THE CHALLENGES AND ECONOMICS OF DRUG DEVELOPMENT IN 2022

Proceedings of the Office of Health Economics
50th Anniversary Conference
8 October 2012
London

Edited by Nancy Mattison

OHE Office of Health Economics 50 YEARS
50 years of research and expertise

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About the Office of Health Economics

Founded in 1962, the OHE's terms of reference are to:

- Commission and undertake research on the economics of health and health care
- Collect and analyse health and health care data for the UK and other countries
- Disseminate the results of this work and stimulate discussion of them and their policy implications.

The OHE's work is supported by research grants and consultancy revenues from a wide range of UK and international sources.

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FOREWORD

The conference reported in this publication was held in October 2012 to celebrate the 50th anniversary of the Office of Health Economics (OHE). In keeping with the spirit of this organisation's long history, the conference's intent was to identify, explore and suggest direction to meet emerging challenges and take advantage of opportunities in the health care environment. As with past OHE anniversary publications, the focus was on identifying the scientific, organisational and economic challenges in the development of new and improved therapies. The implications of these changes for health care systems were an important part of the discussion, ranging from the potential effects on the structure of costs within health care systems to changes in the roles of the public and private sectors that can increase the likelihood of achieving unprecedented advances in therapy for some of the most burdensome diseases.

Nearly 150 participants from a range of public and private organisations and from many countries attended the conference. We thank them for their active participation and differing perspectives, which added to the richness of the discussions.

We were very pleased to have had with us for the celebrations Professor George Teeling Smith, OHE's founder and first director who, sadly, passed on early in 2013. His work at OHE built a strong foundation for its continuing leadership in addressing health care's tough economic issues. We dedicate these proceedings to his memory.

PROFESSOR ADRIAN TOWSE
Director

INTRODUCTION

The Office of Health Economics was created in 1962, at a time when prescription medicines were available only for a limited range of diseases and the development and approval processes still were in their infancy. It was that year when Sir James Black discovered the first clinically significant use of beta blockers, revolutionising the treatment of angina pectoris. The paucity of treatments for most diseases then is highlighted by the fact that bronchitis accounted for "more than one-tenth of the expenditure on prescriptions" in the UK in 1962 (OHE, 1964, p. 20). A 1964 OHE study notes that "expenditure on lung cancer is slight . . . because of the limited therapy possible and the speed with which the condition kills" (OHE, 1964, p. 20).

With respect to the regulatory approval process, it was in 1964 that the UK Committee on the Safety of Drugs was formed in the wake of the thalidomide tragedy. Companies voluntarily submitted products to it for review of safety and efficacy, but it was not until 1968 that the UK Medicines Act made regulatory approval mandatory for marketing.

Concerns about the costs of medicines certainly existed in 1962, as did attempts to control costs for the National Health Service (NHS). A 1963 OHE study, the first to compare health systems in Western Europe, notes, for example, that the health services in most of Western Europe either charged the patient a substantial part of the cost of drugs or restricted the list of drugs available under the service (OHE, 1963). Patients in the UK at that time paid two shillings per prescription; doctors were discouraged from prescribing "nationally advertised or unnecessarily expensive medicines" (OHE, 1963, pp. 15-16).

Fifty years on, the changes in all these areas are vast. Sir James would be amazed at how the advancing understanding of genomics and genetics has changed the entire process of innovation, from discovery through testing and approval and, with companion diagnostics, even clinical practice. Lung cancer, the swift and merciless killer of 1962, no longer is untreatable; indeed, increasing knowledge about the various subtypes of the disease promises ever more successful, non-invasive treatment.

The availability of numerous approaches to treat a widening range of diseases and conditions has created undeniable benefits for patients, but also serious economic challenges for health care systems worldwide. These have not changed in kind since 1962—the basic issue still is how to provide the best care possible with finite resources. What have changed are the tools available to help meet the challenge. Health technology assessment techniques, very limited in 1962, have become increasingly sophisticated in analysing and comparing the costs of alternative therapies. Medicines have been a particular focus. Approval for safety and efficacy, a far more rigorous and nuanced process than could have been envisioned in 1962, now is only the first step in reaching the market in most countries.

OHE's 50th anniversary conference was designed to foresee key aspects of the milieu for drug development ten years out, projecting from the major changes in progress today. Four primary themes ran through the presentations and discussions at the conference.

> **Medicine will be radically transformed** as therapies are more effective in individual patients. This so-called "personalised" or "stratified" or "precision" medicine not only will create medicines that plug into the peculiarities of the patient's and the disease's genetic makeup, but also can be monitored with far greater accuracy and convenience than today. Companion diagnostics are one such method and will take new forms—for example,

"smart pills", already in development, that contain sensors implanted in the medicines themselves that will allow physicians to remotely monitor progress and adjust treatment.

The process of innovation will look quite different in 2022. Over the past twenty years, the process and locus of innovation already have changed substantially. The remarkable explosion in scientific knowledge and technical capabilities have given rise to innumerable smaller firms worldwide that specialise in innovation based on the new approaches.

The larger, traditional pharmaceutical companies have been slower to adapt. Now, however, they are in the midst of embracing change, integrating new technologies, altering internal processes and structures, and changing the type and extent of collaborative efforts within and across the industry. A "volume" mentality, which encouraged testing multiple products and discarding failures, has been replaced with a focus on "quality", which carefully selects specific targets. The idea of working in isolation to produce a startling new blockbuster medicine already seems antiquated.

More inclusive processes for selecting appropriate targets are being tested now, involving a range of stakeholders from both the public and private sectors. The benefits of so doing for the industry are products more likely to be accepted and commercially successful; for the public sector, it means encouraging innovation that targets the more burdensome diseases. It also can aid planning when policy makers know in advance which therapies are likely to appear.

Approval and pricing regimes will adjust in response to the new medicine. The technology for precision medicine is growing at an exponential rate and it is not likely to be science that presents the greatest challenge to recognising its potential. Instead, dramatic new treatments will face familiar dilemmas—how best to evaluate, price and make new treatments available, remaining within finite budgets while still encouraging continuous innovation.

The conference identified several concerns, including the need for flexibility from regulatory authorities and payers. Regulatory bodies will need to adjust personnel and procedures to evaluate, for example, gene-based treatments or medicines paired with diagnostics. Given that newer products may cure, not just treat, disease, availability for some patients before the end of clinical testing may be appropriate. This will require new procedures, for example, to gather necessary information after approval and, in some cases, for limiting use. Moreover, to speed innovation and reduce costs, regulators and health technology assessors need to be realistic in data requests and work towards complementing one another.

For payers, recognising the value of more targeted, precise treatments will require new methods of evaluation and new approaches to pricing. For example, pricing by indication, rather than by medicine, will be important in shaping the innovation agenda so that crucial advances occur.

Perhaps an even more basic concern is realism in projecting what resources will be available to pay for health care by 2022. Critical macroeconomic factors often are inadequately considered. In particular, an ageing

population not only will increase the extent of demand for health care, but also place an increasing burden on the proportionally shrinking working-age population. Efforts to develop and implement new approaches for financing health care are critical.

The focus for innovation and markets will have become even more global. Markets are shifting as, for example, the middle class in the emerging markets grows and increases its demand for health care. In the developing countries, the need for products to treat diseases endemic to those countries will remain; new technology, however, may speed the development of increasingly effective products. The global perspective needs to include a global approach to pricing and reimbursement, one that can both help make more medicines available to more people and also encourage innovation.

The conference considered where the UK fits into the challenges and economics of drug development in 2022. The country has been a remarkably influential source of innovation in medicine for generations—as the example of Sir James Black only begins to suggest. The life sciences sector in the UK, in turn, continues to be very important to the UK economy. Given the UK's relatively small market size, what will it take to ensure the health of this important sector? Recommendations at the conference included making full use of the unique resources of the NHS. This includes in particular its unparalleled potential as a source of data for analysis, from patient and GP records to large-scale clinical studies and approaches to delivering care. Just as important is encouraging the development of clusters of research excellence, learning lessons from what has worked, and what not, in the US and Europe.

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LIST OF ACRONYMS

CASMI	Centre for the Advancement of Sustainable Medical Innovation
CPRD	Clinical Practice Research Datalink
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (US)
GP	General practitioner
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IMF	International Monetary Fund
MHRA	Medicines and Health products Regulatory Agency
MRC	Medical Research Council
NEWDIGS	New Drug Development ParaDIGmS
NHS	National Health Service (in England, unless otherwise noted)
NICE	National Institute for Health and Clinical Excellence (renamed the National Institute for Health and Care Excellence as from April 2013)
OECD	Organisation for Economic Cooperation and Development
OHE	Office of Health Economics
QALY	Quality-adjusted life year

Chapter 1.

EVOLUTION IN DRUG DISCOVERY AND DEVELOPMENT

DR MENE PANGALOS
Executive Vice President of Innovative Medicines, AstraZeneca

A remarkable explosion of scientific knowledge and technical capabilities is changing the landscape of drug discovery and development very quickly. These advances promise important new opportunities for dramatically improving treatment, even for more difficult diseases. For the pharmaceutical industry, meeting these challenges means transforming how we think about R&D, increasing our collaborative networks, and changing the way we work. Only by transforming our productivity can we begin to realize the incredible promise that new medical breakthroughs and understanding of disease pathophysiology hold for everyone, particularly patients.

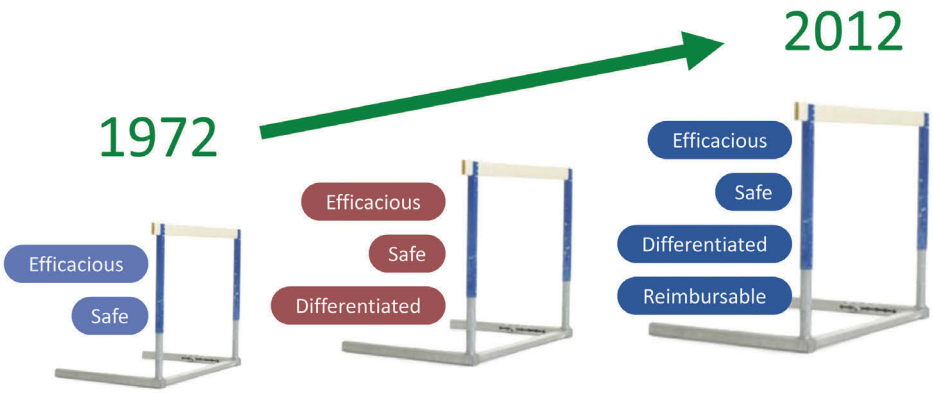
Challenges for the pharmaceutical industry

The environment for the pharmaceutical industry is challenging on several fronts. For example, the general public continues to have misconceptions about the industry. A recent survey by the Association of the British Pharmaceutical Industry (ABPI, 2012) found the following: 35% of those surveyed thought that 20% of the NHS budget is spent on medicines, when it is actually about 12% (DH, 2012); 59% of people believe that it costs less than £10 million to develop a new medicine, when the figure is closer to £1,900 million and climbing (Mestre-Ferrandiz, Sussex and Towse, 2012). The value of medicines does not seem to be in doubt, at least among those who rely on them: the survey found that 77% of patients believe more should be spent on innovative medicines (ABPI, 2012).

The turmoil within the industry is reflected in numerous news headlines that report a flattening or declining R&D spend since 2007, workforce cutbacks of 110,000 in 2009–10 alone, large projected declines in sales as some products go off patent, and the disappearance of entire pharmaceutical companies as the industry seeks to survive through mergers. Companies regularly are questioned by investors and shareholders about continued substantial investment in R&D and the rate of return relative to the R&D investment made.

What's causing this turmoil and financial uncertainty? Figure 1.1 gives a sense of how some of the requirements for market entry have changed for drugs over the last four decades. From the early 1970s to mid-1980s, new products generally reached the market if they were proven safe and effective. Whether the drug was first or fifth in the class, it would be approved and reimbursed. By the 1990s, that was changing. A new product had to demonstrate some type of improvement over the standard of care to gain market acceptance. Today the hurdles are higher still; new medicines must have a clear "value" proposition to be included on formularies around the world.

Figure 1.1. Causes of change in the R&D environment



The costs of amassing the clinical and preclinical data that allow us to surmount these hurdles successfully are increasing. It takes more, often larger, clinical trials and more comparative studies to satisfy regulators, whose risk aversion has increased. One cost factor is time: in the 1970s, it took about 5.7 years to complete the trials necessary to apply for a license for a new medicine; by 2000–2009, that was 6.5 years (Mestre-Ferrandiz, Sussex and Towse, 2012). The average time to complete development today is nearing 10 years—and this does not include the five to seven years of pre-clinical research before development begins. It also does not include the months, or years, that may elapse between licensing approval, assessment by health technology assessment agencies such as the National Institute for Health and Clinical Excellence (NICE) and/or decisions by reimbursement agencies and payers.

Partly as a result of the higher hurdles, the likelihood of a new molecule progressing through the three clinical testing phases has declined. Success rates dropped from 22% in 1983–1994 to 13% in 1997–2007; the decline varies by type of molecule and disease area (Mestre-Ferrandiz, Sussex and Towse, 2012). Some analyses, using different data sources and methods, suggest that success rates have continued to erode to as low as 5.5% in 2010 (Evers et al, 2012).

What must we do differently?

R&D organizations have been challenged by a "volume" mentality. Rewards and incentives have been based on the numbers of compounds entering clinical development and/or the number of compounds entering each development phase rather than the quality or the "value" of the deliverable. The hypothesis was that if one drug is approved for every ten that enters clinical development, then putting thirty drugs into development would produce three approved drugs. Although companies became good at delivering the thirty drug candidates, output remained at one approved medicine. Clearly, this volume-based approach will not work in the future.

The focus of the industry today continues to moving away from the numbers game to a focus on quality. Two years ago at AstraZeneca, we took a critical look at all our decisions over a five-year period in research and early clinical development and questioned why we had made those decisions. We identified five key criteria that we believe will increase our success rates if we focus on them at each step of the research and early development processes.

The five factors we identified were developed into a new framework, which we call the "5R" framework, outlined below. This is fairly intuitive and perhaps not surprising; what was surprising was how few of our programmes consistently incorporated these critical factors into thinking at important investment decision points.

Figure 1.2. AstraZeneca's 5R framework

RIGHT TARGET	• Strong link between target and disease • Differentiating efficacy • Available and predictive biomarkers
RIGHT TISSUE/EXPOSURE	• Adequate bioavailability and tissue exposure • Human PK / PD prediction, PD biomarkers • Drug-drug interaction
RIGHT SAFETY	• Clear assessment of safety risks • Clear understanding of risk-benefit • Availability of predictive biomarkers
RIGHT PATIENTS	• Scientific evidence in lead indication • Risk-benefit stratification of patient population
RIGHT COMMERCIAL	• Differentiated value proposition vs. future standard of care • Market access/payer/provider focus • Personalised health care strategy including diagnostics/biomarkers

In addition, we have established a set of critical capabilities that we believe are important to future portfolio success. These include an integrated payer strategy group focused on working with project teams to identify key questions and development strategies. This group will help create the value proposition for the project and reimbursement dossiers, for both the core dossier and any variations.

Another group is charged with helping teams excel in clinical trial design and interpretation, ensuring that they ask the key clinical questions at the right time and conduct lean and efficient development programmes.

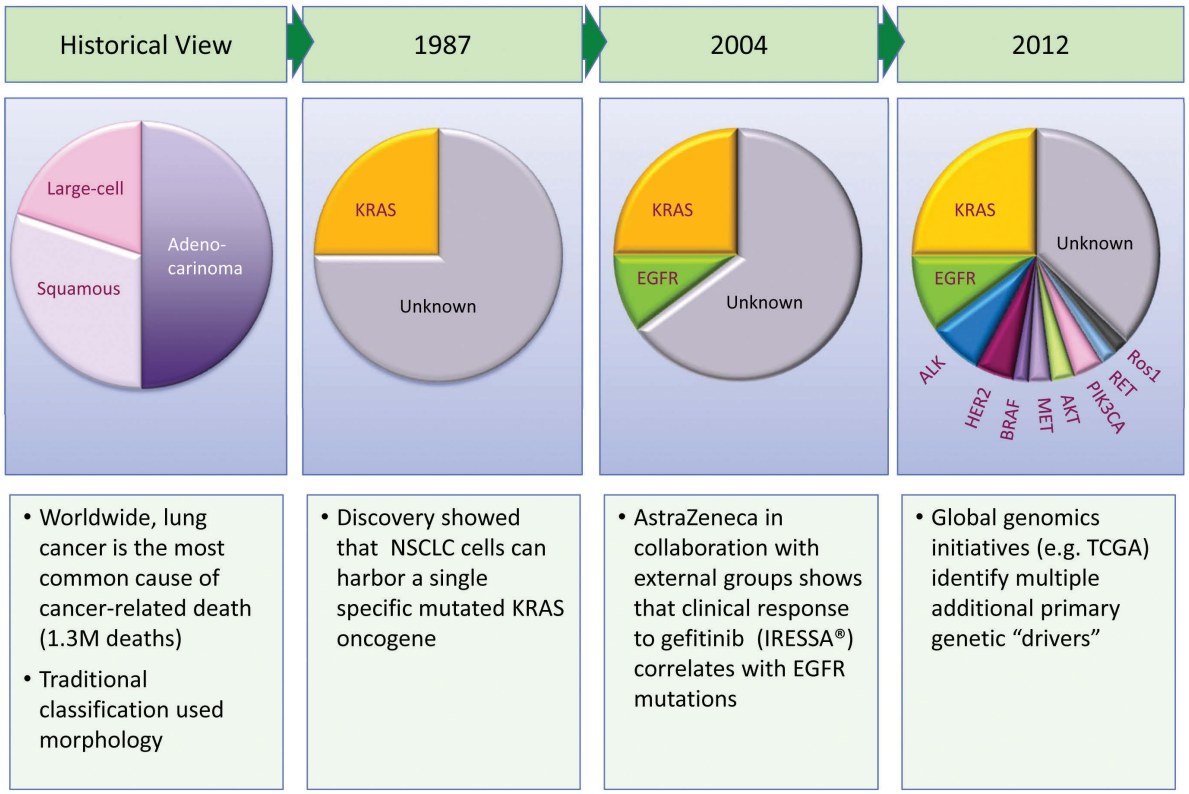
We have built a personalised health care group that is tasked with translating biomarker invention from our laboratories into use in the clinic. Where appropriate, these advances—either as biomarkers or as understanding of patient segmentation—should support the delivery of companion diagnostics used in tandem with new drugs reaching the market.

Finally, we are making greater use of predictive sciences—whether that is predictive toxicology, predictive chemistry, or integrative biology. This will enhance the quality of our research and decisions in both the research and clinical phases.

IMPLICATIONS FOR THE FUTURE

Personalised health care holds great promise—and lung cancer provides an excellent example. As Figure 1.3 shows, in the 1970s and early 1980s, lung cancer was diagnosed primarily through morphology and histopathology—the diagnosis was either large-cell squamous cancer or adenocarcinoma. In the 1980s, the first driver mutation was identified with an oncogene called "KRAS". In 2004, EGFR was first described, leading to treatments, such as gefitinib, which is specific for EGFR-driven non-small cell lung cancer. By 2012, as the figure shows, the landscape has changed very dramatically and in a relatively short time. The unknown segment is shrinking with genomic analysis of tumours and the ability to identify drivers of tumour progression is growing rapidly.

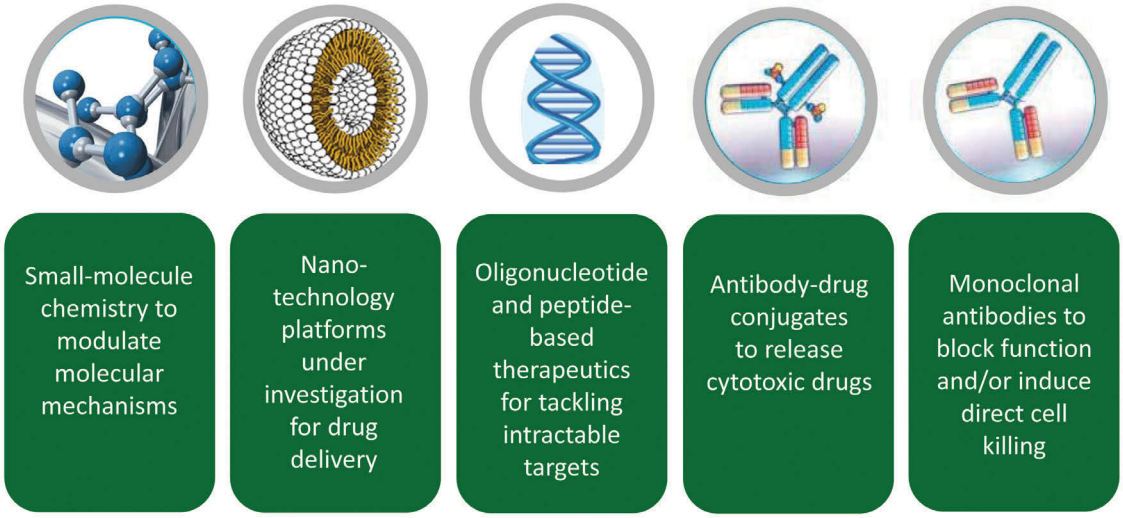
Figure 1.3. Diagnosis of lung cancer and personalised health care



What does this mean for patients? As we have seen with gefitinib, stratifying patients and targeting those who are EGFR-positive has produced a remarkable effect on improving response rates and progression free survival compared to standard chemotherapy (Mok et al, 2009).

The pharmaceutical industry traditionally has worked with small molecules and antibodies, but we now also are exploring macrocycles, peptides and oligonucleotide therapies as depicted in Figure 1.4. It is important we pursue the right targets—not just with the right molecule, but also with the right modality for the particular disease of interest.

Figure 1.4. Access to multiple platforms is important



New models of collaboration

Just as we are changing how we approach R&D internally, the pharmaceutical industry needs to change fundamentally how it works with the external world. Solving the most difficult and complex diseases will require drawing on the brilliance of scientists and physicians across sectors. Partnering is at the core of everything we do at AstraZeneca.

OPEN INNOVATION INITIATIVES

Two ground-breaking examples of AstraZeneca collaboration are arrangements with the Medical Research Council (MRC) in the UK and with the National Institutes of Health (NIH) in the US. These represent a productive new approach to sharing compounds and risks. Some of the best minds in the UK and the US will help identify new uses for compounds and clinical candidates that otherwise would be lost.

Announced in December 2011, our partnership with MRC, the Mechanisms of Disease Initiative, provides academic researchers access to 22 AstraZeneca pre-clinical and clinical compounds that failed for the particular diseases we were targeting (MRC, 2012). The collaboration will produce ideas for possible new uses, based on academic research. To date, 120 project proposals have been submitted across a broad range of disease areas. MRC will provide funding of up to £10 million to support projects selected by an independent review panel. Active collaboration between academic researchers and AstraZeneca is possible under this programme. AstraZeneca will retain the rights to the chemical composition of the compounds; any new research findings will be owned by the academic institution.

In the US, the NIH's National Center for Advancing Translation Sciences (NCATS) launched a similar initiative in May 2012, Discovering New Therapeutic Uses for Existing Molecules (NCATS, 2012). Currently, it involves eight companies: Abbott, AstraZeneca, Bristol-Myers Squibb Company, Eli Lilly and Company, GlaxoSmithKline (GSK), Janssen Pharmaceutical Research & Development L.L.C., Pfizer, and Sanofi. The 58 compounds that have been made available for the pilot programme (14 from AstraZeneca) will be tested by researchers across the US for possible new therapeutic uses. In 2013, for the initial pilot phase, NCATS will provide up to $20 million to fund two- to three-year staged, cooperative agreement research grants through Phase IIa trials. For compounds still under patent, the company has the first option to license the researcher's work; for off-patent compounds, the researcher may find another commercial collaborator.

LEVERAGING COMPOUND COLLECTIONS

AstraZeneca's collaboration with Bayer represents a new approach to making the most of existing compound libraries. Each company has quite distinct and diverse compound collections. Under this agreement, when we identify a target for high throughput screening, but our screen yields no promising leads, we can choose to leverage Bayer's collection—and vice versa. This has enabled us to generate leads and starting points that we would not have found otherwise.

AstraZeneca also works with groups such as the World Intellectual Property Organisation and the Bill and Melinda Gates Foundation, sharing compounds that may prove useful for the development of treatments for diseases prevalent in the developing world, such as tuberculosis, Chagas disease, and malaria (see chapter 4).

PRE-COMPETITIVE COLLABORATION

Making the most of new technologies is the focus of our peer-to-peer collaboration with GSK and the University of Manchester (University of Manchester, 2011). Announced in May 2011, the Manchester Collaborative Centre for Inflammation Research is a translational science centre that will explore new biomarkers, new pathways, and new

ways of stratifying patient populations with COPD and other very complex disease areas. The initial investment by each partner was £5 million over a three-year period. We all benefit; Astra Zeneca and GSK have an opportunity to work with some of the best academics in the world to push our understanding of disease pathophysiology forward.

AstraZeneca is collaborating with Cancer Research UK and Pfizer in pioneering the Stratified Medicines Programme intended to identify new companion diagnostics and biomarkers that can help stratify patient populations. One outcome will be databases of tumour genetic information, treatments and outcomes that can make clinical development more efficient and more successful.

WORKING VIRTUALLY

AstraZeneca has made dramatic internal changes in how we work with external partners. Our approach to research in neuroscience provides an excellent example. Unmet medical need in neuroscience is great; the risks are very high, development times are significantly longer, and expenses higher than for many other therapeutic areas. This year we announced our new "virtual" neuroscience innovative medicines unit (iMed). We have created a small group of 40–50 people, placed in two of the world's academic "hot spots" for neuroscience research: Boston in the US and Cambridge in the UK. This group will work side-by-side with the best academic and biotech laboratories to find new ideas and undertake drug discovery and development projects through collaboration using our functional AZ capabilities. The majority of our R&D spending in the neuroscience area, as a result, is flexible and focused on projects and scientific understanding, rather than on fixed infrastructure costs.

As another example, in July 2012 AstraZeneca announced the formation of the A5 alliance, the first of its kind, which brings together four leading North American academic research laboratories to study a major risk factor for Alzheimer's disease, the apolipoprotein E4 genotype (ApoE). This team of academic scientists with expertise in ApoE biology will focus on identification, validation, and risk reduction of drug targets for treatment of Alzheimer's disease (AstraZeneca, 2012).

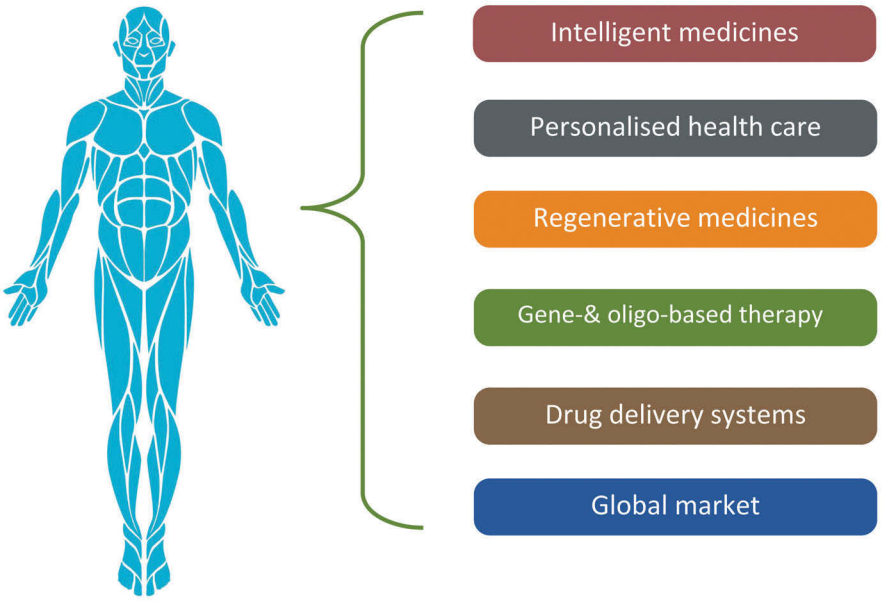
Where will we be in 2022?

Projecting ahead to 2022 is truly crystal ball gazing. Considered below are a few categories where significant change may continue to occur.

Intelligent medicines. Making full use of communications technologies offers great promise. An amazing 72% of the global population currently has mobile phones and billions use social media. The possibilities for both communicating about health and receiving patient-specific information are endless. Already we can monitor cardiac function and blood sugar remotely, for example, producing a dramatic impact by reducing hospitalisation rates. Imagine what would happen in a world where a pill has a censor that can detect blood cholesterol or blood sugar levels, or even take a pulse, and then send a message via a smartphone to the physician, who can decide whether to modify the dose. This is not beyond the realm of possibility; smart pills and medicines carrying sensors are in development.

Personalised health care. We already are making great strides in oncology; and companion diagnostics are being approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) that allow us to treat the right patient with the right drug. Panels of diagnostic tests will become more commonplace as physicians, hospitals and other health care providers gain familiarity with them. In the future, a patient may be offered not just a genome analysis, but also a metabolome analysis, a proteome analysis and others analyses—all stored on a small chip. This would give health care providers a thorough understanding of the disease in an individual patient, which would allow physicians to more effectively tailor available therapies to the patient's particular needs.

Figure 1.5. Looking ahead to 2022



Regenerative medicine. Great progress is being made in this area. A number of heparan sulphate analogues already are used for wound healing. One of the first stem-cell drugs, owned by Osiris Therapeutics, has been approved for graft-versus-host disease, increasing the success of bone marrow transplants in children. More stem-cell companies and stem-cell therapies are entering clinical development.

The understanding of how to use stem cells is growing; they will be used, for example, in regenerative medicine in heart disease and diseases of the pancreas and other organs. Scientists today are able to create tailor-made replica trachea from patient's own stem cells. But using stem cells raises a host of complex challenges—not just to science, but also to perceptions about treatment and about regulation. Efforts should begin in the pharmaceutical industry to develop and grow stem cells consistently; regulators must become comfortable with that consistency. We also must develop ways to produce these products in commercial quantities and make them available around the world.

Gene-based therapies. In July 2012, the first gene therapy in the Western world was recommended for approval by the EMA in Europe and officially approved by the European Commission in November (uniQure, 2012). uniQure's Glybera® treats patients will an orphan disease that affects the pancreas. Gaining approval was a long journey, with many refusals and reconsiderations. In future, as all those involved become more familiar and comfortable with gene-based therapies, moving forward will become easier.

Numerous oligonucleotide-based biopharmaceuticals now have moved into clinical trials. The first antisense oligonucleotide formulation, Vitravene®, has been approved in the US. Multiple oligonucleotide-based treatments are in development at companies such as Alnylam Pharmaceuticals, ISIS Pharmaceuticals and Regulus Therapeutics.

Drug delivery systems. Imagine a small implantable pump the size of a matchstick that could deliver insulin for a year. Such devices are being developed now and could transform the quality of life for patients. Also in development are nanomedicines, with censors embedded to monitor how a patient is responding to a particular therapy. Nanochips and biosensitive devices eventually may monitor disease state and progression. Ultimately, these technologies will help the pharmaceutical industry in improving the benefit-risk profile of drugs even further and increase our ability to target diseases that are difficult to treat.

Global market. The geography of our business will be quite different by 2022. The middle classes are growing in the emerging markets, particularly in the BRIC nations (Brazil, Russian, Indian and China), driving spending on health care. By 2020, for example, health care spending in China is projected to nearly triple, to $1 trillion annually (Bloomberg News, 2012). Projections for Brazil are similarly impressive. In addition, longer life spans will increase demand for treatments for chronic diseases worldwide, a trend already well under way.

Conference discussion

Question: It is exciting to hear about the advances in science. Would you please say a few words about the importance of pricing of innovation?

Pangalos: For any medicine—whether it is a stem-cell therapy, an antibody, a small molecule or something else—we must have a good value proposition. The innovation must be deemed worthy of reimbursement and be priced accordingly. Problems arise when a ground-breaking, innovative medicine that makes a real impact on patients' lives is not reimbursed.

Question: One of the outstanding issues that the pharmaceutical industry needs to address is selecting the wrong targets, virtually ensuring failure from the outset. How can this be addressed?

Pangalos: As mentioned earlier, this is characteristic of the "numbers game" that the pharmaceutical industry has played for decades, where "more in" was assumed necessary to get "more out". We now are focusing on pathophysiology. The emphasis is much less on numbers than on finding the right pathway, the right target. Our alliances and collaborations are one approach to improving basic knowledge about what to target and how. But ultimately our scientists also need to be asking and answering fundamental questions about the biology and pathophysiology of the areas in which we are working. For example, in oncology, understanding driver mutations and how certain tumour types acquire resistance is enabling us to think not just about the right target, but also about the right sequence and combination of therapies.

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Chapter 2.

EFFICIENCY AND PRODUCTIVITY IN R&D

PROFESSOR FABIO PAMMOLLI
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Developments in R&D and innovation in the pharmaceutical industry over the next decade will be affected by three important factors: the macroeconomic environment, trends in the process and focus of R&D, and policies that affect the money available to fund R&D.

Macroeconomic constraints

The macroeconomic environment will continue to influence microeconomic decisions, such as price cuts and cost containment measures, not only in continental Europe, but globally. Two factors have a defining impact on the macroeconomic trajectory: (1) demographics, particularly the ageing of the population and (2) pressures on the sustainability of public financing. The sovereign debt crisis and an increase in welfare expenditure—particularly for pensions and health care—have a powerful impact on public financing that will continue to be felt.

Accurately understanding trends in the macroeconomic environment is essential to effective planning. Until very recently, however, official projections by the European Commission included only the demographic component in health care costs. Income elasticity and technological progress were given inadequate consideration, at best. For example, the EU's Economic and Financial Affairs Council recognised the effect of technological progress only as being slightly cost-reducing for health care and did not incorporate the prospect of growth in expenditure induced by technological progress.

This perspective has created serious disparities between the scenarios produced by the European Commission and those produced by the OECD, the IMF and leading academic researchers. But this is not just an esoteric problem: the figures produced by the European Commission become the official figures that EU Member States use in their stability and convergence programmes. Basing budget planning and constraints only on demographics is myopic.

An accurate assessment of macroeconomic factors is essential to the future of the pharmaceutical industry and health care systems. Both depend on funding that can afford and sustain the real rate of growth in health care expenditure. According to the IMF, "For health care spending, the outlook is much more challenging [than for pensions]. . . . Studies indicate that non-demographic factors—most notably technology, but also income growth and expansion of insurance—explain the vast majority of spending increases in health" (Cottarelli and Schaechter, 2010, p. 16). Although Europe generally has been able to stabilize pension systems through reforms started 15 years ago, sufficient attention has not yet been given to the challenge of financing health care expenditures.

A core issue in solving the challenge is that health care systems in Europe continue to be funded primarily through social contributions and taxation, i.e. in a pay-as-you-go manner. This already is producing a burden on labour productivity and contributing to compressed economic growth. Germany is an interesting exception. In 2001, the pension system was reformed, creating a capitalised fund component not just for the wealthy, but also for workers. More than 11 million workers in Germany now are included in the scheme, which complements the pay-as-you-go system.

European countries must define funding schemes for health care at the macro financial level that are capable of addressing the trends in demand created by the ageing of the population, technological progress and the changing expectations of patients. If this is not accomplished, then pressures on R&D activity and innovation that already are evident will not only continue, but worsen.

Current trends in pharmaceutical R&D

A DECLINE IN PRODUCTIVITY?

Macroeconomic pressures already are having an impact on R&D in the pharmaceutical industry. In particular, R&D projects are becoming more concentrated in therapeutic areas with potentially high return, but also with high risk. In a paper published last year, we analysed these changes based on the success rates, sales and share of R&D in various therapeutic areas (Pammolli, Magazzini and Riccaboni, 2011). What we found was a pronounced increase in the number of projects in therapeutic areas with potentially higher sales, but also considerably higher risk of failure—e.g. antineoplastic and central nervous system agents. More mature areas, such as cardiovasculars, where probabilities of success have been higher, but potential rewards lower, lost ground.

Resource constraints may be responsible for another trend we observed: the number of indications tested per drug declined steadily over time. This means that if a drug should fail for a particular indication, testing for a new indication will take longer and require an entirely new set of clinical trials.

An important question is whether these trends in productivity are observable everywhere, i.e. in companies based in Europe as well in those based in the US. Our analysis showed no systematic difference across countries in the rates of R&D success, despite some difference in the relative riskiness of projects undertaken.

What appears to be a decline in overall productivity in the pharmaceutical industry, then, is not the result of a lack of effort, but is because R&D is targeted at increasingly difficult therapeutic areas. This choice of targets, in turn, is driven by the constraints in the macroeconomic environment that affect markets and, as a result, the resources available for R&D.

Table 2.1. Trends in disease targets: success rate, sales and shares of R&D projects*

ANATOMICAL THERAPEUTIC CLASSIFICATION (ATC1)	NUMB PROJ	AVE SALES (US$m)	AVE POS (%)	PERCENTAGE OF TOTAL PROJECTS 1990–1999	2000–2007	CHANGE
I: Antineoplastic and immunomodulating agents	6,566	105.3	1.80	21.77	29.77	+8.00
Including L01: Antineoplastic agents	5,094	92.0	1.29	16.55	23.43	+6.88
N: Nervous system	3,817	43.5	2.85	14.46	15.55	+1.09
B: Blog and blood-forming organs	822	72.9	3.81	4.11	2.38	-1.73
J: Anti-infectives for systemic use	4,737	82.4	3.92	18.85	18.41	-0.44
M: Musculoskeletal system	1,472	22.6	4.19	6.49	5.10	-1.39
A: Alimentary tract metabolism	2,046	14.8	4.46	7.26	8.82	+1.56
R: Respiratory system	1,165	13.3	4.81	5.07	4.10	-0.97
C: Cardiovascular system	2,139	45.6	4.86	10.72	6.15	-4.57
D: Dermatological	859	4.4	6.64	3.63	3.13	-0.50
G: Genitourinary system and sex hormones	865	2.1	11.75	3.90	2.86	-1.09
Other (H+P+S)§	945	11.2	19.79	3.70	3.73	+0.04

*The top 10 areas in terms of activity are defined according to the top level of the ATC system.
Key: POS = probability of success. ‡All differences are statistically significant (P-value <5%) except for class J and the residual class "Other". §H represents systemic hormonal preparations, excluding sex hormones and insulin; P represents antiparasitic products, insecticides repellents; S represents sensory organs.

Source: Pammolli, Magazzini and Riccaboni (2011)

THE NATURE OF THE R&D PROCESS

Competition and patents are important features of the process of innovation. Patents play two roles. Perhaps the most familiar is that they allow the inventor to expend the resources necessary for R&D. At least as important, however, is that patents disclose information about chemical structures that can give important clues to competitors—and competition can be essential to achieving innovation. For example, camptothecin was discovered in 1966 during a screening of natural compounds for possible anticancer properties. Although the molecule clearly had cytotoxic properties, it also was unstable in its natural form. This prompted several companies to develop analogues of the molecule; a number failed, but those failures provided crucial knowledge that eventually led to two products that were marketed for the treatment of cancer. The prospects for developing successful treatment for a particular disease, then, may depend heavily on a number of companies competing by pursuing similar leads and learning from one another's failures.

Sharing knowledge leads to innovation, whether it is through patents and publications or more directly through collaborative efforts among scientists. Our research on the structure of scientific communities is intended to describe how that happens and suggest ways of encouraging it. We have looked at clusters of activities—e.g. co-authorship of publications and patent co-invention or co-assignment—comparing activity in Europe

to that in the US. What we have found is that, in the US, collaboration occurs rather easily from one site another, integrating knowledge across the continent. In Europe, in contrast, national systems of innovation appear to create rather rigid barriers to collaboration. As a result, Europe lags behind in creating an integrated environment for research and innovation. Change is essential if a true "European Research Area" is to emerge: "a unified research area open to the world based on the Internal Market, in which researchers, scientific knowledge and technology circulate freely and through which the Union and its Member States strengthen their scientific and technological bases, their competitiveness and their capacity to collectively address grand challenges" (European Commission, 2012, p. 30).

Conference discussion

Question: Because of longer development times and costs, it is true that a company tends to focus on a particular indication and that can be risky. At the same time, however, resources are such that we also have to limit the number of therapeutic areas in which we do R&D. Do you see this as an issue? Are we missing opportunities?

Pammolli: Yes, I believe so, and I see another issue: the cost of clinical trials in the later stages of development. Although I do not have actual data, it seems to me that the cost of development for more than one indication for the same drug must be increasing dramatically.

Question: Your points on scientific collaboration were very interesting. What conclusions can you draw from the fact that the US is more integrated? Is this producing more success and more innovation?

Pammolli: The US system is at once both more competitive and more plastic. Collaboration across institutional boundaries, in the US, is driven by competition and creates important synergies. In the EU, the emphasis is on inclusiveness within each Member State, which creates a division of labour based on national borders. This inhibits the kinds of openness that characterises the US. I see this as an issue Europe must address.

Question: I appreciate your analysis, which demonstrates an increasing emphasis on high risk/high return R&D projects. Is this beneficial for public health or should we be considering policy interventions that might change the trend?

Pammolli: The movement into higher risk/higher reward areas seems a natural response to diminishing returns from R&D in the more mature therapeutic areas. Regulation is producing unintended side effects. So, no, it is not a natural progression, but is created by artificial incentives in the market, distortions produced by regulatory systems and by pricing and reimbursement schemes.

The basic problem is in funding; relying entirely on the current pay-as-you-go system for the funding of health is a serious issue. Those currently working are bearing nearly all the burden, which is unsustainable and can lead only to rationing, price containment and an overall disincentive for innovation. There is no easy answer: a different combination of public and private funding, coupled with a different design of the private component, might create better balance. We should explore an intergenerational approach that is realistic about the impact of ageing and the negative macroeconomic effects of relying on pay-as-you-go funding.

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Chapter 3.

LOCATING R&D INVESTMENT TO IMPROVE EFFICIENCY

PROFESSOR SIR JOHN BELL
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The UK continues to be a leader in innovation in the life sciences. As we move forward, armed with the incredible new knowledge and tools that translational research is offering, the challenge is to make the most of a wide range of important opportunities. A year ago, the UK government published a strategy for the life sciences. The aim is to create a much more responsive environment that will not only advance basic knowledge, but also feed commercial development and contribute to economic growth. Core aspects of the effort are outlined here.

The UK's strengths as a science and research base

The research base in the UK is far stronger than the size of its population would suggest. To take a few examples, UK scientists have been awarded over 70 Nobel Prizes and Cambridge University scientists have won more than any other institution worldwide. Four of the world's top ten universities for life sciences are located in the UK. With only 1% of the world population and 3% of the world's GER[1], the UK produces the highest number of science, mathematics and computing graduates annually in the European Union, enough to fuel the UK's life sciences pipeline over the coming years.

The UK hosts 4% of the world's researchers and is rated as the best European location for bioscience, and medical/clinical research. A leading country in the G8 in research productivity, 6% of the world's published articles come from the UK, 9% of usage and 11% of all citations, including 14% of most the mostly highly cited articles. The environment for the innovation agenda in the life sciences in the UK, then, is exceptional.

The commercial side of the life sciences economy also is impressive. The pharmaceutical sector comprises more than 350 companies, employs nearly 78,000 people and has an annual turnover of nearly £32 billion (DBIS, 2011). In the past decade, the industry has grown at a rate of nearly 10% per year, compared to about 4% for the economy as a whole.

R&D spending in the pharmaceutical industry accounts by far for the largest share of any sector in the UK: £4.6 billion, 9%, in 2010. Output is equally impressive. Medicines that originated in UK companies captured a 16% share by value of the world's 100 top-selling drugs in 2008. Overall, life sciences account for almost 9% of UK manufacturing value added.

[1] The Gross Enrolment Ratio (GER) is the total enrolment within a country in a specific level of education expressed as a percentage of the population in the official age group that corresponds to this level of education.

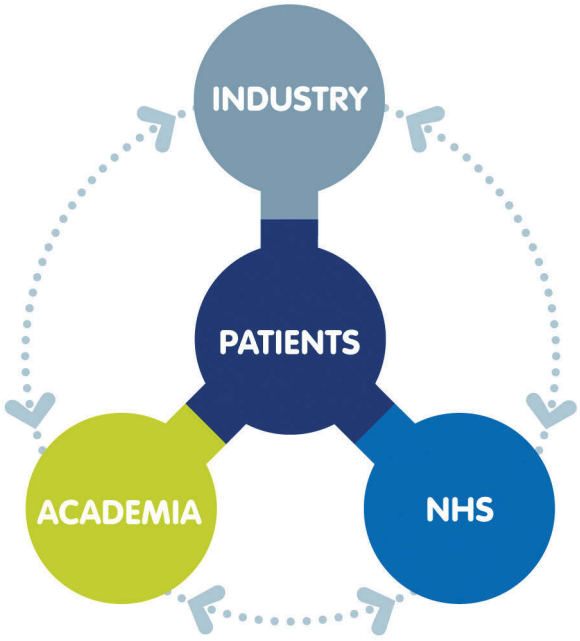
The medical technology and biotechnology sectors (which together with the pharmaceutical sector make up the UK life sciences sector) also are substantial, including over 4,000 companies that employ 87,000 people with an annual turnover of around £18 billion. The UK leads the rest of Europe in the number of molecules that biotechnology companies have in clinical development in Phases I, II and III, accounting for over 20% of the European total in 2010 (Ernst & Young, 2011).

The life sciences business, then, is important to the economic base of this country. But it is facing a dramatically changing environment. This includes changes in the nature of pharmaceutical R&D; pressures on health care budgets within the UK, particularly as the population ages; enticing investment environments outside the UK, especially in emerging markets; and simpler regulatory processes for the development and approval of new therapies in other Western countries.

Aligning for growth

About a year ago, the UK government recognised the importance of creating a more coherent approach to encouraging economic development in the life sciences sector during this period of economic challenge. The fundamental aspects to be emphasised were identified as the academic base, industry capabilities, and the NHS, which has not always been an asset in creating economic growth. The report that sets out the plan, Strategy for UK Life Sciences, brings together these three strands and aims at encouraging both more growth and additional inward investment (Bloor, 2011).

Figure 3.1. Vision for the UK life sciences



Source: Bloor (2011), p. 6

The strategy report contains some 200 recommendations in all. The Prime Minister has asked Chris Brinsmead, Chairman of Proteus Biomedical, and I to help monitor progress. Although we realise that achieving all 200 is not realistic, the plan does contain important core ideas and actions that provide focus. Five are reviewed below: establishing a "global hub" for translational research, creating and using population data, encouraging clusters of research excellence, improving the regulatory and tax environment, and making full use of the NHS.

TRANSLATIONAL RESEARCH

One of the major objectives set out in the strategy report is creating an environment that will further position the UK as a base for the translational activity that transforms basic science discoveries into clinical utility. With that in mind, the government is making investments in a number of facilities and programmes. One of these is the Biomedical Catalyst Fund. Totalling £180 million, it will be managed jointly by the Technology Strategy Board and the MRC. It dovetails with other programmes in the UK already in operation, for example, the Wellcome Trust Discovery funds, the Efficacy and Mechanism Evaluation programme, and the MRC's experimental medicine programme.

The purpose of the Biomedical Catalyst Fund is to provide additional resources to help small companies bridge the financially difficult period of exploratory development, potentially also encouraging additional funding from risk-capital investors. Support will be available for both academically- and commercially-led research and development. Grants will match risk-capital investments, be evaluated quickly by a peer committee from the life sciences industry and will total about 60 over the next three years at about £2.5 million each (TSB, 2011).

Also part of translation research is £50million (£10 million annually for five years) for the Cell Therapy Technology Innovation Centre. Located in London, this facility will focus on the manufacture and development of cell therapy.

Regenerative medicine also is on the list of translation research programmes. A total of £24 million will be invested over five years, apportioned and coordinated through the existing research councils.

Stratified medicine is a substantial focus of the translational medicine effort. With £130 million allotted to it, the intent is to include a range of initiatives and projects. One focus, for example, will be to improve knowledge about how to define disease more accurately so that medicines can be targeted towards precise patient populations. Funding also will support research to define the responder/non-responder populations that inevitably appear for novel therapeutic interventions. The programme will fund collaborations among academia, industry and clinicians. It also includes a unique, £10 million open innovation collaboration with AstraZeneca that provides academic researchers with access to 22 clinical and pre-clinical compounds (see chapter 1).

The concept of precision medicine often is misunderstood. The purpose is better characterisation of patient populations and a refinement of the way diseases are defined, a fundamental change in the practice of medicine. Precision medicine involves being able to identify disease based not on the patient's complains or phenotypic symptoms at the bedside, but instead on an understanding of which pathways are active and how they became active. This was described beautifully in the 2011 US National Research Council report on precision medicine (NRC, 2011). The bottom line is that we need to use all the tools available to improve understanding of the mechanisms of disease because that new classification system is crucial to the more efficient development of therapies.

Lung cancer provides an example. As noted in chapter 1, much progress has been made. Once seen as a single, intractable disease, lung cancer now is being broken down into a series of well-defined diseases. Each is driven by a separate variant and each requires a particular treatment. A very important question is how we progress from this substantial increase in knowledge, acquired in a short period of time, to effective therapies. Of greatest interest are therapies delivered early in the course of the disease that will have long-term impact, replacing the current approach that introduces treatment in the late-stages of disease with relatively little impact on long-term survival.

CREATING AND USING POPULATION DATA

A third major area of action is data, including creating an "information commons" that allows access to a wide range of data of all types. Researchers increasingly are recognising that a wealth of information exists, ranging from routine patient records in the NHS to patient data collected for large-scale studies. Having access to that data could help reveal new definitions of disease and provide new insights into which drugs are working in which patient populations and why.

An opt-out consent system for access to patient data in the NHS has been proposed. The default would become silent consent by patients for use of their anonymised NHS data. This has not yet been implemented, but is likely to be within a year. Various consultations are in progress.

The UK already has a good system for accumulating data from GPs and pharmacies. The plan is to make 25 million GP records available over the course of the next year through the Clinical Practice Research Datalink (CPRD), roughly twice the current number of 12 million records. The HES database, which contains NHS hospitals records, is easily accessible to researchers and widely used.

Building databases also includes a plan to link tertiary treatment centres that have detailed phenotypic data by therapeutic area. Compiling the data from multiple centres would make it possible, for example, to study stroke or various types of cancer in greater depth. Many of these centres already are connected to electronic patient record systems and collating those is a major objective for the next year.

One of the great assets the UK has is Biobank. This contains data collected on a cohort of patients beginning with their initial recruitment and including subsequent encounters with the health care system. Biobank includes the DNA, plasma and urine samples of 500,000 patients and is beginning to be utilised more fully.

INNOVATION CLUSTERS

The concepts of clusters of research and innovation has two prongs—geography and expertise. A closely demarcated geographic cluster allows a community of scientists in academia and industry to work side by side easily. Global experience, however, teaches that although some geographic clusters may be enormously successful, others may not work (see chapter 2). Trying to think through how to create effective geographic clusters is a major objective of the UK's life sciences strategy.

The UK is fairly small geographically. Indeed, it takes about the same time to drive halfway up England as to drive from San Jose to the north side of San Francisco at rush hour. Size has been important in providing opportunities to interact nationally in, for example, efforts such as the translational research partnerships run by the Department of Health.

Criteria of successful clusters that may be particularly important to current UK efforts include the following.

- A strong university research base as the hub of the cluster. Often, the base is engineering, not medicine, with the biomedical component joining later. Perhaps the best examples are the Massachusetts Institute of Technology (MIT) and Stanford University in the US.

- Access to significant sources of risk capital. This currently is in flux worldwide as the nature of risk capital itself is changing.

- Infrastructure to support small- and medium-size companies. This includes science parks, incubator units, and other opportunities where interesting ideas developed in academia can move into a commercial setting.

- Access to human capital. Management is particularly important. Attracting effective managers is facilitated in geographic clusters where experience can move from, say, large companies to small, avoiding the barriers imposed by the disruption of personal lives.

- High-risk science in a low-risk environment. Productive clusters rarely are located in heavily urbanised settings, which represent higher personal risks, particularly for families.

- A multidisciplinary science environment. The role of engineering, IT and life sciences in the most successful clusters is evidence of the importance of this.

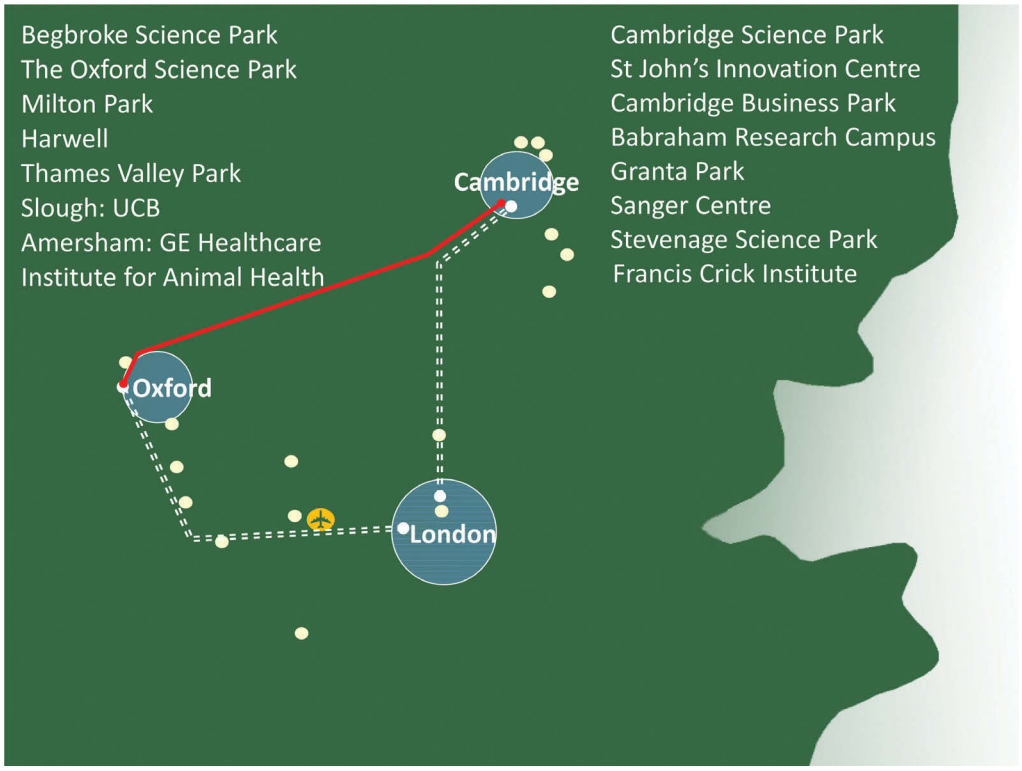
- Recycling. Successful clusters recycle knowledge and skills—intellectual property, management and finance. The latter occurs when those who have profited reinvest in the cluster.

Success is not as formulaic as this, of course. Experience shows striking differences. Using North America for examples, those areas and institutions in North America that have done well include Stanford University, MIT, North Carolina, San Diego, and Vancouver. Those that have a poor record include some top institutions—Harvard University and Columbia University—and major urban centres such as Chicago, Toronto and Los Angeles. The success of Stanford and MIT was built on engineering, not medicine, which developed later. Columbia, located in New York City, may have been less attractive because of the higher risk inherent in large cities. The story here, then, is that developing an effective cluster requires more than just a great university and appropriate expertise. A whole culture, or ecosystem, needs to be in place for a cluster to succeed.

In the UK, Scotland may well be our best cluster in the life sciences. Institutions there work well together and the patient base provides rich data. Manchester and Liverpool form the axis of another cluster, with AstraZeneca being an important participant. South Wales has an excellent environment for small companies and a growing medical technology cluster.

About 60–70% of the research money in the UK, however, is spent in the southeast of England. This potentially very powerful cluster includes a number of outstanding institutions in London, Oxford, and Cambridge and 400 or so biotech companies. As Figure 3.2 suggests, however, the southeast currently is divided into three separate clusters, with Cambridge probably being the most successful. The Thames Valley, then, is much more of an industrial corridor than a life sciences cluster.

Figure 3.2. Thames Valley cluster



One of the problems with developing a broader, Thames Valley cluster is that travelling between Oxford and Cambridge is a complete nightmare. One option for solving that problem is building the "Innovation Line", as it has been called. In Figure 3.2, the red dotted line is a railway line that has been disused for many years. The government recently committed £250 million to reopen it as far as Milton Keynes and Bedford—about half way between Oxford and Cambridge. In discussion now is whether to complete that other half. This would bring together the major hubs and create a network of centres no more than an hour away from one another.

REGULATION AND TAXATION

The new strategy also addresses regulation and taxation. With respect to regulation, recommendations include developing and implementing an adaptive licensing exemplar through the Medicines and Health products Regulatory Agency (MHRA) and making wider use of the expertise of NICE in appraising medical technology. Taxation is a difficult issue at present, given the state of the economy, and providing substantial tax incentives in the near term is unlikely.

Adaptive licensing, if it can be made to work, will be transformative. MHRA has established a committee for innovative regulatory strategy that is considering it. Since the Cooksey report in 2006, interest has grown in creating a regulatory system that allows earlier release of products, as early as after Phase II, in return for additional data being collected in actual clinical practice at the same time that Phase III trials are in progress (Cooksey, 2006). Of course, this would be appropriate only for drugs with evidence indicating high efficacy and acceptable safety. The potential benefits are far ranging: patients would benefit by gaining access to important therapies sooner; health technology assessment would benefit from effectiveness, not just efficacy, data from actual use, something lacking today; and small companies would benefit from being able to generate revenue at an earlier stage.

CREATING MID-SIZE COMPANIES

The UK has few mid-size companies, which is a continuing problem for the economic base. Experience in both North America and Europe has proven that these companies are important for innovation, employment and economic growth. Examples include NovoNordisk and Lundbeck in Denmark; UCB in Belgium; and Gilead, Amylin, and Celgene, among others, in the US. The UK strategy needs to find ways to foster the development of mid-size companies by reducing costs, ensuring revenue streams begin earlier, and developing new forms of equity capital.

THE NHS AT THE CORE

Bringing the NHS into this innovation agenda is one of the most important steps that the current UK government can take. This is a challenge; the NHS understandably is focused more on delivering care than participating in innovation. The potential for useful information from the NHS, however, is immense:

- On average, the NHS serves one million patients every 36 hours, or eight patients every second.
- In 2010, the Clinical Research Networks supported the delivery of 2,500 clinical studies in the NHS.
- In 2010, the Clinical Research Networks supported the recruitment of more than 400,000 patients into clinical trials.
- Each year, 300 million primary care consultations occur in the NHS and nearly 100 million hospital visits.
- The NHS collects data on hundreds of millions of patient episodes of treatments per year.

As noted earlier, these data can be crucial in developing approaches to precision medicine and to other aspects of innovation.

UK leadership in innovation

Some sceptics believe that the UK's research environment is weak, particularly compared to the US. This is not what history shows and not what the future promises. Consider genetics, probably the most transformative technology in the modern life sciences. Darwin was the origin. He may not have known what "genetics" is, but he sure knew about what genetics does. Garrod, who described the genetic basis of disease in 1920, was based in London. England's Crick and the US's Watson worked together in the discovery of the structure of DNA. Britain's Sanger not only is responsible for the discovery of DNA sequencing, but is the only person to have won the Noble Prize for Chemistry twice. Jefferies and Southern, both British, led the way in developing tools for measuring genome variation.

The most important single development in recent years has been next-generation sequencing, which has opened the door wide for affordable personalised medicine. The core technologies upon which it is based have a UK connection. Illumina's sequencing technology, based in San Diego, was discovered by Shankar Balasubramanian from Cambridge University. Chris Toumazou, from Imperial College, developed the intellectual property for the Life Technologies platform, based in the US. Hagan Bayley in Oxford has developed the nanopore sequencing technology.

Thus, a host of activities that have exploited the human genome from its discovery to the current day have been driven by significant science in or from the UK. The ability of this country to deliver innovation is indisputable. We have simply to turn our minds to determining how to do more of that as quickly and efficiently as possible.

Conference discussion

Question: Management is an important aspect of the success clusters. I am interested in your thoughts about how to maximise use of management resources, particularly in smaller companies. I also would like to point out that the Los Angeles area in the US does have an innovation cluster with Amgen and Genentech as nodes.

Bell: One of the models we are pursuing in Oxford now uses the same management team to run two or three companies at the same time. In effect, that's how the multinational pharmaceutical industry operates, with managers who oversee several projects simultaneously. "Sharing" management teams is more efficient and makes better use of experienced managers.

The role of bigger companies in clusters is interesting and warrants further exploration. Certainly, in Silicon Valley, Apple and Google dominate. It would be good to know whether and how they influence the cluster to engender an entrepreneurial culture.

Question: How can research management and leadership in the universities better encourage effective clusters?

Bell: Incentives are very important in spurring people to act and to pursue particular paths. Directed funding can be an important tool. Cultural change also will be necessary. Academics typically have not been inclined to focus on helping the commercial sector or facilitating economic growth.

Question: A few years ago a pilot programme was initiated that was intended to work with large pharmaceutical companies in encouraging R&D in the UK through "translational research partnerships" that, in part, facilitated access to patients for research trials. That seems to have disappeared. What has happened?

Bell: This was an effort of the prior government and appeared to be very effective. Basically, it got lost in the transition from one government to the next. It appears that the Department of Health finally will initiate some new projects in the near future. Unfortunately, this is a very good example of how a change in government, and a consequent change in priorities, can substantially slow progress on worthwhile programs.

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Chapter 4.

THE GLOBAL HEALTH CHALLENGE FOR INDUSTRY R&D AND ACCESS TO CARE

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The conversation about the challenges and opportunities of realising R&D and health delivery goals for the poorest in developing countries fits well within the context of dialogue about the future of the pharmaceutical industry. The global health[2] community can both learn from and leverage the progress that companies are making in improving R&D outcomes and productivity. At the same time, in some areas, the global health community probably is ahead of industry and thus in a position to teach and partner—particularly in addressing issues around global regulatory pathways; product differentiation; and pricing in emerging, developing and developed countries. At a fundamental level, the missions of the global health "sector" and the pharmaceutical sector are similar in that both seek to help secure a healthy, productive life for each person.

The global health community has grown and evolved considerably over the past decade. The Bill & Melinda Gates Foundation specifically has honed and adapted its policy and funding toolkits in response to what has worked and what has not. A decade ago, the focus was on the creation of macro-global structures to improve global health commerce—for example, the GAVI Alliance and the Global Fund to Fight AIDS, Tuberculosis and Malaria (Kettler, 2000). Product development partnerships (PDPs), which are public-private partnerships intended to address gaps in product development, were just beginning to take shape; teams learned how best to contribute to progress through trial and error. Necessarily, a great deal of attention was placed on the significant challenge of raising the funds from public and private sources required to make a difference.

In the past few years, attention in the global health sector has begun to shift away from quantity alone—more money, more products—to include quality—better, more effective, targeted resources and better products. A similar trend is underway in pharmaceutical companies. In part, this is driven by new realities in the global economic climate where funders are becoming more results oriented. It also reflects the fact that the global health community has become more sophisticated in identifying needs and in organizing

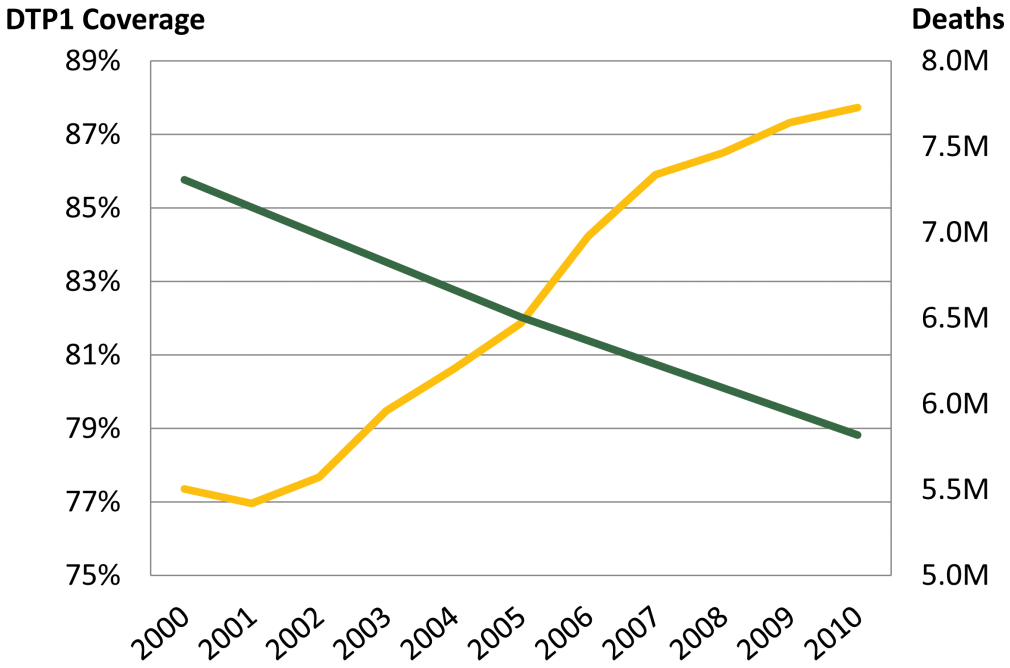
[2] For the purposes of this chapter, "global health" is defined as the health problems that have a major impact in developing countries, but get insufficient attention and funding. Problems persist either because proven, sustainable tools do not exist and need to be developed, or are not accessible to those who need them. The list of health problems includes enteric and diarrhoeal disease, HIV/AIDs, malaria, pneumonia, tuberculosis, neglected tropical diseases, family planning, maternal, neonatal and child health.

efforts to ensure that products are developed specifically to fit those needs. In this context, the engagement of the pharmaceutical industry has broadened, diversified and, arguably, produced more effective partners.

Progress in improving health outcomes is unprecedented

While much remains to be done, we have made significant progress over the past decade against curable diseases and poverty, which can crush even the healthy. Figure 1 shows the effectiveness of just one effort: immunising children less than five years of age. Immunisation alone is not entirely responsible for the decline in child mortality. Malaria drugs, the use of bed nets, and many other factors also contribute. But the correlation is important and results are significant.

Figure 4.1. Effect of immunisation on deaths of children under five years of age



Source: Author's calculations based on UNICEF child mortality indicators and WHO immunization rates, 2010 data

Through partnership alliances such as GAVI, established in 1999, 288 million children have been immunised since 2000, saving over 5.5 million lives. GAVI's initial focus was on boosting routine vaccine immunization rates, for example, for diphtheria, tetanus and pertussis (DPT), and the introduction of hepatitis B and Hib vaccines. Both vaccines had been introduced in the developed world in the 1980s, but still were too expensive for substantive uptake in developing countries. The GAVI model has expanded since 2006 to include newly-registered vaccines for rotavirus and pneumonia and to prepare for the HPV vaccine.

The success of GAVI's interventions can be measured in the number of vaccines taken up, the increasing rates of immunization, the number of lives saved, and the reduction in the number of years that pass between a vaccine's initial launch and its introduction in GAVI countries. In contrast to a decade ago, companies now are introducing products simultaneously in developed and developing countries. This is a critical change that potentially can to reduce the disease burden in developing countries.

GAVI and its funding of vaccines also have helped stabilize the supply side. Throughout the 1990s and into the 2000s, the number of companies engaged in vaccine development and production fell. Sources of supply were becoming tenuous, even for routine vaccines such as those for measles or pertussis, diphtheria and tetanus (TDaP or DTP). Since the establishment of GAVI, and the commercial success of a number of key vaccines, the situation has changed considerably. For most diseases prevalent in the developing world, at least two suppliers exist. Using measles and DTP vaccine again as examples, four suppliers now provide vaccines for measles and eight for DTP. Many of the new manufacturers are in emerging markets, including China, Brazil, India, Indonesia and Mexico.

In R&D, much discussion has occurred, and will continue, about what "narrowing the gap" in access to medicines actually means. Most agree that new tools to treat and prevent priority diseases of the poor are needed and that the pharmaceutical industry had been investing relatively little in these indications, given their relatively low revenue projections compared with non-communicable diseases. Substantial progress has been made over the past decade, resulting in the largest-ever neglected disease pipeline, including vaccines, drugs and diagnostics. Energy, funding and attention is unprecedented; the challenge for the future is to apply the scientific, clinical and health-economic vigour required to ensure that the products developed and registered sufficiently match needs.

Regulatory regimes for testing and approving new drugs also have progressed, as they must. "Adaptive licensing" and other measures that speed relief to patients is nowhere more urgent than in the developing world. For example, tuberculosis treatment is most effective with a combination drug, but regulatory practice had required that each antigen or new compound be tested on its own and then again in combination. Development times, as a result, have been extremely lengthy—stretching to decades. This is beginning to change. In 2009, the US FDA began working with global health agencies to allow companies and non-profits to test combinations without first testing each component (Schoofs, 2010). This is critical to expediting progress, particularly towards addressing tuberculosis.

Meningitis A offers an excellent example of what can be accomplished through partnerships in targeting a specific need. With a grant from the Gates Foundation, organizations contributing to the Meningitis Vaccine Project developed MenAfriVac, a new meningitis vaccine at an affordable price (US$.50 a dose) using a delivery system appropriate for the targeted "Meningitis belt" of sub-Saharan Africa. The key partners involved are the Serum Institute of India, a private for-profit vaccine company based in Pune, India; the World Health Organization (WHO); and PATH, a non-governmental research organisation based in Seattle.

Building an innovative toolkit for problem solving

The Gates Foundation remains at the centre of efforts to leverage these early successes to achieve ambitious goals for the list of the most serious, neglected threats to the poorest. In the case of polio, the Foundation has its sights set on eradication. In HIV/AIDS, its portfolio of investments is focused on significantly reducing HIV incidence at the population level through the development of more effective prevention methods. For malaria, with eradication as a long-term vision, the Foundation is working with partners to identify more effective approaches to diagnosis, treatment and prevention while supporting the efforts of partners to eliminate the disease entirely in eight to ten countries in the near term. Pneumococcal disease, diarrhoeal diseases, and tuberculosis also are priorities, as is eliminating the threat of neglected tropical diseases for the one billion people at risk who live in the poorest regions of the globe.

The Gates Foundation cannot and does not seek to meet these goals on its own. Broad-based collaboration and cooperation are required from all global health sectors, public and private. As noted above, over the past 20 years, a large number of independent, non-profit, global health initiatives have been launched. One example of a PDP in the R&D arena is the Medicines for Malaria Venture (MMV), created in 1999 through the farsighted efforts of the World Health Organisation (WHO), the UK government, the Rockefeller Foundation, and the pharmaceutical industry—specifically, the Association of the British Pharmaceutical Industry.

As they mature beyond the start-up phase, these PDP initiatives face challenges similar to those of small biotechnology companies and larger pharmaceutical companies, as described by Dr Pangalos and Professor Bell elsewhere in this publication (chapters 1 and 3, respectively). Consolidation of key functions, including regulatory and business development, drives efficiency, but indication-specific entities are better advocates for the needs of the different diseases. Standard management practice of driving towards timely results against clearly defined priorities are a greater challenge for non-profits, which often receive issue-specific funds up front rather than in return for milestones met. At the Gates Foundation, new approaches are emerging to provide enhanced push and pull incentives that complement the ongoing grant based programs. For example, on the push side, the Foundation recently has started to leverage its balance sheet to encourage R&D by making select and well-targeted strategic equity investments in biotechnology companies, alongside other venture capitalists. This is in addition to its existing programme of grants. Eligible companies are those that have platforms for projects in areas of interest to the Foundation and a management team with global health as a main strategic focus.

On the "pull" side, the Foundation has offered volume guarantees as part of an effort to secure more affordable prices for developing countries and poor populations in emerging countries. This increases predictability for suppliers and also may encourage the production of larger volumes, which is important in ensuring consistent supply. Early examples suggest this can work in certain circumstances. To take an example, a secure supply of affordable oral polio vaccine (OPV) is essential to eradicating polio. OPV is an unattractive longer-term market for suppliers, however, as inactivated polio vaccine is expected to replace OPV in the coming years. In 2010, The Foundation offered a volume guarantee to one supplier that had intended to exit the OPV market. This secured approximately 20% of UNICEF's OPV procurement needs through 2012. With the market more certain, the supplier also was able to agree to reduce its price by approximately 15%. The volume guarantee closed out in 2012—and because UNICEF purchased all guaranteed volumes, the Foundation incurred no financial costs.

In the case of pneumonia, the Foundation's objectives are not only to ensure the supply of existing vaccines, but also to encourage the development of new types of vaccines to take into account both serotypes neglected in the existing vaccines and growing resistance. We continue to work with private, non-profit and country partners to maintain and expand supply of PCV and antibiotics to Africa and Asia and to reduce costs. Grants and equity investments are being aimed at producing a common protein or whole-cell pneumococcal vaccine that would eliminate the issue of serotypes.

Being able to secure access and shape and support R&D is a luxury the global health community never imagined it would have. The important message for pharmaceutical companies is that the global health community is interested in working in partnership to realise mutually beneficial outcomes. The track record is growing for initiatives where companies are able to both earn a return on investment and deliver an affordable product. Approaches need to be refined and improved, but the growing willingness to engage in partnerships reflects an important cultural shift over the past decade.

On the pharmaceutical industry side, attitudes also appear to have changed—quite dramatically in select cases. A shift has occurred from defensive, reactive responses in global health forums to examples of real, proactive leadership. Serious discussions are occurring across companies about how collaboration can occur in R&D to develop new treatment for, say, lymphatic filariasis. This echoes Dr Pangalos's discussion about the increase in pre-competitive collaboration across companies (see chapter 1).

To avoid losing momentum, especially in the current economic climate, new commitments to global health are crucial. The January 2012 London Declaration is an example of positive industry engagement in collaborating to provide unprecedented resources to combat neglected topical diseases. Party to the agreement are 14 pharmaceutical or device companies[3]; the US, UK and UAE governments; the World Bank; and the Gates Foundation and other global health organisations (Gates Foundation, 2012). The Declaration announces a new, coordinated push to accelerate progress towards eliminating or controlling ten neglected tropical diseases by the end of the decade (London Declaration, 2012).

Another important example of public-private fundraising and visibility is the successful GAVI "pledging conference" held in June 2011 in London where "major public and private donors achieved a milestone in global health . . . by committing [$4.3 billion in] funding to immunize more than 250 million of the world's poorest children against life-threatening diseases by 2015" (GAVI Alliance, 2011). Alongside the global health funds, GSK pledged to supply up to 125 million doses of Rotarix® to developing countries over five years at a price approximately 95% less than for the Western market (GSK, 2011). Both GSK's announcement about differential pricing and the timing of the announcement are clear indications of a new business model.

A third example of new approaches occurred in family planning in July 2012. In spite of tight budgets, new money was pledged by several countries towards the goal of giving 120 million additional women access to family planning tools. Two months later, an innovative partnership was created that allowed Bayer to offer a 50% reduction in the cost of its long-acting contraceptive implant, expected to reach more than 27 million women. For the first time, a country, Norway, intends to be one of the primary guarantors of volume purchasing, representing a new way of contributing to the global health effort (Bayer, 2012).

Leveraging progress going forward

Despite the generosity of donors and innovative approaches to using available resources, funding remains a major issue. R&D is far from being fully funded, and the delivery and implementation of the tools and programmes ultimately is 15 or 20 times the cost of the R&D itself. Donor support will continue to be essential.

[3] Abbott, AstraZeneca, Bayer, Becton Dickinson, Bristol-Myers Squibb, Eisai, Gilead, GlaxoSmithKline, Johnson & Johnson, Merck KGaA, MSD, Novartis, Pfizer and Sanofi

Triangular partnerships are being explored to broaden the donor base and involve important emerging economies, particularly Brazil, China and India. The sides of the triangle are the emerging economies, the traditional donor countries from the developed world, and the Gates Foundation. The emerging economies themselves face many of the priority global health issues, but triangular partnerships go beyond that: the Gates Foundation is seeking new opportunities for R&D and China, Brazil, and India are investing billions in their own biotechnology industries. The foundation is exploring whether this may offer viable new R&D options. Such initiatives will run parallel to continued efforts to secure philanthropic contributions and government aid for R&D and delivery.

The global health community in general, and the Gates Foundation in particular, seeks to broaden and deepen the pharmaceutical industry's engagement in helping solve global health challenges in the years to come. A dedication to partnership has developed, one that is clearer about requests and expectations, but one that also is much more sophisticated in mitigating risks for those who develop and market the tools we need to improve health worldwide. Partnerships with industry in global health have had, and will continue to have, an extraordinary impact on people's lives.

Conference discussion

Question: Whose responsibility is it to monitor the effectiveness and safety of the products in the programmes once the treatment is on the market? Is it the funder, the country or the manufacturer?

Kettler: This varies. Technically and ethically, the companies are responsible, but remember that not all the manufacturers are large multinationals with the resources to do systematic post-approval surveillance or research. Remember, too, that most efforts are partnerships so, for example, the Gates Foundation is supporting some Phase IV studies, particularly in malaria, to attempt to identify what works, and where and why resistance is arising. A working group composed of WHO, the country representatives, the Foundation and companies is exploring the vexing question of sharing responsibility based on the recognition that the capacity for monitoring is under-resourced.

Question: Does the Gates Foundation have an implicit model for support of R&D funding in its equity investments? Are you focusing on large multinationals or smaller biotechnology companies? Where does the Foundation see the greatest promise?

Kettler: In the past, many of the original partnerships were with multinationals because often they already had compounds that were good prospects for development, but had been shelved for commercial reasons. This was particularly true of malaria medicines. For tuberculosis medicines, in contrast, it became clear quite quickly that much less was on the shelf than many thought. In vaccines, the cost of R&D was much greater than the expected size of the potential market and, again, little was waiting on the shelf.

Within the product development partnerships, the initial split between the multinational pharmaceutical industry and smaller biotechnology companies was about 50–50. However, the multinationals offer more in-kind opportunities with lower transaction costs. It was often more efficient economically to work with the larger companies, which do not depend on venture capital for their livelihood. Venture-backed companies have a harder time diverting resources towards products with expected lower rates of return.

The equity investment by the Foundation is a response, in part, to the reality that small companies require additional types of funding opportunities and incentives. In addition, we issue requests for proposals offering small grants to advance a specific aspect of a technology; many biotechnology companies respond. The balance between the two

types of companies is partly practical, and partly a function of what problems are being addressed given the different roles these companies play in the value chain.

Question: Which of the three sides in the triangular partnership seems most vulnerable to the global economic slowdown? How has that affected funding and planning?

Kettler: Certainly, austerity has had a serious impact on the pool of aid dollars from donors, although the changes in the rate and amount vary from one donor to another. With emerging economies, we are looking for partnerships with specific agencies—health or science and technology. Most vulnerable are those developing countries that are highly dependent on aid to fund health care systems and purchase products. We need to create unique, triangular partnerships rather than rely on traditional flows of funds from donor to developing country.

Question: What has happened to funding from donor countries in the current economic climate?

Kettler: It is a mix. Some have maintained their aid budget while others have cut it. The UK is holding to its commitment to donate a set share of GDP, although obviously the absolute amount declines if GDP declines. Norway and the Scandinavian countries, affected less by the slowdown, have maintained their donations. The US continues to be very unpredictable; donations have stopped increasing and, in fact, have started to decline although the US still donates the most in absolute terms. Some countries were just becoming involved, but have now pulled back—Spain, Ireland and Italy, are now out. France's donations are down; Germany never has been a major donor.

Question: The disease areas that are included in your presentation are the traditional concerns for the developing world. Will global health be moving into other areas that also are prevalent in the major markets—chronic diseases and diseases of ageing, such as diabetes, respiratory disease and cardiovascular disease? How might this change the relationship with the pharmaceutical industry?

Kettler: As I noted, we do focus on upper respiratory infection, pneumonia especially, which is a concern worldwide. At the moment, however, there are no plans to move into other disease areas. That is mostly because we are still far away from realising our current goals. So in HIV, for example, we still are working to make progress in developing effective prevention tools—and will be for a while.

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Chapter 5.

MEETING THE SOCIAL CHALLENGES OF HEALTH CARE

Moderator
PROFESSOR TONY CULYER
York University and University of Toronto

Panellists
PROFESSOR PATRICIA DANZON, *Celia Moh Professor and Professor of Health Care Management at The Wharton School, University of Pennsylvania*
DR JENS GRUEGER, *Vice President and Head of Global Health Economics and Pricing at Roche Pharmaceuticals*
PROFESSOR SIR MICHAEL RAWLINS, *President, Royal Society of Medicine*[4]

LEFT TO RIGHT: *T Culyer, J Grueger, M Rawlins, P Danzon*

Introduction

The challenge for any health care system is to provide the best care possible to its user at an acceptable cost. Since OHE was founded in 1962, what that means in practice has changed dramatically. Treatments for diseases are available now that were barely imaginable in 1962. As the health care sector has grown, decisions about how to allocate resources efficiently have become more difficult.

This panel focused on the challenges of achieving value in health care systems, access to treatment for patients, and sufficient returns for encouraging continuing innovation.

[4] At the time of the conference, Sir Michael was Chairman of NICE.

Topics included whether and what role differential pricing for pharmaceuticals can and should play within and across countries at various levels of economic development.

Value based pricing, a variation of differential pricing, was discussed as an approach that will become more important as technology allows medicine to become more personalised. This session explored how that approach affects access, innovation and health care expenses.

Finally, the panel examined what health technology assessment (HTA) can contribute to decisions about value and access in both developed and developing countries.

The lively panel and audience discussion addressed provocative issues raised by changes in health care and identified potential practical sticking points in developing solutions.

Value-based differential pricing: optimal prices for pharmaceuticals in a global context

PROFESSOR PATRICIA DANZON, *Wharton School, University of Pennsylvania*

The issue of pharmaceutical pricing long has been a subject of concern. A variety of approaches has been tried or considered to ensure that pricing allows access for patients and encourages continuing innovation, but does not overburden health care systems. How best to approach pricing has been at the core of some of my recent research, in collaboration with the OHE, and is the basis for this presentation[5].

Three fundamental issues make setting optimal prices for pharmaceuticals difficult. The first is the most obvious—that pharmaceuticals are very R&D intensive. If the standard competitive solution of pricing equal to marginal cost were adopted, R&D would not be covered. The response in all industrialised countries, for all industries, is a patent system that enables companies to charge prices above marginal cost. In principle, at least, this should enable innovators to break even.

The second issue in pharmaceutical markets is the effect of insurance, a factor in most industrialised countries and increasingly in emerging markets. An advantage of insurance is that it makes health care affordable, but it raises a problem from a pricing perspective because it desensitises consumers to price. Payers then act as surrogates for consumers by putting constraints on prices and access.

Finally, pharmaceuticals are global products. To share the burden of paying for R&D appropriately, pricing differentials across countries must be optimal.

OPTIMAL PRICING

For economists, "optimal" prices should achieve two objectives. The first is static efficiency, i.e. a product should be consumed by anyone for whom the marginal benefit exceeds the marginal cost. Obviously, this raises the question of how to define "marginal benefit". In standard markets this is whatever individuals are willing to pay. In health care markets, however, the so-called altruistic willingness of some people to pay for others who are poorer than themselves also must be taken into account.

The second aspect of optimal pricing is dynamic efficiency which produces the appropriate

[5] Danzon, Towse and Mestre-Ferrandiz (2012); Danzon, Towse and Mulcahy (2011); Danzon, Mulcahy and Towse (2011)

investment in R&D. The goal is for firms to invest up to the point where the marginal benefit from R&D is equal to the marginal cost. The way to achieve that is to assure that firms capture the surplus above production costs that is generated by new innovation.

For global products, achieving static and dynamic efficiency requires optimal prices in each country and optimal cross-national price differences.

In all industries, patents are "second-best" optimal in addressing the dual problems of encouraging optimal access and optimal R&D. Patents are in effect for a limited term during which prices can exceed marginal cost. Use will be somewhat less than with first-best optimal pricing, which is a trade off for enabling producers to charge higher prices and thereby recoup the costs of R&D.

OPTIMAL VALUE-BASED DIFFERENTIAL PRICES IN A GLOBAL CONTEXT

For pharmaceuticals, it is important to distinguish between the problem of optimal pricing in countries that have comprehensive insurance and those that do not. Insurance solves the problem of affordability of patented products, but it also creates its own distortion in prices. In self-pay markets, particularly in emerging countries without comprehensive insurance for pharmaceuticals, the question is how achieve a reasonable trade off between affordability and R&D incentives.

Countries with universal insurance

Several prototypes for regulatory systems for countries with insurance exist. Broadly categorised, these include internal reference pricing, external reference pricing and cost sharing. The first, internal reference pricing, bases pricing for new drugs on prices of existing drugs. A new drug will be priced about the same as comparable drugs already on the market, possibly with a mark-up for being more innovative. This is not tied, however, to the notion of efficiency.

External referencing is becoming increasingly common, whereby one country references the prices in other countries in setting its own the price. This approach creates incentives for pharmaceutical companies to target a uniform price across the countries that are being referenced. In practice, if some of these countries cannot afford to pay that uniform price, the drugs will not be not available or be available only after a delay. External referencing undermines differential pricing which is fundamental to a good system, as explained below.

The last of the three, cost sharing, is used most heavily in the US where cost sharing by patients is applied in an attempt to control prices. For expensive drugs, however, that has ceased to work well because cost sharing would be so onerous that the drugs would be unaffordable for consumers. As a result, most insurance plans include catastrophic limits on cost sharing, which means that cost sharing has limited effect on price, at least at the higher ranges.

Using insurance to achieve static and dynamic efficiency in a single country. The problem of how to use insurance to address optimal pricing for pharmaceuticals in a single country has been addressed in some published papers (Garber, Jones and Romer, 2006; Lakdawalla and Sood, 2009). An important concept is that insurance enables a two-part pricing system—a consumer co-pay part and a payer reimbursement component, often called a "top-up". These papers propose that the patient's co-pay be set at a level equal to marginal cost. This would encourage consumers to use drugs up to the static efficiency point where marginal benefit equals marginal cost. The payer then would top up the payment to reach dynamic efficiency. The challenge is how to set that top-up payment. Key objections to this approach are (1) it is very difficult to set the co-pay to be equal to

marginal cost; (2) this could make expensive biologics unaffordable for many patients; and (3) in practice there is no readily available benchmark for how the payer should set the top-up payment, which is critical to R&D incentives.

In theory, the top-up payment should reach the monopoly price that a firm would charge if there were no insurance in the market, if the goal is first-best. However, this uninsured monopoly price is unobservable in countries with comprehensive insurance. Further, there are reasons to argue that the goal should be second-best, not first-best efficiency: that is, optimal utilisation and R&D incentives should be based on the full price to a society, not just the marginal cost.

Optimal price differences across countries. Some prior research supports price discrimination or differential pricing across countries based on the idea that utilisation will be higher and therefore global welfare will be higher with differential pricing than with a single uniform price across countries. Prior research also explores how to apply a theory called "Ramsey optimal pricing" to pharmaceuticals, and concludes that differential pricing is better than uniform pricing. The notion of Ramsey pricing is useful in supporting the idea of differential prices across countries, but it gives us no guidance as to what the absolute price level should be. That is the focus of our current work.

The outline, in brief, of our proposal for countries with universal insurance is that each payer should set an incremental cost-effectiveness ratio (ICER) that is based on its citizens' willingness to pay for health gain. Given this ICER as a condition of reimbursement, manufacturers will be incentivised to set their prices based on the incremental value of their medicine relative to comparator products. Second-best static efficiency and dynamic efficiency, in principle, is achieved if the payer then makes eligibility for reimbursement available to patients for whom the drug is cost effective at the price the manufacturer has chosen, given the payer's ICER.

We include co-pays in this system as a way of raising funds and deterring excess demand, but we do not rely on co-pays to incentivise the right level of utilisation. That is determined by the payer, based on what uses are cost effective.

Our starting point was a paper by Garber and Phelps (1997). That paper addresses the problem of the individual consumer allocating a fixed budget between medical care and other goods and services in a context where medical care has benefit in increasing the probability of survival and raising the quality of life in future periods. Consumption of other goods and services gives utility; the trade off is between how much to spend now on other goods versus how much to spend on medical care that will improve probability of survival and quality of life later.

Garber and Phelps (1997) found that the individual would spend up to the point where willingness to pay for health gain or improved longevity in the future is equal to the ICER, the ratio of the cost of the medical care relative to its expected gain in terms of future quality-adjusted life years (QALYs). The individual's optimisation decision produces the equation below, which sets the ICER equal to individual willingness to pay.

$$\text{ICER} = \frac{w_a}{\left({}^{dQ}/_{da}\right)} = \frac{v}{U_0'} = \text{WTP for health} = \text{K}$$

This can be applied in countries where a payer is trying to determine an optimal criterion for reimbursement. If the payer sets the willingness to pay threshold, K, based on preferences of the representative consumer in this country, then the manufacturer seeking reimbursement will be led to charge a price that reflects its efficacy compared to existing products.

To explain how this works, we begin with the equation below. It defines the necessary condition for a new drug to be deemed cost-effective, where $C_i = P + c$ = cost of treatment, i = n, 0; n = new drug; 0 = comparator; P = price of the drug (new or comparator); c = other direct (and indirect) costs; E = health outcome, e.g. QALYs; K = payer's WTP for health (cost per QALY), for example ~£30,000 for UK's NICE.

Incremental cost-effectiveness ratio (ICER) = $(C_n - C_0) / (E_n - E_0) < K$,

The ICER is the increment in cost of the new drug relative to the comparator relative to the increment in efficacy, which could be measured in QALYs. The drug is cost effective if the ICER is less than or equal to the payer's threshold willingness to pay, reportedly about £30,000 for NICE in the UK.

We can rearrange this equation to see how this criterion for reimbursement constrains the manufacturer's price. The first line is the ICER equation again. On the second line, P_0 = price of comparator; $\Delta c = c_0 - c_n$ = cost savings to payer, if any; and $\Delta E = E_n - E_0$ = health gain to patients. The manufacturer is incentivised to solve that ICER equation for the maximum price at which the product will be cost effective, given any cost offsets and any incremental efficacy. Essentially, the manufacturer is encouraged through the system to choose a price that reflects the incremental value produced by the innovation.

$ICER = \{(P_n - P_0) + (c_0 - c_n)\} / (E_n - E_0) < K$

$Value\ Based\ Price_n^{max} = P_0 + \Delta c + K\ \Delta E$

An ICER constraint on reimbursement eligibility thus indirectly controls price and defines eligibility. In summary, in this approach:

- Each payer in each country sets its own ICER threshold, based on its own citizens' willingness to pay—this cannot be tied to prices or other factors outside the country.
- Manufacturers are incentivised to choose a value based price.
- The payer then sets eligibility based on patients for whom the drug is cost effective at that price and given the ICER.
- Any co-pays are set at a level that is low enough to assure affordability, but still raise some funds.

This should achieve approximate second-best static efficiency and dynamic efficiency and, importantly, the price differentials across countries should reflect their respective willingness to pay, which produces optimal differentials across countries.

Although this is attractive in theory, the issue is whether it is possible in practice. Some modifications we considered are the following.

- In a country with multiple payers, each payer could set its own ICER threshold and prices would vary by health plan. In the US, health plans already pay different prices for the same drug. This is achieved through confidential rebates.

- The ICERs could vary by disease type. If willingness to pay for end-of-life diseases or orphan diseases is higher, then the ICER thresholds could reflect that.

- Patients could top up using their own funds.

- Prices could be adjusted after marketing begins. The initial price would be based on the data available at launch; adjustments could occur as new efficacy data become available.

- In theory, varying prices based on the difference in efficacy of a drug for different indications would be desirable. Essentially, differential pricing across indications would exist based on the differential efficacy of the product. This is difficult to implement in practice, but would get us to first-best in our model.

Countries without universal insurance

Other issues arise in middle- and lower-income countries (MLICs) that do not have universal insurance. Without external reference pricing or parallel trade constraints, a pharmaceutical company might act as a monopolist, setting prices based on a country's average willingness/ability to pay, which reflects average income. But if income distributions are highly skewed, a monopolist would price to the most affluent segment. In practice, however, monopolists do not have a monopoly, but face competition from branded generics. Quality is uncertain because the branded generics are not all required to produce up to regulated quality. Price thus becomes an indicator of quality, and prices are in fact high, relative to average per capita income.

We did a study of the situation in MLICs (Danzon, Towse and Mulcahy, 2011). What we found was very little variation with per capita income, weak competition and high prices. The approach we propose for addressing these problems includes (1) requiring a minimum quality standard for generics and (2) creating institutions that facilitate within-country price differentiation so that prices vary with income.

CONCLUSIONS

To conclude, our research has found that:

- Optimal pricing challenges and solutions are different in countries with and without comprehensive insurance.

- In countries with insurance, second-best static and dynamic efficiency can be approximated if: payers define ICERs unilaterally, based on their citizens' willingness to pay; manufacturers set prices; and payers determine eligibility for reimbursement.

- In countries without insurance, assuring the quality of generics would improve price competition and, so, affordability.

- Policies that facilitate price discrimination between and within countries could increase patients' access to drugs and profits for manufacturers.

Personalised health care and value based pricing: creating access

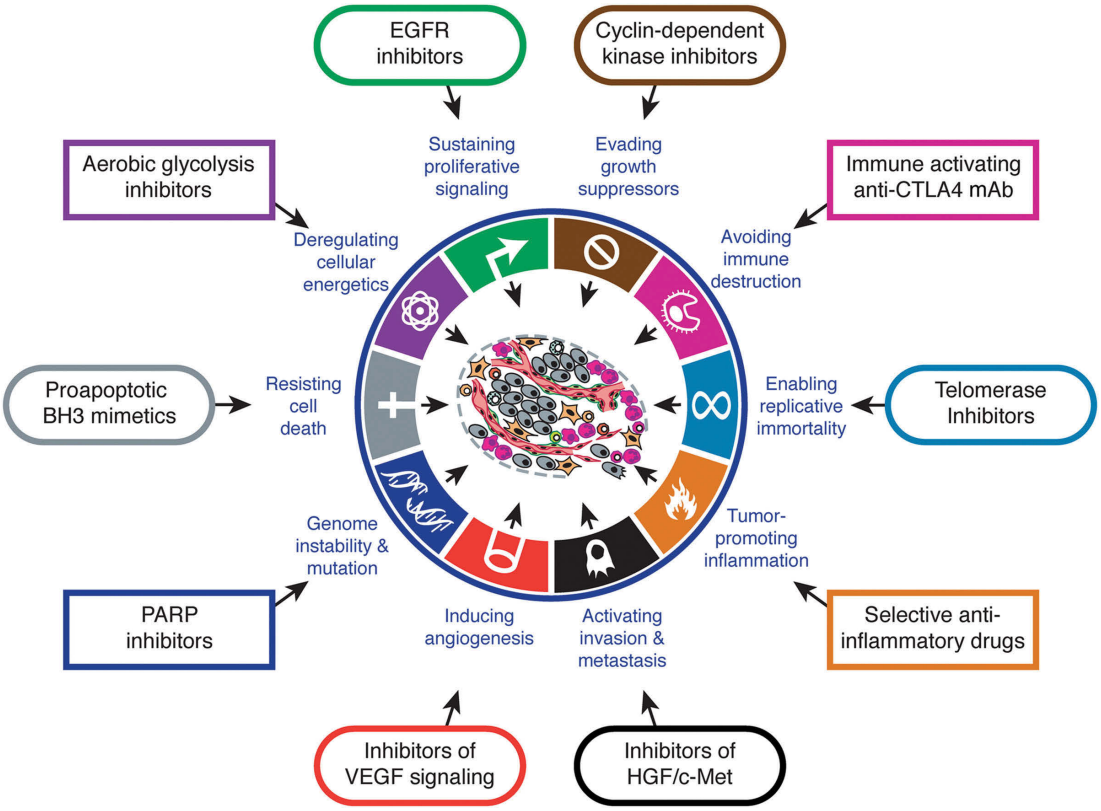
DR JENS GRUEGER, *Roche Pharmaceuticals*

Personalised health care will bring enormous advantages to patients. At the same time, however, new approaches to pricing and reimbursement will be essential to both ensuring access and providing the business incentive to fuel continuing innovation.

The traditional model of pharmaceutical innovation was the "blockbuster" model. The objective was to produce a new drug valuable in a large segment of the population that would be prescribed widely. The statins are an example. For society, this has been successful—not only are these treatments available, but they now are available in generic versions at low cost. Patients continue to benefit greatly; incentives for further research on similar drugs in this disease area, however, have disappeared.

The new, emerging model is based on advances in science that allow us to identify and better understand the pathophysiology of a disease, identifying subgroups of patients and different disease segments. The one-size-fits-all approach is becoming far less relevant. The science behind personalised, precision, medicine is very strong. As Figure 5.1 shows, understanding the hallmarks of disease—cancer, in this case—already is revealing a finite number of pathways and mechanisms of action that are relevant, even across cancers. Different combinations of these approaches may be needed depending on the cancer in the individual patient.

Figure 5.1. Therapeutic targeting of the hallmarks of cancer



Source: Hanahan and Weinberg (2011), n.p.

How much societies will benefit depends on the ability of health care systems to identify and diagnose patients correctly and administer the treatment. In most cases, treatment will include not just a medicine, but an entire process of care—diagnostic, medicine, outcomes indicator and patient care programme.

A NEW REIMBURSEMENT MODEL

Markets long ago ceased to encourage pricing of medicines based on R&D expenditures and risks. Medicine prices today are based on the value that the innovation delivers to patients, providers and societies. In a personalised health care setting, value will depend on the specific use and context of use of the medicine. A medicine may vary in use across cancers or patients, for example, or be used in combination in some cases but not others, or be incorporated in care better in some health care settings or countries than others. In each case, the value will vary; price should vary also.

HTA focuses on setting an average price, or value, per indication. When the availability of generics for the indication is included in the price calculation, the revenue stream for the manufacturer is further eroded. With personalised medicine, this can and should change. Reimbursement levels could be linked to different levels of patient benefit in cases where those vary for specific disease segments within the licensed indication. The focus, then, moves away from a unit- or volume-based approach to a value-based approach that varies with specific use of the medicine.

Multiple prices for the same product based on indication or use are important. A drug may be used for more than one indication, require different doses and vary in its effectiveness across the indications. At present, the price would be same for all indications. If the price is based on the highest-value indication, payers may hesitate to reimburse at that price for other indications. If the price is based on a lower-value indication, then the manufacturer will not realise the return based on the drug's value in other indications. Since personalised medicines populations typically are limited, compensating for lower price with higher volume is not a business option.

What will it take to implement indication-based pricing? A simple but effective data infrastructure will be critical to knowing exactly how these medicines are being used. That requires an IT infrastructure and data collection system that provides basic data about a patient's diagnosis, treatment and outcomes. It also requires a governance structure that controls access to what will be very sensitive data.

This is not just a daydream. In Italy, indication-specific risk-sharing schemes have been implemented successfully since 2006. This is achieved by a simple online registry that tracks utilization of medicines for which a risk-sharing scheme has been agreed. In the UK, the Systemic Anti-Cancer Therapy Dataset now collects information on all drug treatments with an anti-cancer effect in all treatment settings across England (CIU, 2011). The data collected to date appear to be sufficient to implement a multiple indication pricing and/or reimbursement approach in the cancer field.

VALUE BASED PRICING ACROSS COUNTRIES

Prices have varied across countries for decades. In the 1990s, for new drugs launched within Europe, prices varied by about 50% around a median price. Reference pricing existed, but countries realistically referenced those countries with the most similar economic situations.

Since the beginning of the 2000s, two major changes have occurred. First, the Internet has made pricing much more transparent. Second, partly in response to the economic downturn, countries have become irrational in their use of reference pricing and have

been basing prices on countries with very different economic situations. For example, Greece references Romania and Bulgaria; Germany now is including Greece in its basket of countries, which means that the Romanian price influences the German price. The difference in GDP per capita between Germany and Romania is more than fivefold.

What eventually will happen is that lower-income countries such as Romania will lose access to some new drugs because companies will avoid the negative effects of reference pricing by not marketing there. Should such unrealistic referencing continue over time, returns would become so low for companies that investment in R&D no longer would be worthwhile.

As Professor Danzon has noted, differential pricing across countries is advantageous for all concerned. This can be achieved. One option might be confidential commercial arrangements, which have worked with competing payers in the US. Patient access and risk sharing schemes may be appropriate in lower-income countries. Dual brands and localisation of brands, now appearing in the developing countries, is a reaction to the need for differential pricing and should not be necessary. Essential to success is the political will to avoid exploitative practices such as reference pricing and parallel trade.

In sum, personalised health care will require a new reimbursement model in line with value based pricing. This new model will both ensure that patients have access to the best available therapies and provide incentives for industry to develop even more successful approaches. Achieving this requires political consensus about pricing across indications and countries, and strong data infrastructures. All this is familiar—what is new is how much these new therapies can advance treatment for patients and benefit societies.

The role of HTA in the developing world

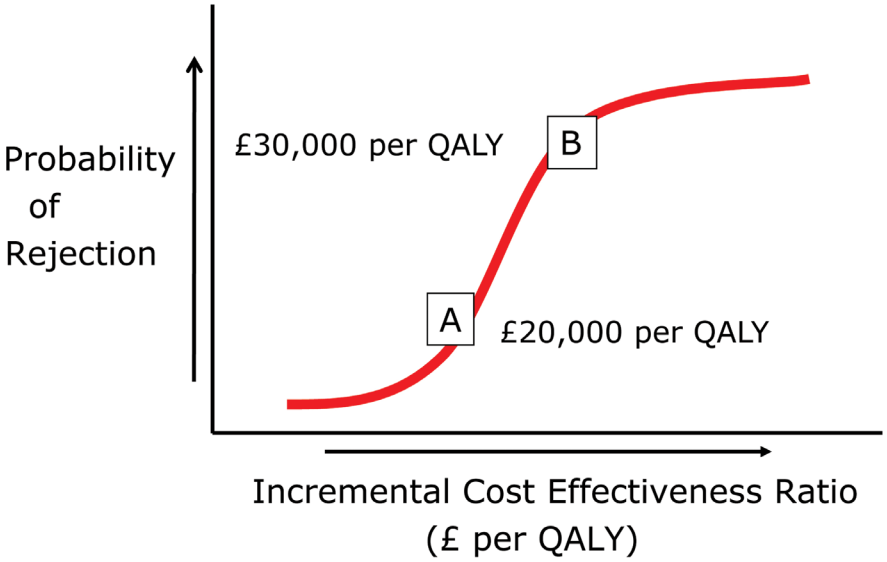
PROFESSOR SIR MICHAEL RAWLINS, *Royal Society of Medicine*[6]

HTA underpins policy decisions about access, reimbursement and, in some countries, pricing. For pharmaceuticals, the process begins once a product has been approved for marketing. The scope and selection of topics to be included in the assessment is followed by evaluations of clinical effectiveness and cost effectiveness. Budgetary impact then is considered, discussions with stakeholders are held and, finally, a decision is made.

CLINICAL EFFECTIVENESS

In determining clinical effectiveness, a number of potential measures can be used: quality adjusted life years (QALYs), disability adjusted life years (DALYs), life years saved/gained, healthy life years saved/gained, and lives saved. As in many countries, the UK uses QALYs. The WHO prefers DALYs, which contain a productivity bonus so that working people receive priority, producing some inequality for the young and the elderly.

Figure 5.2. Determining cost effectiveness in the UK



With cost effectiveness assessments by NICE in the UK, the values at points A and B in Figure 5.2 are critical. Products with a QALY below £20,000, all else being equal, will be regarded by NICE as cost-effective. As the ICER increases, so does the likelihood of rejection, particularly when £30,000 is approached. Nevertheless, in some circumstances, NICE does go above the £30,000 threshold, for example, for particularly severe diseases, end-of-life treatment, or exceptional innovation. Disadvantaged populations and children present problems because measuring QALYs, particularly for children, is a challenge.

No single set of numbers for A and B will hold across countries, of course, because of variations in economic wealth and perspectives as well as attitudes about health and health care. Spending per person even among developed countries varies almost tenfold.

[6] At the time of the conference, Sir Michael was Chairman of NICE.

The same is true in "emerging" markets, which include the states of Eastern Europe, Latin America, and parts of Asia. Thus, for example, health expenditures range from about US$1,500 per capita in Hungary to US$1,000 in Turkey and $50 or so in Pakistan, adjusted for purchasing power parity. In developing countries, although GDP per person is below the levels of the emerging markets, health spending also correlates with GDP. The point here is that finding solutions to questions about how to spend scarce health care budgets gets even more challenging when countries have lower per capita GDP.

For the last four years, NICE International has offered a programme aimed at assisting middle- and lower-income countries. This is meant to accomplish three aims. First, many of these countries wish to better understand HTA—not necessarily how to do it, but how to tell when it has been done properly and how to interpret the results. The second is to respond to frequent requests for recommendations about how to develop clinical practice guidelines. NICE provides evidence tables from its own guidelines and participates in discussions about which components to include. The third component is assisting in setting up versions of NICE—for example in China, Colombia and India. As with guidelines, our role is to provide information and details as background, not design an institution per se.

Most of the countries that NICE has assisted have very little to spend and needs are very basic. For example, average life expectancy in OECD countries is nearly 80 years; in the emerging economies it is 71. Infant mortality in the lower income countries that NICE has visited is about five times that of the OECD average. For maternal mortality, the differences are similar. Given this health landscape, end-of-life cancer therapies will not be high on the list of priorities.

Table 1 provides an example of HTA that might apply in developing countries hard hit by HIV/AIDS. This clearly shows what we might expect, that prevention is more cost-effective than treatment and that certain kinds of prevention—education and condom distribution—are higher on the list.

Table 5.1. Cost effectiveness of HIV-related health service

INTERVENTION	DALYS PER $1,000
Antiretroviral therapy	1
Prevention of transmission during pregnancy	4
Condom distribution	13
Education for high risk groups	28

Source: Based on data from Laxminarayan, Chow and Shahid-Salles (2006)

In summary, HTA is relevant in all countries, regardless of the level of development. Thresholds for cost per QALY or DALY, however, are relevant only in higher income countries. The priority for developing countries is establishing public health priorities at a very basic level, although estimates of QALY or DALY gains will play a role in setting these priorities.

Conference Discussion

Challenges from the moderator and questions from the audience were the basis for a lively discussion session.

PRACTICAL CHALLENGES IN IMPLEMENTING VALUE BASED PRICING FOR PERSONALISED MEDICINE

The rationale for differential pricing based on the value of a medicine for a particular indication is that it encourages companies to develop and market the same drug for more than one use. In theory, this makes sense. But implementing this is practice seems to be fraught with difficulties. Is it really possible?

Probably the greatest hurdle to implementing a pricing system that varies by indication is collecting the data that reliably record use. As Dr Grueger noted in his remarks, the SCAT cancer registry in the UK has been collecting such data for about six months. Other countries have far longer experience. Sweden has had cancer registries for a long time; Italy has been collecting indication-based data for six years. Italy's system includes about 40 medicines under its scheme for coverage with evidence development. The data must be collected in order for patients to get access to the medicines.

The nature of data collection means that payment will not be in real time, at least with today's capabilities. The payer, for example the NHS in England, would make a down payment to the company when products were bought and accounts would be reconciled after the data are analysed. This delayed settlement approach is familiar from DRG-type arrangements (HRGs in the UK) where the insurer or commissioner pays the hospital a per diem rate, then settles up at year end based on actual DRG or HRG use. This could be of benefit to the NHS because it would be paying for value by indication based on actual use, rather than paying an average price based on assumptions about probable extent of use.

Some concern was expressed about "gaming" the system, i.e. someone along the supply chain inappropriately pocketing the difference between a lower-priced indication and a higher-priced one. Although not impossible, this is unlikely in the hospital setting given that payment would be tied directly to patient-level data that include diagnosis and other treatments. "Passing off" a lung cancer patient as a breast cancer patient would be difficult at best. Moreover, many of the products subject to value based pricing schemes will be biologics, which typically are infused in hospital or other care settings where records include far more than just a prescription. "Gaming" has been managed successfully for decades with hospital DRGs (HRGs in the UK). The logistics for indication-based pricing for small molecule drugs available at a community pharmacy, however, would be much more difficult.

Setting and applying HTA thresholds

The argument for value based pricing appears to assume that the cost-effectiveness threshold will be more or less equal to the opportunity cost. So, basically, the NHS would be paying the company an amount equivalent to what it will gain in health benefits (or save in health care costs) by using the new therapy. It could therefore be argued that, for the NHS, there is little incentive to or benefit from moving quickly to adopt therapies that are value priced. Is this a flaw in value based pricing arguments?

Three alternative points were made in during the discussion. First, a societal threshold should set the upper limits of what society is willing to pay, regardless of the budget constrained expenditure replacement effect. The existing health budget should not be taken as fixed or consider opportunity costs only within that health budget and without regard for the economy as a whole.

Second, eliminating current inefficiencies in NHS expenditure on poor-value interventions would make substantial funds available. As in other countries, and other aspects of society, however, eliminating inefficient practice is very difficult.

Third, the debate about a company capturing the NHS's gains is spurious because new therapies always are under patent. Patents are designed to enable the holders to capture surplus, which is essential to justifying investment by companies in new products. The NHS gains substantially when the product goes off patent. It was pointed out that the question of how much of the social surplus to give the company during the patent period (i.e. value based pricing in relation to the threshold) was in principle a separate issue from the case for or against differential pricing. Whatever threshold is used, indications of different value would attract, in principle, different prices under a system of genuine value based pricing.

Without some ability to differentiate by indication subgroup, where appropriate, innovation and access both could be lessened. In effect, if the company is to be allowed only one price, this will influence which indication it chooses to develop. A new indication with potentially high volume, but providing value only at a lower price, will be unattractive for a company if it cannot offer the low price without losing revenue in its existing market for a higher-priced use. A one-price system also will provide reduced incentives to develop a small niche indication that would deliver high health gain and would justify a high price if that higher price will not be achievable because the company already has a lower-priced use. In theory, the company could withdraw the product from the market for the low-priced use so the one price is the high price, but this would deprive patients of access to treatment.

These are not abstract hypotheticals, but the dilemmas of real R&D decisions that affect products appearing on the market and/or being used in certain ways. We need to separate understandable concerns about whether companies may get "too much" as the result of price differentiation from the health care objective of making best use of all products and maximising benefit for patients across a number of indications, which would argue for different prices for different uses.

Applying HTA thresholds in developing countries

The panel discussed whether thresholds are irrelevant in developing countries or whether they have a very different role because of the nature of priority setting in these countries. Health interventions with a low ICER theoretically could be subject to thresholds, although these might be on the order of tens, rather than tens of thousands, of pounds. Clearly, the top priorities in low income countries are basic public health measures such as providing clean water and sanitation. Particularly threatening situations, such as the effect of deaths from HIV/AIDs on the labour force, may warrant a high priority as well. Separating health care from wider social and economic issues is more difficult in developing countries than in developed ones.

In future, HTA may become a more important issue as the epidemiology in emerging market and developing countries changes to include the diseases of great concern in the developed world. For example, obesity is increasing, smoking remains high and the majority of cancer cases, in terms of absolute numbers, now are occurring in middle- and low-income countries. Beginning to plan now for those growing social and economic challenges is important.

Equity, differential pricing and HTA

Some of the arguments in favour of differential pricing are meant to address equity, ensuring access by as many as possible. Emerging markets are showing how this may

work. In Brazil, for example, each drug has one regulatory price for the self-pay private market, based on a European price. A mandatory discount is imposed in the public system that serves lower-income people; some tendering also exists in the public system. The difference in price between the public and private sector is in the order of at least 40%. This option should be very attractive in countries like China and India, which have a large and growing middle class, but a much larger number of people on low incomes. In principle, it can ensure access for both rich and poor people at a lower burden to the system and still provide revenues to support innovation.

It was noted that HTA should be helping reduce inequity in developed countries when used by governments and others to determine coverage. This is not entirely successful, however. Issues arise less from the HTA approaches themselves than from implementation of decisions. In many countries, the decisions about value are meant to apply across the country, but implementation is often left to local or regional bodies that may or may not follow the recommendations closely. When those local bodies have budgetary responsibility, incentives for discouraging use of high-priced, but good-value, products may be serious enough to create access issues. Some central action may be necessary—Germany, for example, identifies particular medicines for which payment is handled centrally, rather than left to local or regional decision makers.

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Chapter 6.

CHANGING THE PARADIGM

Moderator
PROFESSOR ADRIAN TOWSE
Director, Office of Health Economics

Panellists
PROFESSOR SIR ALASDAIR BRECKENRIDGE, *Chairman, MHRA*
DR HANS-GEORG EICHLER, *Senior Medical Officer, EMA*
DR ROB EPSTEIN, *CEO and President, Epstein-French Associates*
MR ROBIN EVERS, *Vice President, Worldwide Regulatory Strategy, Pfizer Inc.*
DR SARAH GARNER, *Associate Director for R&D, NICE, and Project Director for Adaptive Licensing, CASMI*

LEFT TO RIGHT: *R Evers, H-G Eichler, S Garner, A Towse, R Epstein, A Breckenridge*

This panel was charged specifically with considering what aspects of drug development and approval are most in need of change and how that might be achieved. Following the moderator's opening remarks, each panellist was asked to address a specific topic briefly to set the stage for the discussion.

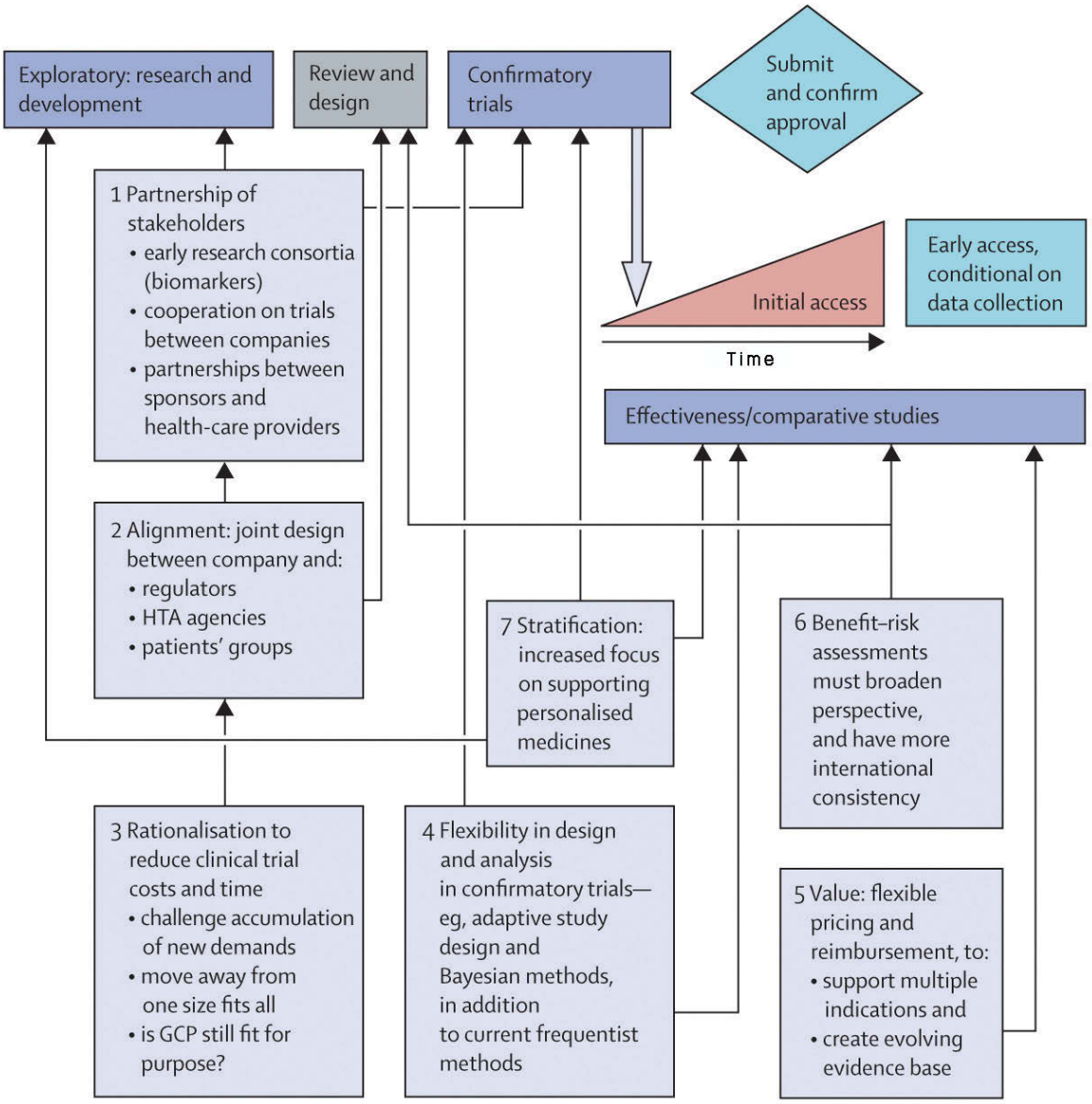
Moderator's introduction

A diverse group of individuals, known as the Athenaeum Group, met in 2009 to consider how the process of drug development might be improved, from identifying the target disease through to approval. The Group included individuals from academia, HTA agencies, the pharmaceutical industry, patients' groups, regulatory agencies, and the UK government. Three of us on today's panel were involved in these discussions.

Figure 1 captures the core ideas that the Athenaeum Group developed, aimed at creating a new paradigm for drug development[7]. It includes an extensive set of innovations in the process of R&D itself, raising a number of questions for the panel to consider, as follows.

[7] For a more complete discussion, see Barker (2010)

Figure 6.1. Proposed flexible blueprint for drug development



Notes: Purple boxes=research. Light purple boxes=proposed new concepts. Diamond=decision point. Pink triangle=effectiveness studies can be started before the end of confirmatory trials and final regulatory trials, to give access to selected populations of patients to the new drug; as time moves on, more and more patients can access the drug. HTA=health technology assessment. GCP=good clinical practice.

Source: Barker (2010), p. 358.

1. Partnership of stakeholders. Three sets of interactions are included. The first is collaboration across companies, which has occurred already with biomarker consortia.

The second foresees expanding the pre-competitive period beyond the current research period to include the early development phases as a way to lessen duplication of effort. For example, could information about early stage trials be shared between companies working in a particular disease area? Or could companies collaborate in pre-launch trials by

including competing new products? Such collaboration has not yet happened—is it feasible?

The third involves companies and health care payers and providers. Could involving payers and providers in clinical development and setting priorities contribute to improving efficiency in drug development in a way that is analogous to the involvement of "launch" customers in new civil aerospace programmes?

2. ***Alignment.*** During the time between exploratory R&D and confirmatory trials could the role for scientific advice from outside be expanded? This might involve not only regulators and HTA agencies providing separate advice to companies, but also a tripartite discussion. Some experiments are taking place along these lines.

3. ***Rationalisation of clinical trial costs and time.*** This has been on everyone's agenda for some time and is linked to the topics of "alignment" of end points and "flexibility" of design.

4. ***Flexibility in design and analysis in confirmatory trials.*** A certain amount of adaptive study design and use of Bayesian methods is occurring now in Phase II. Can that potentially also be applied in Phase III confirmatory trials?

5. ***Value.*** If the evidence base changes over time, can both price and use change in response? If so, companies can accelerate work on both initial and follow indications by avoiding the need to sequence work on indications to deal with pricing rigidities.

6. ***Benefit-risk assessment.*** Can we change the focus of benefit-risk assessments and do more on benefit as well as on risk after marketing begins?

7. ***Stratification.*** Greater emphasis on personalised medicine in theory can improve the process. For example, if effect sizes are larger because of targeting key subgroups, trials can be smaller.

The Athenaeum Group discussions likely will be folded into the work of the Oxford and UCL Centre for the Advancement of Sustainable Medical Innovation (CASMI). Other important initiatives also are in progress including, for example, include MIT's New Drug Development ParaDIGmS (NEWDIGS) programme (CBI, 2012). Two of our panellists have been involved in the CASMI and/or NEWDIGS projects.

Panellists' opening remarks

PROFESSOR SIR ALASDAIR BRECKENDRIDGE, *MHRA*

A gradual shift appears to be occurring away from new chemical entities (NCEs) to biopharmaceuticals or biologics. In fact, some predict that, by 2016, six of the ten best-selling drugs worldwide will be biopharmaceuticals (EvaluatePharma, 2011). This apparent shift has serious implications. Biopharmaceuticals are more expensive to produce than NCEs. The Tufts Center for the Study of Drug Development has calculated that the cost is $1.4 billion for a biopharmaceutical compared to about $1.0 billion for an NCE in 2011 prices (DiMasi and Grabowski, 2007). In addition, the market for biopharmaceuticals always will be smaller. For example, a statin may be prescribed to a million or more people, but a biologic drug for a disease like pulmonary hypertension might treat 1,000 to 2,000 patients. This means that the price of a biopharmaceutical will need to be higher than for a chemical-based drug. The average price of a biological in the United Kingdom at present is £9,500 per patient year compared to £450 per patient for a year for conventional treatment (NICE, n.d.). That is a huge difference.

An important point is that biopharmaceuticals have the potential to cure a disease, not just treat symptoms. This includes diseases that cannot now be cured, such as some forms of cancer and some autoimmune diseases. Given this, both patients and health care professionals are likely to seek to use biopharmaceuticals earlier in the development process than regulators conventionally permit. This may result in various forms of adaptive licensing, which allows earlier marketing subject to specific conditions. This, in turn, will mean additional requirements for post-approval surveillance of both the effectiveness and the safety of these molecules.

How post-approval surveillance will be implemented is the subject of much debate. Options discussed include the use of patient registers, clinical databases such as CPRD, patient reported outcomes, and the like.

We are seeing a change in the business model of the pharmaceutical industry. In the 1980s and 1990s, the pharmaceutical industry concentrated on medicines for chronic diseases that they marketed to doctors, who were the primary decision makers. Attention now is turning to specialist medicines, marketed to payers, which now make the basic decisions. Drug development targets have changed in response to this and to the new approaches that advances in technology have made possible.

DR HANS-GEORG EICHLER, *EMA*

Today, with drug development and licensing, we have a completely binary system whereby a drug is either an experimental treatment or it is a licensed product. There is nothing in between. An unwelcome consequence is a never-ending debate about evidence barriers. Some ask regulators to lower them, others ask us to raise them.

Adaptive licensing is an evolutionary concept that builds on existing experience. It is about better managing the journey of a drug from being an experimental treatment to being a well established and well researched treatment. The idea is to balance timely patient access and sustainability of drug development, on the one hand, against the societal need to have all the necessary information about efficacy and safety, on the other.

The concept of adaptive licensing is iterative—repeat cycles of knowledge generation, followed by regulatory evaluation and licensing. Licensing no longer is a one-off decision, but becomes continuous: initial licensing, re-licensing, re-re-licensing, and so on. Each time, the license is modified based on the information available.

Although this is an intuitively attractive option, it is not without cost. We can allow an increased level of uncertainty when we grant that initial licence only with a commitment to perform further research. In addition, drug utilisation will need to be constrained. If evidence shows that benefit outweighs the risk only in a subpopulation, then the drug should be used only in that subpopulation. This means prescribing restrictions, perhaps enacted by the regulator or required by the payer, or both.

Communication to the public will need to change. Public expectations now are that drugs are safe and effective because they have been vetted fully by the regulator. If we operate under a graduated system, uncertainty must be communicated much more clearly.

Lastly, this can work only with substantial harmonisation between the two key decision makers: the regulator and the payer. This systems approach requires that at least these two parties, and possibly more, act in concert.

DR ROB EPSTEIN, *Epstein-French Associates*

Payers should be viewed as collaborators, rather than ill-informed obstacles for the dissemination of innovation. Their perspectives should be included in the debate around changing the paradigm for drug development for at least four reasons.

First, payers can be very useful in priority setting. Pharmaceutical companies may understand the pathway and the science, but if the problem the product targets is not a real problem for payers, then reimbursement decisions may not meet the company's expectations. Talking to payers about how a potential product fits into their patient management scheme, then, is important.

Second, payers can be very useful in helping determine what the later phase clinical trials need to capture. The few times that company R&D representatives have approached US payers before Phase III, the exchange has been similar to the following: "We have this cake in the oven and you are going to love it when it comes out", the R&D people would say. We would say, "But the ingredients are not right, and you did not come to us soon enough to change that". This applies to aspects such as inclusion/exclusion criteria, choice of comparator, the actual endpoints that are being used, and even the setting of the trials.

Differences in perspective between regulatory agency and payer are common everywhere. In the US, for example, differences about evidence exist between the FDA and CMS, the agency that oversees Medicare, the public programme for people aged 65 and over. CMS may hesitate to include an FDA-approved product on the list of reimbursable drugs if the evidence does not include a subset of people in the 65+ age group. Differences in policy may occur, then, because there has been no conversation about design up front.

Third, payers increasingly can facilitate the cost effective conduct of research itself. Since the early 1990s, all 60,000 pharmacies in the US have been connected in real time. So if a prescription is filled in Hawaii by a patient one day, and another in New York the next day, the New York pharmacist will be able to see any possible drug-drug interactions.

That system also can be used to identify individuals for possible enrolment in clinical trials, an approach that already has been successful. For example, a consortium of about 200 payers was able quickly to identify and enrol volunteers based on an informed understanding of the population and its health characteristics. Payers want to be involved because, in the longer term, it is to their advantage as well. This approach probably is most appropriate from Phase III onwards and also, increasingly, in the post-approval environment for comparative effectiveness studies.

Also with respect to data, merging existing registries could be very cost effective. This would include comparative effectiveness registries, safety registries, genomic registries and outcome registries. Having this data separate seems very inefficient.

Lastly, payers can be collaborators in advocating for the introduction of new technologies that could make a truly big difference. Payers are looking beyond monoclonal antibodies and tyrosine kinase inhibitors. They are interested in genomics, of course, but even epigenetics. They are intrigued by the science of epigenetics and what kind of novel products it may produce.

Stem-cell therapies are at once intriguing and vexing. Partnering early in development for stem-cell therapies is important. Payers are excited about the use of stem cells in pre-clinical toxicity testing since human cells react differently than those of mice or rats. Gene therapy is of great interest to payers. After the introduction of Abraxane®, payers were excited about nanotechnology and are wondering why more products have not appeared.

Payers, then, do not need to be just an audience or a stakeholder; they can be useful collaborators and a great source of advice. It is well worth exploring whether direct interaction between payers and the R&D groups would be useful. Usually, ideas from payers are filtered through companies to R&D; rarely do the two meet face-to-face.

Finally, I agree that aligning requirements and requests across payers is important. In the US, we have many payers and they often have different interests. Some alignment between the payer and the regulatory environment also is needed.

MR ROBIN EVERS, *Pfizer*

By 2022, greater transparency will exist in decision making, both within the pharmaceutical industry and for regulators and payers. Patients, and the general public, will demand more information about how decisions are made and on what basis. Currently, information flow is restricted—industry is limited in Europe as to how much information it can communicate to patients about its products and regulators also are constrained. At the same time, patients are actively seeking information and often are relying on unregulated sources that vary substantially in accuracy.

The shift towards more biologics coming to market presents a different kind of challenge to regulation. Preparing and assessing licensing applications for biologics requires a different knowledge base than for traditional, small-molecule drugs. This expertise may be constrained, in part because so few such products have been developed to date relative to the numbers in development. It will be important to keep this in mind as the approach for assessing new biologic products is standardised.

The regulatory framework also will evolve to take account of using diagnostics in tandem with drugs, particularly biologics, but possibly also traditional small molecule

medicines. Within our company we rely increasingly on diagnostics as a key component for selecting patients and potentially monitoring them after treatment begins. The regulatory framework will need to evolve to ensure that decisions about medicines and diagnostic tests happen in parallel, throughout the entire process—in development and in the approval and post-approval setting.

Lastly, a new challenge will be biosimilars. To date, only a few products have been approved in this category, but many large-market biologics are coming off patent in the next ten years. Potentially, in addition, combination biologics could be developed if lower-cost biologics are available. Regulating those is a very different paradigm to regulating combinations of small molecules because of the potential interactions between biologic mechanisms. Biosimilars also pose questions about whether and what post-approval monitoring might be required, given the characteristics of biologics.

The alignment of benefit-risk assessments across the EU must continue to be a focus, for a variety of reasons. The EMA already has taken the lead in efforts to develop a standardised benefit-risk framework across the EU. Harmonisation with the FDA also will continue, as with other regulatory agencies worldwide—Japan, in particular, and also Australia, Canada, Singapore and others.

For its part, the pharmaceutical industry must work with regulators to understand their requirements with respect to the qualitative and quantitative framework that they would like to see employed. We then need to use this routinely throughout development so that all parties know what to expect in a licensing application. It will be helpful to be able to test the model as data become available during development to gain greater insight into the relative value of the data, which then will enable us to collect only relevant information.

At the same time, the regulatory framework should become a bit clearer so that the questions asked are those that pertain to the actual approved indication and the use of the product, rather than being requests for data that are interesting but not essential. This will be particularly so with progressive or adaptive licensing, which may lead to the temptation to ask broader questions about real-world use than are necessary. The regulatory burden of post approval studies should not become so excessive that it discourages companies from applying for an adaptive license.

DR SARAH GARNER, *NICE and CASMI*

The Centre for the Advancement of Sustainable Medical Innovation (CASMI) at Oxford is an independent think tank. The intent is to create a safe haven where all stakeholders can work together to try to resolve some of the issues with the current R&D paradigm. Figure 6.1 (see moderator's introduction) captures our perspectives and focus. Our mission is to close the innovation gap—the potential in science that is not being translated into improved patient outcomes. We see the issues less as changing R&D than streamlining it.

Bringing stakeholders together is crucially important. Each comes at the problem from a different angle. CASMI's objective is to work through those differences and agree what needs changing and how to begin. For example, regulators, clinicians and patients may have different information needs. Rather than responding by asking for additional information, how can we bring these together to reduce the information burden?

With respect to the interplay between comparative effectiveness research and innovation, the issue is not HTA, but how the current system works. HTA issues simply reflect that the system is creating products that health care payers do not necessarily want at the prices being asked, recognising the opportunity cost of those spending choices. R&D costs are one aspect of price, making discussions about reducing R&D costs important. At the same time, however, it may be time to move away from concentrating on price as the primary way to reward innovation.

Collaboration is absolutely essential for the future of innovation and the future of health care. Historically, the various interest groups and stakeholders have been at odds, sometimes battling, sometimes just talking past one another. These are shared problems, societal issues. We need to take full advantage of initiatives like CASMI to move forward.

Panel Discussion

Questions from the audience were the basis for the panel discussion session. The issues identified allowed the panel to expand on individual remarks, addressing topics of particular concern to the conference participants.

JOINT REGULATORY AND HTA GUIDANCE?

Part of the panel discussion focused on sources of advice for companies during the R&D process. Specifically, two questions were raised: (1) should companies seek guidance from both HTA and regulatory agencies and (2) should this happen simultaneously, that is, with all three parties "in the same room"?

In some cases, panellists noted, companies do seek guidance, certainly with regulatory agencies in the US, Europe and elsewhere. Knowing what data are likely to be preferred means that clinical trials can be designed more efficiently. HTA agencies such as NICE also are being approached for advice about what data may be required. The advantage of having all three parties meet at once presumably would be identifying a set, or limited sets, of data that could satisfy the needs of both the regulatory and HTA agencies. The pharmaceutical industry, however, appears to be uneasy with this idea. Is this an accurate reading and, if so, why the uneasiness?

Generalising is difficult because the R&D process is somewhat different for each molecule; the appropriate time for seeking advice on regulatory matters may not always be the same as for HTA questions. Meeting jointly also may mean less depth in discussions and, perhaps, guidance that is not as useful as that gathered in separate meetings. This is particularly the case since regulators and HTA agencies come from different cultures—regulators are interested in the signal, payers want to understand the noise.

Some companies have found that guidance from some HTA agencies has been less clear than that from regulatory agencies for a number of reasons. One is that regulatory agencies now have had lengthy experience with such interactions and most often can provide clear suggestions that can be implemented. HTA agencies still are building those skills and suggestions may be too imprecise to guide decisions.

The Green Park Collaborative (GPC, n.d.) is one attempt to provide better combined regulatory and HTA guidance. This international pilot initiative, which began in 2010, includes regulatory agencies, HTA bodies, the pharmaceutical industry and academics. Its objective is to explore the scientific feasibility of developing guidance for the life science industry on the design of clinical studies to meet the needs of HTA organisations and coverage bodies. The intent is to develop both "evidence guidance documents" by therapeutic area and general methodological advice applicable across therapeutic areas. Ultimately, this guidance would help reduce uncertainty about the evidentiary

preferences of regulatory, HTA and coverage bodies, improve the relevance of clinical research, and increase patients' access to useful innovations.

In some cases, companies have sought scientific advice jointly from regulators and HTA agencies, or payers, and certainly are willing to do so in future. It may be that companies should make a greater effort to manage the timing so that joint discussions are more often appropriate. The time element, however, is important in another very practical sense. R&D costs are in part driven by time, so delaying decisions by weeks or months until it is feasible for both the regulatory and HTA agencies to meet together with the company may increase costs overall.

Panellists queried whether an underlying issue is an unwillingness to discuss price openly, or even a preference to "divide and conquer". Meetings with the regulatory and HTA agencies, however, focus on data collection, study populations, study design, benefit-risk ratio—but not price, a determination usually made after both regulatory and HTA decisions have been made and often by a different set of decision makers. In addition, no single HTA agency exists for all of Europe or all of the US, for example. It would be impractical, if not impossible, to get together all of the relevant HTA agencies and regulators at one time in one place. Given that countries vary in their data requirements, processes and objectives, such mass meetings are not like to provide useful guidance in any case.

R&D PLANNING AND IMPLEMENTATION

Managing and minimising R&D costs may require more dramatic changes. The traditional model has been for companies to have equal competency in pre-clinical, clinical, and late stage development and marketing—the whole range of activities from target identification through marketing. The panel questioned whether the structure needs to be rearranged, or completely revised. Today, the price/earnings ratio of companies that only license compounds from Phase II onwards are higher than those that do both the basic science and the development. By 2022, less expensive options may have replaced today's comprehensive organisations.

Ensuring the efficient use of limited R&D resources, from a societal viewpoint, may require other innovative approaches. For example, the NEWDIGS programme (CBI, 2012) brings together all stakeholders—payers, regulators, companies and patients—to think through a strategy for development of a molecule for a particular indication. All discussions are entirely confidential, allowing frank exchanges.

INCENTIVES AND TARGETS

As is true of all commercial entities, the pharmaceutical industry responds to economic and financial incentives. Several discussions at the conference highlighted the fact that fewer products on average have been reaching the market in recent years. This is in part a response to new market signals, beginning in the 1990s, that drugs or technologies with minor benefit over existing treatments would not be welcome. As a result, some drugs in development were discontinued. Given that it takes upwards of ten years to complete the drug development process, changes in R&D decisions made in response to the change in incentives will not reach the market for a few years yet.

The lag time between changes in incentives and the ability of any life sciences company actually to develop a product is lengthy—in the meantime, it is possible that the market will have changed its mind again. This is a serious and continuing issue.

It is clear that the real breakthroughs in treatment will occur mostly in personalised health care. That is where the focus of the pharmaceutical industry is now.

EVOLUTION OF PAYER APPROACHES

In response to the far-reaching changes that will take place in R&D in the next ten years, payer expectations and processes also will change. Controlling expenditures through rebates or discounts, as in the US, for example, works well only for medicines with single indications or that treat large populations. In future, products may have multiple indications and the benefit-risk ratio may vary by indication, raising the issue of whether the price also should vary by indication. Already in the US, payers may impose a different co-pay for the same drug for different indications and require prior authorisation for use for some indications, but not others.

Payers often are frustrated by the differences between clinical trial results and real world results, due in part to differences in adherence to drug regimens by patients. In clinical trials, of course, patients must use the product; when the medicine is approved and available to everyone, adherence inevitably slips, in turn affecting the product's therapeutic impact and, thus, its value to the payer. Pharmaceutical companies that invest in companion technologies to improve adherence may be able to command a better price than those that do not.

Outcome guarantees or "risk sharing" arrangements, or a more general use of "coverage with evidence development" requirements, are clearly a potentially powerful tool to bridge efficacy-effectiveness concerns. To date, however, they have had mixed results.

LESSONS FROM OTHER HIGH-TECHNOLOGY INDUSTRIES?

Other high-technology industries may offer ideas for change that are worth considering. Two ideas in particular have arisen in exchanges with other industries, initiated specifically to explore new directions. The conference already has discussed the first: consulting with key customers during the early stages of product development. This a trend that likely will grow within the life sciences industries, although perhaps less through one-on-one discussions than through brainstorming in multi-stakeholder groups, such as the GPC, the CASMI and NEWDIGS.

The second possibility is providing not just a product, but also services for that product after the sale, for example, to support efficient use of or adherence to the product. For the most part, however, this would require a serious change in perspective and in-house expertise. Service and product cultures are very different. Most services companies are customer focused by design; they succeed or fail by providing products based around what the customer wants or needs. Product companies usually are the opposite; they develop products that they believe are cutting-edge, then market them. It is difficult to be both a service and a product company because the orientation, attitudes and range of skills required are very different.

For some disease areas, however, combining produce and service does makes sense intuitively—diabetes, for example, where managing the whole patient is at least as important as any individual product. Whether the pharmaceutical industry should be the one providing this service is another question; whether payers would reimburse for that is yet another.

In future, technology itself likely will drive a change in the product-service balance in the pharmaceutical industry. As new medicines are marketed with companion diagnostics, or have monitoring components literally built in, product and service become more integrated. Data from sensors implanted in treatments, for example, can collect an important set of data about a range of patient actions and responses. In ten years' time, it may be that all new products will have a monitoring component. The potential for improving health care as a result is tremendous.

THE SINGLE MOST IMPORTANT CHANGE BY 2022 . . .

Each panellist was asked to identify the single change that would be most important in improving the efficiency of drug development and use if it were to occur. The combined list is as follows.

- Reduced uncertainty and cost in the drug development system so that new, more effective products based on new technologies are encouraged
- Complementary data requirements from regulators and HTA bodies that allow the most efficient collection of the most important data
- Better communication among all stakeholders to help identify areas of greatest need and greatest promise, as well as approaches to help ensure that the two coincide as far as possible
- More robust and extensive electronic health records that help manage the costs of clinical development, better monitor products after marketing begins, and enable more innovative forms of licensing and reimbursement
- Realistic regulatory and HTA expectations, both for the process of developing a new therapy and the requirements for monitoring during marketing.

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Sir Michael has won several honours and awards, including the Hutchinson and Galen medals. He has authored numerous articles, books chapters and official publications. Sir Michael joined OHE's Policy Board in 2013.

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