

Axiom

Bi-annual newsletter from Pope Woodhead

Edition 5

Spring 2011

Focus on

Real world data

Benefit-risk and value-based approaches are at the forefront of regulators' and payers' minds, and there is much debate within the pharmaceutical industry around how to use 'real-world data' to support the benefit-risk profile of medicines. Turn to page 4 for this issue's lead feature examining future imperatives for real-world data.

Also in this issue:

- EU and US stakeholder real-world data research
- Economic benefits of maintaining a healthy workforce
- Reimbursement opportunities in China

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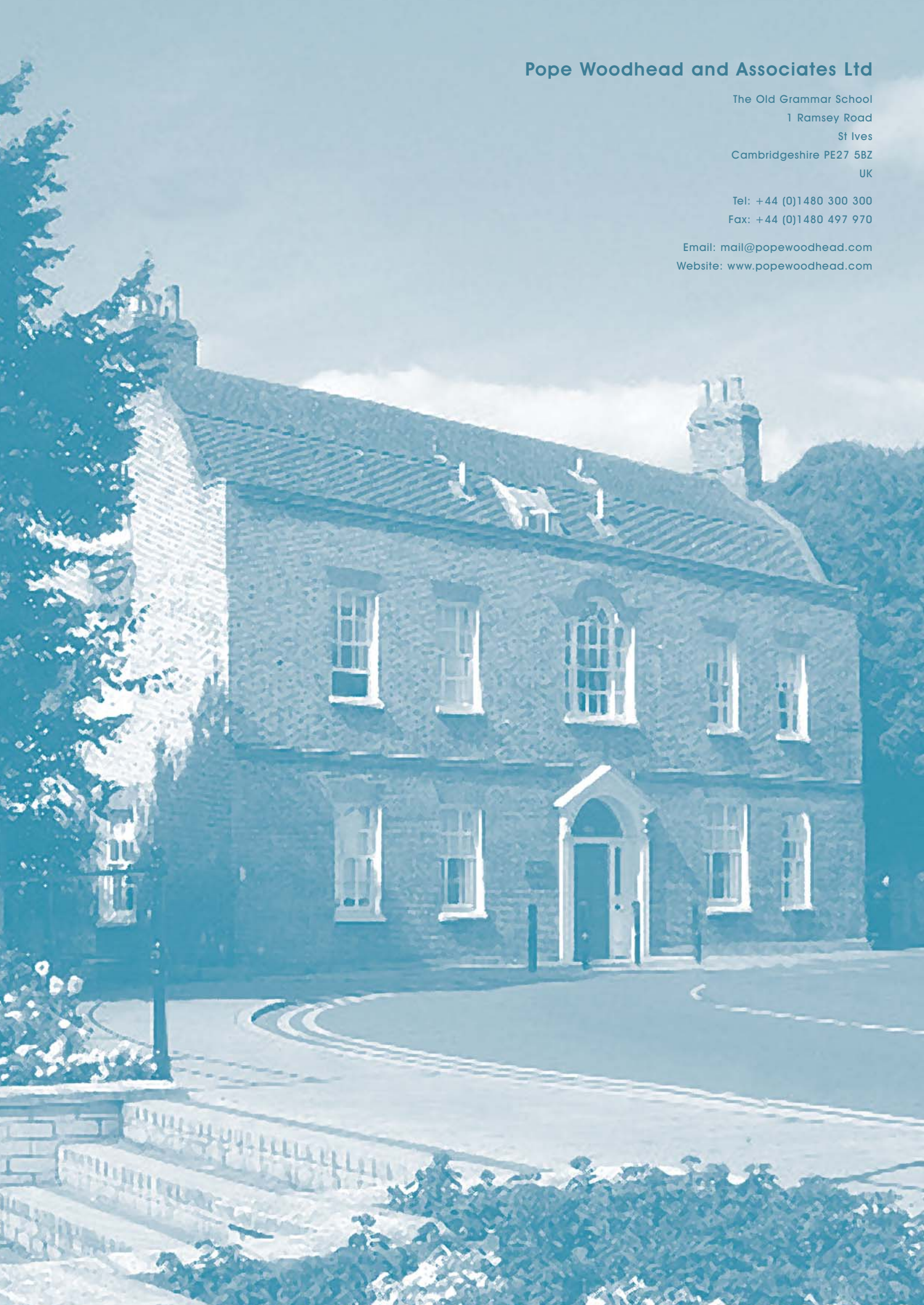


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Foreword by Andrew Hobbs, Managing Director

With benefit-risk and value-based approaches now at the forefront of regulators' and payers' minds, significant pharmaceutical industry attention is being focused on the role and value of post-launch or so called 'real-world' data. For many companies, real-world studies have been somewhat of a Cinderella area until recently, but with external demands increasing and respective budgets growing, most companies are now reappraising how they approach this area. As with any changing environment there is uncertainty about the optimal methods and a shortfall in experienced and suitably skilled people.

This edition of Axiom provides a commentary on the future for real-world data, based in part on research Pope Woodhead has conducted in collaboration with the University of Cambridge. This edition also covers other topical issues we have consulted on in recent months, including an article on the relationship between Western-based companies and their Far-Eastern counterparts. Also, a piece authored by one of our associates, Mark Connolly of Global Market Access Solutions (GMAS), focuses on how the economic benefit of maintaining a healthy workforce should be considered when valuing health technologies.

Pope Woodhead continues to expand its consulting activities. In our news section you can see some of our recent recruits, and we are still looking for more talented individuals to join us.

I hope you enjoy our fifth edition of Axiom and as always I welcome your comments.

Andrew Hobbs
Managing Director
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Focus on

Real world data

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What does the future of real-world data look like?

Based on recent research, conducted in collaboration with the University of Cambridge, this article examines future imperatives for 'real-world data' (RWD) as well as technological advances and political hurdles that will shape its future role.

Pope Woodhead is a long-term advocate of proactively using RWD to support the benefit-risk profile of medicines. It seems that we are no longer alone and RWD is becoming a core element of the evidence generation strategy for many brands. Recent deals (eg, the deal between AstraZeneca and health insurer WellPoint) highlight the additional value of these data in identifying unmet clinical needs and steering drug development strategy.

Real-world data – obligation or opportunity?

Typically, new drugs enter the market with phase III results that don't fully reflect their long-term benefit-risk profile in a broad patient population under naturalistic conditions.

Demand for broader evidence generation through RWD has historically come from two main sources: regulators and payers.

Regulators' requirement for RWD has traditionally been to confirm the drug's long-term safety profile in a typical patient population. However, the European Medicines Agency is now sending a clear signal of its interest in the effectiveness (ie, real-world efficacy) of new treatments to ensure that the balance between benefits and risks is favourable and appropriately managed.

The payer perspective is concerned with understanding in what populations and under what conditions therapies deliver value for money, and the financial impact of new healthcare technologies over time.

The two viewpoints are converging as illustrated in Figure 1.

To date, the pharma industry has often viewed the demands for RWD as obligations (often met with a bare minimum of evidence). However, companies are now starting to see that with well-designed strategies RWD can provide an effective source of competitive differentiation.

In an industry of diminishing pipelines it is critical for companies to maximise value from those drugs that do make it to market, and RWD can be crucial in substantiating the 'promise' of unique or long-term benefits. In addition, real-world evidence can flag further comparative benefits that were perhaps not foreseen at market entry.

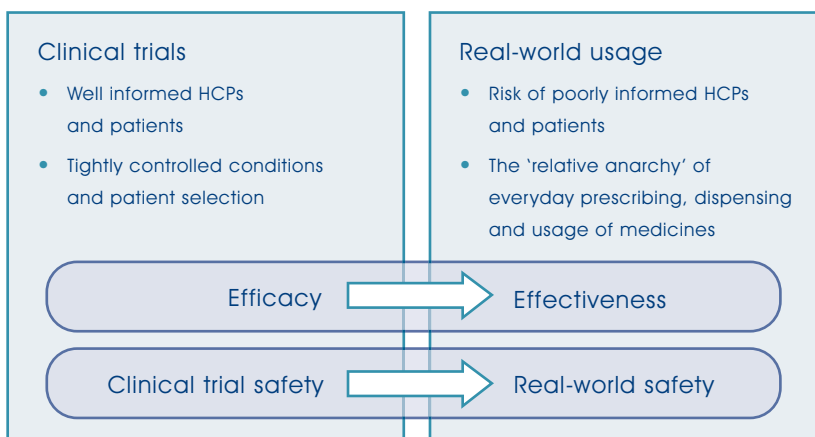


Figure 1. Real-world effectiveness and safety mirror one another

Gauging the evolving perspective on RWD

Literature describes in detail the range of RWD approaches (design, data capture technology, analytical methods, strengths and weaknesses, and constraints/costs of implementation). However, a review of published sources reveals that they fail to answer certain important questions:

- Which RWD strategies are obtaining credence with payers and regulators?
- What approaches are industry willing to undertake?
- What are the main challenges involved in creating and assessing RWD?

In short, what does the future of RWD look like?

To answer these strategic questions, we conducted in-depth discussions with a number of EU and US stakeholders representing a range of regulatory, payer and industry perspectives (respondents were actively involved in generating RWD or making decisions on the basis of these data (see Figure 2 below)).

RWD efficiency through an integrated benefit-risk approach

Regulators and payers are slowly converging towards the requirement for data that establish a positive benefit-risk balance post-launch. During the past few years, regulatory demands for risk management plans and risk minimisation strategies have led companies to invest in post-authorisation safety studies. These sunk costs create the opportunity for these companies to integrate effectiveness and safety endpoints, hence creating powerful RWD at an acceptable cost. There are further opportunities to drive RWD efficiency through integrating post-launch programmes: safety commitments, risk sharing schemes, value-added services and adherence programmes.

Expert group	Number (n) interviewed	Scope of expertise
Data generation		
Third-party research organisations	n = 4	<ul style="list-style-type: none"> • CRO • Database management
Pharma	n = 7	<ul style="list-style-type: none"> • Market access • Pricing and reimbursement • Health economics • Marketing • Regulatory affairs
Data interpretation		
Payers	n = 2	<ul style="list-style-type: none"> • NICE • Sick fund
Academia/advisors	n = 4	<ul style="list-style-type: none"> • Health economics • Healthcare management • Pharmacoepidemiology

Figure 2. Experts interviewed represented a wide range of stakeholders

Key findings from our EU and US stakeholder research

Key finding 1

RWD is an increasingly important complement to randomised controlled trials (RCTs)

The classic approach in drug development has been to rely on phase III RCTs to supply regulatory data needs, and observational studies to support reimbursement. The two sets of data are, however, typically disconnected, falling short of providing the ideal evidence base. To resolve this shortcoming, most stakeholders consulted in our research suggested hybrid approaches for the future.

Respondents all agreed that RCTs remain the gold standard: randomisation is the only sure way to avoid bias and prove the link between a drug and the observed effects. At the same time, they stressed the need for data to be generated in a wider range of patients and routine care conditions. They recognised that this creates a tension because real-world randomised, controlled studies (eg, large 'simple' trials) are particularly complex and expensive – and are therefore rare.

One proposed solution is to increase the external validity of RCTs by giving them 'real-world' features: for example through relaxed inclusion/exclusion criteria, or open-label extensions to the trials.

Focus on



Another solution would be to increase the internal validity of RWD by introducing randomisation in a way that does not threaten the 'real-worldliness' and does not hugely increase the cost of the study. For example, with a 'fire-and-forget' randomisation design, eligible patients are identified automatically by the routine electronic record system; they are randomised to a treatment, but otherwise allowed to interact naturally with the healthcare system. Real-time analysis of linked databases allows these patients to be followed with minimal intervention (see Figure 3).

cost effective: GPRD, Pharmo Institute and the EU-ADR system are good examples of this. The spread of electronic medical records is going a long way to facilitate the acquisition and analysis of RWD; however, the rollout is slow and progress is still patchy in most countries.

Technology will in future allow a richer set of RWD, direct from the patient. Remote monitoring is becoming more common in certain disease areas and novel technology applications are emerging, such as 'smart' pills able to send information to implanted micro receivers to enable tracking of patient compliance and vital signs.

Taking a slightly different angle, web-based platforms like Google Health and Microsoft HealthVault, as well as social media platforms such as PatientsLikeMe utilise the internet to build communities and capture information. This offers the possibility of a vast amount of information from patient-level health records and patient reported outcomes at a much lower transaction cost than is currently possible. Of course, the quality and accuracy of data might be relatively low, but the volume of data in these sources is compelling and they present game changing opportunities and challenges for the industry.

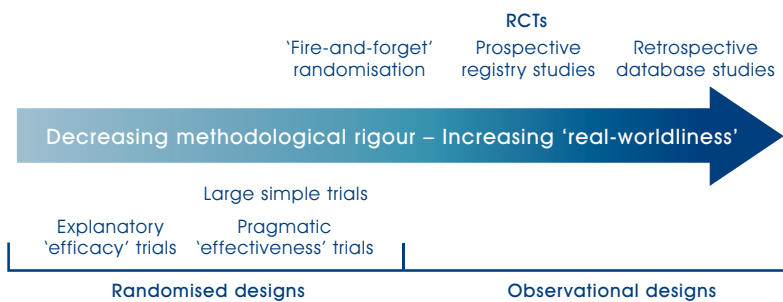


Figure 3. Spectrum of studies that can be used to document the effects of therapies

A third approach would be to use sophisticated statistical analysis and modelling to achieve both internal and external validity. One way of doing this is to conduct indirect comparisons of large, single-arm studies (eg, network meta-analysis). Another way would be to statistically control for bias (eg, via stratification, multivariate analysis or propensity scoring); however these techniques at best reduce some, but not all, of the possible biases.

Newer techniques such as high-dimensional propensity scoring and instrumental variables might be more powerful but are still experimental and are not widely understood.

An alternative strategy does not focus on removing bias from RWD, but on extrapolating RCT data to a wider population; that is, one can simulate large cohorts with a range of patient characteristics and use the RCT data to predict benefit-risk outcomes.

Key finding 2

Technological advances will eventually pave the way for better RWD in greater quantities at a lower cost

Most respondents, especially from the pharma industry, were optimistic about technological progress leading to the availability of more and better RWD. Databases are increasingly exhaustive and integrated, making RWD more

Key finding 3

Companies must address the data ownership and political dimensions to embed new approaches in RWD generation

Our research indicated that companies racing to implement new approaches in RWD generation must overcome two key political hurdles: data ownership and funding concerns.

Taking advantage of technology and electronic databases requires that data are shared between local or regional centres, organisations and even countries. The first challenge here is that local owners may want to hold on to their data (for a variety of reasons, including self-interest); this is particularly true in countries such as Germany and France. An additional challenge is that data privacy laws and regulations may make data sharing and centralisation difficult.

The second major political issue is establishing who should sponsor and fund RWD studies. Since industry, payers and regulators may have different (if not antagonistic) interests, there should be a mechanism to ensure that

governance of the study is equitable. During our discussions, opinions varied about the appropriate sponsor (industry, payers, both, or a third party), reflecting a lack of clarity and consensus. Traditionally, industry has paid for studies to generate RWD, and a number of stakeholders endorsed this view; however others argued that the financial burden should be shared between pharma and payers.

Key finding 4

RWD will be a key component in the value offering for the majority of future products

Having RWD at the time of pricing and reimbursement negotiations is advantageous for pharma, but is challenging given the trend of faster development, complexity in dealing with bias, and the cost of studies.

The findings of our survey suggest that methodological and technological progress will make it increasingly possible (in theory) to obtain appropriate RWD in a reasonable timeframe and at an acceptable cost. However, pharma will need to resolve challenges around appropriate data sharing/ownership and study sponsorship and funding.

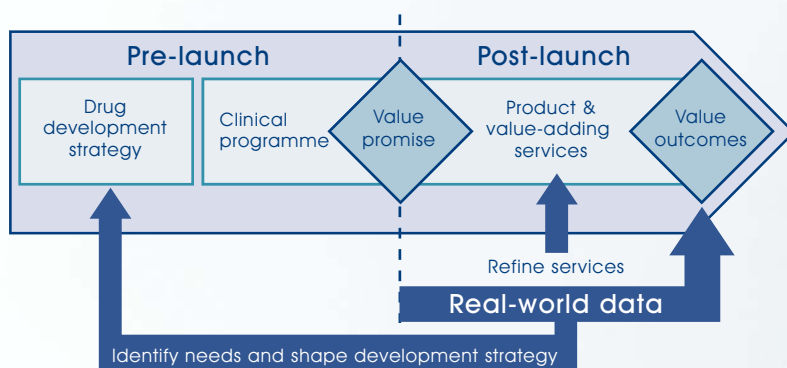


Figure 4. Pharma will increasingly incorporate RWD into 'value packages' together with product and services

As the burden of post-launch commitments grows for companies, many are starting to examine the synergies between regulatory and other commitments.

Our experience suggests that RWD will increasingly become a standard third component of product 'value packages' comprising the drug itself, value-adding services (eg, to improve adherence, mitigate safety risks) and data generated from real-world use that demonstrates the value 'promised' has been delivered, ie, optimal clinical outcomes at an acceptable cost (see Figure 4).

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In mint Condition

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The potential economic benefit of maintaining a healthy workforce should be considered when valuing health technologies.

Establishing the value of medical technologies to paying audiences is critical to the success of all products, but current established methods do not always capture the full economic benefit. Using an alternative approach, such as health investment modelling, could help marketing directors overcome payer challenges.

There is good reason to believe that the relationship between health and economic outcomes, such as increased productivity and economic growth, will become increasingly important in coming years because of the challenges posed by ageing populations. With a shrinking number of working-aged people it will be necessary to capitalise on every available worker in an effort to increase productivity levels and maintain economic living standards – a point acknowledged by the European Commission. In this context, it is worth considering the role of investing in health to maintain a healthy workforce and the possible implications of this for developing and commercialising medical technologies.

Measuring benefits

The health investment framework is based on the idea that health is a form of human capital that can be used to produce economic value (namely in the form of labour force participation) and is normally valued using labour wage rates. Health investment focuses on what happens when an individual returns to work as a result of improved health or avoids a catastrophic health event, and the resulting economic benefits of these outcomes.

The health investment framework varies from the typical analytical approach applied by the National Institute for Health and Clinical Excellence (NICE), which emphasises only health service costs and often excludes the indirect costs of health and illness (see Table 1). Furthermore, the health investment framework, because it emphasises labour productivity, can undervalue technologies because it does not value the intangible benefits of being healthy as occurs with the quality-adjusted life year (QALY) framework. While both health valuation approaches play an important role in decision making, the health investment framework is better equipped to communicate health improvements in economic terms to a range of different audiences eg, politicians, media and the public.

	Technology appraisal organisations (eg NICE)	Health investment framework
Analytical perspective	Emphasis on health service perspective	Emphasis on importance of improved health status on the economy (societal or government perspective)
Measurement of health benefits	Quality-adjusted life years, which are difficult to translate into economic reality	In economic terms, drawing from human capital theory

Table 1. Differences between technology appraisal organisations and health investment frameworks

A clear advantage of the health investment framework is that it emphasises the importance of a healthy workforce, who are able to supply labour to the market and pay taxes to support the growing number of elderly people. To reduce the demands on public resources, governments may have to increase the age of retirement, which can only be achieved if people are healthy enough to continue working.

Setting economic priorities

The government could benefit from allocating resources through a national health service to programmes likely to yield the best economic outcomes. However, using the health service to achieve 'economic priorities' may sometimes conflict with what is customarily considered a 'health priority' based on medical need.

For example, commissioning in-vitro fertilisation (IVF) in the UK is often considered a low healthcare priority with limited funding made available. However, previous studies have shown that National Health Service funded IVF treatments yield an 8- to 10-fold discounted return on investment for government, through the lifetime future tax revenue of an IVF conceived child. This demonstrates a strong economic case for funding IVF, even though infertility is not life threatening. This example is atypical; however, the same tax-based approach can be applied to any health improvement that gets people back to work, improves productivity or avoids premature retirement due to poor health.

The IVF example also illustrates that many investments in health can take many years before they show economic benefit. Health authorities need to take these longer timeframes into consideration when making funding decisions, but budgetary cycles and short-term political goals overlook these fundamentals.

Many will argue against an economic framework for allocating resources – saying that it is inappropriate to use the health service to stimulate economic growth and take resources away from more worthy disease priorities. However, rallying against using the health service to achieve economic goals fails to recognise that the economic rewards can be redistributed in society and that societal welfare can still be preserved.

The major issue in applying a health investment framework to evaluate technology is that it clearly disadvantages people who are not working or are retired. It is important to remember that health services will always be about compassion, improving quality of life and equity, but these goals should not be pursued to the detriment of economic outcomes and sustainability.

Adopting a health investment framework for evaluating technologies should be considered in conjunction with those technical efficiency goals championed by organisations such as NICE. It will help to ensure that obvious choices, with clear economic outcomes, are not under-funded or classified as low healthcare priorities.

Conclusions

Taking the above into consideration, companies should think more clearly about how their product will influence population dynamics and, consequently, economic goals once they enter the market. When benefits are observed beyond timeframes normally considered in clinical studies, there is a need to model future economic outcomes. The health investment framework described here can help companies communicate an aspect of their product value to an audience who are not usually motivated by health economics - particularly politicians and senior health service managers,

"Companies should think more clearly about how their product will influence population dynamics and economic goals."

Furthermore, an appropriate communication strategy is also critical for describing the return on investment from health expenditure. In many cases the strategy should look beyond traditional health ministries and consider making appropriate economic-based arguments to labour ministries, family ministries and even the Inland Revenue Services, which is acutely aware of the tax value of an individual.



China: access all areas?

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China is an intriguing but uncharted territory for many western pharma companies. Across the four most economically advanced provinces where healthcare is most advanced (equating to more than 290 million citizens), the 2009 Chinese medical reform has started to allow the reimbursed use of high-priced drugs that meet important medical needs. Oncology is a case in point.

Pope Woodhead recently discussed the opportunity to access this growing sector with those close to policy reform and the provision of hospital oncology care in China. This market – traditionally dominated by cytotoxics and to a degree traditional Chinese medicine – is now moving towards targeted therapies and orally administered products (as in the West). Together with our local experts, we highlight three key steps on the path to accessing China.

Factor China into the clinical strategy

Clinical data in the local population is mandatory in order to obtain an import licence (requirements are relaxed somewhat for products that already have FDA or EMA approval). Early planning is needed, given the significant time (9 to 12 months) required to get clinical trial approval from the SFDA.

Understand the national context and regional nature of the Chinese market

Drug funding is provided via three main sources: national insurance (eg, government employees, national institutions, schools, universities, military), city social insurance, and employee/company insurance contributions.

The MoHRSS publishes the Catalogue of Drugs for Basic National Medical Insurance that lists all reimbursed products. These are either Type A (fully reimbursed, essential generics) or Type B (patients pay 10 to 20% depending on provincial government policy and insurance coverage).

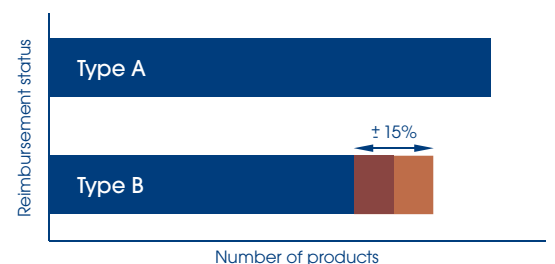


Figure 1. Provinces can customise the central Type B drug list

SFDA, State Food and Drug Administration
MoHRSS, Ministry of Human Resources and Social Security

Importantly, provinces are given the power to customise, expand or reduce the central Type B drug list by up to 15% of products to reflect the local budget and healthcare priorities (see Figure 1). For example, Zhejiang province and the Beijing and Tianjing area have a higher than average rate of lung cancer, and reports indicate that they may supplement the Type B list with newer therapeutics to meet this priority.

Outside the privately insured market, reimbursement is a key determinant of access for costly branded products in chronic indications, given the low ability of patients to pay out-of-pocket. The opportunity for reimbursement is greatest in the four most economically advanced provinces who have the ability and willingness to add or exchange newer products into their Type B list.

"The opportunity for reimbursement is greatest in the four most economically advanced provinces"

Engage locally – regionalise the market access strategy

The lack of a national level mechanism or infrastructure for evaluating product cost-effectiveness or benefit is an area of hot debate among policy makers (ie, whether to introduce a form of NICE adapted to work in the Chinese market). The industry should look to engage with this debate, since it is currently challenging to demonstrate the value of higher priced products to justify reimbursement.

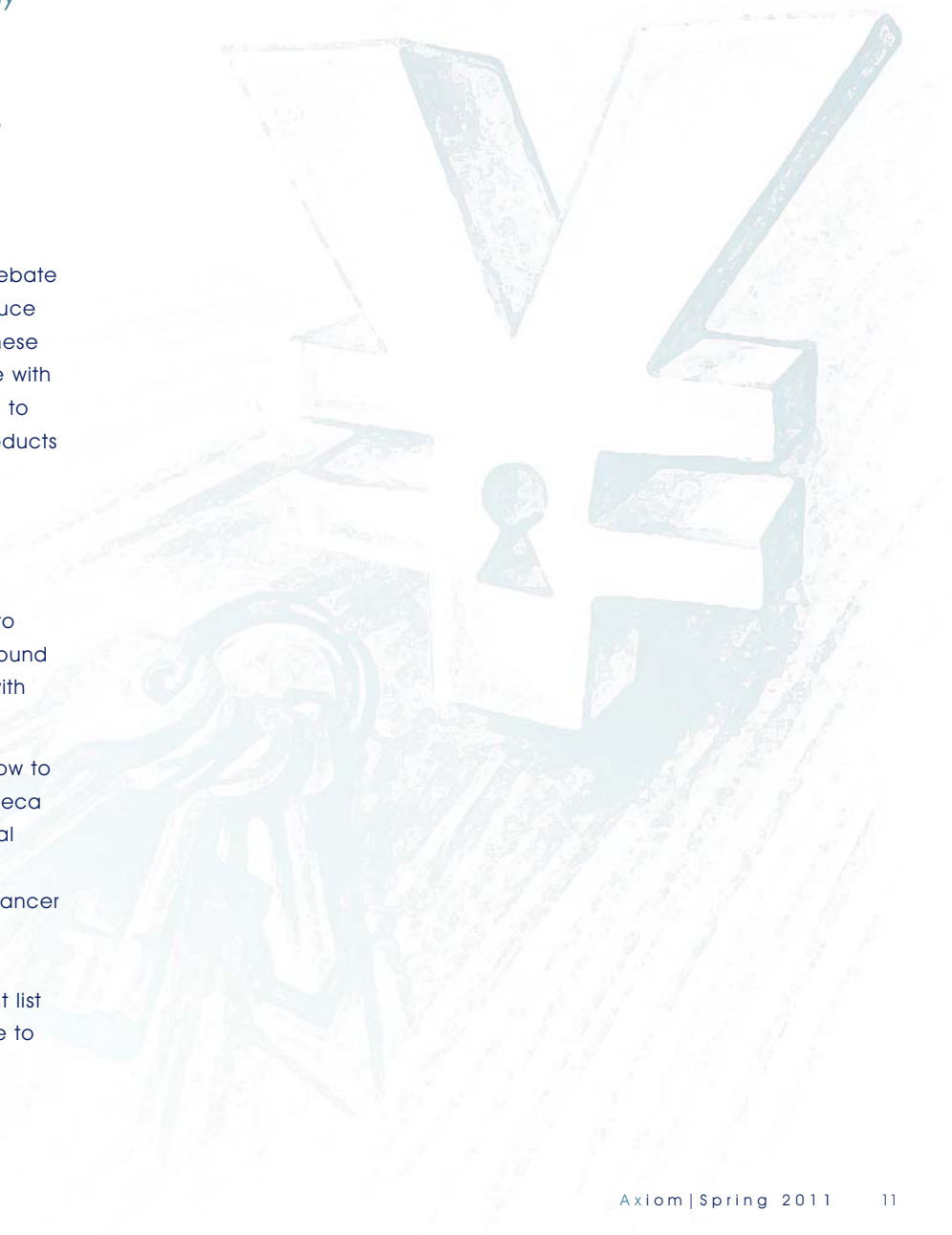
In the absence of a transparent policy, the recent healthcare reform noted that for severe/chronic disease requiring long-term treatment, the government may be willing to explore a 'drug negotiation mechanism' around some form of co-operation or risk sharing with manufacturers.

Leading companies are already learning how to build such initiatives. For example, AstraZeneca organised a summit in 2009 with 400 clinical and academic lung cancer experts in the Guangdong province to discuss targeted cancer therapy and its place in therapy. Iressa® (gefitinib) is now expected to enter the Guangdong province Type B reimbursement list in 2012 (for patients who have low response to chemotherapy or EGRF mutation).

With a few notable exceptions, a navigable route to national reimbursement remains some way off for most high cost drugs. However, Pope Woodhead believes there is a clear opportunity for pharma to work with provincial decision makers to design hospital- or city-based pilot programmes that demonstrate product value to obtain local Type B reimbursement listing. Targeting oncology and other indications of high unmet need appears to be an excellent starting point.

"Unlocking regional opportunities for reimbursement in China is viable"

'Access all areas' is still a little ambitious. However, unlocking regional opportunities for reimbursement in China is viable, given the ability to engage and understand the needs of provincial decision makers and influencers.



Bulletin board

New faces at PW

Wenting Zhang, Rebecca Zhang, Ruth Case and Penny Reeves have joined PW since the last edition of *Axiom*.



Wenting Zhang PhD joined PW in March 2010 as a Writer/Analyst and divides her time across the Market Access and Risk Management Practices. Prior to joining PW, she worked as a part-time consultant in Cambridge Sustainability Research Ltd (CSR) where she was responsible for sustainability strategy and technology communication between industry and academic research.



Rebecca Zhang MD MSc PhD joined PW in January 2011 as a Writer/Analyst and has worked across a variety of risk management activities. Rebecca is a qualified medical doctor, with six years' experience in clinical and biological research and has published her work in peer-reviewed journals. She also has additional experience in clinical development planning for pharmaceutical companies.



Ruth Case BSc PhD joined our People and Process Practice in September 2010 as a Writer/Analyst. She has 13 years' experience in academic biomedical research in both human and veterinary diseases. Ruth has published her work in peer-reviewed journals and is accomplished at writing, editing and proofreading scientific documents and literature-based research.



Penny Reeves BSc returned to PW in May 2010 as a Consultant and Editorial Project Manager. She has 20 years' experience of working in healthcare communications, handling technical, marketing and communications projects for major pharma organisations at both global and affiliate level.

Forthcoming events

DIA EUROMEETING

28-30 March 2011, Geneva, Switzerland

Our consulting team will be participating throughout the three-day programme at the 23rd Annual DIA Eurometing. We hope to catch up with you during the event and can be found at exhibition booth 1480.

Featuring a Pre-Conference Tutorial led by Dr François Lucas – 28 March, 9:00-12:30, 'Risk Sharing and Patient Access Schemes – Their value in reducing uncertainty of the real-world benefits of medicines'

Market Access Summit

31 March 2011, Downing College, Cambridge

On 31 March, Pope Woodhead will host its annual Market Access Summit at Downing College, Cambridge. The Summit is now in its fourth year and provides a recognised high-level forum for senior industry leaders to discuss key issues, trends and proposals relating to market access.

Risk Sharing Masterclass 2011

June 2011, Cambridge

Pope Woodhead will be hosting a one-day masterclass on risk schemes. Key insights include brokering innovative market access agreements in a era of value-based pricing (VBP), understanding where VBP is going, and mastering the practice of patient access schemes (PAS).

Risk Management Colloquium 2011

6-7 July 2011, Downing College, Cambridge

The 5th Pope Woodhead Risk Management Colloquium will be held at Downing College, Cambridge in July. Senior clinical development, safety, risk and regulatory staff are invited to attend this private roundtable event.

Coming up later this year

ISoP (International Society of Pharmacovigilance)

11th Annual Meeting
26-28 October 2011
Istanbul, Turkey

ISPOR (International Society for Pharmacoeconomics and Outcomes Research)

14th Annual European Congress
5-8 November 2011
Madrid, Spain

To register your interest in future Pope Woodhead events, please visit: www.popewoodhead.com/events_register.htm

News

My Career update

In our 2010 Spring edition, we reported that My Career was established across three Novartis Pharma functions and one function had launched across all Divisions. Since then, Novartis has continued to build My Career as 'the way we develop our people', launching in four further functions and with several more under development.