Economics of Innovative Payment Models Compared with Single Pricing of Pharmaceuticals

Amanda Cole a, Adrian Towse a, Paula Lorgelly a, and Richard Sullivan b

a Office of Health Economics, b King’s College London

July 2018

Please cite this report as:
About OHE Research Papers

OHE Research Papers report the results of OHE's research programme. They are subject to review by members of the OHE Editorial Panel.

Views expressed are those of the authors and do not necessarily reflect the views or approval of OHE, its Editorial Panel, Research and Policy Committee, or sponsors.

Funding and Acknowledgements

OHE received funding from IQVIA towards the preparation of this paper. OHE retained editorial control throughout and the content of this paper is the sole responsibility of the authors.

Erratum:

25/07/2018: Please note that this copy of the report (originally published 09/07/2018) has been updated to correct an error in Table 1 (p.9), whereby the results in columns 7 to 9 were in reverse.
CONTENTS

Executive Summary .............................................................................................................. iv
1. Introduction ..................................................................................................................... 1
  1.1. The problem ................................................................................................................ 1
  1.2. The need for change .................................................................................................... 1
  1.3. Differential reimbursement to reflect differential value ............................................ 2
  1.4. Summary of the literature ......................................................................................... 2
  1.5. Structure of the report ............................................................................................... 3
2. The economic arguments: initial static effects ............................................................... 4
3. The case for and against a single-price model .............................................................. 5
  3.1. Bach (2014) ............................................................................................................... 6
  3.2. Chandra and Garthwaite (2017) ............................................................................... 6
  3.3. A critique of the literature ....................................................................................... 7
  3.4. Summary of key points ............................................................................................. 10
4. The economics arguments: longer term dynamic effects .............................................. 11
5. The potential role of competition .................................................................................. 13
  5.1. Two drug classes with multiple indications and competing products ................. 15
    5.1.1. TKIs for CML ...................................................................................................... 15
    5.1.2. PD-1 and PD-L1 inhibitors ................................................................................. 19
    5.1.3. Constructing an example using PD-1 and PD-L1 inhibitors ......................... 21
6. Discussion ....................................................................................................................... 25
7. Conclusion ....................................................................................................................... 27
References .......................................................................................................................... 28
EXECUTIVE SUMMARY

This paper asks: “What are the economic implications of an alternative to the single-price model of payments for pharmaceuticals in oncology? In particular what are the implications for: payer budgets, patient access, and the incentives for innovation?”

Economic theory suggests that the effects of multiple prices for the same product in different uses – for which we use the term indication-based pricing (IBP) in this paper – can improve welfare if it means that more patients get access to the drug. However, prices may also go up for some indications. What happens in practice will, among other things, depend on where the single price is, or would be set by a profit maximising innovator. This is the “static” economic effect, assuming products exist, and prices are set using value-for-money principles or cost-effectiveness thresholds.

Economic theory also suggests that there are two important dynamic (longer term) effects which impact on research and development (R&D) and on pricing. If prices reflect value in particular indications, then R&D investment will be optimal from a societal point of view. With a single price, some (low value) indications may not be developed, even though the incremental value of the drug to patients exceeds R&D and supply costs. Secondly, scientific progress stimulates R&D competition and often leads to several products coming to market in a therapy class. We suggest that IBP makes it more likely (i) that competing products get developed and (ii) that competition occurs in any given indication. Most payers now have mechanisms in place to ensure that competition leads to lower prices for some indications and/or groups of patients.

Bach (2014) described how IBP could lead to lower prices for lower value indications, while Chandra and Garthwaite (2017) argued that IBP would lead prices to rise overall. We set out the different assumptions underlying each analysis and our views on their key points of disagreement.

In order to explore the potential impact of competition, we identify two classes of cancer therapy: tyrosine-kinase inhibitors (TKIs) and PD-1/PD-L1 inhibitors and show how competing products and competing indications have developed over time. In the case of the PD-1/PD-L1 inhibitors additional indications are currently in development with more competing therapies expected to enter the market for several further cancer types. We illustrate how competition by indication in the PD-1/PD-L1 space could, in theory, reduce prices below the value-based price.

We briefly set out the current state of play on the challenges of implementing IBP. As well as having an economic regulatory regime that supports the use of IBP and prevents arbitrage between low value and high value uses, the key challenges are informational. At a minimum, data that tracks use by patient is needed, at least for a sample of patients. Collecting real-world data on the treatment outcomes achieved by patients will increasingly be required, again, at least for a sample of patients. However, proxies for, or surrogate measures of, outcomes can also be used to support the use of IBP, for example on patient duration of treatment as a proxy for patient benefit. Pragmatic approaches have the potential to address health care needs whilst getting better value for money.
1. **INTRODUCTION**

1.1. **The problem**

Medicines have historically been priced on a *per pill* or *per vial* basis. Over time, that price has increasingly been determined by an assessment of the value of the medicine in terms of the health gain it delivers over alternative treatments. The advent of new biological treatments in oncology has led to use of the same molecule in several different ways; for example, in different cancers, at different stages of the same cancer, at different points in a treatment regimen (e.g. first line or second line), and in various combinations with other therapies. In each of these uses, the value – in terms of the incremental health gain delivered to patients – will differ. With a single price per medicine, the relationship between price and value will therefore differ greatly across uses.

“Indication-based pricing”, “value-based pricing”, and “outcomes-based reimbursement” all arise from a desire to better match payment with value. This paper considers:

“What are the economic implications of an alternative to the single-price model of payments for pharmaceuticals in oncology? In particular what are the implications for: payer budgets, patient access, and the incentives for innovation?”

1.2. **The need for change**

The drug development landscape is evolving, particularly in oncology, although the concepts described in this paper are transferable to any disease setting. Drugs are increasingly being found to be of value beyond the indication for which they are initially approved. Over half of major anti-cancer medicines marketed in 2014 were for multiple indications, and by 2020 this is expected to rise to 75% (Aitken, Blansett and Mawrie, 2015). From an oncologist’s perspective, there is increasing experimentation with the use of a medicine at different points in the patient’s pathway or in combination with alternative combinations of other therapies. However, the pricing and reimbursement systems globally generally remain relatively rigid, and therefore inflexible to accommodate changes in, or differences in, value across uses. We consider the impact of a single price framework on access to existing products and on incentives for innovation, for which a longer-term view is necessary. Whilst we cannot provide evidence of indications that are not being developed in order to protect price, we can observe, for example, the phenomenon of effective drugs not being cost-effective even at zero price, e.g. when used in combination with other costly therapies (Davis, 2014; NICE, 2014).

There is increasing interest in innovative payment models for high-cost innovative medicines. The European Commission convened an Expert Panel in 2017 on this subject. The group acknowledged that new strategies to control spending were required, whilst (a) ensuring that patients can access new and effective drugs quickly, (b) providing appropriate research and development (R&D) incentives to the industry and (c) protecting the financial sustainability of both public and private health care systems. The Expert Panel argued that a single payment model is a blunt instrument that is not able to meet all three objectives (EXPH, 2018).
1.3. Differential reimbursement to reflect differential value

The scope of our paper is to investigate the impact of differential reimbursement to reflect differential value. As reflected in the title of our paper, we consider “innovative payments models” as an alternative to single pricing of pharmaceuticals. This could be implemented in a number of ways, for example using a suite of evidence-based list prices at the indication-level, set according to expected value on the one hand, or outcomes-based reimbursement where payments can be based on realised value, determined at the patient-level or implemented retrospectively based on real-world studies at the population level. The challenges in achieving such systems are numerous, such that work-arounds have been proposed. For example, Pearson et al. (2017) describe three options to achieve a price that reflects differential value: a single drug authorised under different brand names with different prices; distinct “discounts” applied to different indications, and a single weighted average price. Research into how differential reimbursement could be operationalised is important but is not the main focus of this paper. Rather, we explore the economic implications of permitting differential reimbursement of a single product. Throughout the paper, we use the term “indication” to denote any “uses” where value differs. We use the term “indication-based pricing (IBP),” which is the term used most prominently in the literature, to denote the concept of paying a different amount for different uses, and “uniform” or “single pricing” to refer to situation where a drug has the same price for each use.¹

1.4. Summary of the literature

Interest in IBP and other forms of differential reimbursement is increasing. We draw on a literature review by Towse, Cole and Zamora (2018) to summarise current literature, which can be split into papers investigating the concept or theory, and those investigating its application in practice.

Yeung, Li and Carlson (2017) outline the differences between using evidence-based prices and outcome-based reimbursement, by applying these two approaches to a specific product. Bach (2014), in a highly-cited article, described the potential benefit of IBP for determining rational prices for expensive cancer drugs, providing four stylised IBP examples for paclitaxel, erlotinib, cetuximab and trastuzumab, based on their costs and survival gains. Messori, De Rosa and Pani (2015) responded to Bach arguing that value-based reimbursement is already operationalised in Italy through a system of rebates associated with performance at the patient-level. Bach (2015), responded that rewarding outcomes on a per patient basis presented higher uncertainty for industry and would be difficult to operationalise in most settings. Subsequently Chandra and Garthwaite (2017) proposed that IBP would lead to higher prices overall and worse value for payers. In Section 3, we revisit the papers by Bach (2014) and Chandra and Garthwaite (2017), adding our perspective on the assumptions made and their implications.

Most examples in the literature of the applications of IBP are theoretical. For example, Hui et al. (2017) present an analysis of the price reduction required to make the treatment brentuximab vedotin cost-effective for use as consolidation therapy, rather than rescue therapy, arguing that if IBP were available treatment access could be broadened. Bach (2016) shows how the price of pertuzumab could be reduced in the less

¹ In practice differences in value could reflect response rates and other patient characteristics within an indication. We use IBP as shorthand for all substantive differences in value.
effective (metastatic) market to reflect its differential cost-effectiveness compared with its use in an adjuvant setting. He notes that this is not, on its own, a solution to the affordability problem. Evaluating the feasibility and attractiveness of IBP in six European countries (Germany, Italy, France, UK, Spain, Sweden) Flume et al. (2016) find data collection and legal and administrative barriers are present in France, Germany, Spain and the UK. Mestre-Ferrandiz et al. (2015) evaluate the potential for IBP in the UK and demonstrate that a single uniform price can have negative consequences for access and drug development. We visit this paper again in Section 4.

There is little discussion in the literature about the potential dynamic effects of IBP. In a discussion piece by Garrison (2010), the author considers the importance of considering the global life cycle of a product, in terms of rewarding value creation to promote innovation in oncology. Garrison points out that fixed pricing on a per-milligram or per-vial basis leads to wide variations in the economic value of a given compound, which provides an inconsistent signal on what society is willing to pay for innovation; a more flexible pricing system would reward innovation on the basis of value created, thus providing the right signals and benefiting patients. In relation to the value-based pricing proposals by the Office of Fair Trade in the UK, Claxton (2007) comments on a concern that under value-based pricing, whereby pricing can differ by indication, manufacturers would capture too much of the social surplus; whilst not inefficient, the author suggest that society should be concerned with how any surplus is distributed, especially as the public sector subsidises R&D in a number of ways. A report by (Rejon-Parrilla et al., 2014) describes the “value footprint” of ten cancer drugs approved by the European Medicines Agency (EMA) between 2003 and 2005, demonstrating that understanding of the value of a particular medicine changes significantly over time and by indication; the authors conclude that pricing and reimbursement decisions can fail to adequately reward important innovation, to the detriment of society, and propose varying price by indication as a possible public policy solution.

1.5. Structure of the report

The paper is structured as follows:

- Section 2 sets out the economic arguments around the initial “static” effects of IBP.
- Section 3 introduces two papers exploring the issue in the context of the US health care system. Both papers consider the potential (static) impact of IBP in terms of indication price and distribution of surplus, but from different perspectives. We explain and critique these perspectives and their inherent assumptions.
- Section 4 extends the economic arguments to consider the dynamic context, and the incentives from pharmaceutical innovation.
- Section 5 looks at the relevance of competition, exploring potential examples.
- Section 6 discusses the practical issues associated with any move away from uniform pricing.
- Section 7 concludes.
2. THE ECONOMIC ARGUMENTS: INITIAL STATIC EFFECTS

IBP involves pharmaceutical innovators charging different prices (or amounts) for the same product in distinct markets where arbitrage between these different markets is not possible. The distinct markets are ones in which the health gain delivered by the same product is different.

This is a specific application of price discrimination and it is helpful to consider the more general situation and then come back to why pharmaceuticals are different, primarily because of the role of third party payers. The effect of price discrimination in a typical consumer market on overall social welfare is ambiguous. On the one hand, the innovator should be better off with the option of price discrimination because, at worst, they can always charge the uniform price in all markets. On the other hand, consumers that are less price sensitive face higher prices under price discrimination, but those consumers that are more price sensitive face lower prices than under uniform pricing. Price discrimination increases welfare if and only if it increases the total volume consumed. The critical issue for social welfare is therefore the impact on volumes.

To put these points in the context of pharmaceuticals:

(i) Third party payers typically choose and pay for the treatments used. Inelasticity of demand is a proxy for the degree of patient health benefit. The more incremental health gain, the higher the price the payer is willing, in principle, to pay.

(ii) If IBP as compared to uniform pricing results in access for more patients to a product that offers them a better efficacy / safety profile than the product they are currently using, then price discrimination is unambiguously better than a single-pricing regime. By contrast, if total use of the drug remains unchanged with price discrimination, then uniform pricing is more efficient in terms of total demand served.

A further consideration for the pharmaceutical market in particular is the perspective of third party payers in health care (the purchasers) who face budget constraints, and who usually exercise some countervailing monopsony power. Increased patient access puts pressure on budgets. However, if the additional use is at cost-effective prices, as determined by the payer’s health technology assessment (HTA) agency, it makes sense for the payer to displace other, less cost-effective activities. There may be short term “affordability” issues if the budget impact is large, but if the effect of IBP is to make

---

2 This is technically third-degree price discrimination.
3 We are assuming that in the case of pharmaceuticals, the innovator sets price but the buyers determine quantity. Thus the innovator will set price taking account of the likely quantities that will be bought. They will also be mindful of the marginal cost (manufacturing and distribution cost) of supplying more or less units of the product. The objective is profit maximisation, conditioned on the product already existing, i.e. we are ignoring incentives for innovation at this point.
4 An unambiguous benefit to welfare is in the case where, under the uniform price regime, only the more inelastic (or higher value) market is served. In this case, price discrimination (IBP) leads to a Pareto improvement since monopoly profits increase, consumer surplus in the previously unserved market is positive, and consumer surplus in the more inelastic market remains unchanged (Church and Ware, 2000; Tirole, 1988).
5 In principle there could be a reduction in use with price discrimination but this is hard to envisage if the payer’s willingness to pay for health gain is well specified and the innovator sets prices that are at or below this level for each use of the drug.
6 It avoids inter-consumer misallocation. For a discussion of this point see Robinson (1969). Note that innovator profits are part of social value, thus, strictly, a rise in price that transferred money from the health care system to the innovator without affecting use of the product would not reduce social welfare.
more cost-effective treatment options available for the payer to approve and clinicians to choose from, this is of benefit.

A related concern for payers is that pricing by indication may lead to higher prices (lower cost-effectiveness) for some indications compared with the profit-maximising uniform/single price, in particular where the size of the market for that indication is such that the uniform price would be set to correspond with the lowest value. The short run tactic for payers with budget concerns would be to seek a uniform price at the price of the lowest value indication, as patient access would be maximised and expenditure minimised.

There are two problems with this stance:

(i) the first is dynamic, which we discuss in Section 4 below. Paying a relatively low uniform price for high value indications may negatively impact on R&D investment decisions.

(ii) the second is that payers are unlikely to be able to enforce such a strategy whilst maintaining access for all indications. They can refuse to reimburse indications which do not represent good value for money at the given (uniform) price, and they can negotiate, but if they seek to impose lower prices (e.g. setting a single price at the lowest value indication) they may find that companies are not willing to supply for some indications at that price, thus denying access to patients who could stand to benefit from the drug.

What payers can do is use competition to drive down prices and reduce growth in expenditure. We discuss in Section 5 the potential for IBP to increase competition.

Throughout the paper we make various assumptions, both around how manufacturers price their products as well as how consumers value them. In the context of a dynamic global pharmaceutical market place, decisions around pricing are very complex. We rationalise (from an economist’s perspective) what the incentives around pricing are, given the health effects and costs observed and valued by payers (representing consumers in this market).

We assume that indication-based pricing is equivalent to value-based pricing but at the indication-level, whereby the patient’s demand curve is replaced by a third party payers’ willingness-to-pay schedule, that can be inferred from an implicit or explicit threshold\(^7\). The threshold should be based on the opportunity cost of spend at the margin. If the intervention is “cost-effective” (falls under the relevant threshold) then it represents good value for payers and a worthwhile investment. We also assume a direct relationship between price and investment in R&D by manufacturers. Finally, we consider a ‘market’ (rather than a single product) analysis.

3. THE CASE FOR AND AGAINST A SINGLE-PRICE MODEL

In this section we set out the cases for and against a single-price model as articulated in two influential papers. The first, Bach (2014), made the case for IBP. The second, Chandra and Garthwaite (2017), made the case for a single or uniform price. We review these and critically assess the assumptions they make. In the following two sections we

---

\(^7\) Later in the paper we will describe the value-based indication-level price can be seen as the “ceiling”, below which competition can drive price down.
then look at the dynamic implications that these papers do not take into account, including a consideration of the potential role for competition.


By describing the survival gains and costs associated with different indications of four drugs (nab-paclitaxel, erlotinib, cetuximab and trastuzumab), Bach demonstrates the (theoretical) impact of IBP obtained by:

(i) anchoring monthly price to that of the highest value indication (i.e. that offering the greatest median survival gain); and

(ii) basing monthly price on a value threshold of $150,000 per life year gained.

He then compares these with the current monthly price of treatment. Anchoring price to the highest value use by definition lowers prices for other indications, and so lowers prices for these indications as compared to their current monthly price. It assumes that what the payer is paying for the high-value indication is appropriate, and therefore that the current price of lower value indications is too high. Perhaps a better test is the use of a threshold (as used in a number of HTA systems including the UK) to generate value-based prices, which the author presents using a threshold of $150,000 per QALY. We discuss one of his examples (cetuximab) in more detail in Section 3.3. below.

Bach finds that although his examples are “crude” they “illustrate that a change to indication-based pricing may be a necessary step toward paying rational prices for expensive drugs used to treat cancer and some other conditions, for which efficacy varies across indications.”

3.2. Chandra and Garthwaite (2017)

In this paper, Chandra and Garthwaite (2017) argue that supporters of IBP “hope that such a system will reduce prices for low-value indications but that prices for high-value indications will not increase”, and they cite the Bach paper at this point. The authors argue that this is not true, by constructing two scenario examples, each with three indications. Both examples show prices for high value indications increasing as a result of introducing IBP. The argument is clear. Whilst Bach shows how IBP can lower prices, Chandra and Garthwaite show how it can raise prices using the examples set out in Figure 1.

In Scenario 1 the profit maximising uniform price is to charge the price of the lowest value indication (Indication C), because the volume of sales is so high relative to the higher value indications that it is the most profitable market. IBP will lead to higher prices for indications A and B. In Scenario 2, the profit maximising uniform price is to set price equal to the value of the middle value indication (Indication B). In this scenario, allowing IBP will lead to a higher price for the high-value indication and a lower price for the lower-value indication.
3.3. A critique of the literature

In their analysis, illustrated in Figure 1 above, Chandra and Garthwaite describe a situation whereby moving from a uniform price to IBP would result in a transfer of surplus\(^8\) from the payer (shaded blue) to the innovator (shaded green). Conceding that in some situations IBP may expand patient access (‘Scenario 2’: the bottom graphs in panels A and B) to indications with low value but a relatively large population, they warn that this benefit may be outweighed by the price increases overall:

"For drugs currently priced so high that they’re unavailable for some indications, it expands access. Drug manufacturers would now be willing to set low prices for low-value indications, since it wouldn’t jeopardize their profits on high-value indications. But the same access-expanding pricing flexibility also allows manufacturers to increase prices for high value indications. Currently, some treatments are priced low enough to be accessible for a wide range of indications, and it is there that we should expect the biggest price increases."

Our perspective differs from those of the authors in three main points. Chandra and Garthwaite state: "...simple economics makes it clear that relative to uniform pricing, indication-based pricing results in...

---

\(^8\) The value of the difference between what patients are willing to pay (or third party payers on their behalf) and what they pay. In this case the consumer surplus accrues to the health system, i.e. the difference between what it pays for a treatment and the value it delivers to its patients (in other words, the maximum it would have been willing to pay).
...higher prices for patients who benefit the most... Our response is: not if the uniform price was already set to correspond with the value for patients who benefit the most;

...higher utilisation by patients who benefit the least... Our response is: absolutely, that is the most important potential of an indication-based pricing system. The point is that a lower price will reflect that lower benefit;

...higher overall spending, and higher manufacturer profits. Our response is: in the static context, this must be the case initially. But in the dynamic context, where we consider the impact of a system of multiple prices on the potential for competition, including facilitating additional entry into the market, the impact is less clear.

All are empirical questions, but the representation of scenarios does not do justice to the economics of IBP. Whilst Chandra and Garthwaite counterpoint Bach (2014), they do not help their readers understand the considerations that should govern whether IBP is likely to lead to more or less consumer surplus, more or less patient access to drugs, and more or fewer new indications.

Both papers described above attempt to illustrate the potential impact on prices, revenues and patient use of the drug by moving from a uniform price to IBP. The crucial difference is the starting point: is the uniform price set at the value of the highest or the lowest value indication. In the illustrative examples the question is an empirical one, but this difference in starting point is critical to our understanding of who benefits. In addition, the context and HTA system in which the drugs are being reimbursed must be taken into account.

Chandra and Garthwaite recognise that IBP “expands access”. We can this see in Scenario 2 of Figure 1 where the uniform price is set at the middle indication that patients for the lowest value indication do not get access. With indication-based pricing they do. However, they argue that “the same access-expanding pricing flexibility also allows manufacturers to increase prices for high-value indications”. This statement is correct, assuming manufacturers can increase prices, but is only relevant if manufacturers have not set the uniform price at the highest value indication. This is an empirical question. Chandra and Garthwaite are correct in seeing IBP as a tool for innovators of “price discrimination to capture more of the overall value created by their products”. However, as they note, it is likely to increase the volume of patients receiving the medicine. If IBP is linked to value as determined by use of an appropriate value-for-money cost-effectiveness threshold, then an increase in the numbers of patients being treated represents a good value use of money by the health system.

The two papers draw on the same example – the data presented by Bach on cetuximab for two indications: (i) first-line treatment of recurrent or metastatic squamous cell carcinoma of the head and neck, and (ii) locally advanced squamous cell carcinoma. Therefore, the huge impact of the different assumptions they make is evident. This is shown in Table 1 below, where the main inputs are summarised in columns 1 to 5, cost per life year gained in column 6, and three alternative representations of a value-based price in columns 7 (Bach’s), 8 (Chandra and Garthwaite’s) and 9 (priced according to a threshold).
Table 1. The cetuximab example

<table>
<thead>
<tr>
<th>(1)</th>
<th>(2)</th>
<th>(3) Survival gain (years)</th>
<th>(4) Total typical treatment cost ($)</th>
<th>(5) Current monthly price ($)</th>
<th>(6) [Indicator of current value: Cost per life year gained (approx.)]</th>
<th>(7) Monthly price based on Indication with most value</th>
<th>(8) Monthly price based on Indication with least value</th>
<th>(9) Monthly price based on value of $150,000 per life year gained</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line – low value indication (LOW VALUE)</strong></td>
<td>(i) first-line treatment recurrent/metastatic HNSCC</td>
<td>0.23</td>
<td>$42,875</td>
<td>$10,319</td>
<td>$190,556</td>
<td>$471</td>
<td>$10,319</td>
<td>$8,123</td>
</tr>
<tr>
<td><strong>Locally advanced – high value indication (HIGH VALUE)</strong></td>
<td>(ii) locally advanced HNSCC</td>
<td>1.64</td>
<td>$14,292</td>
<td>$10,319</td>
<td>$8,706</td>
<td>$10,319</td>
<td>$226,075</td>
<td>$177,798</td>
</tr>
</tbody>
</table>

HNSCC: Squamous cell carcinoma of the head and neck

*The calculations are not exact. We assume that the numbers for survival gains and treatment duration have been approximated to two decimal places in the Table but not for the calculations.

**Source of key inputs** (survival, treatment cost and monthly price): Bach (2014).

The monthly price is the same for both indications: $10,319 (the current “single price” system). It is easy to observe that the value of cetuximab is far higher in the locally advanced indication versus first-line treatment where gains are seven times lower and cost is three times higher, given the longer duration of treatment. An indication of ‘value’ is summarised by the cost per life year gained in column 6, which is $8,706 for the locally advanced high-value indication and $190,556 for first line treatment. The lower the cost per life year gained, the more favourable the intervention, as it represents better value for money.

In order to explore what price changes would ensue from a move to IBP, the two papers take the price currently paid for survival improvements in one of the indications, and apply it to the other. In their analysis, Chandra and Garthwaite take the value assumed by paying a total of $42,875 over 4.16 months in the first-line low value indication to generate 0.23 additional life years ($190,556 per life year gained), and apply that to the 1.64 additional life years generated in the locally advanced high value indication. This is shown in column (8) of Table 1. On the other hand, Bach (2014) presents a monthly price based on the indication with the most value, which suggests a willingness to pay

---

9 1.64 extra years survival at a cost of $14,292 for the locally-advanced indication versus 0.23 extra years survival at a cost of $42,875 for first-line treatment.

10 = $190,556 x 1.64 years ÷ 1.39 treatment duration = $226,075, which Chandra and Garthwaite describe as approximately $220,000 per month.
(WTP) of $8,714 per additional life year and leads to a monthly price for the first-line low value indication of $471 per month. This is shown in column (7) of Table 1.

Chandra and Garthwaite suppose that, as cetuximab is reimbursed for the first line low value treatment, then this is a signal of payer WTP. Therefore, its use in the locally advanced high value indication creates a high level of benefit in terms of life years gained, which is experienced by patients but not captured by the price paid: this represents consumer surplus for the payer. A move to IBP would allow the price in the high value indication to rise to the maximum WTP ($220,000), thus transferring all surplus to the producer. Bach, on the other hand, assumes that the price has been set based on its cost and benefit in the high value indication, and therefore suggests that payers should be willing to spend $471 per month on cetuximab in its low value indication. Bach also uses a WTP threshold of $150,000 which illustrates prices, shown in column (9), that are closer to Chandra and Garthwaite’s assumptions shown in column (8).

3.4. Summary of key points

We argue that there are three critical factors that are not satisfactorily addressed by the current literature, which may limit its applicability, or its transferability to settings outside the U.S.

1. The level of the uniform price that is assumed under a single-price scenario.
   Chandra and Garthwaite (2017) assume that the profit-maximising uniform price will be equivalent to the value-based price of the low-value indication. This means that a move to IBP would lead to higher prices for higher value indications, thus transferring all surplus to manufacturers. Whilst we do not disagree with this basic concept, our point of difference is the starting point: we argue that in many cases, the profit-maximising (uniform) price will correspond with higher value indications, with manufacturers choosing to forgo the lower value indications altogether in order to protect profits. This being the case, price discrimination would permit manufacturers to expand access to patient populations who would currently not have access to the drug, given the modest benefit relative to the (uniform) price; we have already described earlier in this paper that where price discrimination expands access, societal welfare is increased.

2. The presence of an HTA system to modulate price and guarantee value.
   Chandra and Garthwaite challenge the above proposal (that prices in a single-price setting correspond with high-value indications) by saying that “If that were true, it would mean that manufacturers have convinced insurers and patients to consistently pay prices exceeding their products’ value”. In an HTA system that appraises medical interventions on the basis on their cost-effectiveness, this would not be permissible; where a drug was priced higher than the value in an indication, it would simply not be reimbursed for that indication. In addition, it is important to note that, under IBP, even if we assume that (in the static context) companies set differentiated prices to correspond with the maximum WTP for the health gain achieved in that sub-population, then despite all surplus now accruing to the producer, (a) this is efficient and (b) by meeting the threshold, it is a worthwhile and cost-effective way to generate health gains for patients.

---

11 We are assuming that a correct threshold for the value of health gain is used, as discussed in the next paragraph.
3. The role of competition

Analysis by Chandra and Garthwaite explicitly assumes that the producer is a price-setting monopolist. This, particularly in the competitive and busy field of oncology, is unrealistic in most health care systems. A system of IBP would, in the dynamic context, create the R&D incentives required for producers to target further indications / sub-populations, thus facilitating more aggressive competition at the indication-level. We argue that, as a result, the value-based indication prices (based on setting price at the maximum WTP) should be seen as the price ‘ceilings’, and that competition can drive prices down below these levels. We discuss this further in the following sections.

4. THE ECONOMICS ARGUMENTS: LONGER TERM DYNAMIC EFFECTS

Economic theory suggests that there are two important dynamic effects which impact on R&D and on pricing. Firstly, with a single price, some high value or low value indications may not be developed, even though the incremental value of the drug to patients exceeds R&D and supply costs. Secondly, scientific progress stimulates R&D competition and often leads to several products coming to market in a therapy class. We propose that IBP makes it more likely (i) that competing products get developed and (ii) that competition occurs in any given indication. Most payers now have mechanisms to ensure that competition leads to lower prices for some indications and/or groups of patients.

We are assuming that the innovator can choose to set price at the maximum price determined by the HTA assessment of incremental health gain and the willingness to pay for health gain. In some distinct markets (indications) there may be competing products offering very similar incremental health gain. Allowing companies to enter new indication markets without compromising their presence in existing indication markets will likely drive competition. This is because IBP could allow manufacturers to target further (lower value) indications, thus achieving an increase in marginal volume (sales) that does not undermine or compromise existing high-value target indications (to which a higher value and therefore higher price is attached).

Single prices for molecules will impact R&D investment in a number of situations. Mestre-Ferrandiz et al. (2015) present a theoretical analysis of IBP versus uniform pricing. They explore different scenarios to show under which circumstances the introduction of IBP can be beneficial from the manufacturer’s, payer’s and patients’ perspectives. For example, the authors show that if uniform pricing is the only option, fewer indications are available, to the detriment of patients (either because the price is not cost-effective or the manufacturer has not developed them).

Markets that only allow a uniform price create an issue for companies because they won’t necessarily know the full range of future indications when a new drug is released for its first indication, let alone the exact clinical value of those indications, or the extent of any likely competition. Neither will they know how many competitors will be “sharing” the volume in any given indication-market. The decision as to how to set a uniform price, if it cannot subsequently be increased, is hard when all or most possible future indications may not be known at the time of launching the first indication.

---

12 Companies do not have perfect foresight and so the absence of IBP introduces greater uncertainty into decisions to invest in R&D.
The pharmaceutical company faces a problem of trying to optimise access and maximise revenues at a single point in time. This situation puts efficiency at risk, threatening future investments in R&D for new indications. It might also jeopardise early access to the drug by delaying release until the company has a better understanding of market conditions.

Mestre-Ferrandiz et al. (2015) set out possible scenarios when there are two indications, a high value (in terms of quality adjusted life years (QALYs) gained per patient) indication and a low value indication. The findings are set out in Table 2 below. When IBP is not available then there are plausible scenarios in which only one indication is marketed or when only one indication is developed. The optimal short term scenario from the payer point of view – both indications of a single product are developed, and both are sold at the price of the lowest value indication – is not a realistic one on which to base policy, if the objective is to give patients access to cost-effective medicines.

They argue that it will only occur in certain circumstances:

(i) the lower value (QALYs gained per patient) indication has a larger volume such that it is the most profitable market; and

(ii) the development costs of the higher value indication can be recovered at the price of the low value indication (i.e. it is profitable to develop the high value indication even if it can only be sold at a low price); or

(iii) the high value indication is developed first, and it is profit maximising to develop and market the lower value indication subsequently, even though this means the price will be lower for both indications, i.e. the price is high for long enough to provide a return on the development costs of the first indication.

There are likely to be many situations in which these conditions do not hold and indications are not developed and/or not launched, because of the implication for the level of a uniform price.
Table 2. Possible outcomes when multi-indication pricing is not feasible

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Static context</th>
<th>Dynamic context “no-sequencing”</th>
<th>Dynamic context “sequencing”</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-value indication is</td>
<td>The value of</td>
<td>1. The high-value indication is</td>
<td>1. The high-value indication</td>
</tr>
<tr>
<td>marketed</td>
<td>the lower-value</td>
<td>developed first and it is not</td>
<td>is developed first</td>
</tr>
<tr>
<td>indication is relatively</td>
<td>indication is</td>
<td>profitable to develop the low-</td>
<td>and it is not profitable to</td>
</tr>
<tr>
<td>small and the patient</td>
<td>relatively</td>
<td>value indication and market both</td>
<td>develop the low-value</td>
</tr>
<tr>
<td>population is relatively</td>
<td>small</td>
<td>at the low-value price</td>
<td>indication and market both</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>at the low-value price</td>
</tr>
<tr>
<td>Low-value indication is</td>
<td>The patient</td>
<td>2. The low-value indication is</td>
<td>2. The low-value indication</td>
</tr>
<tr>
<td>marketed</td>
<td>population for</td>
<td>developed first but it is</td>
<td>is developed first</td>
</tr>
<tr>
<td></td>
<td>the lower-value</td>
<td>profitable to withdraw it from</td>
<td>and the cost to develop the</td>
</tr>
<tr>
<td>indication is large</td>
<td>indication is</td>
<td>the market and launch the high-</td>
<td>high-value indication cannot</td>
</tr>
<tr>
<td></td>
<td>large</td>
<td>value indication at a higher</td>
<td>be recovered at the low-value</td>
</tr>
<tr>
<td>Both indications are</td>
<td>The value of</td>
<td>The low-value indication is</td>
<td>The low-value indication is</td>
</tr>
<tr>
<td>marketed</td>
<td>the lower-value</td>
<td>large enough and/or the patient</td>
<td>developed first and the cost</td>
</tr>
<tr>
<td></td>
<td>indication is</td>
<td>population is large enough</td>
<td>to develop the high-value</td>
</tr>
<tr>
<td></td>
<td>large</td>
<td></td>
<td>indication cannot be</td>
</tr>
<tr>
<td></td>
<td>and/or the</td>
<td></td>
<td>recovered at the low-value</td>
</tr>
<tr>
<td></td>
<td>patient</td>
<td></td>
<td>price</td>
</tr>
<tr>
<td></td>
<td>population is</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>large enough</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>and</td>
<td>1. The value of the low-value</td>
<td>2. The development cost of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>indication is large enough</td>
<td>the higher-value indication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and/or the patient population is</td>
<td>is small enough</td>
</tr>
<tr>
<td></td>
<td></td>
<td>large enough</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. The development cost of the</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>higher-value indication is small</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>and</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. The low-value indication is</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>developed first and:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>a. The combined revenue from the</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>two indications minus the</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>development cost for the low-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>value indication will exceed the</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>revenue from the high-value</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>indication only, and</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. The development cost of the</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>high-value indication has</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>already been recovered or the</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>additional revenue generated by</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>marketing both indications at the</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>low-value price will allow</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>recovering profitably the part</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>of the development cost of the</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>high-value indication not yet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>recovered</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. The low-value indication is</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>developed first and:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>a. It is profitable to develop</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>the high-value indication</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>and market it at the low-value</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>price.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. This is more profitable than</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>withdrawing the low-value</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>indication and supplying the</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>high-value indication at a higher</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>price.</td>
<td></td>
</tr>
</tbody>
</table>

Source: Mestre-Ferrandiz et al. (2015), Table A1.11. Note that the Table includes numbers in column 3 which relate to a worked example.

5. THE POTENTIAL ROLE OF COMPETITION

The number of competitors, the products substitutability (in terms of its efficacy/tolerability profile), and the position of entry for each indication shapes the type of competition that can take place. We note the interest in competition based on indication from\(^\text{13}\):

\(^{13}\) For more detail and references, see Section 3 of Towe, Cole and Zamora (2018).
• Several US private payers. Examples reported include: Anthem (previously WellPoint) initiating a cancer pathway programme providing information that would enable contracting based on indication; UnitedHealthcare completing in 2014 a cancer pathway pilot which separated oncologist’s income from drug sales, which could facilitate a move toward IBP; CVS entering an IBP programme in 2016 for different indications of Herceptin (trastuzumab); Express-Scripts launching an IBP programme for anti-inflammatories in 2017;

• NHS England’s use of IBP to generate competition and lower prices for hepatitis C drugs. NHS England experimented with different tendering approaches. A key element was a move to tendering by genotype, given that there are six genotypes and not all drugs are effective for all genotypes.

The role of competition in seeking alternatives to the single pricing of pharmaceuticals has largely been absent from the literature, with a couple of exceptions. For example, in his book on the pricing of medicines, Maurice-Pierre Planel suggests that the analysis of price should be carried out throughout the medicine's lifecycle. In addition, he proposes that health authorities should put in place more dynamic regulation strategies that can take into consideration the arrival of new products and allow, in a context of managed prices, competition to lower prices (Planel, 2017).

We looked for examples where IBP could lead to more competition. We assumed this could happen if drugs in the therapy class had some differences in the indications for which they were licensed. IBP would therefore potentially allow more competition than a single price environment.

The difficulty in understanding the potential for IBP is that we do not necessarily know about all potential indications of a drug, as the current system of uniform pricing means that manufacturers are not incentivised to generate evidence in sub-populations for whom benefits would be important but modest compared with other indications. We put this into the context of the discussion of the Bach and the Chandra & Garthwaite papers, by considering a simplified, stylised example of a drug with three different indications. In Figure 2 below, we assume that under a uniform price scenario, represented in (a), the profit maximising price is such that only the high value (HV) indication is marketed. The only patients for whom the drug is used are those with the high value indication (N_U patients). In this case, IBP leads, in the short term, to expansion of access, represented in (b1), and higher spend. Now, a much larger number of patients are served (N_IBP). We assume in the static scenario that the price is set to the maximum WTP of the payer, thereby ascribing all surplus to the producer (represented by the green shaded area). However in the longer term dynamic context, represented in (b2), IBP could lead to increased competition for the medium- and low- value indications, as other manufacturers are also now incentivised to expand access and target these new indications. This could thereby lead to a reduction in price (PMd and PLd respectively) below the maximum value (VM and VL respectively) in those indications. Therefore, comparing this scenario with the uniform pricing situation where the manufacturer has priced at the high value indication, the use of IBP could expand access significantly, whilst at the same time price-based competition could drive prices below the ‘ceiling’ price estimated by a maximum WTP, thus generating consumer surplus for the payer, represented by the blue shaded area in (b2).
5.1. Two drug classes with multiple indications and competing products

Given the increasingly competitive R&D environment nature of drug development for cancer treatments, the analysis of the relative merits of a more multi-price approach needs to incorporate the dynamic picture. We explored two classes of therapy to understand the potential for competition between indications: TKIs and PD-1/PD-L1 inhibitors.

5.1.1. TKIs for CML

The first TKI to be approved for the treatment of Chronic Myeloid Leukaemia (CML) was imatinib (Glivec). It was subsequently also licensed for four further indications beyond CML. Imatinib was followed by six further products with indications that overlapped with one or more of its indications. In order to concretely consider the expansion of indications for imatinib and considerations around reimbursement, we assess indications according to approval by the European Medicines Agency (EMA), and reimbursement considerations by the National Institute for Health and Care Excellence (NICE) in the UK. We illustrate in Figure 3 and set out in Table 3 the indications and timings.
Figure 3. Indications, dates of approval and competitors for Imatinib

Note: different colours represent different products, that were approved with an indications that overlaps an indication for imatinib.

It can be observed from Table 3 that, for reimbursement approvals of imatinib’s competitors, all have been on the basis of a patient access scheme (PAS), usually in the form of a simple discount (which are commercial in confidence). It can therefore be deduced that a discount needed to be offered for the new entrants to secure access to the ‘indication markets’, as list price was beyond the cost-effective price calculated by NICE. In England, only one level of “discount” is permitted, thus this does not represent IBP “through the back door” (although, within the current form of the England CDF, commissioning arrangements can be more flexible).
Table 3. Indications and Competitors for Imatinib (Glivec®), Novartis

<table>
<thead>
<tr>
<th>Indication [date approved by EMA]</th>
<th>Competitors [date approved by EMA] Company</th>
<th>NICE Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CML chronic [Nov 2001]</td>
<td>Dasatinib (Sprycel®) [Sept 2006] BMS</td>
<td>TA70 &amp; TA425 &amp; TA426 Imatinib recommended. Dasatinib and Nilotinib also recommended as options, but only if the companies provide them with the discounts agreed in the relevant patient access schemes “details of which are commercial in confidence” Bosutinib not recommended for first line: only recommended when other TKIs have failed / are not appropriate, and only when offered with discount agreed in the PAS.</td>
</tr>
<tr>
<td></td>
<td>Nilotinib (Tasigna®) [Sept 2010] Novartis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bosutinib (Bosulif®) [Jan 2013] Pfizer</td>
<td></td>
</tr>
<tr>
<td>CML accelerated/blast [Nov 2001]</td>
<td>Dasatinib (Sprycel®) [Oct 2010] BMS</td>
<td>TA70 &amp; TA425 &amp; TA451 Imatinib recommended for patients who initially present in accelerated/blast phase, but high-dose imatinib is not recommended for treating Philadelphia-chromosome-positive CML in adults whose disease is imatinib-resistant. Dasatinib recommended where imatinib has contraindicated or has failed, but only when offered with discount agreed in the PAS. Ponatinib only recommended when patient is resistant to or cannot tolerate dasatinib or nilotinib or where gene mutation T3151 is present, and only when agreed discount is provided through the PAS. Bosutinib only recommended when other TKIs have failed / are not appropriate, and only when offered with discount agreed in the PAS.</td>
</tr>
<tr>
<td></td>
<td>Ponatinib (Iclusig®) [Jul 2013] Takeda</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bosutinib (Bosulif®) [Feb 2018] Pfizer</td>
<td></td>
</tr>
<tr>
<td>ALL 1st line [May 2013]</td>
<td>none</td>
<td>No NICE guidance</td>
</tr>
<tr>
<td>MDS/MPD [Nov 2006]</td>
<td>none</td>
<td>No NICE guidance</td>
</tr>
<tr>
<td>HES/CEL [Nov 2006]</td>
<td>none</td>
<td>No NICE guidance</td>
</tr>
<tr>
<td>Kit (CD117) +ve unresectable and/or metastatic malignant GIST [May 2002]</td>
<td>Only after failure of Imatinib: Sunitinib (Sutent®) [Jul 2006] Pfizer Regorafenib (Stivarga®) [Aug 2013] Bayer</td>
<td>TA86 &amp; TA209 &amp; TA179 &amp; TA488 Imatinib recommended but not as a high dose for tumours who disease has progressed with initial imatinib treatment. Sunitinib is recommended as an option only after imatinib has failed (because of resistance or intolerance) and the cost of the first treatment cycle must be met by the manufacturer.</td>
</tr>
</tbody>
</table>

Economics of Innovative Payment Models Compared with Single Pricing of Pharmaceuticals
<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Kit (CD117) +ve GIST: adjuvant treatment following resection for patients at high risk of relapse [May 2002] | none | TA 326
Imatinib recommended |
| Unresectable DFSP [Sep 2006] | none | No NICE guidance |

CML: Chronic myeloid leukaemia
ALL: Acute lymphoblastic leukaemia
MDS/MPD: Myelodysplastic/ myeloproliferative diseases with platelet-derived growth factor receptor (PDGFR) gene re-arrangements.
DFSP: Dermatofibrosarcoma protuberans
HES/CEL: advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.
GIST: gastrointestinal stromal tumours (GIST)
5.1.2. **PD-1 and PD-L1 inhibitors**

Immuno-oncology research is an innovative class of treatments which uses the body’s own immune system to fight cancer. The most common mechanisms are CTLA-4, chimeric antigen T-cell receptor (CAR-T), and PD-1/L1 cell therapies. The momentum for clinical development of PD-1 and PD-L1 inhibitors has been rapid, with the first (pembrolizumab and nivolumab) being approved by the EMA in 2015. The unprecedented growth in the development of this class of therapies means they offer an excellent example of the role that competition can play in this market, and how this might be impacted by a move away from a single price for a medicine. There is an extensive literature base on the performance and promise of PD-1 and PD-L1 inhibitors; Gong et al. (2018) provide an overview of their development and future considerations, and Alsaab et al. (2017) describe the extent of clinical trials currently underway. There are in the region of 160 agents in clinical/preclinical studies, with 50 in the clinical phase including three in Phase III trials from Sanofi/Regeneron, Novartis and Incyte/Jiangsu, and nine in Phase II (Carroll, 2017). There are over 1,500 clinical trials underway and over 1,000 combination studies in the pipeline. Figure 4 below presents a timeline of agents approved by the EMA, demonstrating the breadth of currently approved indications and the sequence these were brought to market in Europe.

It is clear that the development of PD-1/PD-L1 inhibitors is highly competitive, with many new entrants emerging as well as competition between existing products seeking evidence of benefit in new indications (e.g. sub-populations) (Hayes, 2018a; 2017). NSCLC is the most valuable tumour type for PD-1/PD-L1 checkpoint inhibitors, accounting for almost half of projected sales (Hayes, 2018b). As well as the three PD-1/PD-L1 inhibitors already approved in NSCLC, AstraZeneca’s durvalumab (Imfinzi) is currently under consideration by the EMA for NSCLC and has already been granted accelerated approval by the FDA. Through the PACIFIC trial, durvalumab has demonstrated potential for use earlier in the NSCLC treatment pathway. Trials of its competitors in early-stage patients are at least two years behind (Grogan, 2017; 2018). This is a clear demonstration of companies seeking approval in indications with a current lack of competition (pembrolizumab, nivolumab and atezolizumab are all approved for metastatic stage IV NSCLC).
Economics of Innovative Payment Models Compared with Single Pricing of Pharmaceuticals

Figure 4. Indication timeline for EMA-approved PD-1 and PD-L1 inhibitors

Source: EMA authorisation details and documentation of assessment history, published online
*Note that Avelumab is an orphan medicinal product and has been granted conditional approval by the EMA.
Abbreviations: Non-Small Cell Lung Cancer (NSCLC); Renal Cell Carcinoma (RCC); Squamous Cell Cancer of the Head and Neck (SCCHN); Urothelial Carcinoma (UC); Merkel Cell Carcinoma (MCC).
5.1.3. Constructing an example using PD-1 and PD-L1 inhibitors

To illustrate how pricing by indication might lead to lower prices for some indications by promoting competition, we explored the relative value of indications using evidence from the Institute for Clinical and Economic Review and NICE appraisals.

The Institute for Clinical and Economic Review assesses and produces reports on the clinical and economic value of medical interventions in the United States. In 2016 it produced a report on the treatment options for advanced NSCLC, demonstrating the cost-effectiveness of the treatments at current prices as well as the discount required for prices to be “value–based”. Included in the analysis were the then new immunotherapy PD-1/PD-L1 inhibitors nivolumab, pembrolizumab and atezolizumab. The results are summarised in Table 4, and are relevant for the second line treatment of NSCLC.

Table 4. ICER results for the second-line treatment of NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Incremental costs</th>
<th>Incremental QALYs</th>
<th>ICER at list price</th>
<th>Current list price (per 100mg vial)</th>
<th>Value-based price benchmark (per 100mg vial)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>$205,714</td>
<td>0.87</td>
<td>$236,492</td>
<td>$4,381</td>
<td>$2,694</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>$107,472</td>
<td>0.26</td>
<td>$415,950</td>
<td>$2,470</td>
<td>$1,064</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>$111,785</td>
<td>0.51</td>
<td>$219,179</td>
<td>$8,620</td>
<td>$5,954</td>
</tr>
</tbody>
</table>

*Assumes cost-effectiveness threshold of $150K/QALY, and incorporates an assessment of budget impact


It should be noted that the values summarised by the Institute for Clinical and Economic Review are not directly comparable for the three agents as the populations are slightly different, and may not be transferrable to the European setting today, given differences in the indication approvals (for example the Institute for Clinical and Economic Review analysis assumes that pembrolizumab and atezolizumab require PD-L1 expression test, whereas approval in the EU for atezolizumab does not specify that a test is required).

As evident from the timeline presented in Figure 4 in the EU nivolumab was the first PD-1/L1 inhibitors to be approved for NSCLC in October 2015, with pembrolizumab not receiving EMA marketing authorisation in NSCLC until January 2017, and atezolizumab in September of the same year. However, in the U.S. nivolumab was the first to market for NSCLC in March 2014, pembrolizumab shortly after in October 2015, and atezolizumab in October 2016. Without comparative estimates of cost-effectiveness in the other target indications for the three drugs, it is not possible to compare relative value across indications, and assess how these might be impacted by competition. Other indications have not been assessed by the Institute for Clinical and Economic Review.

We therefore also looked for evidence from NICE in the UK. Table 5 summarises the spectrum of indications for PD-1/L1 inhibitors that have so far been evaluated by NICE, along with the decision outcome, most plausible ICER by NICE where this is disclosed, and the size of the eligible population in England.
### Table 5. NICE Technology Appraisals (TAs) of PD-1/L1 inhibitors

<table>
<thead>
<tr>
<th>Indication</th>
<th>NICE Guidance</th>
<th>Decision</th>
<th>QALY gain (source)</th>
<th>“Most likely ICER”</th>
<th>Eligible population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced (unresectable or metastatic) melanoma as monotherapy</td>
<td>Nivolumab TA384 (Feb 2016)</td>
<td>Recommended</td>
<td>BRAF +ve: 1.82 QALYs (company)</td>
<td>Less than £30,000/QALY</td>
<td>1,100</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab TA366 (Sep 2017)</td>
<td>Recommended only when provided in line with commercial access agreement</td>
<td>BRAF +ve: 0.97 QALYs (company) - 0.79 QALYs (ERG)</td>
<td>Less than £50,000/QALY (including discount)</td>
<td>1,121</td>
</tr>
<tr>
<td>Advanced (unresectable or metastatic) melanoma in combination with ipilimumab</td>
<td>Nivolumab TA400 (July 2016)</td>
<td>Recommended only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme</td>
<td>BRAF +ve: 1.64 QALYs (company)</td>
<td>Less than £30,000/QALY (including discount)</td>
<td>[not included]</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab TA357 (Sep 2017)</td>
<td>Recommended only if disease has progressed with ipilimumab and when provided in line with commercial access agreement</td>
<td>1.19 QALYs (company)</td>
<td>Less than £50,000/QALY (including discount)</td>
<td>600 in year one and 300 thereafter</td>
</tr>
<tr>
<td>Previously treated renal cell carcinoma</td>
<td>Nivolumab TA417 (Nov 2017)</td>
<td>Recommended when provided in line with commercial access agreement</td>
<td>0.61 QALYs (“committee’s preferred analysis”)</td>
<td>Less than £50,000/QALY (including discount)</td>
<td>800</td>
</tr>
<tr>
<td>Relapsed or refractory classical hodgkin lymphoma</td>
<td>Nivolumab TA462 (Nov 2017)</td>
<td>Recommended when provided in line with commercial access agreement</td>
<td>Unknown [QALY estimates redacted from documentation] From Tan et al. (2017): 4.5 QALYs (setting: Australia)</td>
<td>Around £30,000/QALY (including discount)</td>
<td>Less than 50</td>
</tr>
<tr>
<td>Previously treated NSCLC</td>
<td>Squamous NSCLC: Nivolumab TA483 (Nov 2017)</td>
<td>Recommended for use within CDF (if treatment stopped at 2 years and conditions of managed access agreement are followed)</td>
<td>Unknown [not clear from documentation which estimate deemed to be most appropriate] From ICER U.S. analysis: 0.26 QALYs</td>
<td>£50,014/QALY (including discount)</td>
<td>950 over course of managed access agreement (21 months)</td>
</tr>
<tr>
<td></td>
<td>Non-squamous NSCLC: Nivolumab TA484 (Nov 2017)</td>
<td>Recommended for use within CDF (if tumours are PD-L1 positive, treatment stopped at 2 years and conditions of managed access agreement are followed)</td>
<td>Unknown [not clear from documentation which estimate deemed to be most appropriate] From ICER U.S. analysis: 0.26 QALYs</td>
<td>“plausible potential” for cost-effectiveness</td>
<td>350 people over course of managed access agreement (21 months)</td>
</tr>
<tr>
<td></td>
<td>PD-L1-positive NSCLC:</td>
<td>Recommended if treatment stopped at 2 years and provided</td>
<td>0.61 QALYs (company)</td>
<td>£44,490 - £61,954/QALY is company’s assumption. NICE view is “majority of plausible”</td>
<td>2,000</td>
</tr>
</tbody>
</table>
## Economics of Innovative Payment Models Compared with Single Pricing of Pharmaceuticals

<table>
<thead>
<tr>
<th>Drug &amp; ID</th>
<th>Description</th>
<th>Treatment Duration</th>
<th>ICERS</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pembrolizumab TA428 (Sep 2017)</strong></td>
<td>In line with commercial access agreement</td>
<td></td>
<td>ICERS are below the range usually considered to be cost-effective</td>
<td></td>
</tr>
<tr>
<td><strong>PD-L1-positive metastatic NSCLC:</strong> <strong>Pembrolizumab TA447 (June 2017)</strong></td>
<td>Recommended for use within CDF (if tumours are PD-L1 positive, treatment stopped at 2 years and conditions of managed access agreement are followed)</td>
<td>1.06 QALYs (company)</td>
<td>£46,083 - £61,557, but this does not include discount for comparator arm treatment which would raise ICER range.</td>
<td>1,500</td>
</tr>
<tr>
<td><strong>Atezolizumab TA520 (May 2018)</strong></td>
<td>Recommended if treatment stopped at 2 years and discount provided in line with patient access scheme</td>
<td>“similar to pembrolizumab”</td>
<td>“most plausible” ICER “within the range usually considered a cost-effective”</td>
<td>6,100</td>
</tr>
<tr>
<td><strong>Squamous cell carcinoma of the head and neck (SCCHN) after platinum-based chemotherapy</strong></td>
<td><strong>Nivolumab TA490</strong></td>
<td>Recommended for use within CDF (if disease progressed within 6 months of chemotherapy, treatment stopped at 2 years and conditions of managed access agreement are followed)</td>
<td>Unknown [QALY estimates redacted from documentation]</td>
<td>£45,000 - £73,600/QALY, “but closer to the upper end of the range”</td>
</tr>
<tr>
<td><strong>Untreated locally advanced or metastatic urothelial cancer when cisplatin is unsuitable</strong></td>
<td><strong>Atezolizumab TA492 (Dec 2017)</strong></td>
<td>Recommended for use within CDF (if conditions of managed access agreement are followed)</td>
<td>Unknown [QALY estimates redacted from documentation]</td>
<td>Based on list price: higher than £95,211/QALY. Based on discount: not disclosed</td>
</tr>
<tr>
<td><strong>Pembrolizumab TA ID1209 (in development)</strong></td>
<td>[expected publication: June 2018, but already recorded in CDF on 27/04/2018]</td>
<td></td>
<td>Based on list price: higher than £95,211/QALY. Based on discount: not disclosed</td>
<td></td>
</tr>
<tr>
<td><strong>Untreated locally advanced or metastatic urothelial cancer after platinum-containing chemotherapy</strong></td>
<td><strong>Pembrolizumab TA519 (Apr 2018)</strong></td>
<td>Recommended for use within CDF (if treatment stopped at 2 years and conditions of managed access agreement are followed)</td>
<td>0.81 QALYs (ERG)</td>
<td>Confident that it would be higher than the ERG’s preferred ICER of £44,504</td>
</tr>
<tr>
<td></td>
<td><strong>Atezolizumab TA ID 1327 (in development)</strong></td>
<td>[expected publication: June 2018, but already recorded in CDF on 17/05/2018]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. The source of QALY gain is from the presentation of evidence in the TA documentation. Where only one estimate is presented, this is because it was noted by the committee to be the most believable scenario. Where the committee does not express a preference, both sources (company base case or external review group (ERG)) are presented. Where all estimates have been redacted from the documentation, we have sought estimates from the literature. Specific estimates of QALY benefit that go into the decision ICER are also sometimes removed (presumably to avoid back-calculation of price) or difficult to pin down given the uncertainty surrounding the multitude of assumptions and considerations of the NICE committee.

2. England, per year unless otherwise stated.
Using information we have from Table 4 and Table 5 on the differential clinical benefit of drugs in different indications, we can provide a generalised illustration of the potential role competition could have in these markets, if there were to be IBP. Below in Figure 5 we provide an illustration of the (simplified) level of benefit in terms of incremental QALYs and the eligible population in England for three PD-1/L1 inhibitor indications: Hodgkin lymphoma, melanoma, and NSCLC. Our interpretation of the data is that:

- Hodgkin lymphoma is the highest value of the three indications with an incremental QALY gain of around 4.5 QALYs and a population size in England of around 50 patients per year;
- melanoma is the medium value indication with an incremental QALY gain of around 1.5 QALYs and a population size in England of around 1000 patients per year;
- NSCLC is the lowest value of the three indications with an incremental QALY gain of around 1 QALY and a population size in England of around 2000 patients per year.

We assume limited competition for Hodgkin lymphoma (although there are two products currently authorised in Europe for Hodgkin lymphoma, only nivolumab has so far been evaluated by NICE for this indication). As shown earlier in Figure 4, there is competition in the other two indications.

Figure 5. Illustration of the impact of competition with IBP

Thus we suggest that IBP is likely to lead to more competition and lower prices than a single price. Of course, as we have noted, this is an empirical issue. If NSCLC was the largest revenue indication (as market forecasts suggest it might be, because of higher patient numbers) then a requirement for a single price may have led to that single price being the price for NSCLC. In this case it may well be that orphan and ultra-orphan indications (such as Hodgkin lymphoma) are less likely to be developed, as if the only price available for a low value (in terms of QALY gain per patient) indication means that revenues may not cover development costs as patient numbers are low. Of course, it would be preferable to present a real world example of indication expansion when
moving to IBP from a single price scenario, but this is difficult when we live in a single price world. We hope, nevertheless, to have demonstrated the principles.

In summary, the consideration of an IBP policy should adopt a market view, not the optimisation of a single product, on the assumption of a single innovator. A balance between the goals of the payers and of industry could be achieved through IBP, when we consider a competitive set of 'indication markets’. IBP could create financial incentives to expand the cost-effective indications of a product, thereby maximizing health gains and, at the same time, allowing competitive forces to ensure optimal pricing in each 'indication market'.

6. DISCUSSION

Moving away from a single price model would allow reimbursement to reflect differential value of a product when used in different settings or circumstances. Value could differ according to disease (e.g. cancer site, tumour type, mutation), disease stage, line of therapy (i.e. sequencing of use), mode of treatment, and whether used alone or in combination with another therapy.

Examples of the form a multiple-price model could take include:

- Differential payment by approved indication (for example Trastuzumab for HER2+ breast cancer and gastric cancer)
- Differential payment by line of therapy or sequencing of use (for example Trastuzumab in early and late stage breast cancer)
- Differential payment by use as a single or combination therapy (for example product used on its own vs in combination with a competitor product)
- Conditional payment based on cumulative treatment volume (for example a cap on payment above a certain total volume)
- Conditional payment based on treatment completion (for example payment is only made if a patient completes their treatment course)
- Episodic (bundled) payment (for example payment for a six-month period that would include all chemotherapy and administration costs)
- Outcomes-based payment agreements

The limited real-life examples of multiple-price models in any form is indicative of the challenges presented by implementing such arrangements. Bach (2014) identifies some of the practical challenges to implementing IBP in the US. Pearson et al. (2017) have done likewise and Sachs, Bagley and Lakdawalla (2018) have set out how one of the legal/regulatory challenges of the Medicaid best-price rule could potentially be managed. Flume et al. (2016) and Towse et al. (2018) have looked at the position in major European countries. As Towse et al. summarise, in the US and Europe, with the possible exception of Italy (where there are product specific registries, albeit with high cost and some compliance issues with clinicians), practical obstacles remain to implementing IBP in all three areas identified: legal or regulatory hurdles, data collection problems, and contractual or financial flow issues.

We propose a two-step approach:

1. Determining clinically what matters and therefore in what ways the value of a treatment might differ.
2. Identifying what data collection activities can capture that value – directly or indirectly. This could be:

(i) directly, measuring patient quality of life or overall survival;

(ii) using a surrogate – for example completion of treatment course as a proxy for treatment benefit;

(iii) using ex ante evidence of clinical value in a particular treatment or clinical pathway and then identifying whether or not the patient took that treatment or followed that clinical pathway.

Practical implementation issues need to be considered alongside any alternative to the current single-price system. At a minimum, data that tracks use by patient is needed, and arbitrage must be impossible. Chapman and Karlsberg Schaffer (2015) find that in the UK, even establishing what a medicine has been used for (matching a prescription with a diagnosis) can be problematic.

Collecting data on the treatment outcomes achieved by patients will increasingly be required. However, proxies for, or surrogate measures of, outcomes will also be essential, for example on patient duration of treatment as a proxy for patient benefit.

Our view is that introduction of adequate data collection to make IBP work is feasible and, once up and running, data gathering and use to support IBP can be improved. Research into the evidence on the relationship between surrogate measures and final outcome measures should be prioritised.

Beyond the practical challenges, how prices are set (whether in a uniform or IBP setting) has important ramifications and must be considered carefully. In our analysis we assumed that an appropriate cost-effectiveness threshold, which is “known”, can be used to determine price at the indication-level. In some countries, such as England, NICE is transparent in its decision criteria and the cost-effectiveness threshold on which it bases value-for-money decisions. However, the “actual” threshold, which must subsume the opportunity cost of NHS spend at the margin, is notoriously difficult to estimate in practice. If an inappropriate cost-effectiveness threshold is used to determine an indication-specific value-based price, then benefits (in terms of health outcomes) arising from the adoption of innovative drugs could be outweighed by the benefits forgone by disinvestments elsewhere in the health system.

Within IBP, a particular challenge with arguably the most scope for further research and innovative solutions is the issue of differential payments for combination therapies. An analogy can be drawn with how airlines set a price for connecting flights, with different airlines collecting a portion of the total price, or in the telecom industry where consumers’ value of an entertainment channel such as Netflix is conditional on the quality and price of broadband access. Attributing value to the composite elements of a drug combination therapy is likely to be even more complicated, given the interdependence of their effectiveness, and the basis upon which prices are set. The recognised issue of ‘not cost-effective at prize zero’, as discussed in the introduction, is inefficient; a company producing medicine A would sell greater volumes if a further combination medicine B were adopted, and therefore should be willing to concede some margin of value to support medicine B’s introduction. The question is how to attribute the extra value generated. This is especially problematic in cases where combination medicines are produced by different companies, where options could include negotiations between companies, but any suggestion of collusive behaviour on pricing between companies will risk investigation by antitrust bodies.
The notion of differential pricing based on the different demand elasticities is not novel, and has been discussed in relation to the pharmaceutical industry most recently by the Expert Panel convened by the European Commission (EXPH, 2018).\textsuperscript{14} We have set out what we believe to be the main considerations for understanding the implications of a move away from a ‘single price’ model for the reimbursement of medicines. The goal of any health system should be to expand access to and incentivise the development of treatments that can offer important benefits to patients at a cost-effective price. IBP has many operational challenges but, if implemented correctly, could support this goal.

7. **CONCLUSION**

The value of a medicine can vary substantially according to its context of use. Imposing a single, uniform price means that, where a drug is used in multiple contexts, the relationship between price and value may differ. If prices – the key mechanism for incentivising innovation – reflect value generated, then it can be argued that prices should be allowed to differ to reflect these different values. However, pricing and reimbursement systems are not well equipped to handle these variations.

Economic theory indicates that – in the short term – indication-based pricing can improve overall welfare if it means greater patient access, but payers may (or may not) be worse off. However, the potential longer-term (dynamic) effects of IBP are sometimes neglected - optimised incentives for R&D and potential for increased price competition at the indication-level, driving down prices and delivering better value to the health system.

---

\textsuperscript{14} According to the Expert Panel, in order to ensure that differential pricing is welfare improving, the average price weighted across groups of users (indications) should be lower than the previous single price. However this is not the definition linked to economic efficiency that we set out in this paper. For example, a high value indication for a small patient group may not be launched under a single price rule, but would with IBP. Average price would rise but more patients would receive cost-effective care.
REFERENCES


Economics of Innovative Payment Models Compared with Single Pricing of Pharmaceuticals


