbursement risk. In the future, investors could come to differentiate between companies on the basis of this improved visibility.

In the meantime, it is already clear that pharma will need the support of investors to navigate this complex and changing landscape. Being clear about how reimbursement is changing – and the risks and benefits this carries – will be a key part of building this support.

**Conclusion**

An evidence-based system should reduce the risks to pharma and the resulting increase in predictability should help health systems plan the most efficient, timely and cost-effective interventions to the system. Health systems, pharma and their stakeholders face a strategic choice. Either to embrace evidence-based decision-making as an opportunity to agree the true value of pharmaceuticals – with all the implications this has for transparency, pricing and collaboration on outcomes. Or to perpetuate a problematic zero-sum approach to value definition which encourages mistrust and antagonism.

Replacing today’s model of drug development and reimbursement with a new systemic approach would reduce the risk and cost of bringing a medicine to market and increase the likelihood that the medicine will improve productivity and patient outcomes. This result is a value proposition that works for all.
PharmaFutures Participants

**Working Group Participants**

Stewart Adkins, Director, Stewart Adkins Advisors Ltd
Mark Becker, Healthcare Analyst, Fidelity Worldwide International
Dr Scott Braunstein, MD, JP Morgan Asset Management
Joel Emery, VP, Analyst, Fred Alger Management Inc.
Charlotte Ersbøll, Corporate VP Global Stakeholder Engagement, Novo Nordisk
Eddie Gray, President Pharmaceuticals Europe, GlaxoSmithKline
Dr Jane Griffiths, Company Group Chairman Janssen Pharmaceuticals, Europe, the Middle East and Africa, Johnson & Johnson
Charlotte Ersbøll, Corporate VPGlobal Stakeholder Engagement, Novo Nordisk
Eddie Gray, President Pharmaceuticals Europe, GlaxoSmithKline
Dr Jane Griffiths, Company Group Chairman Janssen Pharmaceuticals, Europe, the Middle East and Africa, Johnson & Johnson
Graham Hetherington, CFO, Shire Plc
Prof Sir Michael Rawlins, Chairman, National Institute for Health and Clinical Excellence (NICE)
Dr Jack Scannell, Head of Discovery Research, e-Therapeutics PLC; formally Analyst, Sanford Bernstein
John Schaetztl, Industry Commentator, Independent
Ad Schuurman, President, Medicine Evaluation Committee (MEDEV)
Dan Summerfield, Co-Head Responsible Investment, Universities Superannuation Scheme
Dr Giorgia Valsesia, Healthcare Analyst, SAM Research AG
Stijn Vanacker, Analyst Global Healthcare, Robeco

**Europe Participants and Interviewees**

Dr Peter Anderson, Executive VP, Lundbeck
Dr Richard Barker, Director, Oxford Centre for Accelerating Medical Innovations
Dr Andrew Baum, Associate, Citigroup Analyst
Dr Rafael Bengoa, Minister for Health and Consumer Affairs in the Basque Country, Basque Government
Richard Bergstrom, Director General, European Federation of Pharmaceutical Industries and Associations
Dr Ted Bianco, Director, Technology Transfer, Wellcome Trust
Prof Chas Boutra, Chief Scientist, Structural Genomics Consortium Oxford
Dr Anna Bucsics, Vice Department Head: Department of Pharmaceuticals Affairs, Main Association of Austrian Social Security Institutions
Dr Angela Coulter, Director of Global Initiatives, Foundation for Informed Medical Decision-making
Jim Easton, National Director for Improvement and Efficiency, UK Department of Health
Dr Nick Edwards, Partner, Kinapse
Elizabeth Fernando, Head of European Equities, Universities Superannuation Scheme

Simon Friend, Global Pharma and Life Sciences Industry Group Leader, PricewaterhouseCoopers
Thomas Heynisch, Deputy Head of Unit, European Commission, DG Enterprise & Industry
Dr Alison Hill, MD, Solutions for Public Health
Simon Jose, President, Stiefel, GlaxoSmithKline
Prof Finn Borlum Kristensen, Chairman of the Executive Committee, European Network for HTA
Dr John LaMattina, Former SVP, PureTech Ventures
Natasha Landell-Mills, Senior Analyst, Universities Superannuation Scheme
Colin Pratt, Portfolio Manager UK Equities, Universities Superannuation Scheme
Carl Seiden, President, Seiden Pharmaceutical Strategies
Divya Srivastava, Health Economist, Organisation for Economic Co-operation and Development (OECD)
Chris Strutt, SVP Government Affairs, Public Policy and Patient Advocacy, GlaxoSmithKline
Phil Thompson, SVP, Global Communications, GlaxoSmithKline
Prof Patrick Vallance, President, R&D, GlaxoSmithKline
Jo Walton, Analyst, Credit Suisse
Bo Wesley, Senior Specialist, Innovation and Effectiveness, Novo Nordisk
Dr Paul Wicks, Director, R&D, Patients Like Me

**Emerging Markets Participants and Interviewees**

Dr Jenny Amery, Head of Profession for Health, UK Department for International Development
Dr Ted Bianco, Director, Technology Transfer, Wellcome Trust
Dr Kalipso Chalkidou, Director, NICE International
Dr Wen Chen, Professor, Centre for Pharmacoeconomic Research and Evaluation, Fudan University, Shanghai, China
Dr Fernando Cupertino, International Director, National Council of State Ministries of Health, Brazil
Sabine Dandiguian, MD, Janssen Pharmaceuticals, Europe, the Middle East and Africa, Johnson & Johnson
Antonio Ferreira, International VP, Janssen Latin America, Johnson & Johnson
Prof David Heymann, Head of the Centre on Global Health Security, Chatham House; Professor, London School of Hygiene and Tropical Medicine
Abbas Hussein, President, EMAP, GlaxoSmithKline
Dylan Jackson, Strategy Director for EMAP, GlaxoSmithKline
Dr Sun Jing, Senior Researcher, National Institute of Hospital Administration, Ministry of Health, China
Dr Phua Kai Hong, Associate Professor of Health Policy & Management, Lee Kuan Yew School of Public Policy, Singapore
Dr Hannah Kettler, Senior Program Officer and Economist, Global Health Policy and Finance, Bill and Melinda Gates Foundation

iv, Job titles as at time of participation.
Dr Felicia Knaul, Director, Harvard Global Equity Initiative
Prof Zy Kong, Chairman, China Pharmaceutical Industry Association
Chitra Krishnan, Director of Knowledge and Learning, Ashoka Changemakers
Dr Richard Laing, Medical Officer, Policy Access and Rational Use, World Health Organization
Duncan Learmouth, SVP Developing Countries & Market Access EMAP, GlaxoSmithKline
Laurence McGrath, Exec Director, US Healthcare Analyst, JP Morgan Asset Management
Anthony Nash, Head of Market Access and Pricing Strategy, Europe, Middle East, Africa, Asia-Pacific, GlaxoSmithKline
Stavros Nicolaou, Senior Executive, Strategic Trade Development, Aspen, South Africa
Prof Tikki Pang, Director of Research Policy & Cooperation; Senior Policy Adviser, Innovation, Information, Evidence & Research, World Health Organization
Snehal Patel, MD, Saena Partners, Singapore
Prof Mala Rao, Professor of International Health, Institute for Health and Human Development, University of East London
Dr Tim Reed, Director, Health Action International
Dr Anthony So, Director of Global Health and Technology Access, Duke Sanford College
Jeff Stevens, International Pharmaceuticals Analyst, Fidelity
Billy Stewart, Health and AIDS Adviser, UK Department for International Development, India
Kim Taylor, Company Group Chairman, Asia Pacific, Singapore, Johnson & Johnson
Dr Yot Teerawattananon, Program Leader and Senior Researcher, Health Intervention and Technology Assessment Program, Thailand
Dr Prashant Yadav, Director, Healthcare Research, University of Michigan
Dr Jason Yap, Chief, Health Information and Innovation, Agency for Integrated Care, Singapore

US Participants and Interviewees
Jack Bailey, SVP, Policy, Payers & Vaccines, GlaxoSmithKline
Lauren Barnes, SVP, Avalere Health
Prof Ernst Berndt, Louis E. Seley Professor in Applied Economics, Sloan School of Management, Massachusetts Institute of Technology
Kathy Buto, VP, Health Policy Government Affairs, Johnson & Johnson
Joseph Canzolino, Deputy Chief Consultant, Pharmacy Benefits Management, Veterans Affairs
Dr Benjamin Chu, Group President Southern California and Hawaii, Kaiser Permanente
Dr Molly Coye, Chief Innovation Officer, University of California Los Angeles Health System
Prof Patricia Danzon, Celia Moh Professor of Healthcare Management, Wharton School of University of Pennsylvania
Dave Domann, Director Health Care Quality, Johnson & Johnson

Dr Robert Dubois, Chief Science Officer, National Pharmaceutical Council
Susan Edgman-Levitan, Executive Director, John D Stoeckle Center for Primary Care Innovation, Massachusetts General Hospital
Richard Evans, Founder and General Manager, Sector & Sovereign Research
William Fleming, President, Humana Pharmacy Solutions, Humana Inc
Jason Fletcher, Head of American Equities, Universities Superannuation Scheme
Dr Liz Fowler, Vice President Global Health Policy, Johnson & Johnson
Dr Chester Good, Co-Director, VA Center for Medication Safety, Veterans Affairs
Mary Grealy, President, Healthcare Leadership Council
David Green, Social Entrepreneur, Oxford Lotus Health Fund
John Haney, VP Immunology Marketing, Johnson & Johnson
Roger Longman, CEO, Real Endpoints
Chris McGowen, Director of Government Affairs, Novo Nordisk
Laurence McGrath, Exec Director, Healthcare Equity Analyst, JP Morgan Asset Management
Dr Neil Minkoff, MD, Fountainhead Health
Penny Mohr, SVP, Program Development, Center for Medical Technology Policy
Andy Oh, Research Analyst and Portfolio Manager, Fidelity Plc
Prof Gilbert Omenn, Professor of Internal Medicine, Human Genetics and Public Health, University of Michigan
Steve Phillips, Director Health Policy and Reimbursement, Johnson & Johnson
Joseph Piemont, COO, Carolinas HealthCare Systems
Ginny Proestakes, Director of Health Payments Benefits, General Electric Company
Dr Roger Ray, Executive VP and Chief Medical Officer, Carolinas HealthCare System
Prof Dennis Ross-Degnan, Associate Professor, Department of Population Medicine, Harvard Medical School
Prof Leonard Schaeffer, Judge Robert Maclay Widney Professor and Chair, Sol Price School of Public Policy, University of Southern California
Carl Seiden, President, Seiden Pharmaceutical Strategies
Norman Selby, Executive Chairman, Real Endpoints
Mark Skinner, President/CEO, Institute for Policy Advancement
Jennifer Taubert, Company Group Chairman, North American Pharmaceuticals, Johnson & Johnson
Julie Trocchio, Senior Director, Community Benefit and Continuing Care, Catholic Health Association
Dr Sean Tunis, Founder and Director, Center for Medical Technology Policy
Mike Valentino, Chief Consultant, Pharmacy Benefits Management, Veterans Affairs
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Sophia Tickell
Director, PharmaFutures

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