BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2010.03740.x

Value based pricing, research and development, and patient access schemes. Will the United Kingdom get it right or wrong?

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Keywords
NICE, pharmaceutical industry, value based pricing

Received
6 February 2010

Accepted
23 June 2010

The National Health Service (NHS) should reward innovation it values. This will enable the NHS and the United Kingdom (UK) economy to benefit and impact positively on the Research and Development (R&D) decision making of companies. The National Institute for Health and Clinical Excellence (NICE) currently seeks to do this on behalf of the NHS. Yet the Office of Fair Trading proposals for Value Based Pricing add price setting powers – initially for the Department of Health (DH) and then for NICE. This introduces an additional substantial uncertainty that will impact on R&D and, conditional on R&D proceeding, on launch (or not) in the UK. Instead of adding to uncertainty the institutional arrangements for assessing value should seek to be predictable and science based, building on NICE's current arrangements. The real challenge is to increase understanding of the underlying cost-effectiveness of the technology itself by collecting evidence alongside use. The 2009 Pharmaceutical Price Regulation Scheme sought to help do this with Flexible Pricing (FP) and Patient Access Schemes (PASs). The PASs to date have increased access to medicines, but no schemes proposed to date have yet helped to tackle outcomes uncertainty. The 2010 Innovation Pass can also be seen as a form of 'coverage with evidence development.' The NHS is understandably concerned about the costs of running such evidence collection schemes. Enabling the NHS to deliver on such schemes will impact favourably on R&D decisions. Increasing the uncertainty in the UK NHS market through government price setting will reduce incentives for R&D and for early UK launch.

Introduction

The pharmaceutical industry is driven by profit. What the National Health Service (NHS) rewards it will get more of. What it does not it will get less of. A task of the NHS is therefore to make sure that it rewards the makers of innovative medicines that deliver gains in health and other related benefits to society and that it does not reward those that do not.

The industry is, of course, a global one. The United Kingdom (UK) is a small market but with global reach. The 2007 Office of Fair Trading (OFT) Report [1] calculated that through international reference pricing, UK prices impact around 25% of global sales and noted that 'UK prices, and the assessments of expert bodies such as NICE, are often used informally in price negotiations around the world.' (paragraph 3.24, page 43). The National Institute for Health and Clinical Excellence (NICE) gets many 'hits' on its website from outside of the UK with the US as the biggest customer group. Companies therefore have a choice. They can continue to launch early in the UK (attractive because of the freedom of pricing at launch that the Pharmaceutical Price Regulation Scheme (PPRS) offers) setting a price to just get through NICE (they do not want to 'leave money on the table') or wait until later to enter the UK market. If the former, then anticipation of the decisions of NICE will have an impact on 'go/no go' decisions in development. If the latter, the UK becomes much less relevant. Pricing to get through NICE becomes too expensive in terms of the impact on prices in other markets. The UK will move from being an early launch market to being an afterthought, with implications both for UK patients and for the UK economy.

Why implications for the UK economy? Because there is a link between UK NHS use of medicines and UK Research and Development (R&D) [2]. The UK is good at biomedical research in universities, the NHS and the private sector [3, 4]. The pharmaceutical industry generates value for the UK [5, 6] but much pharmaceutical R&D and manufacturing investment is footloose. When there are competing global

locations offering high quality science, companies take other factors into account. It is irrational, other things being equal, to reward countries that do not want to invest in your products. There are also practical issues. It is difficult to host a clinical trial in the UK against the most effective alternative therapy if it is not being used by the NHS.

This is a familiar litany to those who have been debating these issues for some time, but acknowledging this reality does not mean the NHS should start paying for treatments that are not good value. How do we use Health Technology Assessment (HTA) in the UK in a way that stimulates the right innovation [7, 8]? Can the UK NHS get value and also remain strong in pharmaceutical and clinical R&D? The answer is yes, by being innovative in the way it assesses and uses medicines.

The scope and aim of this paper is to explore how this might be done. In particular it:

- reviews the HTA context, looking at the incentives faced by those reviewing value;
- categorizes the types of uncertainty that can arise for manufacturers in getting recognition for value within the NHS;
- looks at how the changes in the 2009 PPRS were intended to improve the alignment of price and value in the UK NHS and at experience to date;
- suggests a way forward to align better price with value that is likely to benefit the NHS, patients, the industry and the UK R&D base.

Rationing, NICE and the OFT

NICE has done a good job in difficult circumstances. Its technology appraisal programme is intended to ration access to treatments using the price set by the company and a narrow definition of cost-effectiveness. It is not allowed, for example, to take into account the additional benefits of getting people back to work or of saving the time and cost of people providing unpaid care. Yet there remains limited overt political support for rationing. Appraisal Committee members are chosen for their expertise. They are not elected. Hence decision making has to have an element of flexibility and be rationalized by reference to opportunity cost and social preferences as Rawlins *et al*. [9] outline in their paper in this volume. There is a deliberative process [10] in which these criteria are applied and an, initially provisional, judgement made. The Committee gets feedback both on its scientific judgements and on its ethical judgements.

The OFT Report [1] argued for the existing profit control-based PPRS to be replaced by a 'value based pricing' (VBP) PPRS. The OFT report proposed two stages towards government price setting. Initially, using existing legislation, NICE would indicate prices at which a product would be cost-effective in different patient sub-groups and the Department of Health (DH) would then negotiate a price with the company. New legislation was proposed to merge NICE with similar bodies in the other three nations of the UK and give it the DH's power to set prices for medicines supplied to the NHS. To indicate and then set prices NICE would have an explicit cost-per-quality adjusted life year (QALY) threshold (not a range), to be negotiated periodically with the pharmaceutical industry as part of a VBP-based PPRS agreement.

However, combining price setting with the scientific task of assessing costs and effects risks biasing NICE's judgements. This is a concern noted by supporters of the OFT's proposals [11, 12] as well as critics [2, 13]. We can illustrate this point by considering the work of NICE's Appraisal Committees at the moment. They are faced with a technology and a price. In deciding the extent, if any, of NHS use to recommend they have to balance the interests of the NHS in meeting the needs of two different groups of patients. On the one hand there are the patients who would gain from using the treatment. On the other hand there is an opportunity cost, given that the NHS has a fixed budget. Another (unknown) group of patients will not get access to another (unknown) intervention if budgets elsewhere are cut to accommodate the costs of providing the new treatment. If NICE exaggerates the cost-effectiveness of the treatment then it favours the known group of patients against the unknown. If it chooses to take a pessimistic view then it ends up favouring the 'unknown' patients at the expense of the known.

At the present time therefore NICE has an unambiguous incentive to take its 'best guess' as to whether a treatment is cost-effective, i.e. a good use of NHS resources. NICE setting or indicating price or the DH setting price introduces the potential for bias or opportunism. The best of both worlds from a short term NHS perspective can be achieved – a low price and use of the technology – if the scientific review or willingness-to-pay for a QALY is 'rigged' to justify demanding a lower price than the drug is worth to the NHS. But paying less than the drug is worth during the period of patent protection, whilst helping with immediate NHS budget pressures, will reduce the reward to R&D, reducing R&D incentives and leading to less future health gain for NHS patients from new drugs.

Tackling uncertainty in identifying and rewarding value

Company R&D decisions have to take into account both the expected scientific challenges and the expected commercial challenges associated with researching and developing a particular drug. In the context of the NHS we can think of the remaining scientific challenges once the product has been launched as being the uncertainty as to the underlying incremental gain in health and related benefits the product will deliver in routine clinical practice. The

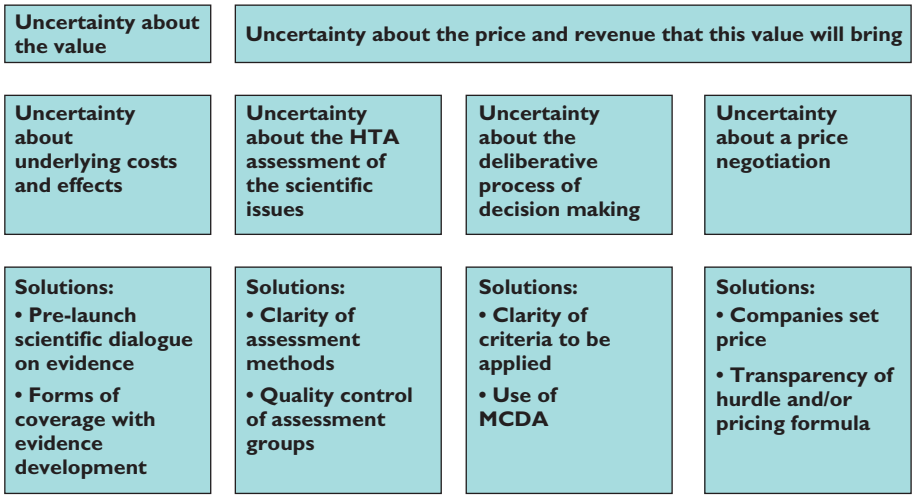

Figure 1
A manufacturer's perspective on VBP and uncertainty

challenge for NICE and the pharmaceutical industry is that establishing the 'value' of a medicine is a process (or journey) of discovery. Not only is a degree of uncertainty about the expected costs and health gain associated with the indication under review, but there may be other indications that come available in the future. Evidence is the key to reducing uncertainty as to underlying value.

The commercial challenge is, given the underlying value, what price and quantity of use can the company get? This will in part depend on competition: what does this therapy add to existing therapies, if any, for the target patient group? It also depends on how the evidence is assessed and decisions made around use. If VBP uses price setting a further uncertainty is introduced.

The sources of uncertainty from a manufacturer's perspective are summarized in Figure 1. It includes a summary of possible ways of reducing uncertainty. The first uncertainty is about the underlying cost-effectiveness of the drug. Better evidence could be collected pre-launch. The offering of early stage scientific advice by NICE to companies will help to achieve this [14]. However, the ability to collect evidence pre-launch will always be constrained by the time cost of delays to market and by the limitations of randomized controlled trials (RCTs) to reflect routine practice in a particular health care system. Hence the attraction of 'coverage with evidence development' (CED), an approach that combines giving patients access to the product ('coverage') with continued evidence collection.

Given the evidence on costs and effects, the second uncertainty is how that evidence will be scientifically assessed. This can be addressed by clear guidance as to the type of evidence required with a standardized approach to evidence review, and also by quality assuring the review teams to ensure reviews are consistent and of high quality. NICE invests much time (and has a deserved international reputation) for the first but invests little in the second. Given the scientific assessment of evidence, the third uncertainty is the deliberative process of decision making to decide if the effects are worth the costs, i.e. should the NHS use the drug? Uncertainty can be reduced by clarity of the criteria to be used and by a transparent decision making process [7] to make clear that all appraisals are being made in the same way using the same criteria with consistency of application. NICE has invested in the first [9] but not in the second. Those involved in NICE decision-making are clear about its strengths. However, these are not visible to external critics. Techniques such as Multi Criteria Decision Analysis (MCDA) could help in this respect. It can help those involved in deliberative decision making to understand the weight they are giving to different factors. This can help them explain the rationale for the decision to others. MCDA is used by the Government in other parts of the public sector [15].

We have already commented on the final source of uncertainty, which would be created by introducing a government price setting role, described by Walley [16] as 'perhaps brave but logical, (to be) regarded as experiments.' (page 344). This uncertainty could be reduced if the current degree of opaqueness around the setting of the threshold cost-per-QALY or willingness to pay for health gain was replaced by a hard number or set of numbers such that once value was established, and any other relevant criteria adjusted for, the price 'fell out' automatically. However, it is difficult to see how this can easily be done. Even if it could be, this would still require the scientific evidence assessment and NICE's decision on value to be 'insulated' in some way from the politics of price setting and, of course, there would be no requirement for the

company to accept the price. As well as uncertainty about price there is uncertainty as to how long the negotiation process will take. In Australia, for example, the Pharmaceutical Benefit Indicators [17] show that only half of major submissions are recommended for listing at first consideration, although 'by the third year after the year of lodgement around 90% . . . have received a positive PBAC recommendation' (page 1).

Pricing to reflect value: the new Pharmaceutical Price Regulation Scheme (PPRS)

One approach to tackling the uncertainty at launch about underlying value was set out in the 2009 PPRS [18] which came into effect on 1 February 2009 for a 5 year period. The DH and the Association of the British Pharmaceutical Industry (ABPI) acknowledged the OFT's desire for a 'value-based approach to pricing' [18] and accepted that 'more could be done to ensure that value is further reflected and better systematized in the PPRS' (paragraph 6.3, page 11). They agreed two new measures to do this. These are set out in Section 6 entitled 'Better Reflecting Value: Flexible Pricing And Patient Access Schemes' '. A joint review of these measures is to be undertaken after a maximum of 2 years. The OFT recommendation for DH or NICE price setting was not accepted [19] and PPRS Section 6 states that 'NICE does not negotiate, set, or publicly indicate prices' (paragraph 6.1, page 11).

There is a fundamental difference between the two new measures:

- Flexible Pricing (FP) is intended to have minimal DH involvement and to be an 'automatic' process involving an adjustment to UK list prices on the basis of new evidence on clinical and cost-effectiveness. NICE has a role in assessing whether the new price and evidence provides value for money. It can veto a UK price increase on an existing indication but not for a new indication. A company can introduce one new indication at a higher price than existing indications (with 'no limit on the price increase' paragraph 6.20, page 13) under a series of conditions notably that the 'price of the original indication must remain the same.' (paragraph 6.21, page 13). No proposals for flexible pricing were made to the DH in 2009 [20].
- Patient Access Schemes (PASs) are initially negotiated between the company and the DH and then referred to NICE for a review of potential use by the NHS in England and Wales. They were intended to be used when NICE has turned down use of a product by the NHS in these two nations and the company is seeking a 'fast track' re-review. PASs have now been introduced by NHS Scotland [21].

However, while the basic principles are driven by the PPRS, as in England, the processes, including the review and decision making are different. Therefore one can expect that some of the conclusions will be different.

Both measures carry a risk of opportunism either by NICE or by a company. In the case of FP a company might collect 'new' evidence simply to trigger a review because NICE in its earlier review found the cost-per-QALY to be lower than the company was expecting. The company is seeking to exploit headroom within the threshold rather than demonstrate a change in underlying cost-effectiveness. However, conversely, NICE may seek to 'move the goalposts' by changing the threshold it applies. The improved cost-per-QALY at the old price is treated as the new (lower) threshold ceiling and the new (higher) price proposed by the company is rejected. The PPRS seeks to address these problems by, respectively, NICE retaining 'the responsibility to decide whether a review is appropriate using its current process involving input from stakeholders' [18] (paragraph 6.11, page 12) and by expecting that NICE's 'assessment of cost-effectiveness will be consistent with that used in the previous appraisal.' (paragraph 6.14, page 12). In the case of PASs the potential for gaming arises from the two stage process. If PASs were routinely proposed to DH and approved by DH then companies would regard their initial submission (without the PAS) as 'an opening bid' and be more likely to propose a price they expected was likely to be rejected. Conversely the NICE Appraisal Committee would be more likely to reject the drug in the expectation that another (lower) offer would be forthcoming wrapped up in a PAS. The end situation is (perhaps) the same effective price but lost time, the use of additional (scarce) NICE resource, and (most importantly) a 'dead-weight loss' to both parties of the ongoing transaction costs of implementing the PAS. This is why PASs are intended to be 'the exception rather than the rule' [18] (paragraph 6.25, page 14) to be proposed by companies 'either: at the outset, when making their initial evidence submission to NICE . . . ; or at the end of the appraisal process, once any appeals have been heard and NICE's final guidance has been issued to the NHS' (paragraph 6.34, page 16). The PPRS states that 'There is no guarantee that patient access schemes will be considered at other stages in the NICE process' (paragraph 6.35, page 16). In other words companies should not expect PASs will be approved by DH until the full NICE process has been completed, and conversely the NICE Appraisal Committee cannot assume a 'better offer' will be forthcoming if they reject the drug as not cost-effective.

Companies can propose a 'financial scheme' involving either (i) an effective reduction in price which could take the form of a list price cut or, more probably, a discount delivered by some form of dose capping or free treatment cycles to reduce mean expected per patient cost, or (ii) some form of patient targeting, such as rebates for non-responders, the effect of which is to lower the mean expected per patient cost. The company is increasing cost-effectiveness by reducing effective price given the evidence of health effect.

Table 1

Patient access by the DH for England and Wales

Drug	Company	Indication under consideration	Details of PAS and of NICE decision including the PAS	PPRS categoriz-ation	TA number	Date of publication of TA or FAD
***Velcade* (bortezomib)**	Johnson & Johnson	Multiple myeloma	Restricted NICE recommendation on condition that company would refund cost of treating non-responders	Financially-based scheme: Response scheme	TA129	October 2009
***Lucentis* (ranibizumab)**	Novartis	Macular degeneration (age related)	Restricted NICE recommendation on condition that company would agree to pay drug cost for treating patients who required more than 14 injections per eye (2 years treatment). Cost effectiveness for treatment beyond this period not established.	Financially-based scheme: Free stock	TA155	August 2008
***Tarceva* (erlotinib)**	Roche	Non small cell lung cancer	Restricted NICE recommendation on condition that the overall costs of treatment would be no more than docetaxel for same indication.	Financially-based scheme: Simple discount	TA162	November 2008
***Stelera* (ustekinumab)**	Janssen-Cilag	Psoriasis	Restricted NICE recommendation based on establishment of cost effectiveness by setting price for dose for patients who weigh more than 100 kg to the lower dose for patients below this weight (essentially provide two vials for the price of one)	Financially-based scheme: Free stock	TA180	September 2009
***Erbitux* (cetuximab)**	Merck Serono	First line metastatic colorectal cancer	Restricted NICE recommendation based on establishement of cost effectiveness following a 16% rebate of the amount of cetuximab used. The scheme requires that patients are treated according to the final NICE guidance and that data should be provided to the manufacturer to show that the NICE guidance has been followed.	Financially-based scheme: Rebate	TA176	August 2009
***Revlimid* (lenalidomide)**	Celgene	Multiple mylenoma in people who have received one prior therapy	Approved by NICE on condition that company agreed to pay drug cost for patients who require more than 26 cycles of 28 days (normally 2 years of treatment)	Financially-based scheme: Free stock	TA171	June 2009
***Tyverb* (lapatinib)**	GSK	Previously treated advanced or metastatic breast cancer	Not recommended for use by NICE as cost effectiveness, including PAS, not established. Terms of proposed scheme acquisition cost for all qualifying patients for up to 12 weeks to be paid by manufacturer. Responding patients continuing treatment to be fully funded by the NHS.	Financially-based scheme: Response scheme	Second FAD	June 2010
***Sutent* (sunitinib)**	Pfizer	Gastrointestinal stromal tumours	Restricted NICE recommendation on condition that company cover costs for first treatment cycle	Financially-based scheme: Free stock	TA179	September 2009
***Sutent* (sunitinib)**	Pfizer	First line treatment for patients with advanced and/or metastatic renal cell carcinoma	Restricted NICE recommendation on condition that company cover costs for first treatment cycle	Financially-based scheme: Free stock	TA169	March 2009
***Nexavar* (sorafenib)**	Bayer	Advanced hepatocellular carcinoma	Not recommended by NICE as cost effectiveness not established. Under proposed PAS, Bayer would provide every fourth pack free of charge or rebate its cost to the NHS.	Financially-based scheme: Free stock or rebate	TA 189	May 2010
***Nexavar* (sorafenib)**	Bayer	Used to treat advanced or metastatic renal cell carcinoma	Not recommended for use by NICE as cost effectiveness, with PAS, not established. Under proposed PAS, company to supply first pack of sorafenib free to NHS per patient.	Financially-based scheme: Free stock	TA178	August 2009
***Avastin* (bevacizumab)**	Roche	Used to treat advanced or metastatic renal cell carcinoma	Not recommended for use by NICE as cost effectiveness, with PAS, not established. Under proposed PAS company rebate of cost of drug after 10 g given to a patient in 12 month period and rebate of cost of IFN-α when given with Avastin.	Financially-based scheme: Rebate	TA178	August 2009
***Avastin* (bevacizumab)**	Roche	Metastatic colorectal cancer	Not recommended for use by NICE as cost effectiveness, with PAS, not established. Company offering to provide Avastin at a fixed cost, even though quantity is dependent upon patient weight. Roche also proposed to provide oxaliplatin free of charge for patients taking Avastin, or to reimburse the hospitals. Further offer to cover the cost of treatment with Avastin for patients needing the drug for more than 12 months (approx. 12–15% of patients go beyond a 12 month course).	Financially-based scheme: Rebate	TA118	January 2007
Cimzia (certolizumab pegol)	UCB	Advanced rheumatoid arthritis	Recommended for restricted use by NICE contingent upon a PAS in which company must cover the cost of the first 3 months of therapy (10 syringes).	Financially-based scheme: Free stock	TA186	February 2010
Yondelis (trabectedin)	PharmaMar/ Johnson and Johnson	Advanced soft tissue carcinoma	Recommended for restricted use by NICE if the company meets acquisition cost if treatment is needed beyond five cycles	Financially-based scheme: Free stock	TA185	February 2010

Sources: Scrip, NICE website and Department of Health.

Companies can, alternatively, propose an 'outcome based scheme,' if they believe that the value of the product exceeds that suggested by the current evidence. Such a scheme is intended to tackle the problem of an inadequate evidence base being available at launch. The company could propose:

1. A risk-sharing scheme in which the price would adjust as new evidence was collected in a way that had been pre-approved by NICE.
2. A rebate scheme in which NICE approved a product on the basis of expected evidence but if, on a NICE reassessment, the evidence did not support the list price, the price would revert to a lower pre-agreed price that was supported by evidence, and the company would pay a rebate.
3. A discounted introductory price with the discount disappearing when the company delivers evidence to support its list price.

A list of schemes where NICE has entered into an arrangement is set out in Table 1. So far 15 PASs have been approved by the DH as workable for the NHS. However, only 10 have been part of positive (including 'restricted' or 'optimized' use) NICE appraisals. NICE has to date rejected the submission including the PAS in five cases. All 15 PASs are financially based, with two (Velcade [accepted] and Tyverb [not accepted]) response related (i.e. given knowledge of underlying cost-effectiveness, use is conditional on targeting of a sub-group of responders with arrangements to ensure the NHS does not pay for non-responders) (see Towse & Garrison, [22]). Only one, Tarceva for non small cell lung cancer, is a simple discount. The other 12 PASs involve rebates or free replacement stock and all except the simple discount scheme require the collection of patient level data. These collection costs have given rise to concern [23, 24]. Although they are taken into account in the assessment of value for money, hospitals are not finding implementation easy. To date only one scheme has been proposed at the start of the NICE process and included in the manufacturer's initial submission. None has been proposed after final NICE guidance has been issued. Fourteen have been proposed immediately prior or after an appraisal consultation document (ACD), i.e. in the middle of the NICE appraisal process.

The innovation pass

The post-PPRS dialogue between the life sciences industries including pharmaceuticals and the Government through the Office of Life Sciences (OLS) [3, 4] has led to the establishment of an 'innovation pass' mechanism to be administered by NICE whereby a small number of new drugs with limited but very positive initial efficacy evidence would be used by the NHS whilst an agreed programme of evidence collection takes place to facilitate a NICE appraisal up to 3 years after launch. An 'exit strategy' is pre-agreed in the event that NICE does not approve the product. Details are still being finalized. Arrangements for Scotland and Northern Ireland are not yet clear.

The way forward?

The NHS and companies are working together to align better price, value and use. It is too early to see if the 2009 PPRS arrangements for FP and PASs and the OLS inspired innovation pass will lead to forms of 'coverage with evidence development' in the UK that will enable patients to access medicines whilst underlying uncertainty about value is reduced. The experience with the multiple sclerosis scheme indicates that both study design to address uncertainty and scheme design to respond to the evidence are not straightforward [25–27] and there is clearly a risk that the FP and 'financial-based' PASs lead to an element of gaming on the part of NICE and/or of companies, in the extreme pushing up NHS and company costs for little gain. The prize, however, for getting 'value based pricing' right is great, not only for NHS patients, companies and the UK economy but in terms of the future impact on companies' R&D decision making and portfolio management. FP and 'outcome-based' PASs offer a potential route forward to match price to real world NHS value in practice. Getting VBP wrong, by resisting coverage with evidence development and introducing government price-setting, risks sidelining the UK. The UK could move down the global launch list, denying NHS patients early access to medicines. The needs of NHS patients will then become irrelevant to R&D decision making and the UK economy will see its biomedical science base erode.

Competing interests

The Office of Health Economics (OHE) receives research funding and consultancy income from the Association of the British Pharmaceutical Industry (ABPI). No separate funding was received for this paper. The views expressed in this paper are mine and do not represent those of either the OHE or the ABPI.

Phill O'Neill and Priya Sharma provided invaluable assistance in the preparation of Table 1. I am grateful to Jon Sussex, Nancy Devlin, Frances MacDonald, Dyfrig Hughes and two anonymous reviewers for comments on an earlier draft. All errors remain mine.

At the time of responding to reviewers comments the incoming UK coalition Government has indicated an intention to introduce VBP. However, no details of any kind have been published.

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