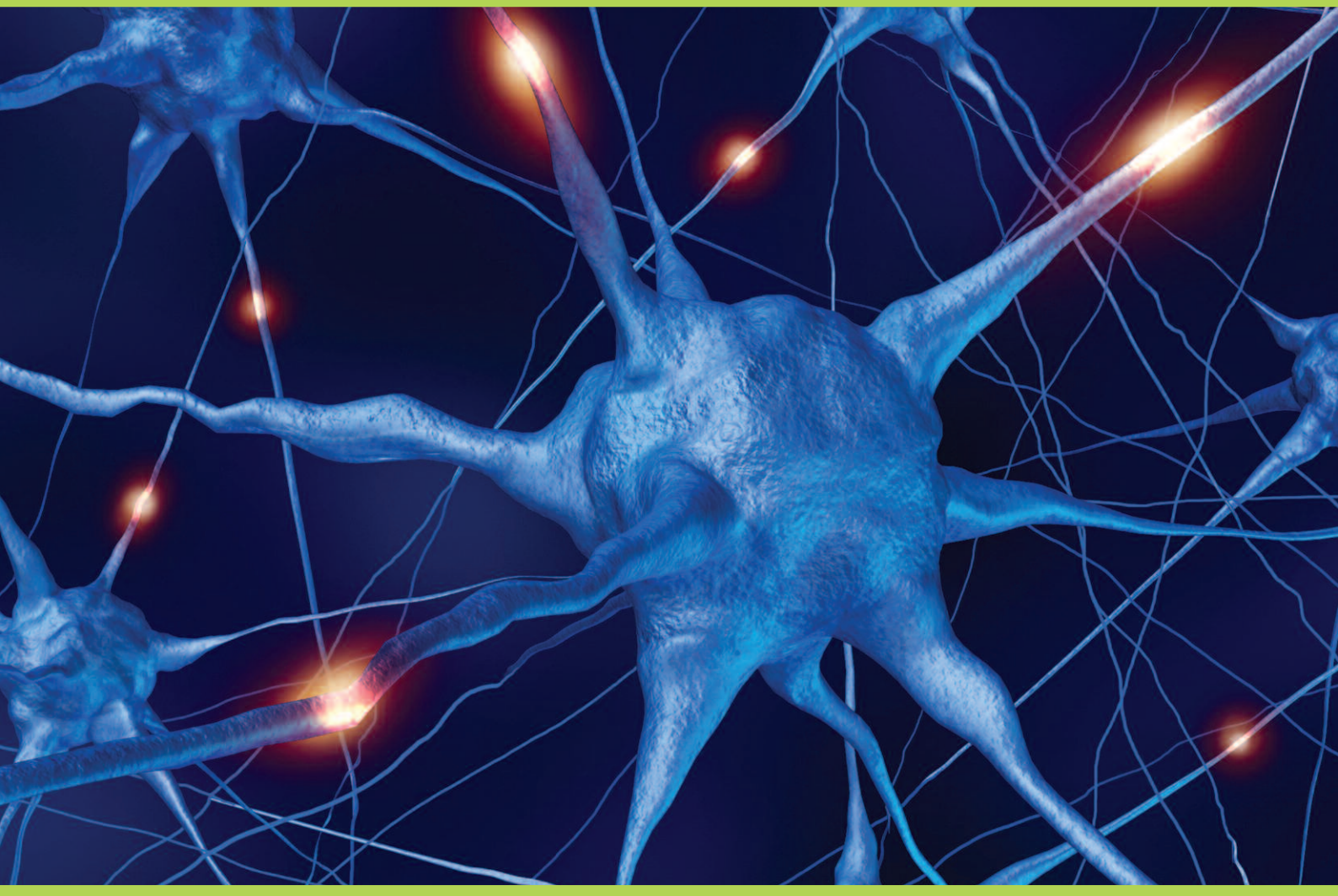
Pharma Futures 4

Shared Value:

Rebuilding Pharma's Contract with Society



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Executive Summary

The biopharmaceutical industry[1] is vitally important to society, a fact that is reflected in the social contract between the industry and society that evolved after World War II. In exchange for developing safe, effective, affordable and innovative treatments for unmet medical need, society rewards the industry in the form of markets, intellectual property and market exclusivity for its products. The industry's social contract generally functioned to mutual satisfaction in the industrialised markets until the mid-1990s. Since then, concerns over increasing prices, intellectual property claims and access in the developing world have combined with increasingly complex science, costly regulatory requirements and changing payer behaviours to place the social contract under severe strain.

Despite this, the importance of the sector is growing as requirements for new treatments for the rapidly growing incidence of chronic diseases worldwide combine with the urgent need for new antimicrobials and therapies for neurodegenerative diseases, such as Parkinson's and Alzheimer's Disease, for an ageing population. The industry has unique skills to translate academic discovery and research into safe, effective products. It has specific competencies for taking products through complex regulatory processes and it has a wealth of knowledge about disease states. It has a scale and reach that allow it to understand and respond to globalised disease trends. It is therefore in the interest of patients, regulators, health workers, health insurers, industry and shareholders to reframe relationships and make the social contract work again.

This report of discussions between the industry and its investors outlines two major challenges to the industry's ability to successfully develop treatments for unmet need. It analyses first the continuing challenge of R&D productivity and second the changes to how medicines are paid for. It then reviews the relationship between the two.

The R&D Challenge

Over the last ten years R&D expenditure has increased dramatically, whilst new medicine approvals have decreased and the mix of product approvals has shifted towards speciality drugs, many with lower commercial potential than earlier blockbusters. This has led to a "productivity drought". Intense attempts by the industry to address this have led to an increase in the number of new drugs emerging from Phase 1 trials and many company pipelines look promising. Despite this, the attrition rate is higher now than it was ten years ago; meaning that the probability of success is lower than it was previously. The R&D challenge is a multi-faceted problem that cannot be reduced to a single explanatory variable. However, the following five contributory factors have been particularly significant.

1. This report covers the broad category of biopharmaceutical industry which includes both large pharmaceutical companies and the newer biotech companies.

Industrialisation

Traditional drug discovery in the 1950s and 1960s relied heavily on an understanding of animal physiology, strong pharmacology skills and labour-intensive chemistry. In the 1980s and 1990s the industry embraced new industrial techniques (e.g. automated drug libraries and high throughput screening) for drug discovery. In the process, the skills bias within the industry moved away from traditional pharmacology and physiology. Many chemists were replaced by machines and personnel budgets were instead spent on molecular biologists and bio-informaticians who were needed to help interpret the next wave of technology – genomics and new target discovery. This increasingly reductionist approach led to a loss of focus on integrated biology and experimental medicine, and an over-reliance on the belief that identifying the molecular target would be sufficient to produce a drug.

Duplication

Another result of the widespread application of industrial techniques was the evolution of a "shots on goal" mentality in which the number of things being worked on became a surrogate for their quality and validity. Once a target had generated useful data, the industry came to hunt as a pack, focusing on a relatively small number of validated targets. The result was the race to the finish line to launch significant improvements on the drugs that had been successfully launched as first in class pioneers. Some were indeed best in class but many proved to offer only modest clinical differences. The consequences of companies "working under the lamp post", with large areas of medical need unexplored, have become serious in the last two decades. It has led to a diminishing focus on more intractable disease states, such as neuropathologies, which lack good biomarkers.

Risk Aversion

The commercial success of the multiple drugs focused on validated targets encouraged many stakeholders, including investors, to believe that such success was the norm. Though industry did try to identify novel targets, increasingly through genomics, they proved to be even higher risk, partly because they were not fully validated. Thus, when faced with a choice of predictable returns from successful validated targets or exploration of new ones, industry prioritised the former and was rewarded by investors for doing so. The result was a consolidation of effort on those self-same targets and a reduction in the breadth of the portfolio.

Consolidation

The wave of mergers and acquisitions from the 1980s onwards also contributed to a reduction in R&D productivity as the act of consolidation, rather than enhancing productivity, proved to be an organisational disruption which reduced the pipeline, created distractions and fostered an organisational structure at cross-purposes with product-driven value creation.

Regulatory Requirements

The final cause of productivity decline was found to be the growing requirements of regulators who have raised the standards of safety and efficacy, particularly for primary care, obliging companies to gather much more clinical data from many more patients. The increased costs of late stage clinical trials, together with higher hurdles for success, have required companies to make tougher choices about which projects have the best chance of success for a given R&D spend.

The ecosystem of innovation includes Big Pharma, biotech and academia. Identifying the most efficient and productive role for each of these multiple creative players is leading to calls for significant rationalisation. Perhaps the most critical decision facing the industry today is the extent to which excess capacity in the R&D function can be reduced without a resultant loss of core industry competency and further damage to R&D productivity. Different companies have signalled radically different approaches to this. At one extreme has been the defence of a broad portfolio and an accompanying warning to investors to lower their profit expectations. At the other has been a radical reduction in R&D expenditure. Investors still appear to lack conviction that the current R&D strategies of the industry can provide a sustainable and increasing return, though there are early signs of increasing confidence.

The Reimbursement Challenge

R&D productivity is intimately linked with corresponding willingness and ability of the payer to pay. The 1980s and 1990s marked a "Golden Age of Pharmaceuticals" during which the payer seemed to have a limitless appetite for new drugs. Although the race was for first and best in class, second, third and fourth could find a market too. The doctor decision-makers were persuaded of the value of the new generations of medicines, compared to the old and accepted product to product differences. As a consequence their prescribing practices expanded utilisation and the range of products used. While doctors seemed unconcerned about the price implications, the payers were too dispersed to do anything other than passively endorse higher prices for the new medicines and the annual price increases (in the US) thereafter. Where the US led, Europe followed, and there too the industry proved able to increase sales volumes without too much pushback on pricing.

During this era of first and best in class, regulatory hurdles were relatively low and pipeline pruning took place only if the drug was particularly unsafe or ineffective. The market signalled its willingness to pay for multiple products in key therapeutic areas and so industry responded to these large markets with clear targets by focusing its attention on them in a logical deployment of capital.

The expansion could not last. The increasing cost burdens of rising prices and expanding volumes (associated with life-long chronic disease therapies) led first to modest and then to more intense pushback. Trust began to erode as the price of incremental innovation in the new "me-too" therapies came to be perceived as over-reach for the limited added value they offered.

Payer pushback was first felt in Europe where there were a range of attempts to hold down escalating pharmaceutical budgets, including the introduction of black lists, negative lists, price cuts and jumbo groups (groups of drugs in the same therapeutic class, reimbursed at the same level irrespective of differences in clinical effect).

At the same time, the new discipline of pharmacoeconomics began gaining ground and the language of doubt began creeping into the vocabulary in payer efforts to make qualitative assessment, to define value for money and to establish evidence-based protocols.

More recently, there has been a big increase in the generation of head to head comparative data on different therapies and more and more payers have begun to insist on generic substitution. Over time, decision-making has gradually passed from the physician to the payer – a shift that has taken place in both Europe and the US, despite the highly politicised nature of the debate about choice in the US market. In the process, the demand for evidence has become institutionalised to varying degrees and in different forms, across the range of payers globally, and is increasingly a condition of reimbursement.

Rethinking the Model

The result has been to find ourselves at a crossroad in which the relationships between the industry and its stakeholders have fundamentally changed. In the previous model, corporate and venture investors confidently allocated capital to R&D on the understanding that the industry's judgement about what would succeed in the market was sound. The appetite of the payers for the products coming online ratified these assumptions. In the new model, in which payers are demanding evidence of value, particularly of incremental innovation and increasingly linked to price, sources of capital have become increasingly risk averse, no longer confident of industry's ability to predict what payers will be prepared to pay for.

Despite first appearances, this impasse presents the most significant opportunity facing the industry today as it dawns on the many players who will influence what happens next, the degree to which they share a common interest in finding solutions. The growth in patient groups, newly empowered by online information; the rise of the consolidated payer; the increase in the quantity and quality of real data about the comparative effectiveness of medicines, as well as efficacy and safety; and the fact that the industry is already being heavily discounted by the financial markets provide not a threat, but an unprecedented opportunity to collaborate with other actors in the marketplace to identify the medicines society needs, and is able and willing to pay for. The definition of innovation, having passed from industry to payers, could become much more aligned with what payers want, what prescribers want and what industry scientists want: to make a difference with a new medicine. This could evolve into a "Shared Value" model in which the social contract is renewed to the mutual benefit of industry and society.

Recommendations

Determined to contribute to a "Shared Value" model the *PharmaFutures* Working Group identified the following responses from society, industry management and investors that it considers most likely to result in mutually beneficial outcomes. These would ensure that the industry is rewarded commensurately for meeting unmet patient need while providing appropriate returns for investors and recognising the constraints on society's ability to pay.

Role of Societal Stakeholders

- **Signal priority unmet needs and priority focus for treatments**
- **Coordinate work of Agencies dealing with the Pharmaceutical Industry**
- **Be prepared to collaborate with Industry**

Government Agencies

1. Articulate a clear healthcare strategy that gives a well-defined picture of what you see as the appropriate balance of health interventions, including prevention, treatment and cure across and outside the health system.

2. Encourage debates about future health policy which incorporate discussions about efficiency savings involved in preventative and early interventions.

3. Clearly signal areas of unmet need in timely fashion to Industry to enhance the industry's ability to make appropriate investment decisions. Recognise that decisions about today's application also serve as guidance for products just entering early development. In the absence of direct guidance about those early candidates, the signals are easily misunderstood.

4. Enhance multilateral collaboration in signalling unmet need, e.g. at European level.

5. Expand collaborations with industry on non-commercial unmet need which will require risk-sharing between government and industry; identify milestones for collaboration; collaborate earlier in the development process, especially with R&D departments.

6. Coordinate health, regulatory and reimbursement policies and practices so that they combine appropriate rewards for innovation with the need for pricing discipline.

Regulators, HTAs and Payers (Public and Private)

1. Collaborate to minimise unnecessary duplication.

2. Harmonise assessment criteria and rationalise data requirements across regulatory and health technology assessment entities (HTAs) throughout the development process, including streamlining pathways to approval which minimise unnecessary differences in filing formats, deadlines and requirements and post-marketing surveillance.

3. Enhance channels for providing scientific advice, particularly at the earliest stages when advice and guidance (even tentative and subject to revision) is most valuable, e.g. multi-country/single-stakeholder collaboration (HTAs, Payers and Regulators, plus individual company) multi-stakeholder/ multi-country collaboration (HTA, Payers, Regulators, plus multiple companies).

4. Expand and increase alternative approaches to approval and reimbursement including early conditional approval for specific patient sub-populations; reimbursement with evidence over time, where evidence can be generated post-launch and post initial reimbursement; and support research of products into higher risk areas of unmet medical need through enhanced exclusivity periods and/or priority regulatory review.

5. HTAs: consider a common format for any reimbursement criteria.

6. Regulators: acknowledge the cost–benefit equation in risk assessment and that the expense of longer studies to identify smaller differences leads to more expenditure on post-marketing surveillance and reduced expenditure on innovation.

7. Regulators: engage with industry to reconcile the balance between patient risk (side effects) and reward (clinical benefit) particularly in those cases where the commercial opportunity is not large enough to justify the additional development expense, despite a meaningful unmet medical need.

Role of Biopharmaceutical Industry Management

- **Enhance the credibility of management**
- **Improve innovation in the Biopharmaceutical Industry**
- **Rebuild the social contract through collaboration on value and reimbursement**

Enhance the Credibility of Management

1. Define the company's core competence. Review, rethink and rearticulate what the company does well; and how the business model is designed to exploit that skill/competency.

2. Reconsider the business model. Acknowledge that long-standing business models may not be suited to deliver innovation and growth.

Begin to reframe the model through:

- Experimentation that supports the removal of excess capacity without undermining core competencies
- Expansion of new R&D collaborations
- Expansion of the collaboration in the pre-competitive space to improve understanding of disease biology in areas of unmet medical need, up to, in some cases, proof of concept in humans.

3. Be explicit about the capital allocation philosophy. Identify where the company wants to invest, how it makes those decisions, define the required returns, outline the company's track record and the future milestones, specify how shareholders should factor these considerations into their decision-making.

4. Be significantly more consistent and transparent in communications. Identify your strategy, communicate its evolution, be clear about the rationale for any changes, and communicate your core competencies. Allow regular access to management beyond the C-Suite to enhance investor confidence in process and capabilities.

5. Be bold. Consumer perceptions and capital market valuations of the industry are at all-time lows so the risks of bold action are low. Don't be afraid to break from the pack, be proactive not reactive. For example, consider new product and service offerings, combined with medtech delivery systems; offer lower margin products in higher volume markets; build ties with truly independent patient groups and philanthropic entities.

6. Aggressively manage internal assets to create value. Be prepared to make necessary efficiency cuts, monetise non-productive assets, increase transparency. Explore new risk-sharing models.

Improve Innovation in the Biopharmaceutical Industry

1. Identify a clear R&D investment process. Articulate it internally and externally, particularly to investors who will use it to judge future value. Once in place use it and don't ignore it.

2. Retool R&D to increase externalisation, increase experimentation and expand R&D collaborations. This should include partnerships between companies, licensing, pre-competitive partnerships and, where possible, a general expansion of the pre-competitive space. Consider increased patent pooling, including areas of increasing commercial potential.

3. Streamline internal R&D to attract and retain talent. Build on existing initiatives to create the right environment for scientists to flourish, prevent the flight of talent post-consolidation, give scientists more "bench time" and fewer meetings, and outsource fixed cost infrastructure.

Rebuild the Social Contract through Collaboration on Value and Reimbursement

1. Foster collaborations designed to agree criteria on what constitutes value and price accordingly.

2. Continue to provide greater pipeline transparency with the timely posting of trial results, including failures.

3. Build on existing collaborations on unmet medical need such as those designed to develop products for diseases of the developing world and neglected diseases.

4. Undertake risk-sharing partnerships including novel clinical trial approaches and risk-sharing reimbursement agreements based on agreed outcomes.

5. Undertake early engagement with payers and regulators to streamline regulatory requirements, throughout the development process, including post-marketing surveillance while meeting safety, efficacy and cost-effectiveness concerns.

6. Engage with regulators and payers to rationalise data requirements across regulatory and HTA entities.

Role of Investors in the Biopharmaceutical Sector

- **Continue to play a critical role in funding new drug discovery**
- **Use activist tactics to support sustainable R&D models and help bring change in its absence**
- **Retain a focus on the long term to achieve sustainable returns**

Venture Capital and Private Equity

1. Continue to play the critical role of funding new drug discovery platform technologies and novel products, in categories with unmet need. These investments often in start-ups and "biotech" companies, consortiums and public private partnerships increasingly provide the leads which feed development for Big Pharma. Any slowing of investment at this stage will directly reduce the eventual pipeline at those larger companies.

2. Be prepared to support new exploratory models of risk-sharing both within and outside established biopharmaceutical companies, to break the pattern of poor historic returns.

Specialist Healthcare Investors (long only and hedge funds)

1. Proactively articulate a strategic viewpoint to companies.

2. Where necessary, use activist tactics to help bring change to companies without a sustainable R&D model.

3. Evaluate companies on the basis of overall portfolio to allow for different volume/price trade-offs in different therapeutic areas to address unmet medical need.

4. Give clear signals to companies. Make sure companies executing well know that they have the support of their shareholders.

Generalist Investors

1. Retain the focus on the return on R&D investment and the ability to achieve a sustainable return above the company's weighted average cost of capital. This will allow long-term, self-funded re-investment into R&D on an ongoing basis.

Investor Foreword

As the investor participants* in the fourth project of the *PharmaFutures* series we collectively represent approximately £1700bn in assets under management. This significant increase in the value of the funds participating since the last *PharmaFutures* project signifies a notable shift in investor interest regarding the issues affecting the pharmaceutical sector. The dialogue confirmed the importance and effectiveness of the *PharmaFutures* forum in allowing these issues of concern to be addressed with pharmaceutical executives* in an in-depth, confidential and constructive manner.

For those of us involved in *PharmaFutures* from the outset, there has been an increase in the level of trust developed between investors and pharma executives as both sides have sought to build consensus through the *PharmaFutures* initiative. This is largely due to the increased recognition of the overlap of the key challenges facing both sides.

This *PharmaFutures* dialogue was initially designed to focus on three game-changing developments including the Natural Environment. In the course of the discussions, it became apparent that although the environment conversation was extremely important, it was worthy of a separate dialogue. This work is now under way and will be released as a separate report.

The participants ultimately honed in on two key challenges facing the industry and those who have a vested interest in getting the pharmaceutical sector back on track in creating value for investors and fulfilling its social contract. Although the model is not broken, it is in need of reformation particularly with regard to reframing relationships among its key constituents. R&D productivity and changes to how medicines are paid for, and by whom have the potential to become game-changers for the industry and present significant opportunities if collective solutions are found.

The value drivers themselves may remain the same, but the operating environment in which they play out is constantly changing. *PharmaFutures 4* provided an opportunity for companies to build on earlier discussions about R&D productivity and reimbursement, in order to consider how the changing background of advances in technology, new approaches to collaborative innovation, and a rapidly consolidating payer would impact the long-term prospects for the industry.

The investors and industry participants in this project were keen to ensure that there would be practical recommendations emanating from the key findings which would be aimed at each stakeholder group. No single explanation can be found for the many problems experienced by the sector nor is there a magic bullet. There are instead a number of interrelated issues and it will be for each investment house and pharmaceutical company to decide how best to develop their own approach going forward.

The investor participants in this project are grateful to the participating representatives of the pharmaceutical companies for their candour and honesty during the course of our deliberations. The discussions enabled us to identify collectively some of the key challenges facing the sector and informed the drafting of the conclusions and recommendations.

Of course, none of this would have been possible without the vision and leadership of the project director, Sophia Tickell, and her team at Meteos. Their professionalism and commitment to the success of the project ensured that *PharmaFutures 4* joins its three prequels in being ahead of the curve of most commentators on the sector and in suggesting a road-map to take the industry forward.

Dr Daniel Summerfield. USS
On behalf of the investor participants

* See Appendix 1

Introduction

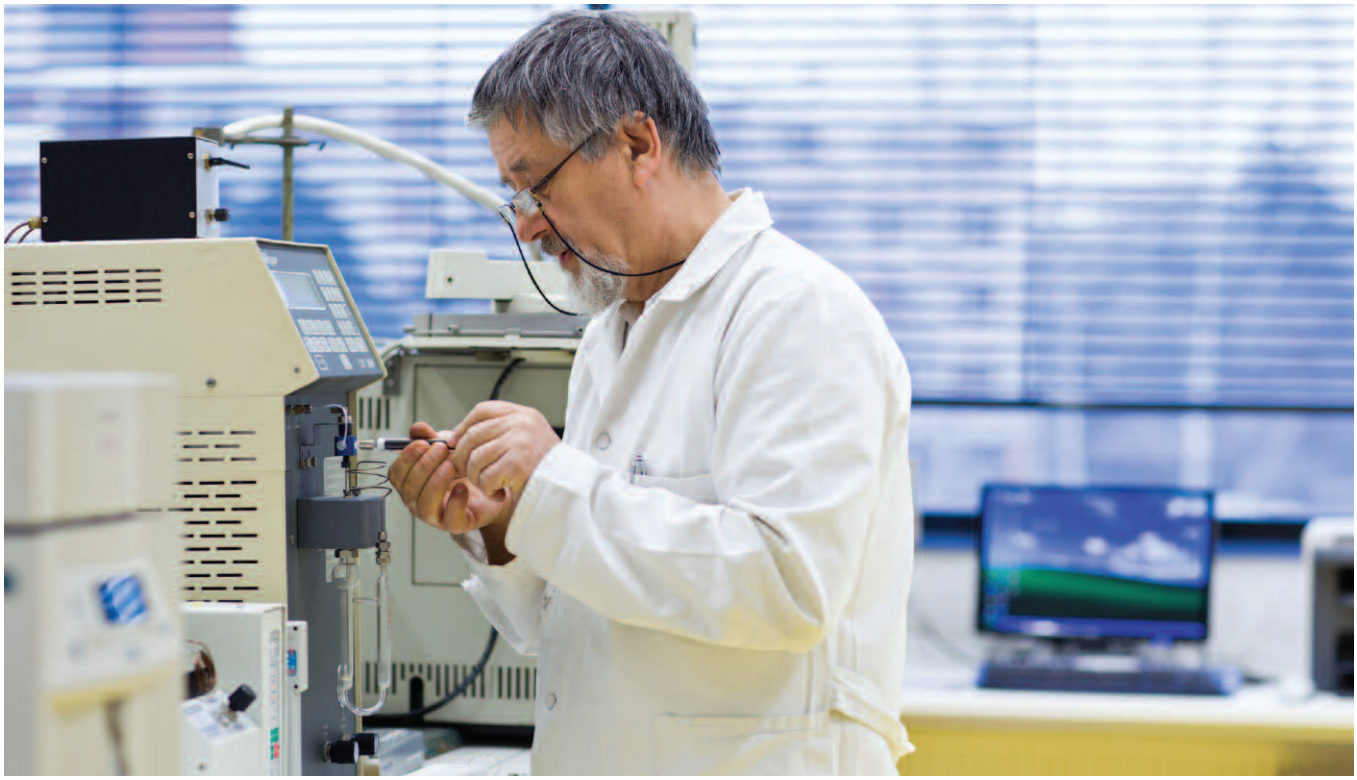
The biopharmaceutical industry is vitally important to society, playing a critical role in the development and delivery of treatments for the prevention, treatment and cure of disease. This social purpose is reflected in a social contract that evolved after World War II with a system of societal rewards to the industry of markets, intellectual property agreements and market exclusivity, in exchange for the industry providing society with safe, effective, affordable and innovative treatments for unmet medical need. The importance of the sector has only increased in a context of growing need for treatments resulting from the rapid worldwide spread of chronic diseases; the urgent need for new antimicrobials; and the mounting societal pressure for therapies for neurodegenerative diseases, such as Parkinson's and Alzheimer's Disease, for an ageing population.

The industry's social contract functioned to mutual satisfaction in the industrial markets of Japan, Europe and the United States until the 1990s and early 2000s, when concerns over increasing prices, intellectual property claims and access in the developing world combined with increasingly onerous and costly regulatory requirements and changing payer behaviours to place the industry under severe strain. This coincided with increasingly complex science and an investment market that discouraged research into therapeutic areas with unpredictable commercial returns.

It is in the interests of all patients, regulators, health workers, health insurers, industry and shareholders to reframe relationships to make this social contract work. The industry has unique skills to translate academic discovery and research into safe, effective products. It has specific competencies for taking products through the complex regulatory processes and it has a wealth of knowledge about disease states and clinical practice. It has scale and reach that allow it to understand and respond to a globalised context of disease.

These skills are needed to address an already high level of unmet medical need that is projected to grow and become more complex. Smoking, sedentary lifestyles and new eating patterns are leading to an exponential growth in chronic diseases, particularly in developing countries. Resistance to existing antimicrobial treatments is growing and there is an urgent need for research into new antibiotics to deal with the rapid spread of new pathogens in our globalised era. There are many diseases of the developing world that still lack basic treatments.

This report explores the roots of the current crisis of confidence in the social contract. It traces the evolution from the abundant years of the 1980s and 1990s to the present day. This evolution was largely a result of the ability and willingness of hundreds of thousands of US doctors to quickly adopt and widely prescribe new therapies, requiring third-party payers to pay ever-higher prices on ever-increasing volumes. The report then proposes elements of the solution,



which, ironically, lie in the pressures amplified by the austerity years of the 2010s. The combination of risk-averse investors who require greater fiscal discipline around capital allocation and a retooling of R&D; cost-conscious payers who require evidence of clinical value to part with their money; more demanding patients and concerned regulators could strain the contract to breaking point. These factors could, alternatively, precipitate a much-needed collective rethink about how to prevent a reverse in the (terminal, according to some) decline of this essential industry.

This report reflects the findings of a year-long dialogue between senior pharmaceutical executives and institutional investors, which were complemented by the views of senior experts across the public and private sectors, primarily in the US and Europe. It is structured to present the findings of the dialogue and the many interviews we undertook with the Working Group and external experts throughout the project, using direct unattributed quotes. Sections One and Two provide a historical overview of the evolution of two core value drivers: innovation and reimbursement. Section Three explores the links between them, the resultant business model and how it might evolve. Finally, Section Four summarises the conclusions of the dialogue and makes recommendations about the future.

This report is intended to contribute to a reframing of the social contract to produce mutually beneficial outcomes, in which the industry is rewarded commensurately for meeting unmet patient need, where investors are provided with appropriate and predictable returns, and in which the constraints on society's ability to pay are factored into pricing.

Section 1

The R&D Challenge

R&D Productivity Decline

A recent Bernstein report[2] makes clear the extent of the R&D productivity crisis facing the pharmaceutical sector. It highlights that over the past 60 years, the number of new molecules brought to market by the biotech and pharmaceutical industry, per billion dollars of R&D expenditure, has fallen by a factor of 100 in inflation adjusted terms. It goes on to argue that returns on investment on small molecules is probably already negative at an industry level, and it warns that if these productivity trends persist, then biologics[3] which have continued to deliver value, will follow.

> "In the last 20 years of biomedical research worldwide, there's been a huge investment in biomedicine in the universities, in the research institutes and so on, which has led to an unparalleled increase in biological knowledge. And yet, that's been accompanied by a deficit in the ability to translate that into new medicines.[4]"

Over the last ten years R&D expenditure has increased dramatically whilst new medicine approvals have decreased (see Fig. 1) and the mix of product approvals has shifted towards specialities, many with lower commercial potential. This has led to the "productivity drought" in the sector.

Determining the best to way to address this productivity drought has, arguably, been the key challenge facing senior pharmaceutical managers for the past two decades.

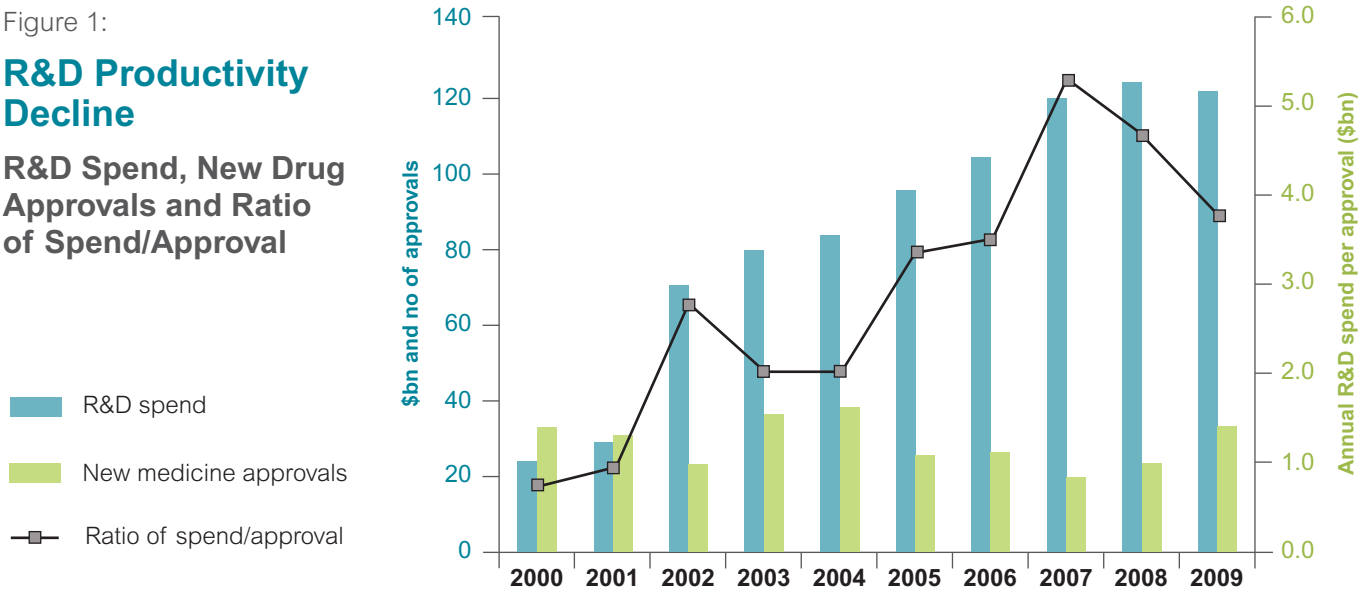
Drug discovery and development is a complex, risky business. Scientific expertise is required first to identify a target (a receptor, enzyme or signalling molecule) in the human body and then to discover a molecule or compound with a mechanism of action capable of entering the human body, finding that target, being strong enough to defend itself against degradation within that organism and by the body in general, and, without being too toxic, prove capable of modifying a system that is critical for the patient's survival.

Big Pharma, academia and biotech are all involved in the innovation process, with discovery of promising targets for drug

Figure 1:

R&D Productivity Decline

R&D Spend, New Drug Approvals and Ratio of Spend/Approval



2. *The Long View: Pharma R&D Productivity – When the Cures Fail It Makes Sense to Check the Diagnosis*, Bernstein Research, September 30th 2010

3. Traditionally large molecules that are protein, peptide or nucleotide based, rather than small molecules made from chemical synthesis.

4. This and subsequent quotes are unattributed direct quotes stemming from the PharmaFutures interviews and dialogue.

development historically falling to the pharmaceutical industry and academia, with the latter playing an increasingly important role. Due to the high costs involved, the process of taking resultant promising leads through the complex development process of preclinical and clinical trials to produce a therapeutic medicine is largely undertaken by the biopharmaceutical industry. The social contract between this industry and society is a mutual agreement that the industry's risk-taking will be rewarded with various intellectual property and market exclusivity arrangements and a degree of liability insurance in exchange for successfully bringing to market affordable, innovative treatments for unmet medical need.

Intense attempts by the industry to address productivity have led to a significant increase in the number of new drugs emerging from Preclinical and Phase 1[5] trials into Phase 2, and many company pipelines look promising. Despite this, the attrition rate in Phase 2 is higher now than it was ten years ago, meaning that a much smaller proportion of drugs in Phase 2 enter Phase 3 and the number making it to market is barely changed (see Fig. 2). Even biotech, significantly the most productive part of the pharmaceutical sector, has shown signs of declining productivity in recent years.

The R&D challenge is a multi-faceted problem that should not be reduced to a single explanatory variable. However, there was a remarkable level of agreement between the *PharmaFutures* Working Group and the experts we interviewed, who between them have decades of scientific and commercial experience. The following five contributory factors have been particularly significant.

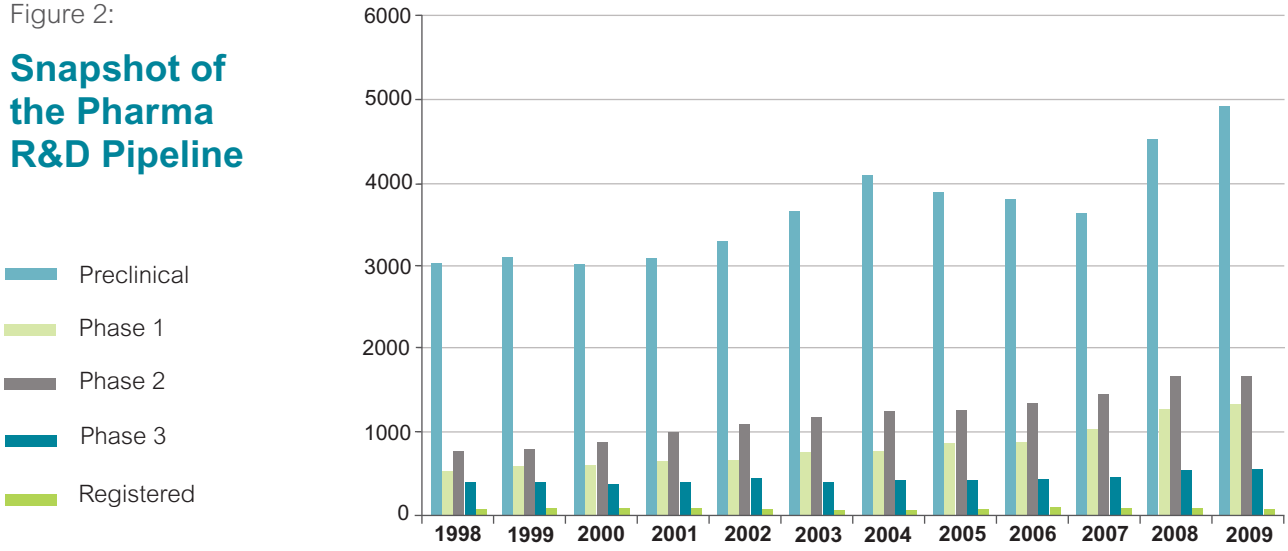
Industrialisation: the gap between discovery and invention

The first contributory cause to productivity decline was the industrialisation of the R&D process. Traditional drug discovery in the 1950s and 1960s relied heavily on an understanding of animal physiology, strong pharmacology skills and labour-intensive chemistry. In the 1970s and 1980s the industry embraced new industrial techniques for drug discovery. High throughput screening (HTS) created the ability to test batches of compounds for binding or biological activity against target molecules at industrial scale. This process was accompanied by advances in medicinal chemistry which made available huge new chemical libraries, allowing companies to search for drug hits and develop candidate drugs rapidly. The advent of genomics[6] and related technologies in the 1990s further consolidated this trend, as target discovery shifted from exploring mechanisms of action that worked

> "Molecular biologists are now two a penny. I'm not interested in cells. I'm interested in coughs. Show me a cell that coughs!"

Figure 2:

Snapshot of the Pharma R&D Pipeline



Source: Parexel's Bio/Pharmaceutical Statistical Sourcebook 2009/10 p. 64

5. Phase 1 trials are studies to gain evidence of effectiveness and pharmacologic actions of drugs in humans; Phase 2 trials are controlled clinical studies to evaluate the effectiveness of a drug for a particular indication in patients with the disease under study, to determine the common short-term side effects or risks; Phase 3 are expanded trials after preliminary evidence of effectiveness has been obtained and intended to evaluate the overall benefit–risk relationship of the drug and provide an adequate basis for physician prescribing. Phase 4 refers to post-marketing studies done to provide further information about the drug's risks, benefits and optimal use.

6. The application of knowledge of the DNA sequence of an organism's genes, especially disease genes, to find drug targets.

> "At a certain point after the genomic revolution, when there were lots of new techniques for high throughput screening, people like Richard Sykes and George Post took the view that 180 molecules + X years = a blockbuster. The issue became efficiency of process and was solved by putting more molecules through the system. So, we replaced people with robots and machines and HTS but what we really got rid of was biology. Chemists think that lots of data tells you something that it doesn't. The problem is that there are not sufficient people in control of the purse strings who understand that it's to do with biology."

on the surface of the cell to those that work inside it, leading to the employment of more biochemists.

In the process, the skills bias within the industry moved away from traditional pharmacology and physiology. Many chemists were replaced by machines and human resource budgets were instead spent on molecular biologists and bioinformaticians who were needed to help interpret the next wave of technology – genomics and new target discovery.

Although the number of potential drug targets increased enormously as a result of genomics, many of these were not fully characterized or "validated" as legitimately "druggable" targets. This meant that lead drug candidates that had not been validated could go through to proof of concept[7] and then fail in late stage development. In this process a great deal of time (up to ten years) and money was wasted.

This increasingly reductionist approach led to a loss of focus on integrated biology and experimental medicine, and over-reliance on the belief that identifying the molecular target would be sufficient to produce a drug.

> "For some of the new diseases, depression, for example, the level of target validation you have is virtually zero. [This means] that the established pathways won't help, and you have to go for a new pathway. The animal models are completely non-predictive. The clinical read-out simply says 'yes, you've got a drug-like molecule and it gets into the brain.' So, ultimately, once you pull the trigger, you're going right the way to Phase III, because you've got nothing in the middle that tells you you're completely wrong."

Duplication

Another result of the widespread application of industrial techniques was the evolution of a "shots on goal" mentality in which the number of things being worked on became a surrogate for their quality and validity. Once a target had generated useful data, the industry came to hunt as a pack, focusing on a relatively small number of validated targets. The result was the race to the finish line to launch best in class improvements on the drugs that had been successfully launched as first in class pioneers. Some were indeed best in class, but many proved to offer only modest clinical differences.

As examples of this dynamic, during the 1970s through to the 1990s, the first H2 antagonist cimetidine, primarily prescribed for the treatment of stomach ulcers, was followed into the market by ranitidine and famotidine. Close on the heels of the cardiovascular disease calcium channel blocker, nifedipine, came nitrendipine. Other examples include the developments within serotonin reuptake inhibitors (SSRI), and serotonin–norepinephrine reuptake inhibitors (SNRIs) for the treatment of depression, the ACE inhibitors for hypertension, the proton pump inhibitors primarily used in the treatment of stomach acid and the antiretrovirals for the treatment of HIV/AIDS. The duplication of efforts against the same validated targets was successful in producing the so-called "low-hanging fruit" of pharmaceutical development, but it also had the unintended consequence of leading companies to avoid the risks involved in the exploration of other targets and considerable inefficiencies inherent in duplication of effort (see Fig. 3).

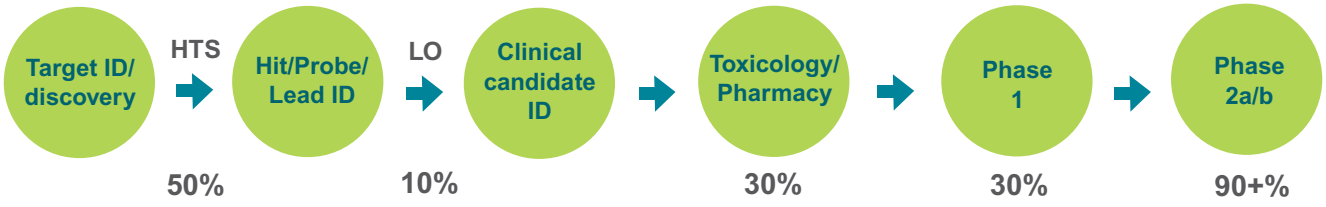
7. Evidence that the medicine treats the disease.

The consequences of companies "working under the lamp post" on a limited number of targets have become more serious in the last two decades. It has led to a diminishing focus on more intractable disease states such as neuropathologies, which lack good biomarkers. Attrition rates for novel targets are highest during the clinical proof of concept phase (i.e. when the weight of evidence is sufficient to test the ingredients for success) leading some scientists to propose much greater cross-industry collaboration in early stage research through to Phase 2 in order to reduce the cost of undertaking the same research in multiple companies.

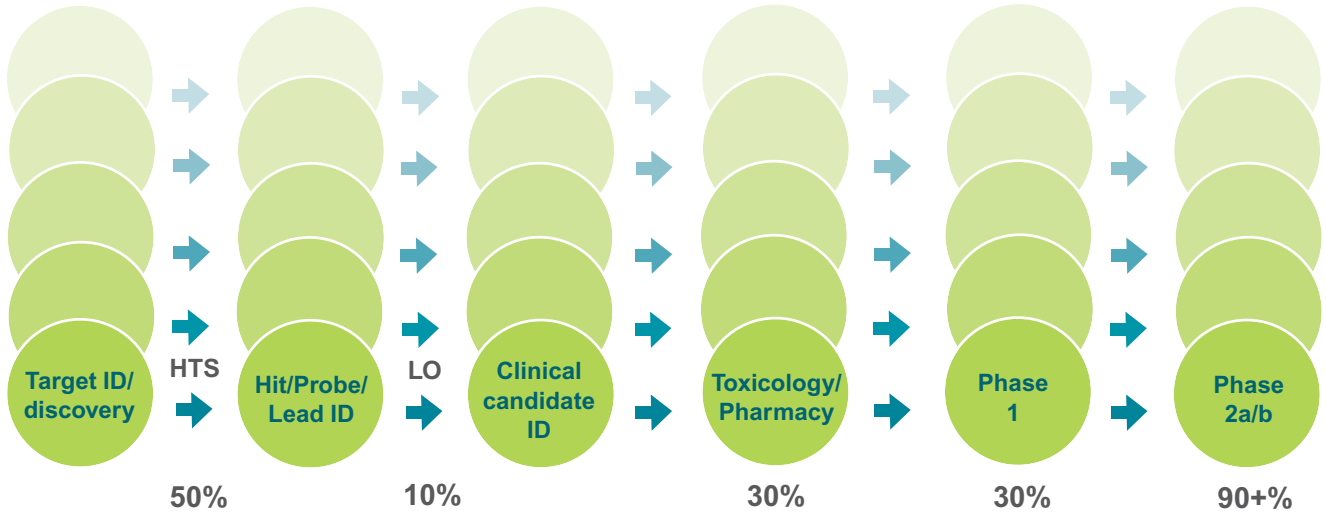
Figure 3:

Attrition Rates and Duplication

Attrition rates for novel targets is at clinical proof of concept



And the failure is duplicated, many times



Source: Chas Bountra, Structural Genomics Consortium, 2011

The "Catch 22" of Risk Aversion

The commercial success of the focus on validated targets encouraged many stakeholders, including investors, to believe that such success was the norm. Though industry did try to identify novel targets, particularly though genomics, they proved to be even higher risk, partly because they were not fully validated. Thus, when faced with a choice of predictable returns from successful validated targets or exploration of new targets, industry prioritised the former option, and was rewarded by investors for doing so. The result was a consolidation of effort on those self-same targets and a reduction in the breadth of the portfolio. In the 1980s and 1990s, the industry focused on cardiovascular diseases (CVD – particularly hypertension and hypercholesterolemia), diabetes, acid-related diseases and the central nervous system (CNS) (depression, schizophrenia and anxiety). Despite urgent unmet medical need in other areas, for example neurodegenerative conditions and antimicrobials, in the past decade most pharmaceutical research efforts have reduced to a focus on three major disease areas: cancer, metabolic syndrome and autoimmune diseases.

The comparative commercial failure of the genomic era disillusioned many investors. Many venture capital

> There is an inverse relationship between spending and output for Big Pharma. A consequence of scale is that more prioritisation (a euphemism for pipeline cuts) must take place. This happens after every merger and now happens routinely given the cost of Phase 3 trials. Furthermore, big companies find so many ways to distract scientists with non-scientific things to do and this leads to lower productivity. Big Pharma can only take so many products into Phase 3 and so ends up cutting significantly at Phase 2.

firms (VCs) were unsuccessful in that era of investment and both VCs and their investors reduced their commitments to drug development. There was a flurry of interest in platform technologies for drug discovery, but this gave way to more downstream and less risky investments as the upstream failure rates increased. An estimated half of the healthcare VCs failed between 2007 and 2009. The slowing of investment in very early stage biopharma is deeply relevant to Big Pharma as the lack of early stage innovation shrinks the overall pool from which the industry can draw.

> One very simple consequence of scale is that more prioritisation will occur and therefore fewer medicines will make it to patients. Scale leads to demands for focus and prioritisation. Portfolio management is a euphemism for killing products early. Attrition in development is the way that the results of innovation are compromised.

> Companies are now overly bureaucratic. The sheer size of them means that drugs have to have a massive market to justify even starting. The decision point used to be whether you had something useful in three to five years' time. Now you have endless meetings justifying your work.

> The practice of invention has not increased or decreased. You can't make people more or less inventive. What you can do is distract them.

Consolidation: M&A

The fourth contributory factor to reduced R&D productivity were the wave of mergers and acquisitions from the 1980s onwards, driven in part by the need for a competitive US market presence and R&D scale. Ironically, the act of consolidation, rather than enhancing productivity, has proved to almost guarantee a reduction in the size of the pipeline and to create more distractions from value creation.

Progressively Higher and Tougher Regulatory Requirements

The final cause of productivity decline was found to be the growing requirements of regulators who have simultaneously raised the standards of safety and efficacy, particularly for primary care, while increasing the data required to demonstrate approvability. This has meant companies have to gather much more clinical data from many more patients. The increased costs of late stage clinical trials, particularly for chronic use medicines, together with higher hurdles for success, have required companies to make tougher choices about which projects have the best chance of success for a given R&D spend.

This is particularly true of primary care products where the expectation of widespread prescription by family doctors requires stringent safety testing. The industry is consequently focusing on speciality/secondary care, where the costs of clinical trial are much lower, since the risk–reward balance is very different. Since specialities are, by definition, for smaller patient populations this tends to mean lower peak sales. To counter this, there has been a tendency to push price per patient to its limit in some markets (particularly the United States). This emphasis on high price,

most obvious in orphan diseases, but manifest also in oncology and rheumatoid arthritis, may have increased mistrust as the value proposition for these medicines was not always clear. Furthermore, it is widely acknowledged that there has been additional pruning of Phase 2 candidates that don't meet the more differentiated Target Product Profile than that required in the past. In addition, there are growing requirements for monitoring once the product is in use. For example, companies producing therapies for Type 2 diabetes now have to monitor these therapies for cardiovascular risk for ten years after the medicine is authorised for the market.

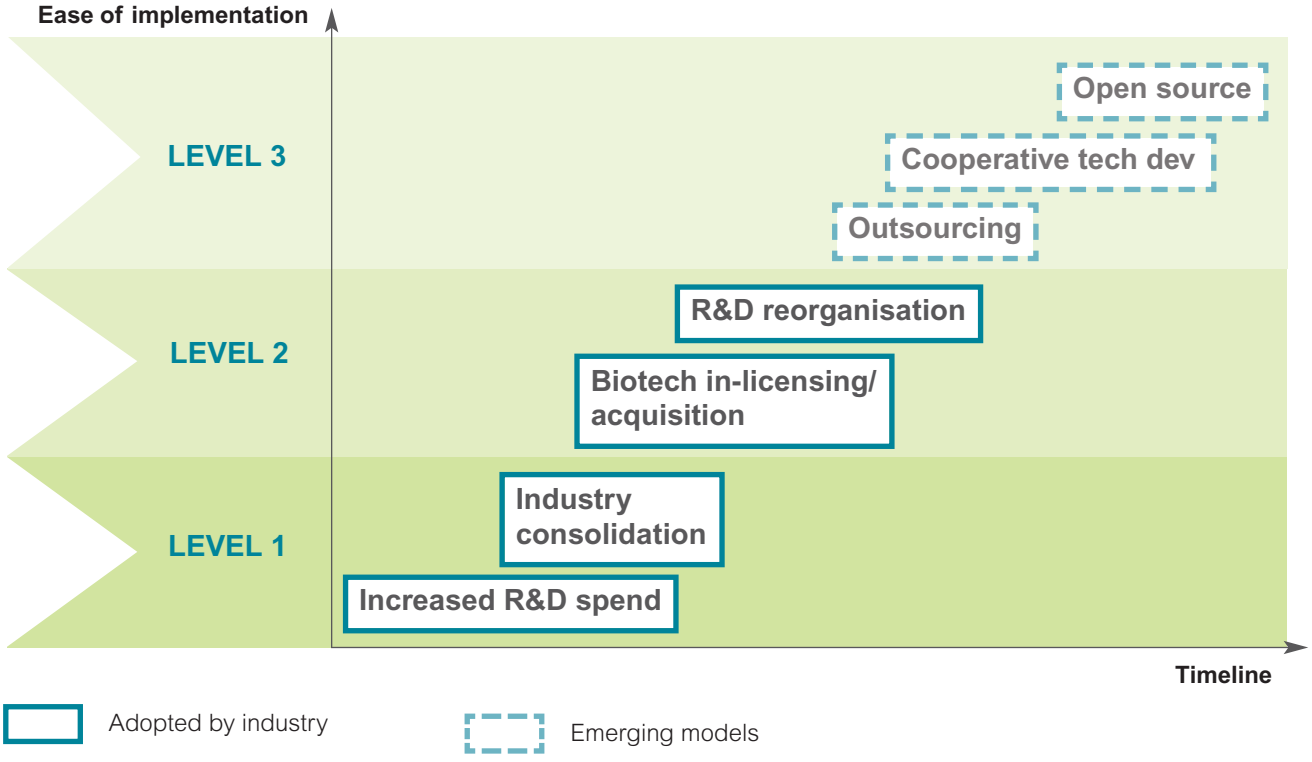
Strategic Responses to the Problem

Of course, the industry has not been passive in the face of these challenges and there have been many strategic responses to R&D capital allocation. Many companies have restructured in-house R&D, trying to create nimbler, more creative discovery units. There is a growing tendency to supplement in-house R&D capacity and indeed almost all are shifting the balance significantly to a greater focus on in-licensing and externalisation. Many companies are experimenting with open innovation, which has been the source of considerable added value in other industries, including agriculture, food and beverage, and ICT, and holds promise as a game-changer in terms of approaches to IP management and networked collaboration. Additionally, companies are beginning to explore partnerships with government, e.g. the European Innovative Medicines Initiative (IMI), to tackle some of the less commercial therapy areas.

Figure 4 shows strategic responses to the R&D productivity crisis. Increased R&D spend, industry consolidation, biotech in-licensing and R&D reorganisation have been the primary responses from industry in the last decade. Emerging responses are found in outsourcing, cooperative tech development, and open-source/open-innovation approaches.

Figure 4:

Different models of innovation



Source: Hu, Michael, et al., *The Innovation Gap in Pharmaceutical Drug Discovery and New Models for R&D Success* (Kellogg School of Management, 2007), p.6. Available [online] at http://www.kellogg.northwestern.edu/biotech/faculty/articles/newrdmodel.pdf.

The Ongoing Challenge: R&D Capital Allocation

The ecosystem of innovation includes Big Pharma, biotech and academia. Identifying the respective roles of these multiple creative players in the most efficient and productive way is leading to calls for significant rationalisation. Perhaps the most critical decision facing the industry today is therefore the extent to which excess capacity in the R&D function can be reduced without a resultant loss of core industry competency. Different companies have taken radically different approaches to this. At one extreme has been the ardent defence of a broad portfolio and an accompanying warning to investors to lower their profit expectations, e.g. in February 2011 Merck withdrew its profit forecast rather than reduce investment in promising experimental medicines in its pipeline. At the other extreme has been a radical reduction in R&D expenditure, e.g. within days of Merck's decision, Pfizer announced its decision to cut 2012 R&D expenditure by a quarter (US$2bn of US$8bn) of total spend.

Investor confidence that the industry can provide a sustainable and increasing return remains in doubt, however, leading them to signal that if the industry cannot deliver, they will require their investment to be returned, to be invested elsewhere. In response, several companies have indicated their willingness to step up share buy-backs, emphasise dividend payouts and pull back from non-core areas (though the definition of non-core may be changing). However, this route has its dangers. As we will see in Section 4, whether the combined forces of industry, investors and society are capable of coming to agreement on the skill mix will determine whether we appropriately slim down or, inadvertently, slay the goose that lays the golden egg.

Section 2

The Reimbursement Challenge

The Evolution of the HTAs

Between the 1950s and the 1990s, the point at which the R&D landscape became progressively more challenging, the payer landscape too was relatively stable. The industry proved adept at driving volume without too much price control in its major market of the USA, while coping with frequent but small and usually ad hoc price cuts in Europe and Japan. Collectively these markets represented 20% of the world's population and 95% of the global pharmaceutical market.

Product choice was made by large numbers of geographically dispersed doctors whose prescribing practices effectively endorsed the emergence onto the market of multiple products to treat the same conditions. These physicians prescribed products that progressively demonstrated incremental value over competing products already on the market and in doing so they also effectively supported the definition of these products as breakthrough innovation. For the industry this meant that there were practically as many opportunities to win a sale as there were patients.

As a result, while profits remained high, it was logical for the industry to spend more and more on R&D for multiple candidates within a single drug class, combined with investments in the sales and marketing "arms races" to influence the incredibly valuable doctor decision-makers. The most significant thing about this market during this period was that decision-making was highly dispersed and totally uncoordinated.

Since then the market has changed from being composed of a large number of single doctors, firstly to groups of doctor decision-makers, such as those contracted by Health Management Organisations (HMOs), working for Physician Practice

The Evolution of the Reimbursement Landscape

Europe: the Evolution of Compulsory and Tax-funded Health Insurance

Timeline	Critical Events
Late 19th century – WWII	Voluntary social foundations for sickness funds for certain groups of workers supplemented by state subsidies and gradually extended to include other sectors of the population
1939–1949	Northern European countries adopt a model of compulsory health insurance that post WWII becomes universal, covering regular workers below a fixed income threshold, their dependents, the unemployed and pensioners
1948–1973	First wave of countries move from Social Health Insurance to fully tax-based system (including Denmark, Finland, Sweden and UK where the first payer pushback was expressed in the form of the shilling co-pay)
1978–1986	Second wave (Italy, Portugal, Greece, Spain)
1940s–1990s	Austria, Belgium, Germany, Netherlands retain strong commitment to self-regulated social health insurance model
1990s–2000s	Liberalising reforms in many member states to create more market-driven approaches within social health insurance systems, but principle of social solidarity retained
1999	Creation of UK NICE (National Institute of Clinical Excellence), providing national guidelines for treatment of diseases, combining desired clinical outcomes with cost-effectiveness
2001	Creation of MEDEV (Medicines Evaluation Committee) – an informal subscription-paying group of (originally German-speaking) insurance companies that meets every two months to discuss relative effectiveness, added therapeutic value and pricing strategies (and cost-effectiveness assessments in particular)
2004	Formation of German Institute for Quality and Efficiency in Health Care (IQWIG)
2006	EUnetHTA created of government-appointed HTAs and academics

Management Groups, and then to the Health Technology Assessors (HTA) and payers of today. These groups not only seek an evidence base for their reimbursement decisions, but also actively encourage generic substitution with a view to lowering costs.

Europe

Following early efforts to control prices in Australia in the 1950s, it was in the socialised medicines markets of Europe that HTA bodies first emerged to undertake pharmacoeconomic research linked to reimbursement decisions. This trend is now firmly established in these markets. In some instances payment decisions have been centralised in a single body, e.g. the UK's NICE (National Institutes of Clinical Excellence) which produces evaluations that link clinical outcomes with cost-effectiveness for the country's National Health Service (NHS). In other countries, such as France and Germany, reimbursement and evaluation functions are separate, but there is a high degree of coordination between these bodies. Whether funded by social health insurance or general taxation, the consolidation of technology evaluation and reimbursement is under way in all European Member States.

The consequences for the industry have been significant. Across Europe there is a degree of coordination through networks such as the Medicine Evaluation Committee (MEDEV)[8], an informal network for information exchange between European health insurers and companies, and the European Network of HTAs (EUnetHTA), a formal Member State led network of HTAs and academics. There are also moves to standardise scientific evaluation. However, any devolution of decision-making to a single Europe-wide body is unlikely to happen in the foreseeable future.

United States: The Evolution of Health Insurance

Timeline	Critical Events
1930s & 1940s	Several large life insurance companies enter health insurance field
1932	Blue Cross and Blue Shield offer group health plans based on discounted contracts with doctors and hospitals
1940s & 1950s	Employee Benefit Plans proliferate. Wage controls introduced during WWII, expanded after 1954 when employer paid insurance premiums become employee income tax-free
1950s & 1960s	Government programmes expand and disability benefits included in social security coverage for the first time
1965	Medicare and Medicaid programmes created (but 75% of all healthcare costs still paid privately)
1980s & 1990s	In response to rising healthcare costs, majority of employer sponsored group insurance plans switch from "fee for service" to cheaper "managed care"
1990s	Pharmacy Benefit Managers (PBMs) created and institute 15% claw back and most favoured nation pricing
1990s	Growth in HMOs subscribers doubles
2001	Florida limits Medicaid formulary, followed by State after State
2004	Medicare Part D initiated, allowing for restricted coverage in all but six classes (antipsychotics, anticonvulsants, anticancer, immunosuppressants, antiretrovirals and antidepressants)
2010	Patient Protection and Affordable Care Act (PPACA) includes Accountable Care Organisations provision for Medicare to provide high-quality care while keeping costs down

8. MEDEV publishes extensive criteria (www.esip.org) of what is required of a medicine including: effectiveness – i.e. the medicines effectiveness in clinical practice, not pre-launch; insured, i.e. should it be insured; feasibility, i.e. it may have the appropriate evidence base, but is it too expensive?; and cost effectiveness, i.e. what is its added value in relation to additional cost, compared to normal existing treatments.

United States

> The standard line is that people don't want to be restricted by the government in managing their care.

The US market, still the biggest pharmaceutical market by some margin, is moving in a similar direction. As a result of the Patient Protection and Affordable Care Act (PPACA), within five years the US marketplace is likely to be divided, with half of the population and a little more than half of the healthcare costs being paid by the government, either directly or through private entities. The move towards evidence-based decision-making will not be immediately apparent, due to the highly politicised nature of the US public system and the legal impediments to linking reimbursement to price in the public system. However, it is clear that all payers in the US are becoming more demanding on price and efficacy. New product uptake is slowing, as the US market shows increasing preference for generics as first line treatment. Generics now account for 75%[9] of prescriptions (in the US market) and the figure is rising, leaving the more expensive and newer treatments for smaller populations with greater capacity to pay.

The unfunded liability for Medicaid and Medicare currently stands at more than US$30 trillion making disruption to the system highly probable. Given the political sensitivities around public provision in the US, the appearance of a market-based system will almost certainly be retained. However, it is likely that evidence-based reimbursement will be sought for direct government programmes as well as by the newly formed Accountable Care Organisations (ACOs), groups of healthcare providers who pool together to offer care pathways including prevention, primary and secondary care, and other bodies to whom the government is outsourcing its cost decisions.

The private system, by contrast, which covers half the population via employer or individually provided private health insurance, is already embracing an evidence-based approach to reimbursement. Pharmacy Benefit Managers (PBMs) are increasingly making assessments based on best practice and efficacy, combined with information systems across pharmacies that consolidate compliance data for use in pharmacoeconomic analysis and to rationalise reimbursement decisions.

Views differ on whether changes to the US system (created by pressures on price and demands for more data) will be gradual or abrupt and the degree to which they could modify the market-based nature of the system. The lack of transparency about the degree to which decisions in the public system are already being taken on the basis of cost and efficiency will make conversation about moving from price and access to value more difficult. It is for this reason likely that government programmes will outsource decisions about cost-effectiveness and best clinical practice to private sub-contractors less vulnerable to political decision-making. Despite this, these trends within both public and private markets indicate that we are likely to see the whole US market evolve towards evidence-based pricing (a US version of "HTA" controlled) by 2015, the year in which the US healthcare reform will be implemented.

> We have a baseline advantage in this country and I see us evolving in a more aggressive way because we have technology in place that allows for the wired system.

> We have not in the US figured out a way to address cost at all. You don't need to look any further than healthcare reform. The initial objectives of healthcare reform were to reduce cost, improve quality, and improve access. But it has really been more about insurance reform. It's dropped the ball on reducing cost and improving quality.

> Any real cost controls result in accusations of rationing, so we need to come up with a new word for cost; something closer to allocation. But to be honest, it's more likely that cost-saving ideas will come from the private sector because they have fewer constraints.

9. Source: www.phrma.org/three-quarters-us-prescriptions-are-filled-generics

The Emerging Markets

While the mature US and to a lesser extent European markets still represent the industry's largest markets, the emerging economies, particularly in Asia and Latin America, are rapidly growing in size. These markets were reviewed in depth in *PharmaFutures 3* (www.pharmafutures.org) which concluded that they are still largely characterised by out of pocket expenditure and therefore today resemble the doctor-led model of prescriber choice. However, these markets remain heavily genericised for the majority of the population.

In the wealthier private markets, expanding private insurance coverage and increased government focus on cost reductions are leading to an early interest in pharmaco-economics and an evidence-based approach to reimbursement. In many low-income countries which combine high levels of disease and levels of aid dependency, there is also an increasing focus on reining in cost. NICE International reports a growing interest from countries as diverse as Thailand, Singapore, Colombia, Brazil and Tanzania, pointing to a growing trend across the emerging and developing economies.

> "The pressures on healthcare systems around the world are not that different in their fundamentals. The scale and particular expressions of these pressures are different, but at the core, all systems are facing a mounting disease burden, increasing consumer demand, and within a budgetary future that will be incapable of meeting that need. Something will have to give."

The Implications of the Rise of Evidence-based Reimbursement

> "On scientific [issues] an informal level of collaboration is possible. But legally and politically, it is complicated. HTAs will share assessments on relative effectiveness and added therapeutic value and continue to exchange information on strategy for negotiation, pricing on particular products [and] cost effectiveness assessments. But it will remain ad hoc and not systematic as it gets too complex."

The most significant consequence of these developments is that payers and governments have, so far, looked to health technology assessment agencies, either directly or indirectly, to help them contain costs. In particular, they are being used as a bargaining tool to evaluate the true price of incremental innovation. On the one hand the industry argues that it makes a vital contribution to the development of disease understanding and treatment. On the other, payers are demonstrating a growing reluctance to pay premium prices for what they describe as "me-toos", arguing instead that incremental pricing is only appropriate for incremental innovation, irrespective of research costs. And this push-back is now extending to entirely novel medicines as well. In some countries the incremental price is benchmarked against patent-expired generic therapies.

Another consequence of the rise in HTAs is the growing appetite for transparency about the clinical trial process, the findings it yields and increasingly in what causes compounds to fail. Technology assessors have evolved an increasingly sophisticated understanding of how the clinical trial process works, leading to a growing HTA interest in clinical data from the upstream research process and downstream findings of efficacy and effectiveness once the medicine is on the market. A standardisation of data requirements would undoubtedly decrease the onus on companies to provide multiple data sets for multiple agencies. The provision of scientific evidence in particular could be relatively straightforward. If managed well, this provides an opportunity for industry, HTAs, payers and regulators to streamline data requirements, to reduce costs and improve clinical outcomes. Managed poorly, it could result in a cacophonous call for data that swamps an already squeezed industry.

The third implication arises from the political consequences of harmonisation across the HTAs. Both European Member States and different US healthcare providers have developed their own standards of care and delivery, and merging them is likely to prove highly problematic if not downright impossible. There is a danger that harmonisation of HTAs could lead to further information requirements, simply adding another European or Federal regulatory hurdle on top of those required by individual Member States or States in the US. It is also possible that harmonisation could result in the standardisation of a model which is averse to the adoption of new technologies due to price considerations.

> "Harmonisation does not necessarily lead to higher profit margins, though it can certainly help to create more predictability, which is good for companies and for healthcare systems. Harmonisation can help create value by advising companies on what is needed in early stage development and what society will value. It could help us move away from current focus on "me-toos", which increasingly are not being reimbursed, and away from current litigation trends."

Responses to Date

The industry has responded to this changing landscape both proactively and defensively. On the positive side, a growing number of companies are experimenting with trust-building exercises that entail using different models of information exchange to make market access and reimbursement more predictable and more likely. These range from bilateral company initiatives to a range of collaborations between companies and payers, HTAs and governments. Across Europe a number of new pricing agreements have been established that are based on a common definition of changing value provided by a treatment. At the same time, however, there are a growing number of legal challenges to HTA and payer decisions, which are likely to decrease trust and could lead to further onerous data requirements.

Section 3

Cause and Effect in Innovation and Reimbursement

The Evolution of the Market

R&D productivity is, of course, intimately linked with willingness and ability of the payer to pay. As outlined in Section Two, the 1980s and 1990s marked a "Golden Age of Pharmaceuticals" during which the market seemed to have a limitless appetite for new drugs, irrespective of cost. Though the race was for first in class and best in class, second, third, fourth and fifth could find a market too. The doctor decision-makers were persuaded of the value of the new generations of medicines, compared with the old, and accepted product to product differences. As a consequence their prescribing practices expanded utilisation and extended the range of products used. While doctors seemed unconcerned about the price implications, the payers were too dispersed to do anything other than passively endorse higher prices for the new medicines and the annual price increases (in the US) thereafter. Where the US led, Europe followed, and there too the industry proved able to increase sales volumes without too much pushback on pricing.

During this era of first and best in class, regulatory requirements were relatively low and pipeline pruning took place only if the drug was unsafe or ineffective. The market signalled its willingness to pay for key therapeutic areas and so industry responded to these large markets with clearly identified drug targets by focusing its attention on them in a perfectly logical deployment of capital.

Perhaps inevitably, the expansion could not last. The cost burdens of rising prices and expanding volumes (associated with life-long chronic disease therapies) led first to modest and then to more intense pushback. Trust began to erode as the price of incremental innovation in the new "me-too" therapies came to be perceived as over-reach for the limited added value they offered. At the same time, there was growing disillusion with sales and marketing behaviours, which entailed the employment of multiple and overlapping sales forces, sales tactics designed to break the appointment system and direct to consumer advertising that risked trivialising the ethical nature of the industry. The financial market's refusal to accept lower profits even

Figure 5:

Payer responses correlates with market expansion of me-too classes (selected classes)

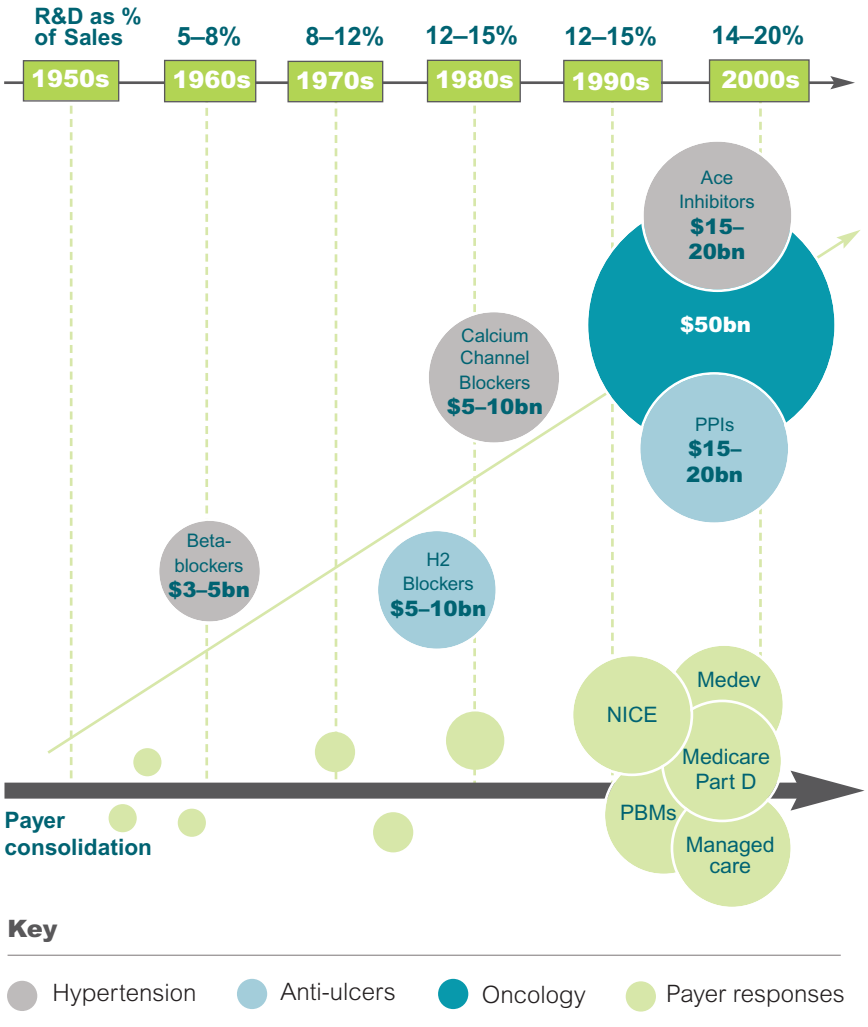


Figure 6:

"Golden Age" model: 1980s & 1990s

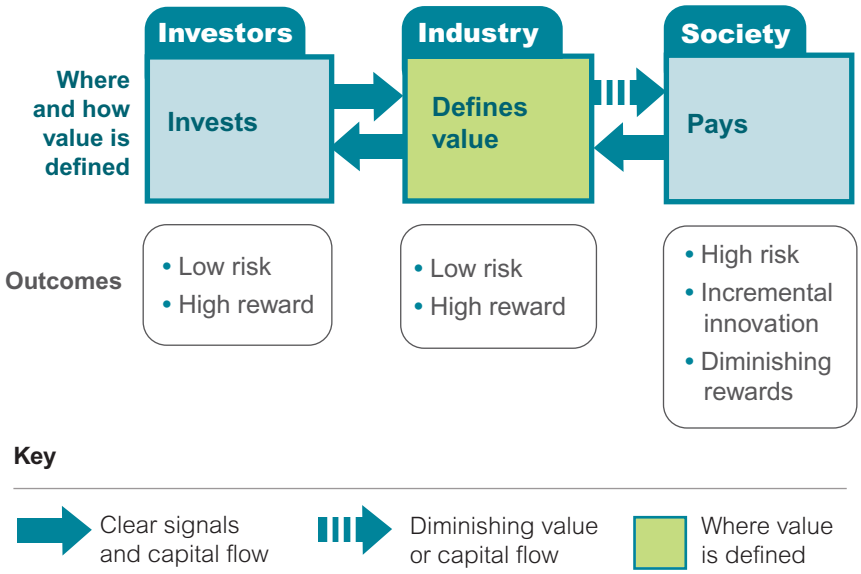
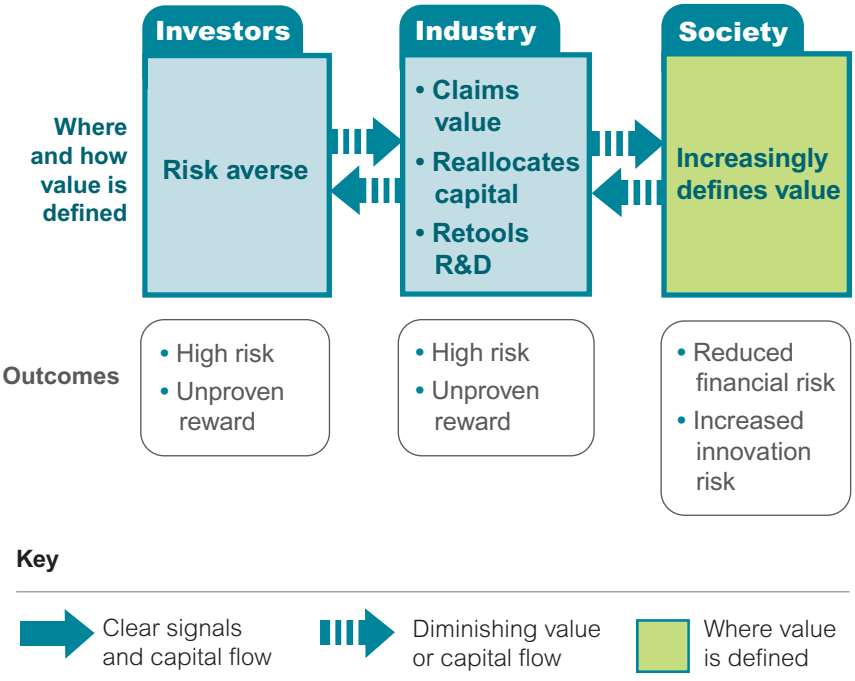


Figure 7:

"Show Me the Value" Model: 2000s to Today



though R&D productivity was lower combined with ever-more stringent and fragmented regulatory requirements to make sales forces more aggressive and to drive prices further upwards. The upshot was that the pushback was harder and faster than it might otherwise have been.

Although the growth in the market was led by expansion in the US, it was in Europe that payer pushback was first felt. Before the US Pharmacy Benefit Managers started making their demands, and before the advent of the HTAs, Europe introduced a range of attempts to hold down escalating pharmaceutical budgets, including the introduction of blacklists, negative lists (pharmaceuticals which could not be reimbursed by the statutory health insurance bodies), price cuts and jumbo groups (reference price groups including patented and non-patented medicines).

At the same time, the new discipline of pharmacoeconomics began gaining ground and the language of doubt began creeping into the vocabulary in payer efforts to make qualitative assessment, to define value for money and to establish evidence-based protocols. More recently, there has been a big increase in the generation of head-to-head comparative data on different therapies.

Simultaneously, more and more payers began to push for generic substitution[10]. The rise of tiered formularies in the US HMO/PBM was just such an attempt to make patients pay a higher co-pay for a branded choice, when a generic may have been clinically appropriate. Over time, decision-making gradually passed from the physician to the insurer and/or payer – a shift that took place in both Europe and the US, despite

10. Generic substitution is the practice whereby the pharmacy is assumed to provide the generic version of a given treatment, unless specifically directed not to by the prescribing pharmacist.

the highly politicised nature of the debate about choice in the US market. In the process, the demand for evidence has become institutionalised to varying degrees, and in different forms, across the range of payers globally, and is increasingly a condition of reimbursement. The correlation of payer pushback to the market expansion of incremental innovation is captured in Fig. 5.

The result has been a fundamental change to the business model in which the definition of innovation was controlled by the industry during the "Golden Age" Model of the 1980s and 1990s to one in which innovation is defined by the payer in the "Show Me the Value" Model of today (see Figs. 6 and 7).

The Implications of the "Show Me the Value" Model

This change towards the consolidated, institutionalised payer, who requires evidence of substantial incremental value in safety and efficacy over existing therapies as a condition of reimbursement, has led to a serious weakening of what had become the core market competency of the industry: namely companies' ability to influence the product choice of the prescriber. This adjustment is not necessarily negative; the balance between a research focus that pursues predictable, but duplicative, commercial outcomes and one which addresses truly unmet medical needs to be shifted back in favour of the latter.

The danger, however, is that the new decision-makers in the market place are not clear enough about what they will be prepared to pay for a predicted possible advantage to justify the decision to embark on the enormous investment costs involved in pursuing the associated medicine through multi-year development. Already the new market is signalling its unwillingness to reimburse incremental innovation for "satisfied" classes and there is growing unease about high prices, even for breakthrough medicines, where the value proposition has not been clearly elaborated. The major players – innovators, payers and health assessors – are only now beginning early dialogues about the contribution incremental innovation makes to the body of medicinal knowledge.

The absence of an agreement about what constitutes value could combine with what are perceived as weak and ambiguous market signals to inadvertently weaken the industry's *raison d'être*: its R&D capabilities. Already R&D expenditure has been reduced. Some reduction of R&D capacity that was created in an era of plenty, and which perhaps lacks the discipline more austere circumstances require, is a welcome rationalisation of excess capacity. The danger, however, is that it results in an unhealthy stand-off with neither industry nor payers prepared to consider the long-term consequences of failing to achieve the appropriate balance between industry incentive and societal reward.

This gradual, selective withdrawal from R&D poses a grave concern as to who will research unmet medical need at precisely the time of a growing appetite for treatment, resulting from the rapid worldwide spread of chronic diseases; the urgent need for new antimicrobials; and for therapies for neuro-degenerative diseases, such as Parkinson's and Alzheimer's Disease, of an increasingly elderly population.

Section 4:

Conclusions:

From Challenge to Opportunity

The Challenges of the New Era

The result has been to find ourselves at crossroads in which the relationships between the industry and its stakeholders have fundamentally changed. In the previous model corporate and venture investors confidently allocated capital to R&D, on the understanding that the industry's judgement about what would succeed in the market was sound. The appetite of the payers for the products coming online appeared to ratify these assumptions. In the new model, in which payers are demanding evidence of value and linking it to price, sources of capital have become increasingly risk averse, no longer confident of industry's ability to predict what payers will be prepared to reimburse. In the long run, however, this model in which payer cost constraints dominate is unlikely to ensure that the needs of all patients are met, any more than the previous model in which industry and its investors benefitted from a focus on incremental innovation.

Most Significant Opportunity

Despite first appearances this impasse arguably presents the most significant opportunity facing the industry today, as it dawns on the many players across the drug discovery and approval system that they share a common interest in finding solutions. The growth in patient groups, newly empowered by online information; the rise of the consolidated payer; the increase in the quantity and quality of real-world data about the comparative effectiveness of medicines, as well as their efficacy and safety; and the fact that the industry's capital market valuation is already heavily discounted by the financial markets, all provide an unprecedented opportunity to collaborate, in order to incentivise and reward research and development into unmet medical need.

A critical challenge will be to find a way for all stakeholders to acknowledge that they operate within a system in which the realisation of their needs has implications for other parts of the system. The way Western societies have chosen to discover, develop and deliver medicines sought to match affordability for patients with reward for industry by pooling risk in taxation, or privately funded social insurance systems. The upshot was that, apart from the industry, no other player has full oversight of the process which, colloquially, is divided between those who choose (doctors), those who use (patients) and those who pay the dues (payers).

Balancing the competing demands of the multiple beneficiaries of a thriving biopharmaceutical industry will require collaboration between those parties. If this is not achieved the result could be a Show Me the Money business model in which 'investors' insist on a monetisation of assets for near-term returns and society equates value as being synonymous with cheap (see Fig. 8). In this, they could unwittingly combine to preside over the dismantling of the core R&D capabilities on which the future of the industry depends.

There is, however, an alternative. The austerity era offers a significant opening for all stakeholders who stand to benefit from collaboration on a mutually agreed definition of value. Managed boldly and carefully, the current "Show Me the Value" market could evolve into a "Shared Value" model in which industry and payers balance incentives for true innovation with a desire to ensure prices are affordable within hard-pressed health systems (see Fig. 9). The focus on innovative medicines for unmet need could lead to greater investor confidence that judicious R&D capital allocation will be predictably reimbursed. It could even result in regulators agreeing cheaper, smaller clinical trials that are both more agile and focused, in which there is a greater sharing of results so failures are not replicated, at the cost of both developers and patients. Ultimately, such an arrangement would lead to the alleviation of pain, prolongation of life and management of disease for patients.

To make this happen, society will need to send strong signals about what it considers to be priority unmet medical needs for which it wants treatments, now and in the future. The industry will need to retain a core R&D competency if it is not to lose its lifeblood, while at the same time, fulfilling patients' expectations that it will fulfil an ongoing need for primary and secondary care products. Achieving the right balance between adopting new approaches to R&D and maintaining its centrality to the company will be one of management's toughest challenges. On reimbursement, the industry's task is to engage wary and disparate payers in multiple markets about the

Figure 8:

"Show Me the Money" Model

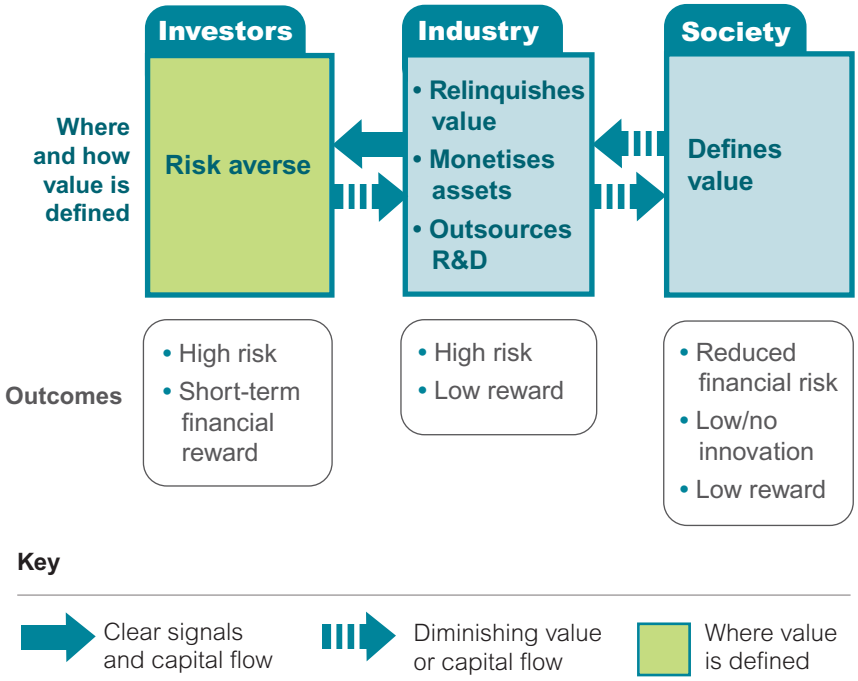
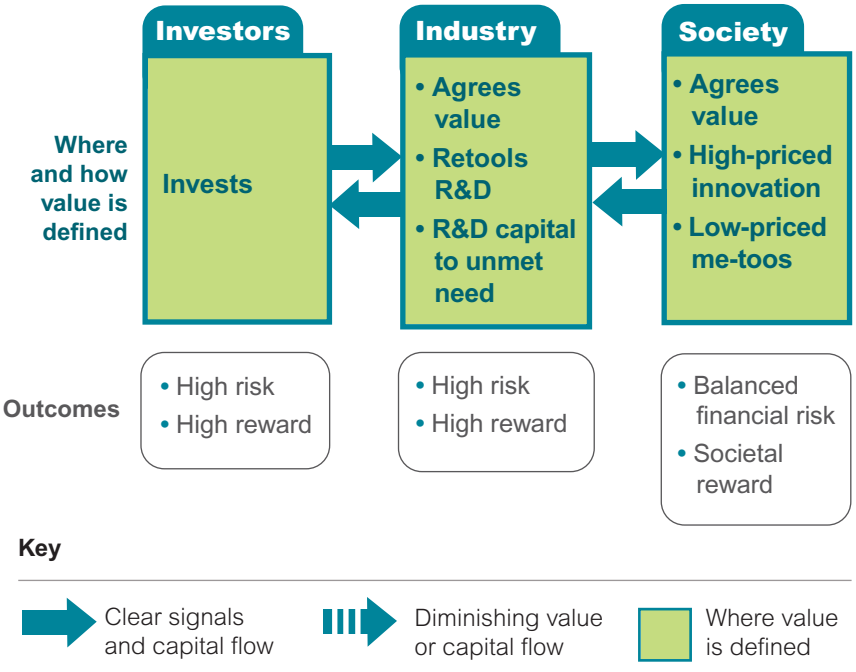


Figure 9:

"Shared Value" Model



value it offers to patients, health systems and to society as a whole. And simultaneously, it will have to ensure that investors understand the changing reimbursement landscape and its implications.

The role of investors in supporting this outcome will be critical. Capital markets are very heterogeneous. Specialist investors want companies to become better allocators, stewards and defenders of capital. They believe industry as a whole to be ex-growth in primary care and want this reality to be reflected in changes to capital allocation. Generalist investors who pick the industry as much as they pick the stock are asking to see a credible model that links the high cost of R&D to marketable products with some degree of predictability over what is often a decade-long product development cycle. Both have an interest in a successful biopharmaceutical industry, but require change to be convinced that this is imminent.

Recommendations

Determined to contribute to a "Shared Value" model the *PharmaFutures* Working Group identified the following responses from society, industry management and investors that it considers most likely to result in mutually beneficial outcomes. These would ensure that the industry is rewarded commensurately for meeting unmet patient need while providing appropriate returns for investors and recognising the constraints on society's ability to pay.

Role of Societal Stakeholders

- **Signal priority unmet needs and priority focus for treatments**
- **Coordinate work of Agencies dealing with the Pharmaceutical Industry**
- **Be prepared to collaborate with Industry**

Government Agencies

1. Articulate a clear healthcare strategy that gives a well-defined picture of what you see as the appropriate balance of health interventions, including prevention, treatment and cure across and outside the health system.

2. Encourage debates about future health policy which incorporate discussions about efficiency savings involved in preventative and early interventions.

3. Clearly signal areas of unmet need in timely fashion to Industry to enhance the industry's ability to make appropriate investment decisions. Recognise that decisions about today's application also serve as guidance for products just entering early development. In the absence of direct guidance about those early candidates, the signals are easily misunderstood.

4. Enhance multilateral collaboration in signalling unmet need, e.g. at European level.

5. Expand collaborations with industry on non-commercial unmet need which will require risk-sharing between government and industry; identify milestones for collaboration; collaborate earlier in the development process, especially with R&D departments.

6. Coordinate health, regulatory and reimbursement policies and practices so that they combine appropriate rewards for innovation with the need for pricing discipline.

Regulators, HTAs and Payers (Public and Private)

1. Collaborate to minimise unnecessary duplication.

2. Harmonise assessment criteria and rationalise data requirements across regulatory and health technology assessment entities (HTAs) throughout the development process, including streamlining pathways to approval which minimise unnecessary differences in filing formats, deadlines and requirements and post-marketing surveillance.

3. Enhance channels for providing scientific advice, particularly at the earliest stages when advice and guidance (even tentative and subject to revision) is most valuable, e.g. multi-country/single-stakeholder collaboration (HTAs, Payers and Regulators, plus individual company) multi-stakeholder/ multi-country collaboration (HTA, Payers, Regulators, plus multiple companies).

4. Expand and increase alternative approaches to approval and reimbursement including early conditional approval for specific patient sub-populations; reimbursement with evidence over time, where evidence can be generated post-launch and post initial reimbursement; and support research of products into higher risk areas of unmet medical need through enhanced exclusivity periods and/or priority regulatory review.

5. HTAs: consider a common format for any reimbursement criteria.

6. Regulators: acknowledge the cost–benefit equation in risk assessment and that the expense of longer studies to identify smaller differences leads to more expenditure on post-marketing surveillance and reduced expenditure on innovation.

7. Regulators: engage with industry to reconcile the balance between patient risk (side effects) and reward (clinical benefit) particularly in those cases where the commercial opportunity is not large enough to justify the additional development expense, despite a meaningful unmet medical need.

Role of Biopharmaceutical Industry Management

- **Enhance the credibility of management**
- **Improve innovation in the Biopharmaceutical Industry**
- **Rebuild the social contract through collaboration on value and reimbursement**

Enhance the Credibility of Management

1. Define the company's core competence. Review, rethink and rearticulate what the company does well; and how the business model is designed to exploit that skill/competency.

2. Reconsider the business model. Acknowledge that long-standing business models may not be suited to deliver innovation and growth.

Begin to reframe the model through:

- Experimentation that supports the removal of excess capacity without undermining core competencies
- Expansion of new R&D collaborations
- Expansion of the collaboration in the pre-competitive space to improve understanding of disease biology in areas of unmet medical need, up to, in some cases, proof of concept in humans.

3. Be explicit about the capital allocation philosophy. Identify where the company wants to invest, how it makes those decisions, define the required returns, outline the company's track record and the future milestones, specify how shareholders should factor these considerations into their decision-making.

4. Be significantly more consistent and transparent in communications. Identify your strategy, communicate its evolution, be clear about the rationale for any changes, and communicate your core competencies. Allow regular access to management beyond the C-Suite to enhance investor confidence in process and capabilities.

5. Be bold. Consumer perceptions and capital market valuations of the industry are at all-time lows so the risks of bold action are low. Don't be afraid to break from the pack, be proactive not reactive. For example, consider new product and service offerings, combined with medtech delivery systems; offer lower margin products in higher volume markets; build ties with truly independent patient groups and philanthropic entities.

6. Aggressively manage internal assets to create value. Be prepared to make necessary efficiency cuts, monetise non-productive assets, increase transparency. Explore new risk-sharing models.

Improve Innovation in the Biopharmaceutical Industry

1. Identify a clear R&D investment process. Articulate it internally and externally, particularly to investors who will use it to judge future value. Once in place use it and don't ignore it.

2. Retool R&D to increase externalisation, increase experimentation and expand R&D collaborations. This should include partnerships between companies, licensing, pre-competitive partnerships and, where possible, a general expansion of the pre-competitive space. Consider increased patent pooling, including areas of increasing commercial potential.

3. Streamline internal R&D to attract and retain talent. Build on existing initiatives to create the right environment for scientists to flourish, prevent the flight of talent post-consolidation, give scientists more "bench time" and fewer meetings, and outsource fixed cost infrastructure.

Rebuild the Social Contract through Collaboration on Value and Reimbursement

1. Foster collaborations designed to agree criteria on what constitutes value and price accordingly.

2. Continue to provide greater pipeline transparency with the timely posting of trial results, including failures.

3. Build on existing collaborations on unmet medical need such as those designed to develop products for diseases of the developing world and neglected diseases.

4. Undertake risk-sharing partnerships including novel clinical trial approaches and risk-sharing reimbursement agreements based on agreed outcomes.

5. Undertake early engagement with payers and regulators to streamline regulatory requirements, throughout the development process, including post-marketing surveillance while meeting safety, efficacy and cost-effectiveness concerns.

6. Engage with regulators and payers to rationalise data requirements across regulatory and HTA entities.

Role of Investors in the Biopharmaceutical Sector

- **Continue to play a critical role in funding new drug discovery**
- **Use activist tactics to support sustainable R&D models and help bring change in its absence**
- **Retain a focus on the long term to achieve sustainable returns**

Venture Capital and Private Equity

1. Continue to play the critical role of funding new drug discovery platform technologies and novel products, in categories with unmet need. These investments often in start-ups and "biotech" companies, consortiums and public private partnerships increasingly provide the leads which feed development for Big Pharma. Any slowing of investment at this stage will directly reduce the eventual pipeline at those larger companies.

2. Be prepared to support new exploratory models of risk-sharing both within and outside established biopharmaceutical companies, to break the pattern of poor historic returns.

Specialist Healthcare Investors (long only and hedge funds)

1. Proactively articulate a strategic viewpoint to companies.

2. Where necessary, use activist tactics to help bring change to companies without a sustainable R&D model.

3. Evaluate companies on the basis of overall portfolio to allow for different volume/price trade-offs in different therapeutic areas to address unmet medical need.

4. Give clear signals to companies. Make sure companies executing well know that they have the support of their shareholders.

Generalist Investors

1. Retain the focus on the return on R&D investment and the ability to achieve a sustainable return above the company's weighted average cost of capital. This will allow long-term, self-funded re-investment into R&D on an ongoing basis.

Methodology

The *PharmaFutures* series was created in 2003 to allow investors to hold a sustained dialogue with senior pharmaceutical managers about how they were seeing and responding to challenges in the external operating environment. The dialogues aim to validate the business case for adjusting the biopharmaceutical industry business model to more effectively balance changing market realities and societal expectations. At its heart, *PharmaFutures* seeks to enhance a business model that combines sustainable shareholder value and strong patient health outcomes. It aims to build trust and foster an environment in which collaborations and partnerships between industry and key stakeholders can flourish.

At the heart of each *PharmaFutures* dialogue is an expert Working Group, formed of senior pharmaceutical executives and institutional investors, which provides the project's intellectual steer through face-to-face workshops and ongoing research and dialogue. The exchanges of the Working Group are enhanced by inputs from a group of senior expert practitioners who have years of experience of working in pharmaceutical R&D and as healthcare evaluators and payers (see Appendices 1 & 2).

This *PharmaFutures* dialogue was initially designed to focus on three game-changing developments in the external environment; the rise of the HTAs, Open Innovation and the Natural Environment. All three were discussed at length by the group. In the course of the discussions, it became apparent that there was a symbiosis between the innovation and payer discussions that merited detailed exploration. The environment conversation was considered extremely important, particularly by the industry participants, but worthy of a separate dialogue. This work in now under way and will be released as a separate report.

PharmaFutures dialogues are run by Meteos Ltd, a not for profit company formed specifically to seek cross-sector collaborations to solve complex problems. Our investor dialogues are a supplementary research tool, which use direct dialogue between companies and their investors to generate new and original insights, in order to enhance strategic planning and investment decision-making.

For each of our dialogues we create a Research team, made up of in-house and external experts who design the process, undertake supplementary research and seek to provoke the generation of new and original insights to enhance strategic planning and investment decision-making. The Research Team in *PharmaFutures 4* included Stewart Adkins, Becky Buell, Alexa Clay, John Schaetzl and Sophia Tickell.

Appendix 1

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Acknowledgements

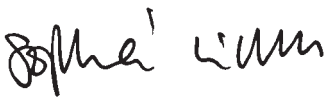
This report is a record of the fourth iteration of the *PharmaFutures* dialogue between pharmaceutical executives and institutional investors. The dialogues are run by Meteos Ltd, a not for profit company formed specifically to seek cross sector collaborations to solve complex problems. Our investor dialogues are a supplementary research tool, which use direct dialogue between companies and their investors to generate new and original insights, in order to enhance strategic planning and investment decision-making.

This report is the result of a team effort. For each Meteos dialogue we bring together in-house and external experts, to provide research and facilitation skills, to provide a strong intellectual underpinning to any findings and to ensure that the conversations are as probing and challenging as possible. In this dialogue, the Meteos team (Becky Buell, Alexa Clay, Sharon Williams and I) was joined by John Schaetzl and Stewart Adkins.

So, first, I would like to thank Stewart and John, who brought to the project invaluable intellectual insights drawn from decades of experience of pharmaceutical analysis, utter dependability and an enormous sense of fun. The contribution their knowledge brought was invaluable in the underpinning research to the project and for the Synthesis and Workshop Meetings; and it has been invaluable for this report. Secondly, it has been a treat to work with Alexa Clay, our research lead, whose originality of thought and rigour ensured that we do not get complacent about what we know or what might happen. Thirdly, I would like to thank Sharon Williams, who embraced the complexity and considerable administrative demands of a project of this nature with complete efficiency, and also with tremendous calm, particularly when under greatest pressure. And finally, I turn to my Meteos co-founder and Director, Becky Buell, who has brought not only intellectual rigour and strong project management skills to the project, but is also, simply, one of the best facilitators I have ever met. It has been a privilege to work with each of them.

Beyond the *PharmaFutures* Team, I would like to thank both the members of the Working Group and the other expert interviewees whose views and perspectives underpin this report. As with previous iterations of PharmaFutures, these people *are* the project. The respectful but frank and open exchange of views between different constituencies is what these projects are about. This was a particularly good team and it was an honour to get to know them.

As author of the report, any errors of omission or commission are mine alone.



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