
STRATEGIC ANALYSIS

Pricing and Reimbursement: Innovative Risk-Sharing Strategies

Ensuring market entry through risk-sharing schemes

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In an increasingly cost-sensitive environment, it is becoming more difficult for highly priced innovative drugs to gain positive reimbursement status.

Pharma is now moving towards a value-based pricing system, opting for risk-sharing schemes in an effort to improve equitable access to effective care.

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ABOUT DATAMONITOR HEALTHCARE

Datamonitor Healthcare provides a total business solution to the pharmaceutical and healthcare industries. Its services reflect its expertise in therapeutic, strategic and eHealth market analysis and competitive intelligence. For more details of Datamonitor Healthcare's syndicated and customized products and services, please refer to the Appendix or contact:

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About the Strategic Pharmaceutical Analysis Team

Datamonitor's Strategic Analysis team led by Alistair Sinclair includes both analysts and senior analysts. In addition to prior experience in bioinformatics, pharmaceutical consulting and medical market research, the team's educational backgrounds span a variety of science and business based degrees (BSc, MSc and PhD) from universities in the UK and abroad. The team focuses upon providing in-depth strategic insight through syndicated reports in the following five key areas:

- **Healthcare Systems and Markets** – analysis of strategic issues ranging from emerging markets to the changing pricing and reimbursement environments in the major pharmaceutical markets and their impact on the industry as a whole;
- **Research and Development (R&D)** – coverage of topics including strategies aimed at improving R&D productivity and the impact of emerging technologies;
- **Corporate Strategy** – providing understanding behind corporate development strategies such as mergers and acquisitions and licensing/alliance networks, plus major trends impacting business models;
- **Sales and Marketing** – examining issues affecting sales and marketing, from strategies to improve sales force effectiveness to the impact of new media;
- **Lifecycle Management** – offering insight into the opportunities presented by reformulations or OTC switching, in addition to providing up to date coverage of the rapidly evolving generic and biosimilars markets.

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CHAPTER 1 EXECUTIVE SUMMARY

Strategic scoping and focus

Datamonitor's report, *Pricing and Reimbursement: Innovative Risk-Sharing Strategies* provides an overview of the different types of risk-sharing agreements adopted by manufacturers and an insight into the utilization of such schemes in the UK, US, Italy and Australia. The pros and cons of risk-sharing agreements are discussed and key strategic recommendations are presented as how to best optimize risk-sharing strategies, supported by in depth case study analysis.

Key findings

The growing number of niche biologic products entering the market require high price points in order to provide manufacturers with a return on investment given the expensive developmental processes and often limited size of target patient populations. However, with heightening regulatory scrutiny and increasing cost-pressures, a balance must be struck between incentivizing Pharma to develop novel drugs with high unmet needs, and that of the healthcare payers which fund healthcare costs.

While pharmacoeconomics plays a key role in reimbursement decisions, a number of European Medical Agency (EMA) approved drugs have failed to achieve reimbursement status on first submission to the UK's National Institute of Clinical Excellence (NICE), exceeding cost-effectiveness measures defined as quality-adjusted life years (QALY), which has an upper limit of £20,000–30,000 (\$37,104–55,655) per QALY (NICE, 2008; www.nice.org.uk). In light of these factors, greater weight is now being placed on health outcomes as the industry shifts towards a more value-based pricing system in order to reflect the claimed effectiveness of a drug (www.onlymedics.co.uk/servecontent.asp?contentid=245).

Innovative pricing and reimbursement schemes such as risk-sharing agreements are particularly useful for costly innovative drugs that have some degree of uncertainty associated with their clinical outcomes, and spreads the risk between Pharma and the payer. In this manner, a win-win situation is created: pharma companies secure market entry, the payer is financially protected from patients who fail to respond to drug treatment, and patients gain access to innovative therapies.

Datamonitor's recommendations for optimizing risk-sharing agreements include:

- **identifying a suitable agent** – a drug should fulfill specific criteria in order to be suitable for a risk-sharing agreement;
- **deciding on which type of risk-sharing agreement to adopt** – when devising a risk-sharing scheme manufacturers must carefully measure the trade-offs between health benefits and costs of their drug, and also the type of reimbursement used;
- **timing of risk-sharing scheme implementation is critical to its success** – be that for market entry approval or as part of a lifecycle management strategy;
- **strong head-to-head clinical data are required to support risk-sharing applications in the UK** – these are critical to increasing NICE's cost-effective appraisals of a drug;

- **identifying key stakeholders and developing a pilot program** – the use of an independent third party, such as a university, can be useful in order to ensure academic rigor and balance the interests of Pharma and the health authority;
- **investigating all regulatory and legislative avenues that could support access to market** – the new NICE end-of-life guidance legislation can be useful for drugs struggling to gain a positive NICE opinion in patients with a few months to live;
- **not underestimating the influence of patient advocacy groups on reimbursement approval** – strong patient advocacy groups (PAGs) helped in overturning a NICE's initial decision on Velcade, highlighting the importance of working with these prominent groups in order to increase disease awareness.

This report is produced in two parts:

1. Word document: contains key conclusions and a summary of the current market and future opportunities and threats, outlines the assumptions and events utilized in forecasting the market assesses strategic case studies to provide insight into potential market strategies;
2. PowerPoint executive presentation: shares Datamonitor's key insight into the market with supporting data and recommendations.

Related reports

Datamonitor report, *Future Pharmaceutical Industry Trends: Long-term opportunities tempered by short-term challenges*, April 2009, DMHC2497

Datamonitor report, *Pricing & Reimbursement: Seven Major Markets Update*, May 2008, DMHC2397

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CHAPTER 2 INTRODUCTION TO RISK-SHARING AGREEMENTS

Key findings

- Due to the high R&D costs and small patient pool, many novel drugs for niche indications command a high price, one that is often calculated to exceed the UK National Institute for Health and Clinical Excellence's (NICE) threshold for cost-effectiveness. Therefore, in order for patients to gain access to these novel therapies, but without compromising National Health Service (NHS) budgets, one of the most recent tools introduced to contain pharmaceutical costs in the NHS has been the approval of risk-sharing schemes by NICE. Such schemes will stimulate innovative R&D and the launch of novel drugs in the UK, while fostering the pricing of drugs based on their therapeutic value and cost-effectiveness. In doing so, the new UK Pharmaceutical Price Regulation Scheme (PPRS) protects the NHS from drugs that are not cost-effective, while accommodating the rise in price of expensive novel drugs such as biologics.
- In Italy, a monitoring system has been set up to control the number of patients and the clinical outcomes, known as the Register of Oncology Medicines (Registro Farmaci Oncologici sottoposti a Monitoraggio, RFOM). In addition to registering and monitoring patients receiving treatment with these drugs, the database also allows pharmacies to deal with administrative procedures. This allows the monitoring of the whole process, from diagnosis to drug dispensing in the hospital pharmacy, thereby creating an electronic record for each patient, including data on severity of disease, progression, side effects, brand and dose of drug. The RFOM has proved essential to building risk-sharing agreements in Italy, supporting the development of all schemes for innovative oncology drugs in the country.
- If an Health Technology Assessment (HTA) body is introduced in the US, it could create a more cost-effective use of current healthcare resources, however it is important to note this will increase the burden on Pharma to produce data. More importantly, as the HTA would be linked to pricing and reimbursement decisions, it would lead to greater controls for branded pharmaceuticals, in turn resulting in a controversial loss of the free market pricing in the US. Ultimately, the actual implementation would present a considerable challenge given the expected level of resistance.

Key types of risk-sharing agreements

A risk-sharing arrangement is a specific form of conditional therapeutic coverage that entails a contractual agreement between a payer and a healthcare supplier or manufacturer (Pouvourville, 2006). These arrangements are based on a 'guaranteed' outcome resulting from the treatment, be that based on clinical, financial or cost-effectiveness criteria. If the outcome is achieved the payer will pay, if not, the pharmaceutical company refunds the payer for the cost of the drug (Ehreth and Williams, 2009). Risk-sharing agreements add a new dimension to pharmaceutical pricing, distributing the risk between the payer and the provider, and represent a useful tool, particularly when there is insufficient information available on a new drug and how it will perform in the real-world setting.

Pharmaceutical companies are increasingly turning to risk-sharing agreements as a means of increasing the chance of gaining positive guidance from the UK's National Institute for Health and Clinical Excellence (NICE) and uptake by health insurance agencies in the US, providing patient access for expensive novel drugs. These schemes also encourage responsible prescribing by healthcare professionals and ensure resources are not wasted on ineffective treatments. By addressing payer concerns regarding both economic and clinical outcomes, risk-sharing schemes have the potential to change the pricing landscape of high-cost drugs.

The first scheme to pave the way for risk-sharing agreements began in 2002 in the UK, after NICE's negative guidance on four drugs for the treatment of multiple sclerosis. Biogen's (now Biogen Idec), Avonex (interferon beta-1a), Schering AG's (now Bayer Schering), Betaferon (interferon beta-1b), Serono's (now Merck Serono), Rebif (interferon beta-1a) and Teva's Copaxone (glatiramer acetate) were not deemed sufficiently cost-effective, and were therefore not eligible to be funded through the National Health Service (NHS). This resulted in considerable opposition from patient and professional organizations and pharmaceutical companies. NICE therefore recommended that the Department of Health and the four pharmaceutical companies should find a way to make their respective drugs available on the NHS in a cost-effective manner. The multiple sclerosis risk-sharing scheme was born, whereby the four manufacturers agreed to lower prices of their drugs if they failed to meet a cost-effectiveness threshold of £36,000 (\$66,786) per quality-adjusted life year (QALY), with disease progression monitored in a minimum of 5,000 patients over a 10-year period (Pickin *et al.*, 2009). Clearly, this was beneficial for both patients and the pharma companies:

"If we didn't enter into the risk-sharing scheme, we wouldn't really have a market here in the UK."

Pete Smith, manager for Biogen Idec UK (Pollack, 2007)

Today, pharma companies as well as providers are more than willing to share the risk in order to bring a novel drug with a high unmet need to market, as there are potential benefits to both sides: sales and profits for Pharma, and an overall reduction in total healthcare costs for the provider. Given that NICE has been accused of slow assessment and the NHS of sluggish uptake of new drugs, risk-sharing agreements should speed up patient access to potentially life-saving drugs in the UK.

However, Pharma and stakeholders must appreciate that these schemes can require burdensome administration and their introduction is complicated by a variety of funding arrangements, each of which has specific implications. For example, the managing of patients' outcomes involves tracking and monitoring large sets of data, which can be even more challenging if objective and reliable biomarkers are not available. It is also important to ensure the appropriate prescribing of the drug, so

that the scheme is not used as a platform to promote the drug involved in the scheme. Furthermore, the decision on what type of risk-sharing scheme to implement and the associated outcome parameters require significant research and analysis in order to balance the risk between pharma company and provider.

Three key risk-sharing agreements

The three of the most common types of risk-sharing agreements are:

- **clinical risk-sharing:** sharing the risk associated with the therapeutic performance of a product. If the drug fails to meet a clinically defined outcome, the payer will typically receive a refund from the manufacturer;
- **cost-effectiveness risk-sharing:** setting a target for drug cost-effectiveness, whereby if the threshold is not met the payer will typically receive a refund from the manufacturer;
- **fixed budgets/price and volume agreements:** prior agreements are set with regard to utilization and price, and can include provisions such as price caps, utilization caps and budget caps. Financial-based contracts offer greatest risk and reward potential to both the manufacturer and the contracting partner, as the basis of the agreement is price and/or expenditure.

Table 1 illustrates a number of recently implemented risk-sharing strategies in the UK, enabling patient access to drugs which would otherwise likely receive negative guidance from NICE due to issues over price or cost-effectiveness.

Table 1: Evolution of approved risk-sharing agreements in the UK, 2007–09					
Date of approval	Drug	Indication	Company	Type of risk-sharing agreement	Strategy
July 2007	Velcade (bortezomib)	Multiple myeloma	Janssen-Cilag	Clinical risk-sharing	NHS would continue to pay treatment in responding patients, while Janssen-Cilag would reimburse the NHS for non-responding patients
August 2008	Lucentis (ranibizumab)	Wet age-related macular degeneration	Novartis	Fixed budget/price and volume agreement	The NHS pays for the first 14 treatments, and if further injections are required, Novartis will pay the rest
November 2008	Tarceva (erlotinib)	Non small cell lung cancer (NSCLC)	Roche	Cost-effectiveness risk-sharing	Lowered price by 7.5% for all NSCLC patients, in order to bring the price in line with rival Taxotere (docetaxel)
March 2009	Sutent (sunitinib)	Renal cell carcinoma	Pfizer	Clinical risk-sharing	5% price cut and one free course of treatment (6 weeks). The NHS will then pay for the treatment in responding patients
April 2009	Revlimid (lenalidomide)	Multiple myeloma	Celgene	Fixed budget/price and volume agreement	The NHS pays for treatment for the first 2 years in patients who have received at least one prior therapy. If treatment is required after the 2 years, then Celgene will cover the costs
June 2009	Erbitux (cetuximab)	Metastatic colorectal patients, in combination with chemotherapy	Merck Serono	Fixed budget/price and volume agreement	16% rebate on the amount of Erbitux used on a per patient basis

NHS = National Health Service

Source: Datamonitor

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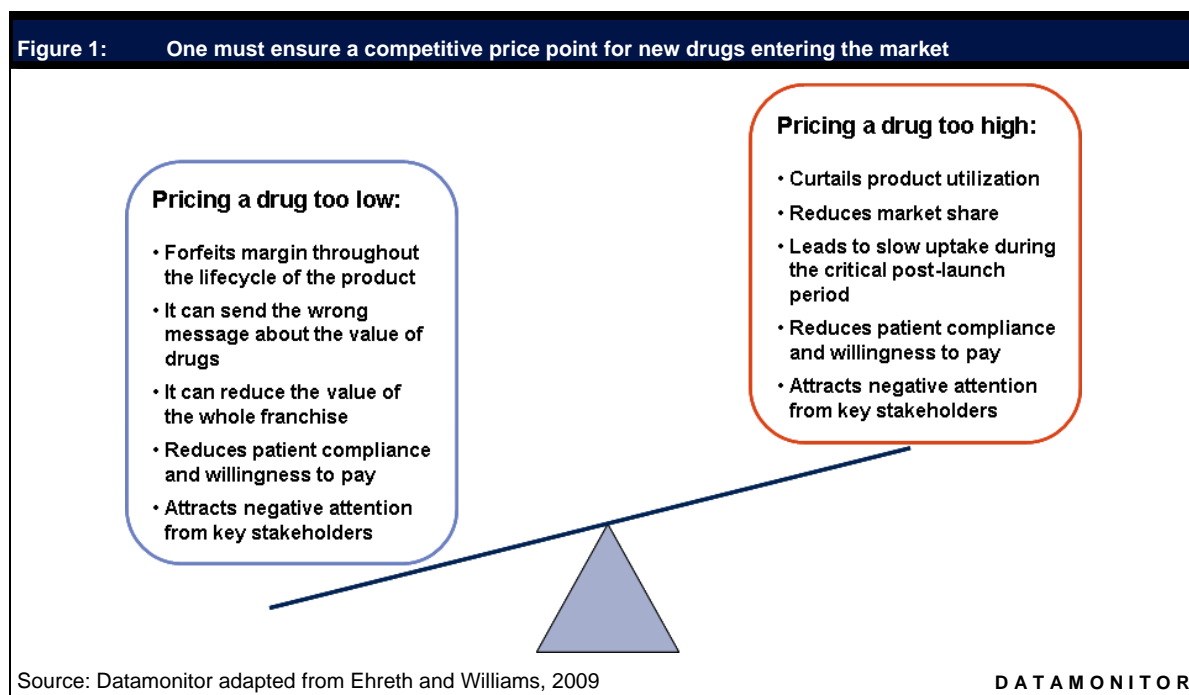
The evolution of risk-sharing schemes in the UK

The UK's healthcare system is essentially based on the tax-funded National Health Service (NHS). Although the NHS has kept its spending on prescription drugs relatively low in comparison to other countries, its drug spending has risen from £4 billion (\$7.4 billion) to £8.4 billion (\$15.6 billion) in the 10 years to 2007 (OECD Health data, 2007; www.oecd.org). This is driven by an increasingly aging population, which in turn leads to higher demand for costly drugs to treat chronic diseases such as cancer, diabetes and arthritis. With drug expenditure only contributing to approximately 10% of healthcare costs, and with other costs escalating year-on-year, a number of cost-containment strategies aimed at controlling pharmaceutical spending have been implemented by the NHS, spearheaded by the National Institute for Health and Clinical Excellence (NICE) since its formation in 1999.

The goal of NICE is to provide guidelines for fairer and more efficient utilization of pharmaceuticals (and medical devices) by the NHS, principally by using cost-effectiveness and pharmacoeconomic analysis to compare costs and benefits of different products. NICE's primary purpose is (Pharmaceutical Price Regulation Scheme, 2007; www.of.gov.uk):

- to improve the quality of care provided by the NHS;
- to secure value for money;
- to ensure treatments are available equally across the UK (to eliminate postcode prescribing).

Pricing of a drug at its launch is a critical decision for drug makers as summarized in Figure 1. However, due to the high R&D costs and small patient pool, many novel drugs for niche indications command a high price, and one that often exceeds NICE's threshold for cost-effectiveness; this is primarily calculated through quality-adjusted life years (QALY) as a measure of quality and length of life lived.



In order for patients to gain access to these novel therapies, but without compromising NHS budgets, one of the most recent tools for containing pharmaceutical costs has been the approval of risk-sharing schemes by NICE. These allow manufacturers to launch their novel, high value products in the NHS setting, but involves an aspect of cost and risk mitigation in order to reduce the burden on the NHS.

Factors driving the introduction of risk-sharing agreements in the UK

This provides an insight into factors that have driven the implementation of risk-sharing schemes in the UK's NHS:

- NICE's QALY limit too low to permit approval of certain high value, life-saving drugs;
- lack of coordination between Health Technology Assessments (HTAs) leads to disparate access to novel drugs;
- delays in issuing guidance is disadvantageous to both Pharma and the patient;
- lack of transparency makes stakeholders question the value of QALYs;
- excessive cost-containment measures have hindered access to innovative life-saving drugs.

NICE's QALY limit too low to permit approval of certain high value, life-saving drugs

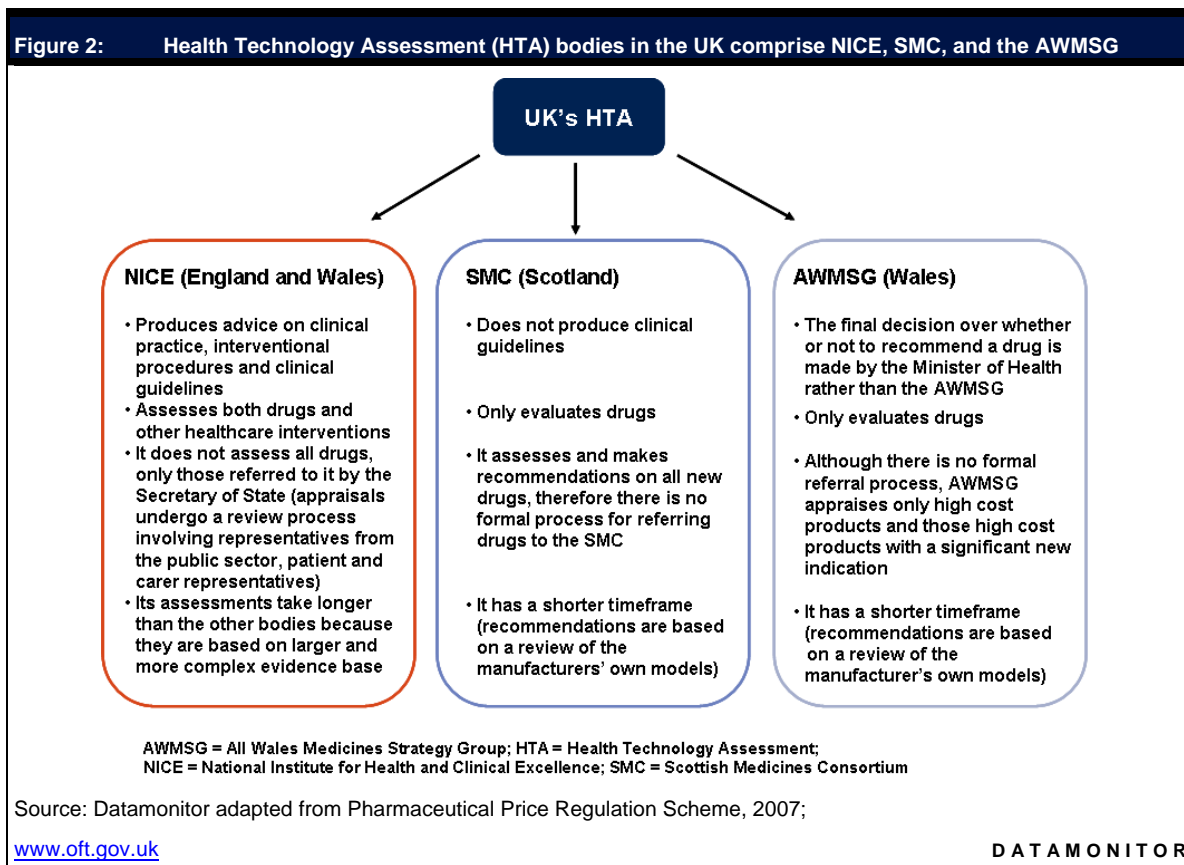
Historically, NICE is renowned for its detailed pharmacoeconomic assessments, where a technology is assessed. This has given rise to its health technology appraisals—where the evidence is evaluated and the decisions are made—with its recommendations subsequently being used and referenced globally. Cost-effectiveness is analyzed using various tools, including measuring extension of life and improvements in the quality of life, commonly expressed in terms of quality-adjusted life years (QALYs). Despite being an effective strategy for cost-containment, it remains a controversial tool, as novel life-saving drugs (such as orphan drugs) are frequently not deemed sufficiently cost-effective to be listed for reimbursement owing to their high price. Although no formal cost-effectiveness threshold is set and each drug is considered on a case-by-case basis, NICE stipulates the range of acceptable cost-effectiveness as being in the range of £20,000–30,000 (\$37,104–55,655) per QALY (Pharmaceutical Price Regulation Scheme, 2007; www.offt.gov.uk). This means the probability of rejection increases as the cost per QALY rises for each drug. Other factors such as burden of disease and uncertainty regarding safety and efficacy are also factored into NICE's final decision, although lack of clarity still surrounds this issue.

For example, the beta-interferons and glatiramer acetate for the treatment of multiple sclerosis exceeded the threshold by a substantial margin—of up to £700,000 (\$1.3m) per QALY (Appraising orphan drugs, 2006; www.nice.org.uk). These drugs were initially given negative guidance by NICE, but subsequently were approved as part of the UK's first pharmaceutical risk-sharing scheme.

Lack of coordination between Health Technology Assessments (HTAs) provides disparate access to novel drugs

Health Technology Assessments (HTAs) were introduced to enable health policymakers, clinicians, payers, hospital managers and government leaders to make informed decisions on whether to develop a technology (drug/device), allow it on the market, and to pay for its use. Specifically, the HTA was set up in an effort to provide information about clinical effectiveness, cost-effectiveness, and the broader impact of drugs and medical technologies.

The UK has three national bodies to carry out cost-effectiveness evaluations: NICE, the Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG)—these have differing models for assessing cost-effectiveness, whose roles and differences are summarized in Figure 2. Despite their diversity, their common aim is to promote cost-effective prescribing and to serve as a centralized source of advice.



Differences between NICE, AWMSG and SMC have highlighted issues that need to be addressed; for example, encouraging more consistent implementation of guidance and greater co-ordination between the bodies. This is illustrated by Bristol-Myers Squibb/Merck-Serono's Erbitux (cetuximab), which is available in Wales (for colorectal cancer) and Scotland (for head and neck cancer), in addition to its availability in most other EU countries, but was initially rejected by NICE for both indications. Only through a risk-sharing scheme was the drug finally approved for use in England's NHS in June 2009.

Delays in issuing guidance is detrimental to both Pharma and the patient

NICE has been heavily criticized by Pharma, the government and patients over the length of time it takes to evaluate each drug, sometimes taking up to 3 years after a drug has been approved (Sikora, 2009), with only 30% of approved drugs receiving NICE approval for full use. Clearly, this has repercussions for both the industry and patients alike: delays and drug rejections can severely limit patient access to a life-saving drug, raising further emotive issues when NICE's decision is not in line with other HTAs. From an industry perspective, delays translate in shortened patented life on the market, impacting a drug's sales.

The use of risk-sharing schemes can help speed up a drug's access to market due to the more dynamic nature of the negotiation process between Pharma and NICE. This may reduce the need for a second round of negotiations, as amendments to the agreement can be settled directly. In fact, three new measures were announced in March 2009 in an effort to increase patient access to new drugs in the UK, which should also positively impact risk-sharing negotiations. These include (Bruce, 2009b):

- a faster system for referring drugs for NICE appraisal through the introduction of joint Department of Health–NICE exclusion and prioritization criteria;
- an additional appraisal committee is to be set up ensure NICE can assess new drugs and treatments as quickly as possible;
- guidance on how primary care trusts (PCTs) should handle decisions on new drugs.

Lack of transparency makes stakeholders question the value of QALYs

NICE's overreliance on QALY criteria is another cause of concern for Pharma, as this measure does not take into account certain issues such as disease severity, which leaves Pharma to query the validity of the agency's guidance. To reduce NICE's reliance on QALY, it has been proposed that a more holistic approach should be taken, incorporating different aspects of a disease, examining: progression-free survival; disease-free survival; the severity of illness; and take into account overall costs and savings to patients, caregivers and society (Pharmaceutical Price Regulation Scheme, 2007, www.oft.gov.uk).

Questions have also been raised as to how drugs are assessed. For example, in February 2009, Servier challenged the Institute over its decision to only recommend the company's Protelos (strontium ranelate) in limited circumstances for the second-line treatment of a subset of osteoporosis patients. Servier, supported by the National Osteoporosis Society, challenged the guidance on three grounds: that it was discriminatory, that some of the evidence had not been handled properly, and that it was unfair because consultees did not have access to a fully executable version of the economic model (Mills, 2009c). The judge only ruled in favor of the company on the last point, but this, nevertheless, highlighted the lack of QALY transparency.

Furthermore, in a recent string of rejections, NICE issued positive guidance for just one out of four of renal cell carcinoma drugs, recommending Pfizer's Sutent (sunitinib), while Roche's Avastin (bevacizumab), Bayer's Nexavar (sorafenib), and Wyeth's Torisel (temsirolimus) were rejected as first-line treatments in draft guidance (in addition to Sutent and Nexavar also receiving negative guidance as second-line treatments) (Mills, 2009b). As a result, NICE has come under attack from

oncologists, patients, carers and politicians who were concerned that the NHS would have very few treatment options for renal cell carcinoma if its draft guidance were confirmed. Roche stated its disappointment (Mills, 2009b):

“Avastin plus interferon has demonstrated a similar cost and clinical cost effectiveness to the recently approved sunitinib and has a different adverse event profile which may make it more suitable for some patients. NICE’s negative decision in this appraisal is not about affordability to the NHS as the additional budget impact of making Avastin available is minimal, nor about the cost of clinical effectiveness of Avastin, but about the way in which NICE has applied its own end-of-life criteria.”

John Melville – General Manager, Roche UK

However, while there is still a lack of transparency over the calculation of QALYs, the use of risk-sharing agreements can support discussions over drug recommendation. For example, Janssen-Cilag’s Velcade (bortezomib) for the treatment of first relapse in multiple myeloma was rejected by NICE in 2006 based on its overly high QALY. But following further negotiations regarding the terms of the risk-sharing agreement (see Chapter 3 for further details), the drug’s QALY was reduced to approximately £20,700 (\$38,402) per year and was subsequently approved (Bortezomib monotherapy for relapsed multiple myeloma, 2007; www.nice.org.uk).

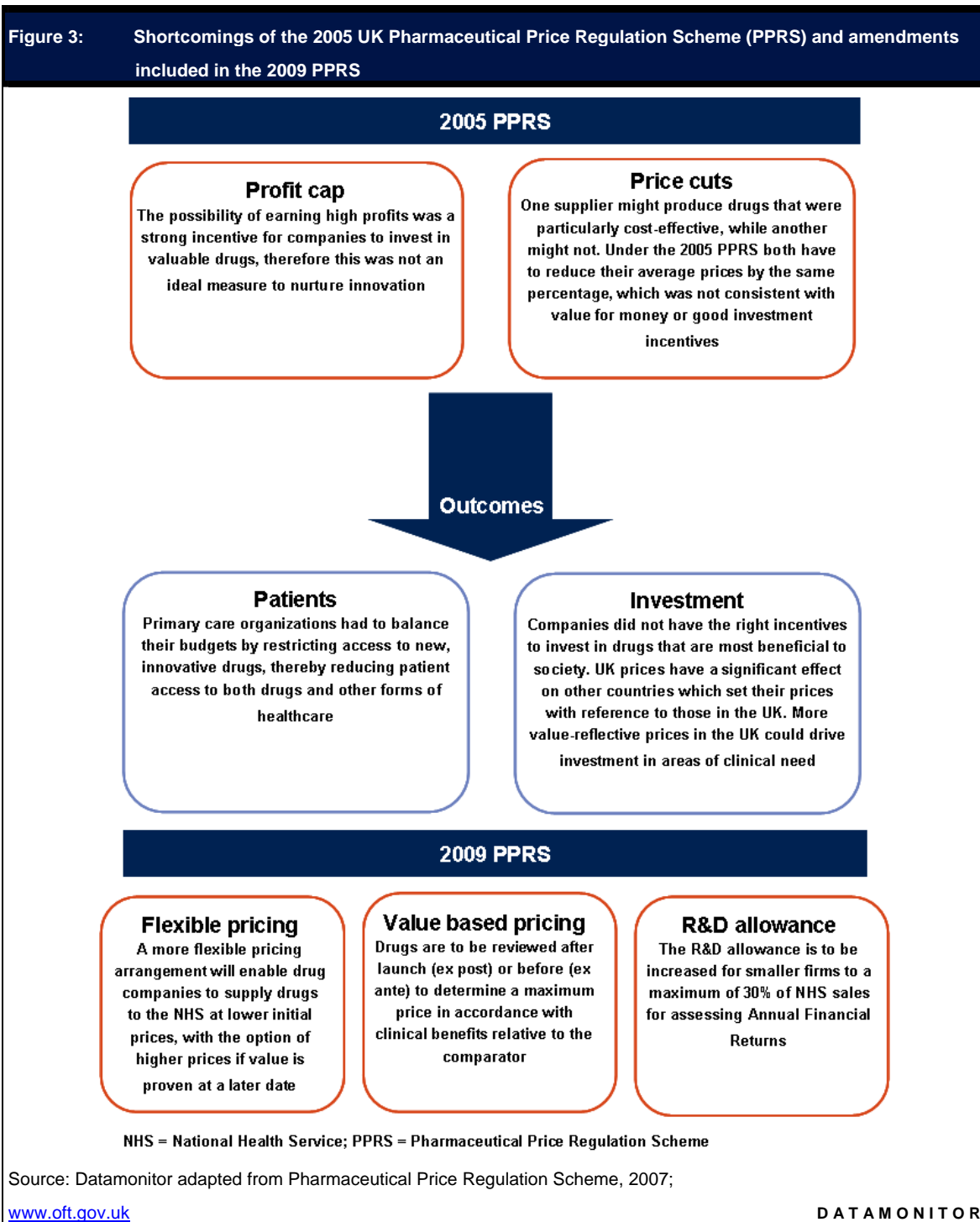
Excessive cost-containment measures may hinder access to innovative life-saving drugs

The Pharmaceutical Price Regulation Scheme (PPRS) was set up in 1957 in order to allow the NHS to access branded drugs at reasonable prices, in addition to incentivizing Pharma to invest and develop innovative drugs. This regulation is updated every few years, with the 2009 PPRS replacing the 2008 regulation, which was an interim scheme after the 2005 scheme ended.

Following its revision, the two key components of the 2005 PPRS were:

- **profit caps** – this set a maximum threshold on profits earned from supplying drugs to the NHS (if this level is exceeded, excess profits must be repaid to the Department of Health);
- **price controls** – this gives companies freedom to set the initial price for a new drug, but imposes restrictions on subsequent price increases.

However, there was concern that neither measure secures prices that reflect the therapeutic value of a product, and therefore fails to incentivize companies to invest in innovative drug development (Figure 3).

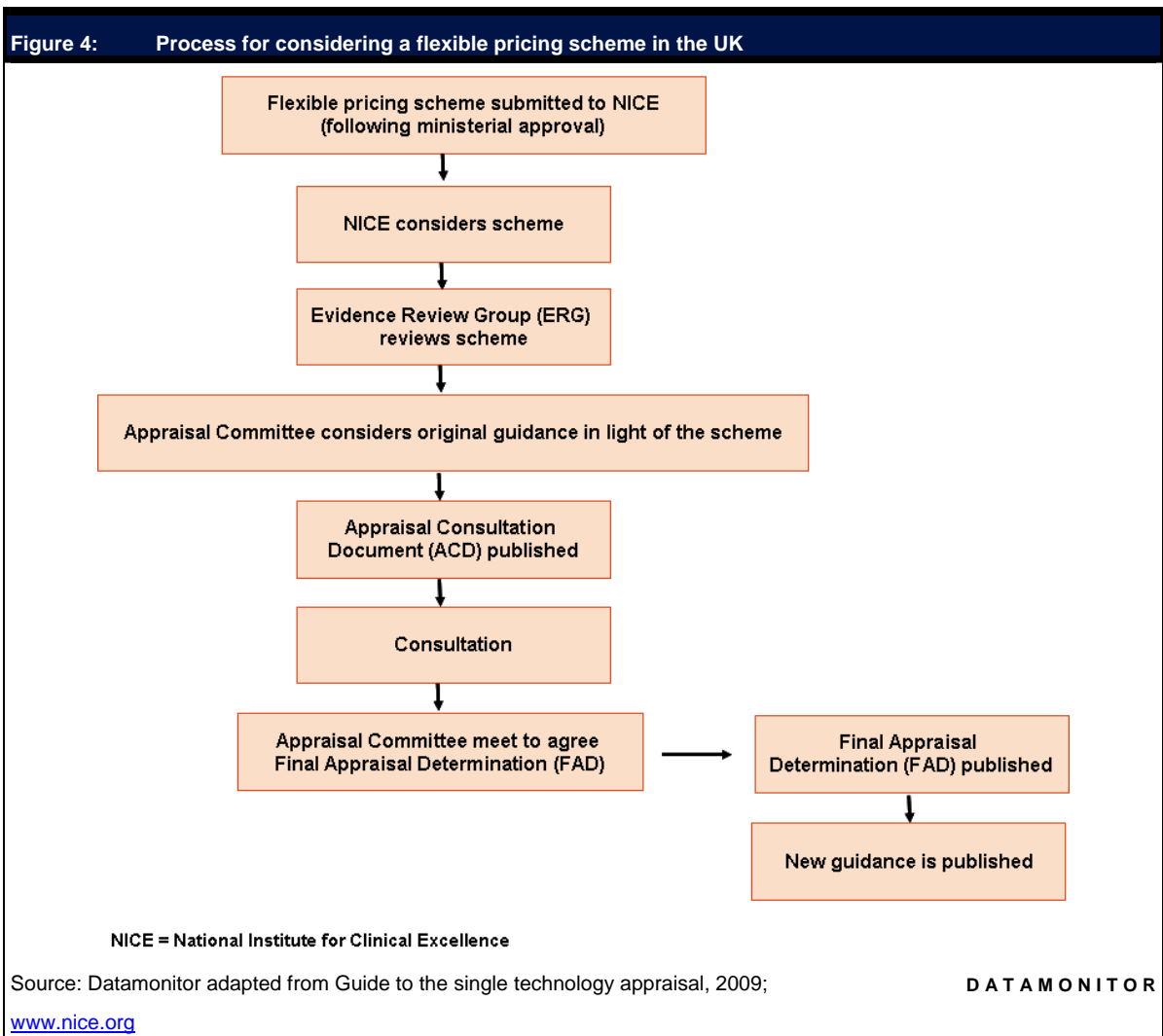


In the latest revision of the PPRS in 2009, despite the announcement of price reductions for branded drugs, a number of incentives have been introduced with the aim of stimulating innovative R&D and the launch of novel drugs in the UK. This will foster pricing of drugs based on their therapeutic value and cost-effectiveness, reinforcing the use of risk-sharing schemes. In doing so, the new PPRS protects the NHS from drugs that are not cost-effective, while accommodating the rise in price of expensive novel drugs such as biologics. Amendments to the 2009 PPRS include:

- **Flexible pricing** – more flexible pricing arrangements will mean that drug companies will supply drugs to the NHS at lower initial prices, with the option of higher prices if their therapeutic value is proven at a later date. Essentially, the new scheme allows potential price rises when significant new evidence is produced, changing the value of a product. A new price may also be designated when a new indication is approved, although this only applies to new active substances launched after January 1, 2009. For new indications, companies are free to set the price, but the drug must also be discounted so that the NHS pays the original lower price for the first indication (Ehreth and Williams, 2009).
- **Value based pricing** – historically, value-based pricing for medicines has been mostly applied in smaller markets such as Australia, Canada and Sweden. However, due to the importance of the UK market for international pricing reference, the UK Office of Fair Trading (OFT) report has suggested that drugs should be reviewed after launch (ex post) or before (ex ante) to determine a maximum price in accordance with clinical benefits relative to the comparator drug (defined as the current best available treatment) (The Pharmaceutical Price Regulation Scheme, 2007; www.of.gov.uk). As such, value-based pricing should encourage incremental improvement in treatment, as superior products will receive higher payment. Also, more value-reflective prices would achieve a better outcome for patients by increasing access to drugs they are currently denied; in addition to securing better value for money for the NHS.
- **Greater R&D allowance for smaller companies** – the R&D allowance is to be increased for smaller firms to a maximum of 30% of NHS sales for assessing annual financial returns (Taylor, 2008).

Under the new PPRS, the manufacturer can change the price of a drug when new evidence emerges. However, this flexible pricing arrangement can only be considered by NICE after ministerial approval and confirmation from the Department of Health.

Figure 4 illustrates the process used by NICE to review a flexible pricing scheme in the UK.



Italian risk-sharing agreements are optimized through the Register of Oncology Medicines (RFOM)

In order to address the challenge of pricing novel innovative oncology drugs, the Italian Agency for Pharmaceuticals (Agenzia Italiana del Farmaco, AIFA) assesses risk-sharing programs based on two main principles (De Ambrosi, 2008):

- oncology drugs are reimbursed only if significant efficacy is demonstrated, as the Italian Health Service (Servizio Sanitario Italiano, SSN) cannot bear the risk and cost of clinical failure (non-responding patients);
- clinical procedures are introduced to follow up patients who respond to treatment.

While in the UK, risk-sharing agreements are often based on pre-established outcomes, where the risk is shared between the National Health Service (NHS) and the pharmaceutical company until the end of treatment, in Italy payment by results are mostly based on rebates. This is because the SSN would not be able to afford such high prices for innovative drugs given that Italy has smaller budgets than the UK. However, the main differentiator between the two countries is that while the National Institute for Health and Clinical Excellence (NICE) often rejects novel drugs which do not meet quality-adjusted life year (QALY) targets, Italy prefers to approve these drugs for all patients (Table 2) but only reimburses treatment for patients who respond.

For example, in 2009, UK's NICE rejected Bayer's Nexavar (sorafenib) for the treatment of both kidney and liver cancer patients in England and Wales as it was not deemed cost-effective. In Italy, however, two risk-sharing schemes for Nexavar were proposed and later accepted, one for the treatment of each type cancer (Staton, 2009). In November 2006, Nexavar was given market authorization in Italy for the second-line treatment of advanced renal cell carcinoma, under the condition that the company offered the SSN a 50% discount during the first 3 months of treatment, and that after the treatment period, the SSN is fully reimbursed for responding patients, typical of many risk-sharing schemes adopted in Italy. Similarly, the liver cancer risk-sharing scheme proposed in June 2008 involves the SSN paying the full price of Nexavar for the first 2 months of treatment, after which the patient is assessed, and in cases where no responses to the drug is observed, treatment is stopped and the pharmaceutical company offers reimbursement or a credit note (De Ambrosi, 2008).

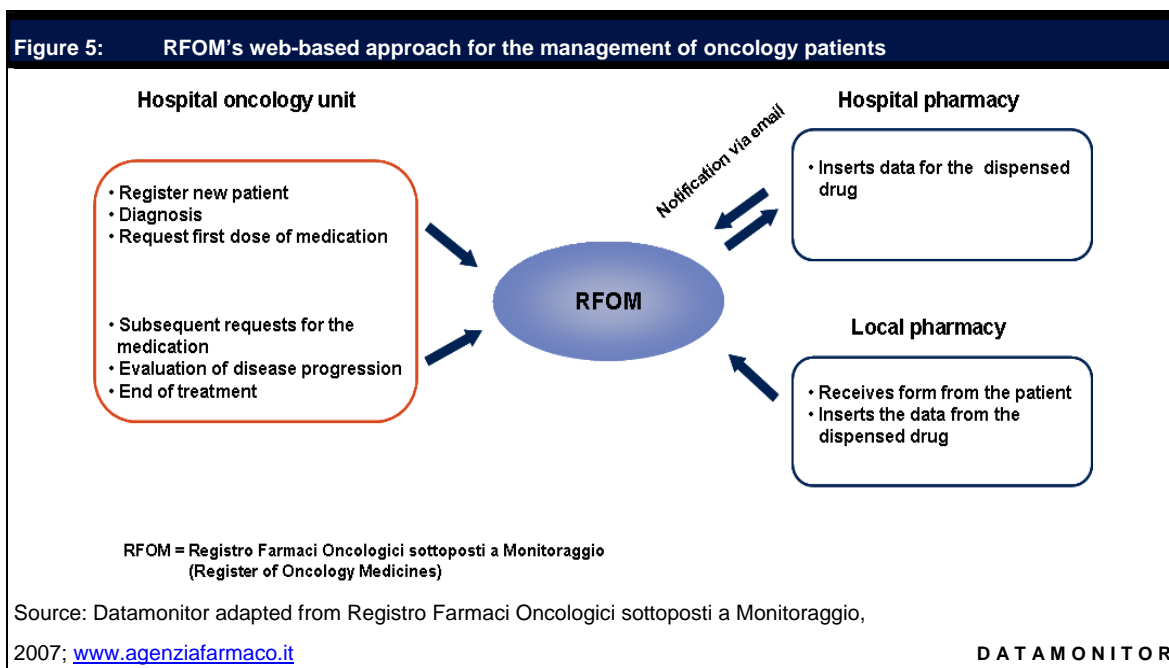
Table 2 shows Italy welcomes new pricing plans to guarantee access to oncology drugs, while the UK is more restrictive.

Table 2: Market access restrictions for oncology drugs in Italy and the UK, 2009		
Brand	Italy	UK
Herceptin (trastuzumab)	No restriction	Positive review took 2 years
Avastin (bevacizumab)	>6 month delay between EMEA approval and launch	Rejected by NICE and SMC
Erbix (cetuximab)	Price volume agreement Observational studies Prior authorization	Rejected by NICE and SMC
Vectibix (panitumumab)	None	Rejected by NICE and SMC
EMEA = European Medicines Agency; NICE = UK's National Institute for Health and Clinical Excellence; SMC = Scottish Medicines Consortium		
Source: Innovative approaches to pricing, 2007; www.imshealth.com		DATAMONITOR

Due to the high cost of oncology drugs and the poor correlation with their clinical value, ensuring risk-sharing programs are optimized is of prime importance for AIFA. A monitoring system to control the number of patients and the clinical outcomes has been set up in Italy, known as the Register of Oncology Medicines (Registro Farmaci Oncologici sottoposti a Monitoraggio, RFOM). The database was initially rolled out in December 2005 as a Herceptin registry, but was launched online in April 2006 to also monitor Avastin (bevacizumab), Eloxatin (oxaliplatin), Emend (aprepitant), Erbitux (cetuximab), Faslodex (fulvestrant), Foscan (temoporfin), Gliadel (carmustine), Zevalin (ibritumomab), Kepivance (palifermin), Tarceva (erlotinib), Nexavar (sorafenib), Sutent (sunitinib) and Sprycel (dasatinib) treatments. In addition to registering and monitoring patients receiving treatment with these drugs, the database also allows pharmacies to deal with administrative procedures. As such, it allows the monitoring of the whole process, from diagnosis to drug dispensing in the hospital pharmacy, thereby creating an electronic record for each patient, including data on severity of disease, progression, side effects, brand and dose of drug (Godman, 2009). This can then be used to optimize future risk-sharing strategies in Italy by:

- providing guidance on the appropriateness of drug administration;
- speeding up drug dispensing;
- enabling the use and costs for each drug for each hospital to be traced;
- centralization of oncology drugs, thereby easing collaboration and communication between the physician and the hospital pharmacist.

Figure 5 summarizes the interaction and flow of information between key stakeholders and the RFOM.



Despite the benefits of the system in streamlining procedures and increase efficiency, there is still room for improvements to RFOM, such as updating patient files (which burdens physicians and pharmacists), in addition to other technical aspects regarding data collection and input. Going forward it is important that such a registry can be flexible to adapt to the different characteristics of oncology drugs (Registro Farmaci Oncologici sottoposti a Monitoraggio, 2007; www.agenziafarmaco.it).

Nevertheless, the RFOM has proved essential to building risk-sharing agreements, supporting the development of all schemes for innovative oncology drugs in Italy (Table 3). Consequently, a novel oncology drug has a greater chance of launch in Italy than in the UK.

Table 3: Evolution of approved risk-sharing agreements in Italy, 2006–08			
Date	Brand	Indication	Strategy of risk-sharing agreement
July 2006	Tarceva (erlotinib)	NSCLC after previous treatment with chemotherapy	50% discount for SSN for the first 2 months/two cycles of chemotherapy. Follow up after 8 weeks treatment
September 2006	Sutent (sunitinib)	Advanced and/or metastatic renal cancer (for first and second-line treatment)	50% discount for SSN for the first 3 months/two cycles of therapy
September 2006	Nexavar (sorafenib)	Renal cancer (second-line)	50% discount for SSN for the first 3 months/three cycles of therapy
June 2008	Nexavar (sorafenib)	Liver cancer	SSN provides full treatment for the first 2 months, subsequently, the pharma company reimburses with credit note for non-responding patients
May 2007	Sprycel (dasatinib)	Chronic myeloid leukemia and acute lymphoblastic leukemia	50% discount for SSN for the first month/first cycle of treatment but only after ensuring progression of disease (non-responders)
July 2008	Tasigna (nilotinib)	Chronic myeloid leukemia for Philadelphia-positive (Ph+) adult patients whose disease has progressed	SSN provides full treatment for the first month, subsequently, the pharma company reimburses with credit note for non-responding patients
June 2008	Avastin (bevacizumab)	Colorectal cancer in combination with chemotherapy	50% discount for SSN for the first 6 weeks of treatment. Responding patients will get free treatment after the 11th cycle
June 2008	Avastin (bevacizumab)	Metastatic breast cancer in combination with paclitaxel	50% discount for SSN for the first 6 weeks of treatment. Responding patients will get free treatment after the 11th cycle
June 2008	Avastin (bevacizumab)	NSCLC plus platinum-based chemotherapy	50% discount for SSN for the first 6 weeks of treatment. Responding patients will get free treatment after the 11th cycle
June 2008	Avastin (bevacizumab)	Advanced and/or metastatic renal cancer in combination with interferon alpha-2a	50% discount for SSN for the first 6 weeks of treatment. Responding patients will get free treatment after the 11th cycle

NSCLC = non-small cell lung cancer; SSN = Servizio Sanitario Italiano

Source: Datamonitor adapted from De Ambrosi, 2008

DATAMONITOR

Will a NICE-like model succeed in the US?

Under President Obama, the US is now aiming to deliver more affordable and equitable healthcare. However, the country faces spiraling healthcare costs, which currently consumes 18% of the US economy and could rise to 34% by 2040 (Gaouette and Litvan, 2009). US drug prices and administrative costs are the most expensive in the seven major markets, made worse by physicians overcharging for outpatient services due to the discretionary nature of the fee-for-service reimbursement system (Why Americans pay more for health care, 2008; www.mckinseyquarterly.com). Furthermore, the introduction of more expensive drugs and devices has also made a significant contribution to the rise in healthcare costs. For example, global sales of \$111 billion for biologics (therapeutic proteins, monoclonal antibodies and vaccines) were accrued by the top 50 global pharma companies in 2008 alone (company reported data, PharmaVitae Explorer). Consequently, there is a need to curb spending and control costs which in part could be achieved through the creation of a Health Technology Assessment (HTA) body in the US which would formalize the process for gathering information on comparative effectiveness.

Congress is therefore focusing on understanding the UK's HTA organization—the National Institute for Health and Clinical Excellence (NICE)—as this is generally regarded as the most sophisticated institution that assesses clinical and cost effectiveness of new drugs and treatments. However, given the significant differences between the healthcare systems in the UK and the US, it remains unlikely that the NICE model will be copied directly in the US, as NICE is designed around the UK's public National Health System (NHS), whereas the US has a fragmented private-based system. In addition, there are social and cultural differences that can obstruct the introduction of a NICE-like model, particularly the willingness to accept explicit restrictions on access to services and the concern about extensive government involvement in healthcare (Sorenson *at al.*, 2008). Nevertheless, the US already has HTA-like organizations: the Centers for Medicare and Medicaid Services (CMS) has the Medicare Coverage Advisory Committee (MCAC); each of the 50 state Medicaid programs has some form of HTA procedure for drugs; and 13 states participate in the Drug Effectiveness Review Project. Furthermore, many private health plans and pharmacy benefit managers (PBMs) also manage HTA-like programs.

In order to examine NICE and its implications for comparative effectiveness reviews in the US, the National Pharmaceutical Council (NPC) commissioned a project through LSE Health and Social Care (LSEHSC). The following observations were made for introducing a hypothetical NICE-like model in the US (Sorenson *at al.*, 2008):

- **Structure and composition** – although the UK's NICE is funded by the Ministry of Health, it has a distant relationship from the government and it is seen as an independent body. In the US, decisions affecting governance, funding and organization of any HTA body would depend on where it is located, i.e. whether it should be a new federal agency, part of an existing agency, or outside of the government. Subsequently, if the agency is to inform the federal government alone, it would result in a similar relationship between NICE and the Ministry of Health in the UK. On the other hand, if an HTA body were to report to a wider range of payers, a broad spectrum of funding and organizational options would be available, such as a mixture of public and private funding.
- **Responsibility** – analysis of a drug's clinical and cost effectiveness forms the core of NICE's remit. On an international level, however, NICE is one of the few HTAs (together with Australia's and Canada's national formulary committees) to clearly state its remit. In contrast, many other agencies promote a more general 'quality in healthcare' or 'care of an international standard', but by doing so, they engender a high level of uncertainty. This issue has been subject to debate in the US with the Comparative Effectiveness Research Act of 2008. For many,

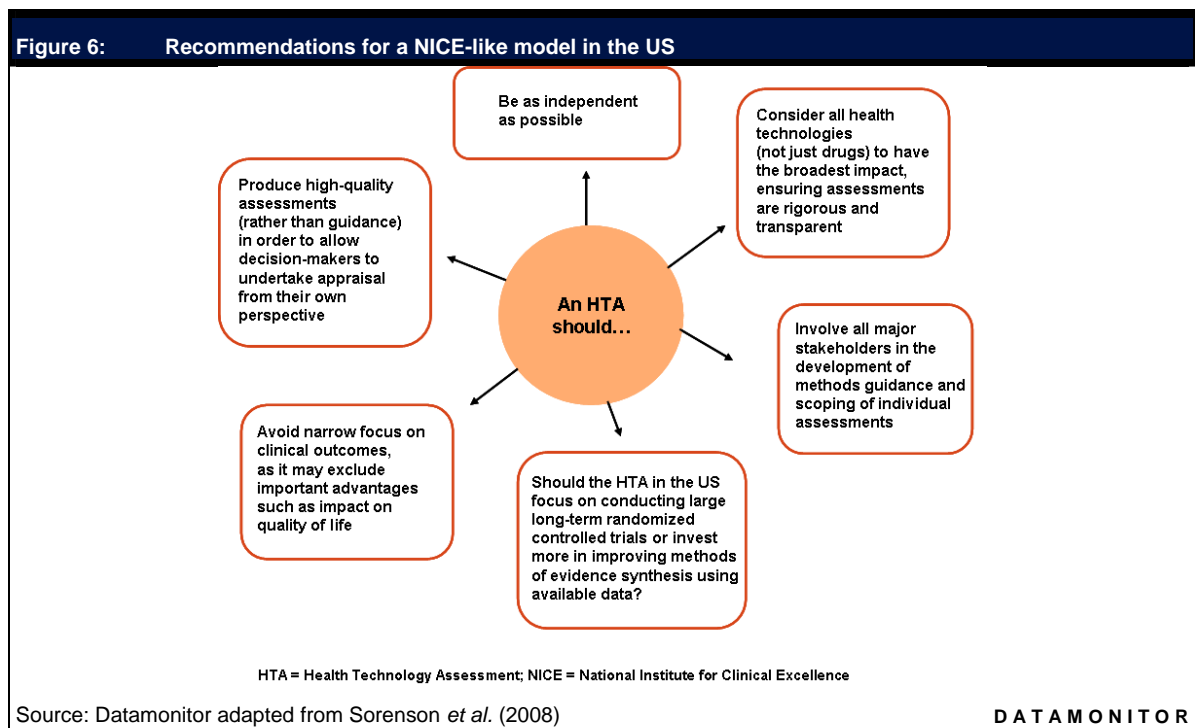
Introduction to risk-sharing agreements

the term 'comparative effectiveness' should involve only clinical outcomes through conducting clinical trials to compare alternative technologies. On the other hand, others believe comparative effectiveness should also consider costs.

- **Assessments versus appraisals** – NICE clearly distinguishes between assessments (where a technology is assessed) and appraisals (where the evidence is evaluated and the decisions are made), and also relies on an external panel of experts during its decision making process. The challenge in a market such as the US is whether an HTA body would have a decision-making role at all, as the US healthcare system is so diverse.
- **Cost effectiveness threshold** – ultimately, NICE's decisions are based on its £20,000–30,000 (\$37,104–55,655) per quality-adjusted life year (QALY) threshold. No official threshold exists in the US, although in health economics literature a threshold of \$100,000 per QALY is usually referenced (Sorenson *et al.*, 2008). If a threshold is ever to be confirmed in the US, it will probably vary between the different sectors of the healthcare system depending on the level of budget available. Nevertheless, an HTA entity is likely to limit its role to assessments rather than making appraisals.

Overall, an HTA body could create a more cost-effective use of healthcare resources in the US, however it is important to note this will increase the burden on Pharma to produce data. More importantly, as the HTA would be linked to pricing and reimbursement decisions, it would lead to greater controls for branded pharmaceuticals, in turn resulting in a controversial loss of the free market pricing in the US. Ultimately, the actual implementation would present a considerable challenge given the expected level of resistance.

Despite the substantial differences between the UK and US, important lessons can be drawn from the NICE model, if this is to be introduced in the US. These are illustrated in Figure 6.



Risk-sharing agreements could help reduce costs of universal healthcare in the US

Besides comparative effectiveness, President Obama is also aiming to introduce direct price negotiations with the federal government in an effort to control costs and reduce wastefulness in the US healthcare system. Pharma is expected to strongly oppose this as it could potentially have a dramatic effect on the industry's profits given the government would then dictate drug prices. Consequently, risk-sharing agreements in the US act as a middle ground, and enable the prescription of high priced drugs, while offsetting cost against their therapeutic effect and outcome in specific patient populations. US state health insurance programs have covered pharmaceutical expenses for the elderly and the poor through Medicare and Medicaid, respectively; but with plans to cover all currently uninsured patients under a universal healthcare scheme, this will drive up the country's healthcare bill. Therefore, this represents an additional area where risk-sharing agreements could be implemented, providing cost savings in patients who fail to respond adequately to novel, high value drugs.

Currently, companies must refund Medicaid either with a flat sum consisting of a minimum rebate amount (15.1% of the average manufacturer price) for a branded drug, or the difference between the average manufacturer price and the best price extended to any private buyer. The problem with introducing UK-style risk-sharing in the US, is that it can change the per-unit pricing on products, resulting in a steep increase in rebates or even reduce reimbursement under the average sales price (Senior, 2009). In the Medicare Payment Advisory Commission's (MedPAC) discussion on biosimilars, the idea of risk-sharing for some costly biologics was suggested, which is a notable divergence from the US's private-based system. Although the proposal is still in its infancy, its consequences must be carefully evaluated since it is a radical change from the country's traditional principles of healthcare provision.

Although risk-sharing remains uncommon in the US, a small number of such deals have been introduced. The pharmacy benefit management division of Cigna, for example, can be credited with an innovative and risky deal, whereby it signed a pay-for-performance deal with Merck & Co., in order to control costs and increase access to Januvia (sitagliptin) and Janumet (sitagliptin and metformin) for type 2 diabetes patients in the US. Under this scheme, Cigna will receive a discount on the drug if a patient's blood sugar falls. Nevertheless, critics firmly believe that state regulations and marketplace pressures make it impossible for an insurer to refuse to pay for an US Food and Drug Administration (FDA)-approved drug (Pollack, 2007), reflecting the poor leverage of individual health plans. As such, skeptics remain doubtful that risk-sharing schemes are likely to work on a larger-scale in the US, which has been historically dominated by a private system—in stark contrast to UK where the government is the primary payer. Consequently, until the roll-out of universal healthcare in the US, the uptake of risk-sharing will be simply based on financial incentives to payers for the time being.

Australian risk-sharing schemes allow market access in the face of low cost-effectiveness thresholds

Historically, Australia has had similar a similar healthcare system to the UK:

- both countries currently have a total expenditure on health as percentage of gross domestic product (GDP) of roughly 8% (www.who.int);
- like the UK, Australia's healthcare system is based on public health insurance (Medicare), which provides universal subsidy schemes through the Pharmaceutical Benefits Management (PBM);
- Australia appraises new drugs through the Pharmaceutical Benefits Advisory Committee (PBAC) much like the UK through the National Institute for Health and Clinical Excellence (NICE).

Nevertheless, criteria covering the recommendation of new drugs for use within the two public healthcare systems differ slightly between Australia and the UK. Firstly, PBAC appraises all drugs, while NICE evaluates only those referred to it by the government. Another significant difference is that the cost-effectiveness threshold in Australia is A\$42,000 per quality-adjusted life year (QALY) (equating to \$35,824) whereas NICE's threshold is £20,000–30,000 (\$37,104–55,655) (Raftery, 2008). In fact, Australia has a notoriously tough pricing and reimbursement system, as evidenced by Datamonitor primary research (Datamonitor, *Pricing and Reimbursement in Key Asia Pacific Markets*, January 2009, DMHC2478):

"The cost-effectiveness barriers [in Australia] are some of the hardest in the world."

Greg Cook, Bristol-Myers Squibb

"The level of data required [in Australia to prove cost-effectiveness] is quite high compared to other countries."

Cammy Yuen, Sanofi-Aventis

The first risk-sharing scheme was introduced in Australia in October 2003, and by 2008 14 schemes were in place (Carapinha, 2008), such as that for Actelion's Tracleer (bosentan) (see Chapter 3 for more information). Risk-sharing agreements in Australia allow the government to claw back the cost of highly priced medicines from manufacturers if annual expenditure for those drugs exceeds pre-defined budgets. For example, if the annual government budget for a new medicine is A\$250m (\$213m) and the actual expenditure is A\$270m (\$230m), a proportion of the A\$20m (\$17m) would be recouped from the pharmaceutical company (Carapinha, 2008).

The Department of Health in Australia receives monthly data from Medicare for each drug covered by a risk-sharing agreement, and uses the data to track actual usage and expenditure against the usage and expenditure agreed in each risk-sharing agreement. This is supplemented by quarterly data from the States and Territories regarding drugs that are prescribed in public hospitals, and allows the Department of Health to monitor and inform the PBMA of the uptake and effectiveness of drugs prescribed under a risk-sharing scheme.

Summary of risk-sharing agreements across key markets

Table 4 summarizes the various types of risk-sharing schemes between pharma companies and payers in the UK, US, Italy, Germany, and Australia.

Table 4: Examples of pharma risk-sharing agreements in Australia, Germany, Italy, the UK and US, 2005–09						
Date of guidance	Decision	Drug	Indication	Company	Type of risk-sharing agreement	Country
December 2005	Approved	Tracleer (bosentan)	Pulmonary arterial hypertension (PAH)	Actelion	Clinical risk-sharing	Australia
July 2007	Approved	Velcade (bortezomib)	Multiple myeloma	Janssen-Cilag	Clinical risk-sharing	UK
October 2007	Approved	Aclasta (zoledronic acid)	Osteoporosis	Novartis	Clinical risk-sharing	Germany
November 2006	Approved	Nexavar	Renal cell carcinoma	Bayer	Clinical risk-sharing	Italy
June 2008	Approved	Nexavar (sorafenib)	Liver cancer	Bayer	Clinical risk-sharing	Italy
March 2009	Approved	Sutent (sunitinib)	Renal cell carcinoma	Pfizer	Clinical risk-sharing	UK
March 2009	Rejected	Tyverb (lapatinib)	Advanced or metastatic breast cancer, in combination with Xeloda (capecitabine)	GlaxoSmithKline	Clinical risk-sharing	UK
April 2009	Approved	Januvia (sitagliptin)	Type 2 diabetes	Merck & Co.	Clinical risk-sharing	US
April 2009	Approved	Actonel (risedronate sodium)	Osteoporosis	Sanofi-Aventis	Clinical risk-sharing	US
November 2008	Approved	Tarceva (erlotinib)	Non small cell lung cancer (NSCLC)	Roche	Cost-effectiveness risk-sharing	UK
February 2008	Approved	Avastin (bevacizumab)	Breast cancer	Genentech	Fixed budget/price and volume agreement	US
August 2008	Approved	Lucentis (ranibizumab)	Wet age-related macular degeneration	Novartis	Fixed budget/price and volume agreement	UK
April 2009	Approved	Revlimid (lenalidomide)	Multiple myeloma	Celgene	Fixed budget/price and volume agreement	UK
June 2009	Approved	Erbix (cetuximab)	Metastatic colorectal patients, in combination with chemotherapy	Merck Serono	Fixed budget/price and volume agreement	UK

Source: Datamonitor

DATAMONITOR

CHAPTER 3 OPTIMIZING RISK-SHARING AGREEMENTS

Key findings

Risk-sharing agreements are designed to align the interests of payers and Pharma, in order to allow a drug access to a specific market, thereby improving health outcomes for patients. In order to optimize such agreements, the following recommendations are made:

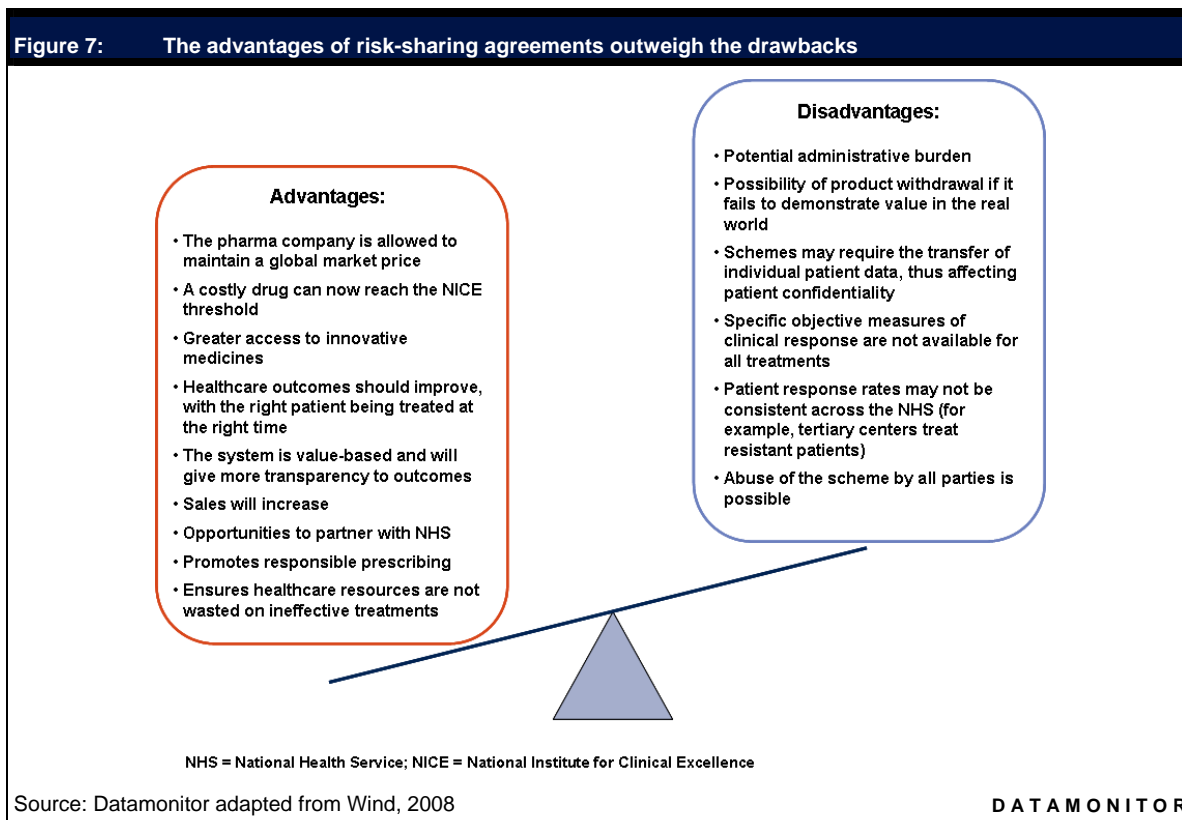
- **identify a suitable agent** – a drug should fulfill specific criteria in order to be suitable for a risk-sharing agreement;
- **decide on which type of risk-sharing agreement to adopt** – when devising a risk-sharing scheme manufacturers must carefully measure the trade-offs between health benefits and costs of their drug, and also the type of reimbursement used;
- **timing of risk-sharing scheme implementation is critical to its success** – be that timing of market entry approval or as part of a lifecycle management strategy;
- **strong head-to-head clinical data are required to support risk-sharing applications in the UK** – these are critical to increasing the National Institute of Clinical Effectiveness's (NICE's) cost-effective appraisals of a drug;
- **identify key stakeholders and develop a pilot program** – the use of an independent third party, such as a university, can be useful to ensure academic rigor and balance the interests of Pharma and the health authority;
- **investigate all regulatory and legislative avenues that could support access to market** – the new NICE end-of-life guidance legislation can be useful for drugs struggling to gain a positive NICE opinion in patients with a few months to live;
- **do not underestimate the influence of patient advocacy groups on reimbursement approval** – strong patient advocacy groups (PAGs) helped to overturn NICE's initial decision on Velcade (bortezomib), highlighting the importance of working with these prominent groups in order to increase disease awareness.

The pros and cons of entering risk-sharing agreements

Risk-sharing agreements are designed to allow high priced drugs to gain access to a new market (often without the need for additional clinical data) following negative approval from a health authority such as the National Institute of Health and Clinical Excellence (NICE) in the UK. Risk-sharing agreements can also provide a form of lifecycle management strategy, incentivizing the prescription of an already marketed drug, as observed in the US market with agreements between pharma companies and insurance providers. These strategies share the risk between the pharma company and the provider, but ultimately they enable patients to gain access to an innovative drug that would otherwise be rejected or stalled by protracted negotiations. Risk-sharing can therefore improve health outcomes while reducing overall healthcare costs.

Such schemes also typically allow a drug quicker access to market following initial rejection by authorities, involving a dynamic process, principally consisting of negotiations between the two parties over drug cost-effectiveness, involving bartering over drug price and rebates. This is often preferred to the long and expensive route of producing additional clinical trial data to support a second market approval application. Risk-sharing schemes also allow companies to maximize global sales of a given drug. If a company were to simply lower the price of its drug in a key reference market such as the UK, in order to reduce its quality-adjusted life year (QALY), this would affect the price of the drug in the numerous countries that use the UK price as a benchmark in their own pricing negotiations. Additionally, NICE is prohibited by law from negotiating drug prices with a company (Breckenridge and Walley, 2008).

The advantages and disadvantages of risk-sharing agreements are summarized in Figure 7.



Despite the benefits of risk-sharing agreements, they must be managed correctly to ensure they do not become a burden to healthcare systems. In fact, these schemes can be labor-intensive for pharmacy, clinical and financial staff. The administration of risk-sharing agreements is complicated further by the several types of funding arrangements possible, which in turn can lead to multiple risk-sharing programs across a single drug for different indications. Given it is already challenging to administer rebates and track outcomes, the greater the variety of schemes available, the harder they become to manage. Another drawback is that it may be difficult to conclude if such pricing schemes actually work in practice, especially as it may be hard to objectively measure a clinical response to a drug. However, the risk to Pharma could fall as physicians gain more confidence with the drug regimen, with costs to the payer increasing. Alternatively, if clinicians use a drug therapy more widely because of its low perceived cost, if treatment fails, costs incurred by the manufacturer could rise.

Key recommendations developing risk-sharing agreements

Risk-sharing agreements are designed to align the interests of payers and Pharma, in order to allow a drug access to a specific market, thereby improving health outcomes for patients. In order to optimize such agreements, the following recommendations are made:

- **identify a suitable agent** – a drug should fulfill specific criteria in order to be suitable for a risk-sharing agreement;
- **decide on which type of risk-sharing agreement to adopt** – when devising a risk-sharing scheme manufacturers must carefully measure the trade-offs between health benefits and costs of their drug, and also the type of reimbursement used;
- **timing of risk-sharing scheme implementation is critical to its success** – be that timing of market entry approval or as part of a lifecycle management strategy;
- **strong head-to-head clinical data are required to support risk-sharing applications in the UK** – these are critical to increasing the National Institute of Clinical Effectiveness's (NICE's) cost-effective appraisals of a drug;
- **identify key stakeholders and develop a pilot program** – the use of an independent third party, such as a university, can be useful to ensure academic rigor and balance the interests of Pharma and the health authority;
- **investigate all regulatory and legislative avenues that could support access to market** – the new NICE end-of-life guidance legislation can be useful for drugs struggling to gain a positive NICE opinion in patients with a few months to live;
- **do not underestimate the influence of patient advocacy groups on reimbursement approval** – strong patient advocacy groups (PAGs) helped to overturn NICE's initial decision on Velcade (bortezomib), highlighting the importance of working with these prominent groups in order to increase disease awareness.

Identify a suitable agent

A drug should meet the following criteria in order to be suitable for a risk-sharing agreement:

- target an area of high unmet need – drugs for the treatment of small and niche populations are particularly suitable;
- target the treatment of severe life-threatening indications;
- offer an objective and measurable outcome of treatment, ideally where biomarkers can be reliably monitored. If there are less objective measures of response or long periods of treatments (such as the multiple sclerosis scheme in the UK) risk-sharing schemes are less practical (Beckenridge and Walley, 2008);
- present an innovative treatment for which there is uncertainty over the expected risks and benefits;
- have a high cost and therefore large impact on potential healthcare budgets;
- be supported by strong political and/or patient demand for drug access.

Many of these attributes are met by oncology drugs, which form the bulk of risk-sharing schemes implemented, with five of the six risk-sharing schemes approved by the UK's National Institute of Health and Clinical Excellence (NICE) since 2007 designated for the treatment of various types of cancer.

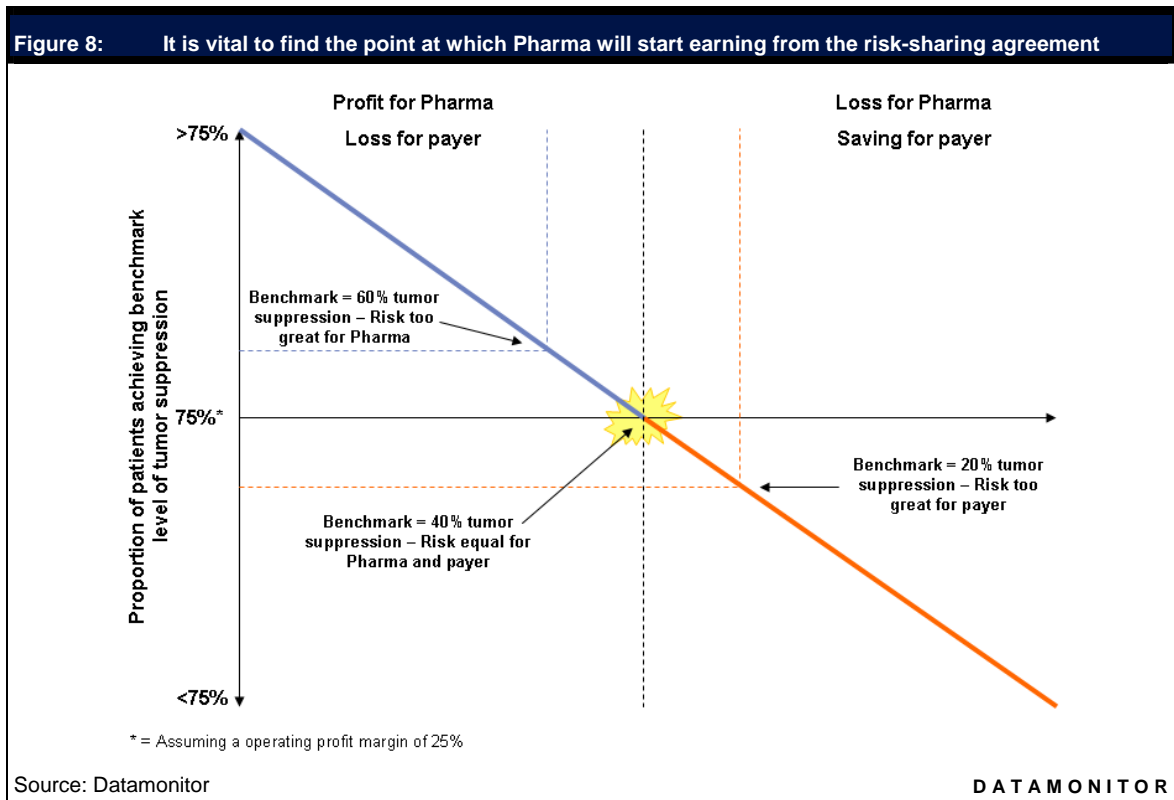
Deciding on which type of risk-sharing agreement to adopt

The three types of risk-sharing schemes available to Pharma are clinical, cost-effective and fixed budgets/price/volume agreements, although there are numerous variations of each, all with their own pros and cons. When devising a risk-sharing scheme, manufacturers must carefully measure the trade-offs between health benefits and costs of their drugs, as well as the type of reimbursement used. This can take the form of a rebate from the manufacturer or a future payment from the payer once treatment effectiveness has been determined. Ultimately, manufacturers need to devise a matrix from which a threshold level of cost-effectiveness can be defined. For example, if the risk-sharing program is based on clinical outcome guarantees, forecasts of the proportion of patients expected to reach the target must be calculated.

Figure 8 illustrates an example of a risk-sharing deal based on therapeutic outcomes, where the pharmaceutical company will not charge the payer for patients who do not reach the clinical goal (for example, 40% tumor suppression within 6 months). Therefore, it is crucial to find the point at which the company will start making a profit. For example, assuming an operating profit margin of 25%:

- if more than 75% of patients respond with 40% tumor shrinkage, then the company will make a profit;
- if fewer than 75% of patients respond to treatment, the company will make a loss;
- if exactly 75% of patients respond positively, then the company will break even.

Figure 8 illustrates the importance of finding a middle ground where both Pharma and the payer benefit from the risk-sharing scheme.



Examples of risk-sharing schemes that are based on cost and price rather than cost-effectiveness include Roche’s Tarceva (erlotinib) risk-sharing agreement for second-line non-small cell lung cancer (NSCLC) in the UK and Genentech’s Avastin (bevacizumab) agreement for breast cancer in the US. Schemes for Novartis’s Reclast/Aclasta (zoledronic acid) and Sanofi-Aventis and Procter & Gamble’s Actonel (risedronate sodium), both for the treatment of osteoporosis, demonstrate the use of pay for non-performance risk-sharing.

Tarceva’s risk-sharing scheme focuses on bringing costs into line with rival Taxotere

Roche’s Tarceva (erlotinib) is a once-a-day treatment currently approved for two types of cancer: non-small cell lung cancer (NSCLC) and pancreatic cancer. NICE’s evaluation of Tarceva began in November 2006, although following several rounds of appeals and negative guidance, the Institute continued to deny the drug access to the NHS market for the second-line treatment of NSCLC patients in England and Wales. In January 2007, Tarceva was finally approved in mainland Europe for the treatment of metastatic pancreatic cancer in combination with gemcitabine, even though it had been rejected the previous year.

Unhappy with NICE’s decision, Roche decided to follow in the steps of Velcade’s risk-sharing scheme in order to ensure patient access to Tarceva. In May 2008, the company wrote to the Department of Health proposing an arrangement that could guarantee positive guidance until definitive head-to-head data between Tarceva and Sanofi-Aventis’s Taxotere

(docetaxel) become available (in 2011 or thereafter). This scheme was proposed due to the lack of existing comparative data between the two drugs (Mills, 2008), and as Tarceva was then only recommended in the second-line as an alternative to Taxotere in treating NSCLC patients who have failed one chemotherapy regimen.

Roche estimated that a reduction of 14–15% equating to £1,036 (\$1,922) would be required to bring the cost of Tarceva treatment in line with the £6,714 (\$12,456) cost per cycle for Taxotere (Costing Statement: Erlotinib for the treatment of non-small cell lung cancer, 2008; www.nice.org.uk). On this basis, NICE issued positive guidance for Tarceva in November 2008, approving the drug for use in the treatment of second-line NSCLC, but only on condition that the overall treatment costs (including administration, adverse events and monitoring costs) were equal to that of Taxotere. Despite the discount, Tarceva is still more expensive than Taxotere. However, Tarceva has lower administration costs because it is an oral drug which does not require outpatient hospital trips, as well as generating fewer side effects, which brings its total costs into line with Taxotere which must be infused intravenously. Unlike other risk-sharing schemes which have a pre-arranged rebate for the 'non-responder' group of patients, Tarceva's scheme offers a lower price for all NSCLC patients to ensure positive guidance by NICE and increase patient access.

One reason for adopting this risk-sharing scheme rather than Velcade's, for example, could be the fact that Tarceva's response rate for the treatment of NSCLC is 12% across all patients (Perez-Soler, 2004) as compared to the 33% treatment rate for Velcade in multiple myeloma (Scientific discussion of Velcade, EMEA, 2004; www.emea.europa.eu). Consequently, due to Tarceva's lower response rate, a price reduction allows the company to sell more product than under the Velcade type scheme, which only charges for positive responders.

Avastin risk-sharing scheme based solely on price and not cost-effectiveness

Genentech's blockbuster monoclonal antibody Avastin (bevacizumab) has been approved for colorectal cancer, NSCLC, and breast cancer. The drug was initially approved in Europe for breast cancer in 2007, however, the US approved the drug a year later due to indecisiveness over the 5.5 months of progression-free survival it offered to breast cancer patients, and whether this benefit offset the severe side effects.

Upon launch, the drug was subject to a severe media backlash owing to its high price of approximately \$7,700 a month or \$84,700 for an average 11-month course for breast cancer (Chase and Wilde Mathews, 2008). The high cost specifically for the treatment of breast cancer is because this indication requires a higher dose, thereby pushing up the price. Consequently, Genentech proposed an innovative scheme to lower patient out-of-pocket spending once the drug received US Food and Drug Administration (FDA) approval for breast cancer. The company capped the cost of the drug to \$55,000 per year for patients with advanced breast cancer who meet certain criteria, including having an annual income of less than \$100,000 (Chase and Wilde Mathews, 2008). In addition, the company also doubled its contribution to independent charities that provide co-pay assistance. This was a landmark move and demonstrates that risk-sharing agreements can be achieved based solely on price without the need for a NICE-like organization to enforce cost-effectiveness.

Aclasta's and Actonel's money-back guarantees for treatment failure offer an alternative risk-sharing option

In Germany, Novartis has implemented a pay for non-performance risk-sharing agreement for its osteoporosis drug, Reclast/Aclasta (zoledronic acid)—marketed as Reclast in the US, and Aclasta in Europe, whereby the company refunds the costs of the drug to health insurance agencies if a patient experiences an osteoporotic fracture within a year of taking the drug (Novartis Annual Report, 2008).

Similar to the agreement for Aclasta, in April 2009 Sanofi-Aventis and Procter & Gamble rolled out a pay for non-performance risk-sharing scheme for their drug Actonel (risedronate sodium) in the US, used in the treatment and prevention of postmenopausal osteoporosis. If a patient insured by insurance company Health Alliance suffers any fracture (except a spinal chord fracture) despite faithfully taking Actonel, the pharmaceutical companies will pay for the required medical care. Clearly this deal has several terms and conditions, whereby reimbursement to the US insurer occurs only for the cost of treating non-spinal osteoporosis-related fractures in post-menopausal women taking Actonel.

This type of plan penalizes poor therapeutic responses and lowers the cost for payers. In Aclasta's case, Health Alliance members would receive a rebate for the average cost of a small fracture (\$6,000) and up to \$30,000 for a hip fracture from the pharma companies, while the insurer would reimburse co-payments made and any cost-sharing the patient incurred related to the fracture, from prescriptions to hospital stays (Faigen, 2009). In the long run, it also lowers costs for Health Alliance, a small health insurance in Iowa and Illinois covering roughly 310,000 members. Sanofi-Aventis and Procter & Gamble also benefit, as the deal can reduce the incentive for the insurance company to move patients off Actonel to a less expensive generic alendronate, since the risk of covering the cost of a fracture offsets the prescribing of a cheaper drug (Pollack, 2009).

Such schemes also offer a type of lifecycle management strategy. Actonel's pilot risk-sharing scheme was introduced 9 years after its launch, reflecting a defense strategy in an effort to compete against generic incursion, exemplified by Teva's recent patent infringement of Actonel, and the resulting lawsuit, which was won by Procter & Gamble. With the forecast launch of Amgen's monoclonal antibody osteoporosis drug denosumab, currently under US Food and Drug Administration (FDA) review, such risk-sharing agreements should incentivize physicians to prescribe Aclasta and Actonel, providing differentiation from denosumab in the future. Furthermore, the success of Actonel's pilot program could lead to agreements with other healthcare providers in the US, eventually even offering a program to Medicare, potentially revolutionizing provision of healthcare in the US, where insurance companies do not have national monopolies.

Timing of implementation of risk-sharing schemes is critical to their success, be that for market entry approval or as part of a lifecycle management strategy

The timing of implementing a risk-sharing scheme is critical to its success, but also to its role in the lifecycle of the drug.

- **Gaining market access** – risk-sharing schemes like those typically used in the UK should be considered during the development of the drug and not as a last resort, or as a shortcut to market. This is particularly important if the drug is expected to command a high price. The National Institute of Health and Clinical Excellence's (NICE's) CEO Andrew Dillon has said it is preferable if a company approaches NICE earlier than expected to ask for consideration, particularly if the pharma company believes the scheme is part of the solution to market access (NICE's growing influence on UK drug pricing, 2009; invivoblog.blogspot.com). If risk-sharing is not proposed as soon as possible, it could delay a potential approval and unnecessarily extend the process. A significant advantage can be gained through first-to-market status for a drug accessed through a risk-sharing agreement—especially if multiple drugs initially receive negative approval from NICE for the same indication—not only in terms of patient numbers, but also in terms of setting a benchmark for future risk-sharing schemes. This is illustrated below by Novartis's Lucentis (ranibizumab), which secured first-to-market status for wet age-related macular degeneration (AMD) ahead of Pfizer's Macugen (pegaptanib), after both received negative NICE guidance.
- **Incentivizing drug prescribing once at market** – risk-sharing schemes of the type used in markets like the US and Germany should be considered before the launch of potential branded competitors. For example, by implementing a risk-sharing scheme, pharma companies can further incentivize their products by offering discounts, rebates, and pay-for-non-performance, strengthening the case to prescribe a given drug over competitor products which may not offer such incentives. These strategies have been used by Merck & Co. for Januvia (sitagliptin), Novartis for Aclasta (zoledronic acid), and Sanofi-Aventis for Actonel (risedronate sodium) to incentivize drug prescribing.

Lucentis's first-to-market advantage for wet age-related macular degeneration

Following NICE's negative guidance for two wet age-related macular degeneration (AMD) drugs—Novartis's Lucentis (ranibizumab) and Pfizer's Macugen (pegaptanib), Novartis proposed a dose-capping scheme for Lucentis, which led NICE to reverse its assessment of the drug. This enabled the drug to secure reimbursement in England and Wales from August 2008 (Ranibizumab and pegaptanib for the treatment of age-related macular degeneration, 2008; www.nice.or.uk). This marked a significant shift and demonstrates the power of risk-sharing schemes. Lucentis's approval was based on the condition that the NHS pays for the first 14 treatments for the first eye affected by wet AMD, and if further injections are required, the company will pay for the rest. Furthermore, treatment on the NHS will be free only after numerous specific criteria are met showing strong disease progression, otherwise patients are not eligible to receive the drug. With Lucentis's dose-capping scheme, Novartis bears the risk, but also has the chance to maximize sales in this treatment-naïve patient population.

Access to Pfizer's Macugen in England and Wales remains blocked, despite the fact that both drugs are available in Scotland, and that Macugen is actually cheaper than Lucentis (Table 5). However, according to NICE, Lucentis has a more favorable profile, and despite its increased price was deemed more cost-effective, hence its approval.

As illustrated in Table 5, it is unexpected to see Lucentis approved, when it has higher costs than Macugen.

Table 5: Comparative snapshot of Lucentis versus Macugen		
Key parameters	Lucentis (ranibizumab)	Macugen (pegaptanib)
Price per injection (\$, excluding VAT)	1,412	954
2-year treatment, projected number of injections	14–24	18
2-year treatment, estimated cost (\$)	19,850–33,949	17,253

Source: Ranibizumab and pegaptanib for the treatment of age-related macular degeneration, 2008: www.nice.org.uk

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In light of these factors, Macugen would benefit from a risk-sharing agreement to facilitate market access. However, if Pfizer were to adopt a similar type of risk-sharing scheme to the Lucentis model, it might need to offer more weeks of free Macugen treatment than Lucentis, since Macugen is viewed as having a less favorable profile by NICE, although this may disincentivize treatment with Pfizer's drug altogether.

This highlights the importance of first-to-market status for a drug accessed through a risk-sharing agreement, especially if multiple drugs initially receive negative approval from NICE for the same indication. Consequently, second-to-market players should consider developing alternative risk-sharing agreements. This will prevent like-for-like comparisons with approved drugs (also accessed through risk-sharing schemes), which may disincentivize prescribing of the second-to-market entrant. However, as risk-sharing schemes are already presenting a burden to stakeholders, agencies such as NICE may limit the types of risk-sharing agreement employed within a given indication. This could further hamper market access and uptake of second-to-market therapies if they are deemed less favorable than the initial market entrant.

Merck & Co. incentivizes Januvia uptake providing bigger discounts on positive clinical outcomes for diabetes patients in the US

In April 2009, Merck & Co. signed a pay-for-performance deal with the pharmacy benefit management division of Cigna, in order to control costs and increase access to Januvia (sitagliptin) and Janumet (sitagliptin and metformin) for type 2 diabetes patients in the US. Under the deal, Cigna will receive a discount on the drug if a patient's blood sugar falls (regardless of whether the improvement is through Merck & Co.'s drugs or competing medications). Cigna will receive further discounts if patients adhere to compliance program and take the drug as prescribed (Pollack, 2009).

Ultimately, this is beneficial for Merck & Co, Cigna and the patient:

- when the patient buys more Januvia/Janumet, Cigna will receive a larger discount and Merck & Co. will increase its profits;
- Merck & Co. will improve its placement for Januvia/Janumet on Cigna's formulary, translating into a lower co-payment for patients than a number of other branded competitors;
- patients taking the drug diligently will keep low blood sugar levels.

This bold and innovative move from Merck & Co. highlights the company's confidence in its drugs, and therefore the risk it is willing to take in order to increase access to its medication; betting the drugs' therapeutic and financial offerings against competitor products.

Strong head-to-head clinical data are required to support risk-sharing applications in the UK

In addition to timely planning of risk-sharing strategies, is the need to present such proposals supported by strong head-to-head clinical trial data, in order to prove a drug's effectiveness against the current standard of care. By combining these two strategies, Pharma can maximize a drug's time at market and therefore its sales.

"I have a very strong opinion about when risk-sharing should be taken into consideration. It must be done as soon as possible via head-to-head studies. The only problem is that these types of studies can be initiated after FDA approval, so Pharma must begin to plan a head-to-head study by the end of Phase III."

Anonymous Pharma executive

For example, as demonstrated by the case studies below, while GlaxoSmithKline's Tyverb (lapatinib) was rejected by NICE due to insufficient demonstration of cost-effectiveness and additional efficacy over the standard treatment, Merck Serono's Erbitux (cetuximab) received NICE approval for patients with advanced head and neck cancer in April 2008. Erbitux's success followed the production of new clinical data coupled with a cost-sharing program proposed by the company, which resulted in NICE re-evaluating its initial negative guidance.

NICE continues to reject Tyverb due to cost-effectiveness issues despite a proposed risk-sharing scheme

In July 2008, NICE issued the first negative guidance for GlaxoSmithKline's Tyverb (lapatinib), marketed as Tykerb in the US, for its use in combination with Roche's Xeloda (capecitabine) for the treatment of advanced or metastatic breast cancer. NICE concluded that the extra efficacy at an additional cost of £25,207 (\$46,763) per year compared to Xeloda alone did not justify the use of the new drug in England and Wales (Jack, 2009). Despite this, Tyverb was reimbursed in several other European countries, including Austria, Denmark, Germany, Greece, Ireland, Luxemburg and Switzerland.

In response to the negative assessment, GlaxoSmithKline proposed a scheme by which it offered to supply Tyverb free of charge for the first 12 weeks of therapy, thereafter the NHS would pay for continued therapy in positive responders. However, despite the efforts to increase patient access to Tyverb in England and Wales, as of March 2009, NICE still deems the drug not to be cost-effective (NICE refuses funding for advanced breast cancer treatment Tyverb, Press Release, 2009; www.gsk.com). NICE's decision has yet again brought the organization under further scrutiny and sparked criticism from Pharma, healthcare professionals and patients, especially in view of GlaxoSmithKline's proposed arrangements. However, clinical data suggest that Tyverb in combination with Xeloda only provides an additional 8 weeks median survival time over Xeloda alone (74 weeks versus 66 weeks, respectively) (Datamonitor, *GlaxoSmithKline: NICE says no to Tyverb*, July 2008). This was not deemed a sufficient improvement by NICE, with the negative guidance further justified by Tyverb's high price, which in combination with Roche's high-priced Xeloda would have significantly increased the cost of the combination therapy, beyond NICE's upper threshold.

With this disappointing result, GlaxoSmithKline is considering appealing once again and plans to offer its scheme to individual NHS trusts to help ensure Tyverb is available to women who could benefit from it (NICE refuses funding for advanced breast cancer treatment Tyverb, Press Release, 2009; www.gsk.com).

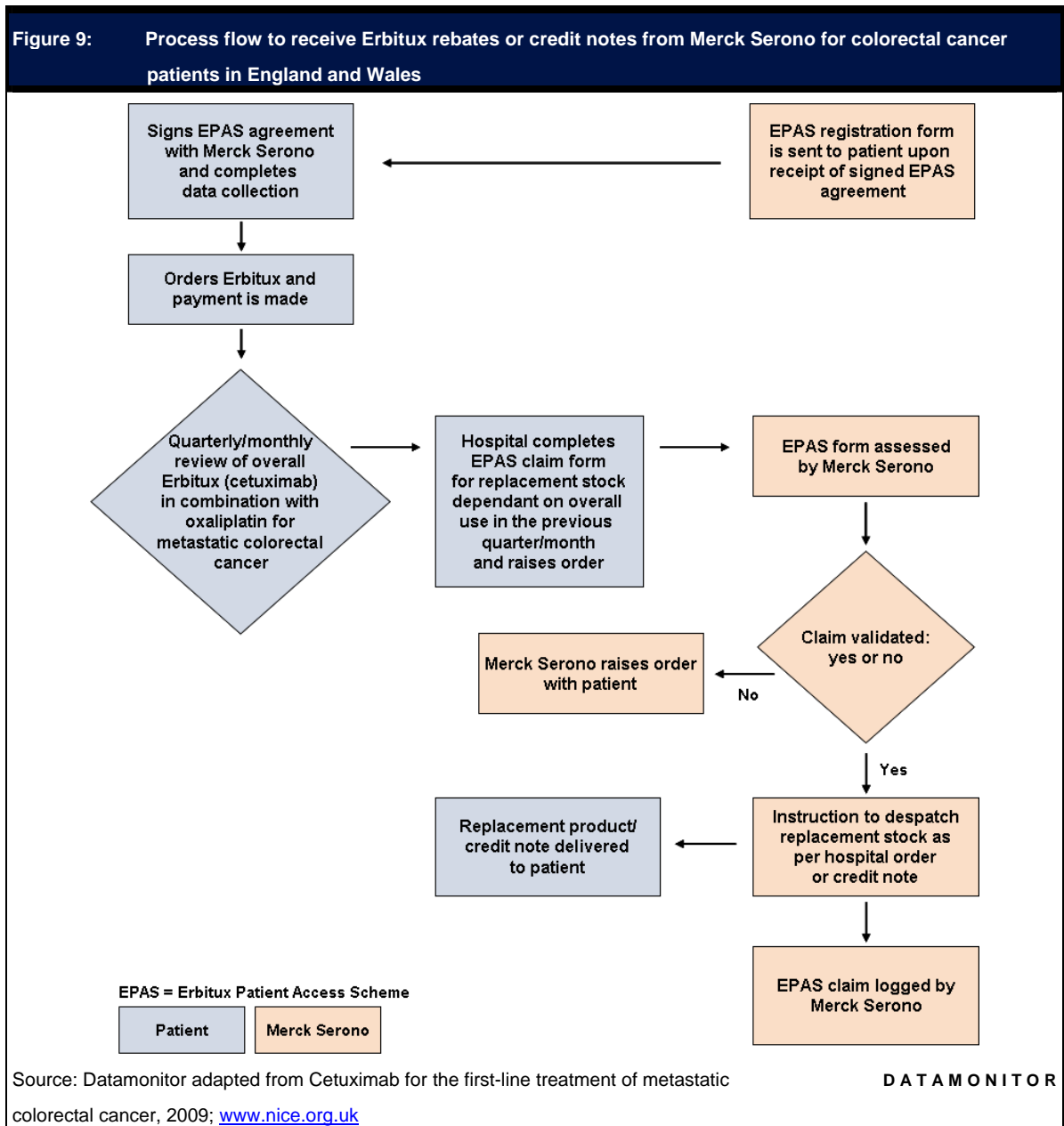
Erbix's positive NICE re-evaluation based on new clinical data and a proposed risk-sharing scheme

Although Merck Serono's Erbitux (cetuximab) received NICE approval for patients with advanced head and neck cancer in April 2008, it was previously rejected for the larger indication of colorectal cancer, as a first-, second- and third-line treatment due to a lack of perceived cost-effectiveness. Appeals against the appraisals were unsuccessful, however new clinical evidence, coupled with a cost-sharing program proposed by the company, has since resulted in NICE re-evaluating its negative guidance.

Pivotal new data (Cetuximab in Neoadjuvant Treatment of Non-Resectable Colorectal Liver Metastases – CELIM study) investigating the efficacy of Erbitux in combination with two different chemotherapy regimens (FOLFOX—based on oxaliplatin; and FOLFIRI—based on irinotecan) in patients with unresectable colorectal liver metastases, have improved the drug's cost-effectiveness assessment by NICE. Furthermore, Merck Serono has proposed a risk-sharing scheme for Erbitux in combination with oxaliplatin for the first-line treatment of patients with metastatic colorectal cancer (but only for patients whose cancer has spread to the liver), known as the Erbitux Patient Access Scheme (EPAS), which was later approved in June 2009. Essentially, Erbitux (when used in combination with oxaliplatin) is rebated at a rate of 16% in the form of free stock for the NHS for all patients within the scheme on a per patient basis—this equates to a rebate of one vial per every eight vials used (Cetuximab for the first-line treatment of metastatic colorectal cancer, 2009; www.nice.org.uk). Alternatively, credit notes may be given if another reimbursement method is needed in case stock is not available.

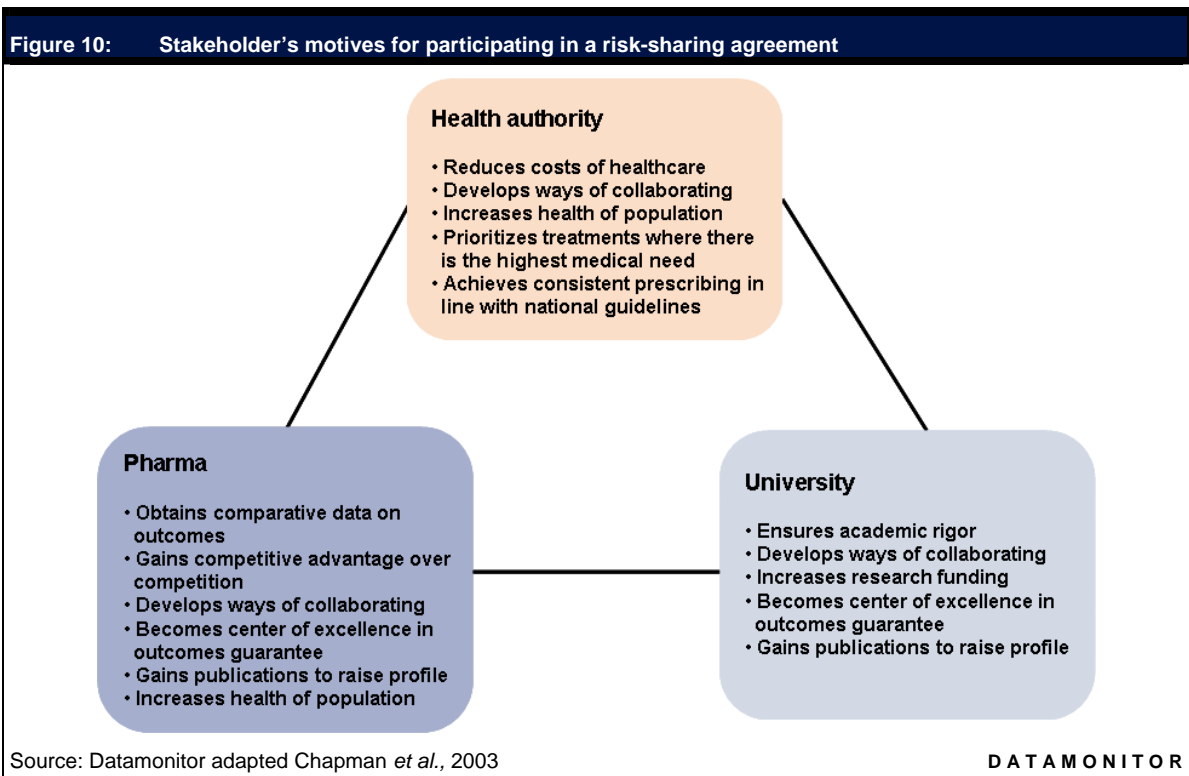
As a result of the new clinical data and proposed risk-sharing scheme, Erbitux is now the first targeted therapy approved by NICE for the first-line treatment of colorectal cancer (NICE recommends Merck's Erbitux for advanced colorectal cancer, 2009). This was a welcome decision by patients and cancer charities, as the drug has been licensed in the UK for 5 years, but before this risk-sharing agreement, it was only available through private health insurance.

Figure 9 illustrates the cost-sharing program, which is based on refunding primary care trusts for the cost of vials used by patients who do not respond to Erbitux after a treatment course of 6 weeks.



Identify key stakeholders and develop a pilot program

It is critical to define specific roles for stakeholders during risk-sharing schemes, in order to avoid duplication of work and avoid potential conflicts of interest. Key motives for the various stakeholders participating in a risk-sharing agreement are summarized in Figure 10. Some agreements may prefer to include an independent third party, such as a university, in order to ensure academic rigor and balance the interests of Pharma and the health authority. These may be especially useful in managing large registries or to act as a steering group to agree on inclusion criteria and develop a project outline. This is the role undertaken by the Centre of Clinical Research Excellence in Therapeutics (CCRE Therapeutics) at Monash University in Melbourne, which independently monitors Actelion’s Tracleer (bosentan) Bosentan Patient Registry (BPR), as part of the drug’s risk-sharing scheme in Australia. Hospitals and primary care practices are also formally invited to contribute to the development of pilot risk-sharing on behalf of the health authority. Participating practices are encouraged to carry out audit and intervention programs—often devised by the independent monitor—to ensure the project does not incentivize the physician to prescribe the drug in question.



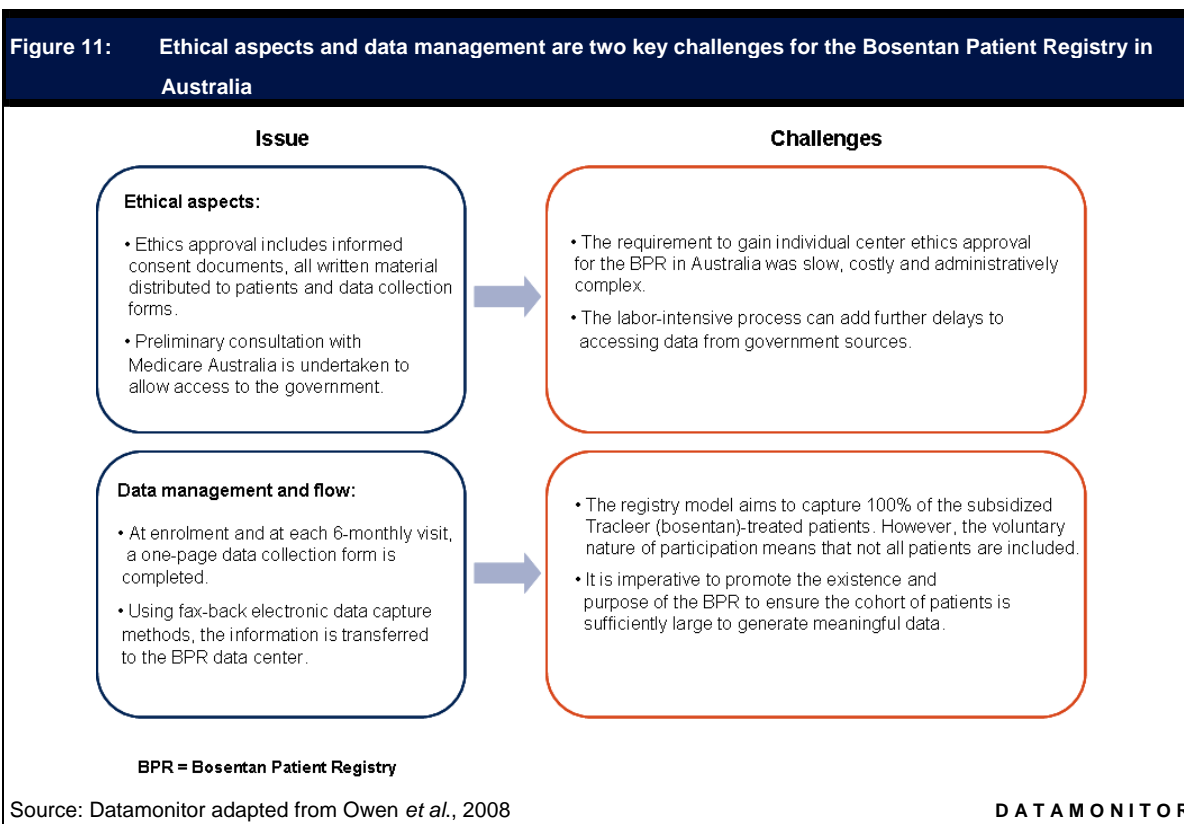
The Bosentan Patient Registry in Australia allows systematic drug evaluation as part of Tracleer’s risk-sharing scheme

Actelion’s Tracleer (bosentan) is a vasoconstrictor used for the treatment of pulmonary arterial hypertension (PAH), which has shown to improve symptoms, quality of life, and delay clinical worsening. Tracleer was approved in Australia in March 2004, however, recommendations to include the drug on the national formulary—the PBS—were based on improvements in life expectancy, even though these had not been confirmed in long-term controlled clinical studies (Owen *et al.*, 2008).

Consequently, Actelion proposed a risk-sharing agreement, whereby the future price of Tracleer would be in proportion to the mortality of patients treated with the drug under the PBS; in this way, clinical evidence was gathered to support its claimed effectiveness. The proposal includes the establishment of a registry, the Bosentan Patient Registry, to collect survival outcome data of Tracleer patients, through a collaboration between Australia’s government, Actelion and a steering committee comprised of clinicians involved in treating PAH patients. The registry is maintained by an independent party—the Centre of Clinical Research Excellence in Therapeutics (CCRE Therapeutics) at Monash University in Melbourne, in order to maintain impartiality (Owen *et al.*, 2008).

Although Tracleer is now reimbursed in Australia, prescribing guidelines are very restrictive. As part of the risk-sharing scheme, the prescription of Tracleer is limited to specialist clinicians from hospitals approved by the Department of Health. In order to access subsidized Tracleer, the PAH patient must initially complete a written form including results of a right heart catheter, echocardiogram, and results from a 6-minute walk test, which is required to be updated every 6 months. Like other pay-for-performance risk-sharing agreements, the subsidized treatment of Tracleer will cease if the physician determines that the patient has not demonstrated improvement or stability with the treatment.

In the establishment of the Bosentan Patient Registry, a number challenges have been identified, as summarized in Figure 11, such as patient privacy and data management. While such a registry has the potential to be used to evaluate high-cost drugs systematically, and provides researchers and clinicians with information to improve evaluation of the clinical prescribing guidelines in the management of rare diseases, data collection and management must be streamlined in order to maximize efficiency and reduce costs (Owen *et al.*, 2008).



Investigate all regulatory and legislative avenues which may aid access to market

Manufacturers should fully investigate all regulatory and legislative avenues which may assist in the positive approval of a drug, whether through the use of risk-sharing agreements or otherwise. One such piece of legislation which has helped a number of drugs gain a positive assessment by NICE following the proposal of risk-sharing schemes has been the recent introduction of end-of-life guidance which came into effect from January 2009. These new guidelines address the use of expensive drugs for terminal illnesses affecting a small number of patients. If such a drug can extend life by at least 3 months compared to standard NHS treatment, it can be approved even if deemed not cost-effective (Appraising life-extending end-of-life treatments, 2009; www.nice.org.uk). Two examples of drugs that have used end-of-life guidance to gain market access are Pfizer's Sutent (sunitinib) and Celgene's Revlimid (lenalidomide).

These cases show how the new NICE end-of-life guidance legislation can be useful for drugs struggling to gain a positive NICE opinion in patients with a few months to live. By targeting terminal patients with months to live, such drugs can achieve market access and a route into the treatment of other stages of a disease or new indications, but only in conjunction with additional concessions to reduce a drug's quality adjusted life year (QALY) threshold.

Sutent's and Revlimid's risk-sharing scheme and end-of-life guidance pave the way for positive NICE guidance

In August 2008, Pfizer's Sutent (sunitinib), along with three other kidney cancer drugs—Avastin (bevacizumab), Nexavar (sorafenib) and Torisel (temsirolimus)—were all rejected by NICE due to their high QALY values. Nevertheless, the implementation and synergy of two new strategies resulted in a reversal of NICE's assessment for Sutent. The two key events were:

- Pfizer's determination to increase access to patients by supplying Sutent free-of-charge to regional health commissioners directly in the UK;
- NICE's new end-of-life guidance rules for all life-saving treatments published in January 2009.

In order to make its drug available for use on the NHS, Pfizer began offering Sutent for free following NICE's negative assessment, which also provided an opportunity to gather further evidence of clinical outcomes. This move prompted NICE to re-evaluate its guidance on Sutent, at the same time as the organization simultaneously rolled out new rules regarding end-of-life appraisals for pharmaceuticals in the UK (Submission to the National Institute for Health and Clinical Excellence, NICE, 2009; www.nice.org.uk).

As Sutent has been demonstrated to increase overall survival by 0.82 years in first-line patients and by 0.77 years in second-line patients with kidney cancer (Submission to the National Institute for Health and Clinical Excellence, 2009; www.nice.or.uk), it met the new end-of-life guidance criteria. Furthermore, Pfizer proposed a 5% price cut and one free course of treatment (6 weeks)—worth £3,139 (\$5,823)—to every eligible UK patient, helping reduce the financial strain on the NHS and sealing the deal with NICE, giving an estimated saving of 19–29% per patient, depending on the stage of their tumor (Hill, 2009). Sutent was subsequently issued with positive guidance in March 2009 for first-line treatment of advanced and/or metastatic kidney cancer, in patients who are already receiving immunotherapy. After the initial free course of treatment, as part of a pay-for-performance scheme, if patients show signs they are responding to Sutent, the NHS pay for additional treatment at the agreed discount price of £24,000 (\$44,524) per year (Rose, 2009). Subsequently,

in May 2009 Sutent was also approved by NICE for advanced gastrointestinal stromal tumor (GIST) in patients who develop resistance to imatinib. Although approval for GIST is not based on a risk-sharing scheme, due to NICE's end-of-life guidance, patients in the terminal stages of the disease will have access to a treatment option to prolong life.

Similarly to Sutent, Celgene's Revlimid (lenalidomide) was initially rejected by NICE in October 2008 on the grounds that it was not deemed cost-effective; in Revlimid's case this was for the treatment of second-line multiple myeloma, despite the fact that was shown to extend the lives of such patients by up to 3 years. The rejection was based on Revlimid's costs of £36,000 (\$66,786) per patient per year (Smith, 2008). Due to NICE's negative guidance, UK charities urged Celgene to propose a risk-sharing agreement and subsequently in April 2009, Celgene offered to refund the NHS for non-responding patients as part of a price-capping scheme under which the NHS pays for the treatment with Revlimid for the first 2 years in patients who have received at least one prior therapy. Although, if treatment is required after the 2 years, then Celgene will cover the costs (excluding related costs such as hospitalization), thereby reducing the financial burden on the NHS. As a result, in June 2009 NICE issued a positive final guidance for approval in the second- and third-line in combination with dexamethasone (Lenalidomide for multiple myeloma in people who have received at least one prior therapy, 2009; www.nice.org.uk). This was also aided by the new end-of-life rules permitting the approval of high cost drugs that extend the lives of terminally ill patients, and which positioned Revlimid favorably according to NICE's assessment.

Importance of not underestimating the influence of patient advocacy groups on reimbursement approval

The importance of patient and physician support to increase access to new drugs cannot be underestimated, as observed with Janssen-Cilag's multiple myeloma drug Velcade (bortezomib) discussed below. Although multiple myeloma accounts for only 1% of all cancers, its strong patient advocacy groups (PAGs) helped to overturn a major decision, highlighting the importance of working with these prominent groups in order to increase disease awareness (Datamonitor, *Patient Empowerment*, July 2007, DMHC2320).

NICE U-turn over Velcade driven by implementation of risk-sharing scheme and patient support

When Janssen-Cilag's multiple myeloma drug Velcade (bortezomib) received negative guidance from the UK's National Institute of Health and Clinical Excellence (NICE) in October 2006, it attracted criticisms as the drug had shown statistically significant improved survival in patients who received it compared with a traditional myeloma therapy (high-dose dexamethasone). Furthermore, Velcade was already approved in Scotland, but due to NICE's decision, patients in England and Wales were denied treatment owing to its high cost—of approximately £3,000 (\$5,566) per cycle of treatment. Consequently the incremental cost-effectiveness ratio ranged from £33,000 (\$61,221) to £38,000 (\$70,497) per quality-adjusted life year (QALY), exceeding the NICE threshold of £20,000–30,000 (\$37,104–55,655) (Risk-sharing for NICE and the pharma industry, 2007; www.ibmedical.com).

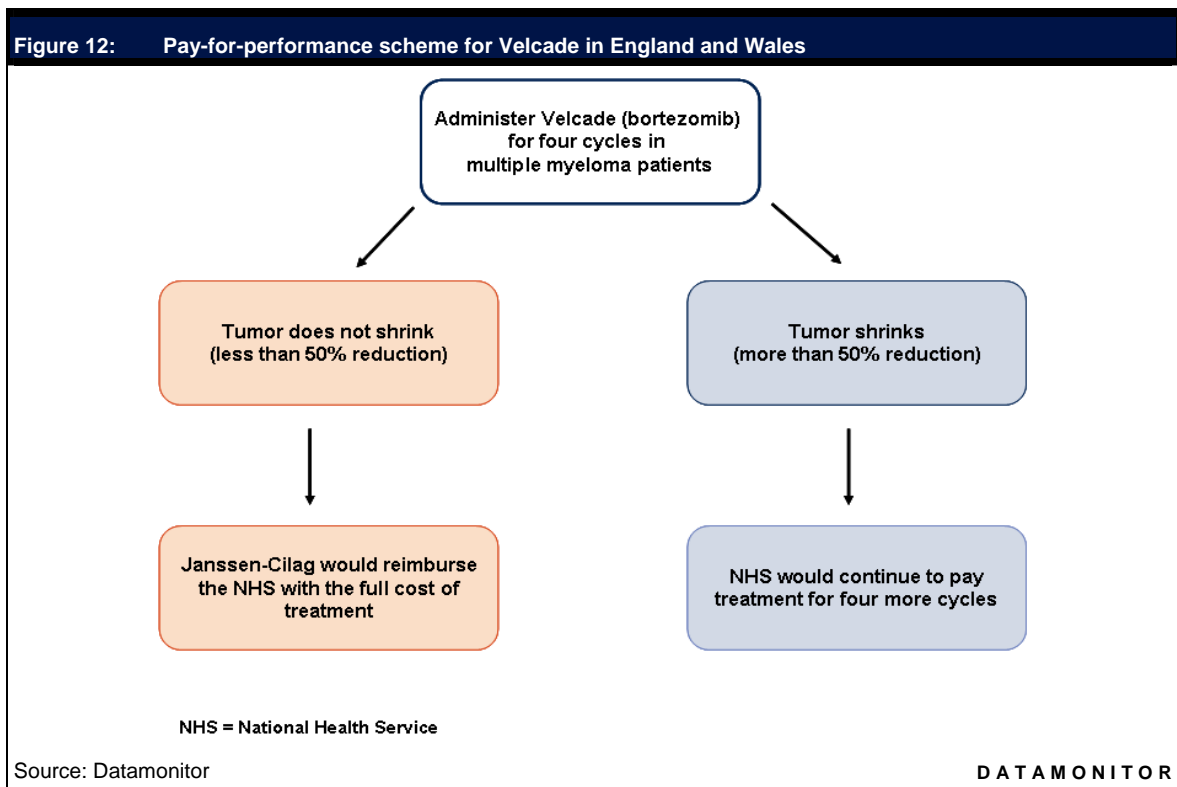
After the initial rejection, and following an appeal from the British Society for Hematology and the Royal College of Pathologists, supported by further complaints from Cancerbackup, Leukemia CARE and Myeloma UK, Janssen-Cilag and NICE agreed on a risk-sharing scheme. The scheme proposed that the National Health Service (NHS) only pay for Velcade in patients who benefit from the drug, while the company would refund the money spent on patients whose tumors did not shrink sufficiently after four cycles of treatment. Considerable debate ensued regarding the degree of cancer reduction: Janssen-Cilag demanded that a 25% reduction (a "minimal or minor response") should be sufficient. However, NICE

proposed at least a 50% reduction (a “partial response”) in serum M-protein, which would result in a cost per QALY of approximately £20,700 (\$38,402) falling within NICE’s maximum QALY quotient (Beckenridge and Walley, 2008).

Finally in July 2007, it was agreed the company would reimburse the NHS with the full cost of treatment for those patients whose tumor did not shrink (less than 50% reduction) and treatment would stop. On the other hand, the NHS would continue to pay treatment for those patients with a reduction of 50% or more. This risk-sharing agreement became known as the Velcade Response Scheme and is deemed particularly appropriate for this drug due to the rapid response rate shown by patients prescribed Velcade.

Patient groups and cancer charities saw NICE’s landmark U-turn on Velcade guidance as a significant development, particularly as the drug can prolong life of patients with an incurable disease. Following NICE’s guidance, over 80% of UK hospital trusts have signed up to the Velcade Response Scheme, thus boosting access to Velcade in England and Wales (10 months on from NICE guidance on Velcade, 2008; www.velcadethree.co.uk).

The decision-making process for the Velcade Response Scheme is summarized in Figure 12.



The future of risk-sharing agreements

In the UK, given the National Institute for Health and Clinical Excellence (NICE's) lack of transparency over its stringent cost-effectiveness analysis, coupled with the multiple molecular targets for innovative drugs which provide an opportunity for objective biomarker analysis to monitor a drug's therapeutic response, risk-sharing agreements are expected to become an increasingly viable option for novel expensive targeted therapies.

Future risk-sharing candidates in the UK?

Examples of two drugs that Datamonitor expects to adopt risk-sharing strategies are Novartis's Afinitor (everolimus) and Dendreon's Provenge (sipuleucel-T).

- **Novartis's Afinitor** – in June 2009, Novartis's Afinitor received a positive opinion from the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) for the treatment of second- and third-line patients with advanced renal cell carcinoma. This will be followed by a decision by the European Commission recommending market authorization across Europe. In the US, where the drug received US Food and Drug Administration (FDA) approval in March 2009, it is currently priced at \$5,500 for 4 weeks of treatment (Guha, 2009b). This equates to approximately £3,347 (\$6,209), or £40,164 (\$74,511) per year, which exceeds NICE's cost-effectiveness threshold. Consequently, the potentially high UK price expected to be set for Afinitor and its treatment of a niche population makes this novel drug an ideal candidate for a risk-sharing scheme. However, NICE has recently issued negative guidance for three out of four renal cell carcinoma drugs, approving only Pfizer's Sutent (sunitinib) as first-line treatment while rejecting Roche's Avastin (bevacizumab), Bayer's Nexavar (sorafenib), Wyeth's Torisel (temsirolimus) as first-line treatments in draft guidance. In light of these factors, Novartis may have adopted a highly cautious approach when devising a risk-sharing agreement, including significant benefits to the NHS for patients who fail to respond adequately to the drug in order to gain positive guidance from NICE.
- **Dendreon's Provenge** – Dendreon's experimental drug for prostate cancer Provenge is poised to become the first vaccine to fight cancer, despite being initially rejected by the FDA in May 2007, as more evidence was required. Recently however, the company has unveiled positive new results, which are likely to lead to a US approval. In the pivotal Phase III clinical trial (IMPACT study), the drug showed an improved overall survival of about 4 months in men with advanced hormone-refractory prostate cancer (Guha, 2009a). Nevertheless, despite the potential to become a groundbreaking drug, it has a complex manufacturing process. The antigen-presenting tumor cells are withdrawn from the patients, then transported to Dendreon's manufacturing facility to produce the vaccine, and finally delivered to the physician's office for infusion into the patient; this process is performed three times over the course of a 4-week period, upon which treatment is completed. This is certain to add to the yet undisclosed price of the drug, which is already expected to have a high price point, comparable at least to other biologics that prolong survival. Similarly to Afinitor, Provenge also makes a good candidate for a risk-sharing agreement given this innovative drug targets a small population and is expected to be costly. Although a risk-sharing agreement may be the only way forward for Provenge, its barriers to market entry will hinder approval of such a scheme.

Strategies to minimize risk-sharing burden on healthcare payers and providers

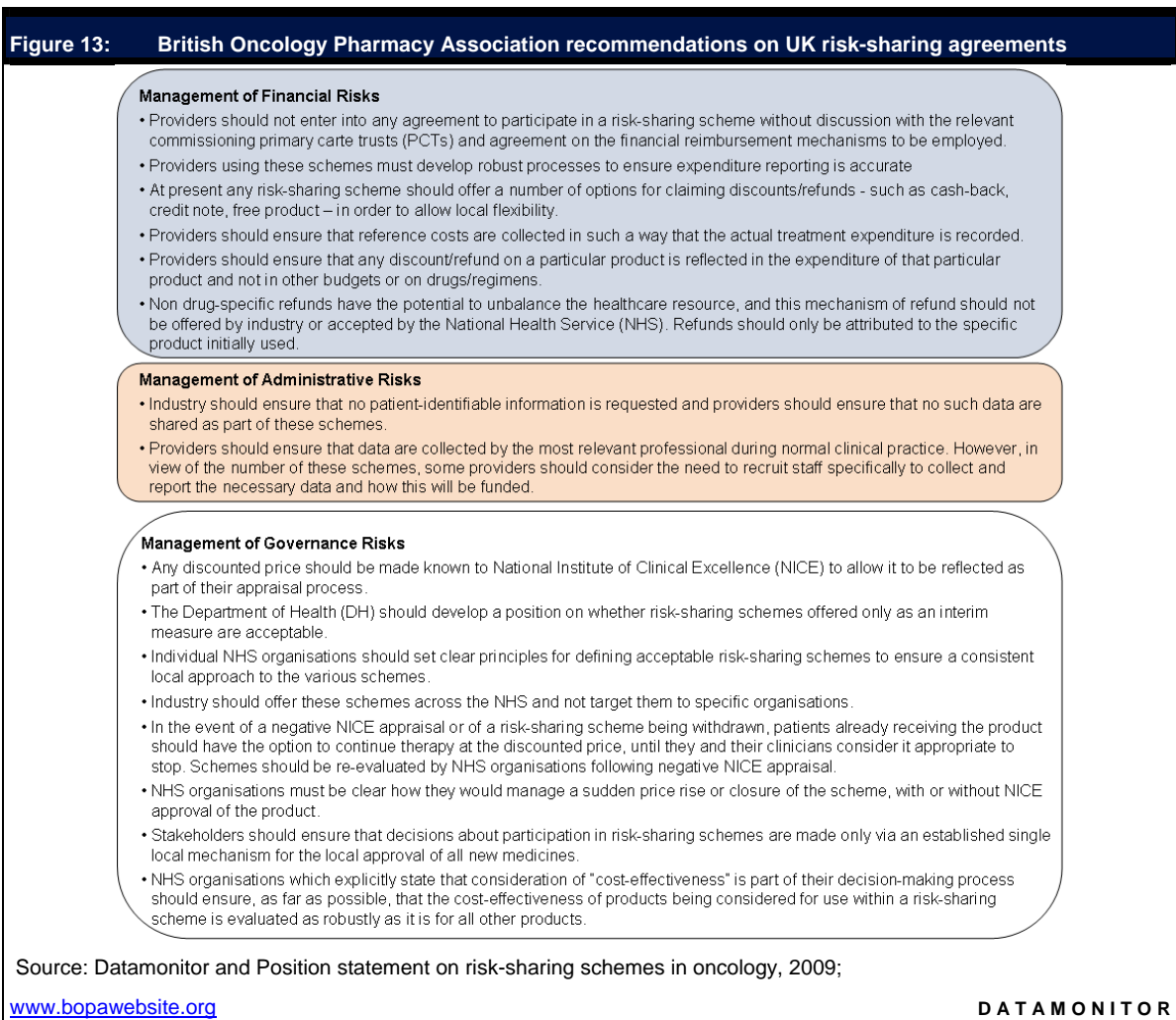
Risk-sharing schemes are already an established route to National Health Service (NHS) access for a number of expensive biologic drugs, which otherwise would not have access to the UK market. However, there is growing concern among healthcare payers and providers that such schemes are too diverse and may not offer sufficient benefits to the NHS:

“Risk-sharing schemes are multiplying rapidly, are not consistent in the way they work, and this lack of consistency increases the financial, administrative and governance risks to NHS organizations.”

David Thomson, Lead Pharmacist, Yorkshire Cancer Network

(Position statement on risk-sharing schemes in oncology, 2009; www.bopawebsite.org)

Consequently, the British Oncology Pharmacy Association has produced a position statement to provoke wider debate around the risks of such schemes at both local and national level, and has also made the following recommendations on the management of these risks (Figure 13).



The future of risk-sharing agreements in the US

Unlike the single payer system in the UK, numerous different payers and other stakeholders are involved in healthcare decisions in the US, and consequently, risk-sharing schemes are less common. When they are implemented this is carried out on a localized basis. However, as the US embarks upon a universal healthcare coverage plan for all patients who are currently uninsured, and in conjunction with the increasingly integrated nature of the US healthcare system, more risk-sharing schemes are expected to be implemented in the future, although overcoming existing decentralization will be the rate-limiting step.

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APPENDIX***Contributing experts***

Anonymous UK Pharma executive

Exchange rates

Table 6 shows the exchange rates used.

Table 6: Exchange rates, 2008		
Country	Currency	Exchange rates*
UK	GBP (£)	1.85518
Australia	AUD (A\$)	0.85296
US	USD (\$)	1

* National currency units per USD (average for 2008)

Source: www.aonda.com

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