

# The Debate on Indication-Based Pricing in the U.S. and Five Major European Countries

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and Bernarda Zamora

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## Funding and Acknowledgements

This study was commissioned and funded by AstraZeneca.

Karla Hernandez Villa-Fuerte, Francois Maignon, and Margherita Neri undertook the research on Germany, France, and Italy respectively. Any errors or omissions remain the exclusive responsibility of the authors.

### **Please cite this report as:**

Towse, A., Cole, A., and Zamora, B. (2018). The Debate on Indication-Based Pricing in the U.S. and Five Major European Countries. OHE Consulting Report, London: Office of Health Economics. Available at: <https://www.ohe.org/publications/debate-indication-based-pricing-us-and-five-major-european-countries>

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## 1. INTRODUCTION

### 1.1 The purpose of the report

This report sets out the results of two pieces of work. First, we identify and summarise a number of key published papers in the area of Indication-Based Pricing (IBP) in order to set out the current state of debate and understanding around the issue. Then, we consider the possibilities for undertaking IBP in six countries – France, Germany, Italy, Spain, UK and US – exploring the formal regulatory framework. Finally, we set out the key issues to be debated in order to take IBP forwards.

The purpose of this report is to leave the reader with a better understanding of the state of the debate on the merits and demerits of moving from a price for a drug to a price for each use of a drug. Such a move is predicated on an assumption that price should reflect incremental value. By incremental value we mean the additional health and health-related gain delivered to the patient over and above the current standard of care. We take this approach as a given, although it is not accepted by all stakeholders, some of whom argue for cost-based pricing. The case for and against an alternative perspective to value-based pricing is not addressed in this paper.

We use the term Indication-Based pricing (IBP) throughout the report except where the papers we report use a different term. Other terms that are used include multi-indication pricing (MIP) and indication-specific pricing (ISP).

### 1.2 Issues that arise in considering the pros and cons of a move to IBP

Issues arising tend to centre on two aspects:

**Who benefits and who loses?** Charging different prices for different indications is seen by economists as a way of increasing the revenues to the manufacturer from a product. It is a form of price discrimination. However, it may also provide opportunities for payers to get more competition for some indications, and so lower prices. This could arise if some indications have competing drugs available but others do not. If a drug has to address all indications, then only one will do. If drugs are priced by indication, then having products competing for some indications may reduce prices. Irrespective of the impact on overall revenues, economists would expect two additional benefits from IBP:

- there is a short run benefit, in that more patients get access to a drug. If companies have to have a uniform price, they may choose a high price, leading to payers restricting use to indications with a higher value. IBP enables them to also have a lower price for a lower value indication, so giving further patient access to that treatment.
- there is a long run benefit, in that the correct signals are sent for future R&D investment. Revenues reflect the incremental benefits to patients from all of the indications, and companies will invest in molecules that bring the most benefits, irrespective of the number of indications.

**Can it be implemented in practice at an affordable cost?** The challenge for many health systems is that, even if it is accepted as a model that benefits patients, there are obstacles to achieving IBP. These comprise one or more of:

- legal or regulatory hurdles. For example, a public payer is only allowed to set one price for a drug, or there is a link between the discounts given in the private sector and the price that must be offered to the public sector;
- data collection problems. It may be difficult to identify the use to which a product has been put. It may only be possible to do this by incurring significant additional cost.
- contractual or financial flow issues. In most systems the manufacturer does not sell the drug directly to the care providing institution or clinician prescribing the drug. Intermediaries such as wholesalers are usually involved. The payer who agrees the price with the manufacturer may be reimbursing the care provider who in turn pays the wholesaler who pays the manufacturer. Even where the data exists at the provider level, ensuring the correct payments reach the provider and the manufacturer may not be straight forward.

There are also a number of additional issues:

- whether an IBP uses:
  - (i) Evidence-based prices, based on expected value using RCT and other evidence to identify ex ante what additional benefits a drug may bring in a particular indication or
  - (ii) Outcomes-based reimbursement, based on realised value, i.e. identifying ex post what value was delivered to a patient. Outcomes-based agreements in turn can be at the individual patient level response, i.e. payment is triggered if a patient hits a particular pre-agreed target outcome, or at a patient population level, i.e. outcomes data is pooled to find an average response which determines the price paid. The main challenge with outcomes based agreements is ensuring they can practically be implemented.
- how IBP is operationalised? IBP can be delivered in one of four ways:
  - (i) different brand names or delivery / dosage forms which separate the product according to the indication for which it is used. Significant investment may be needed to achieve this, and there is still a risk of arbitrage if there are large price differences between the different indications;
  - (ii) an average weighted price or a “blended” price reflecting the prices appropriate to the different indications, and the volumes associated with each indication. Volume data and price will need to be periodically updated. One challenge to this approach is that the prescriber and budget holder faces an average price and not the price that is relevant for the indication for which they plan to use the product.
  - (iii) differential discounts from a single list price. The list price is set at the level that is appropriate for the highest value indication and use of the product in lower value indications attracts discounts to bring the net price or transaction price for each indication in line with the value of the indication. Use needs to be tracked and payment / reimbursement mechanisms implemented.

(iv) outcomes-based payments. As we have indicated these can be difficult to negotiate and implement. In addition to use tracking and having payment / reimbursement mechanisms in place, outcomes to track need to be agreed and whether patients achieve them needs to be measured.

### **1.3 Structure of the Report**

The report is structured as follows:

- Section 2 identifies and summarises a number of key published papers in the area;
- Section 3 considers the possibilities for undertaking IBP in six countries;
- Section 4 briefly summarises the issues to be debated in order to take IBP forwards.

## 2. KEY PAPERS

The search strategy is set out in Section 2.1 and the 11 papers are individually summarised in Sections 2.2 to 2.12.

### 2.1 Search strategy for key papers

The remit was to identify key papers that illustrate the issues around IBP and could contribute to an understanding of the debate about the potential value of using IBP. The search strategy is set out in Table 1 and the results are set out in Figure 1. We identified 11 papers which, together, give an overview of the current debate on the use of IBP.

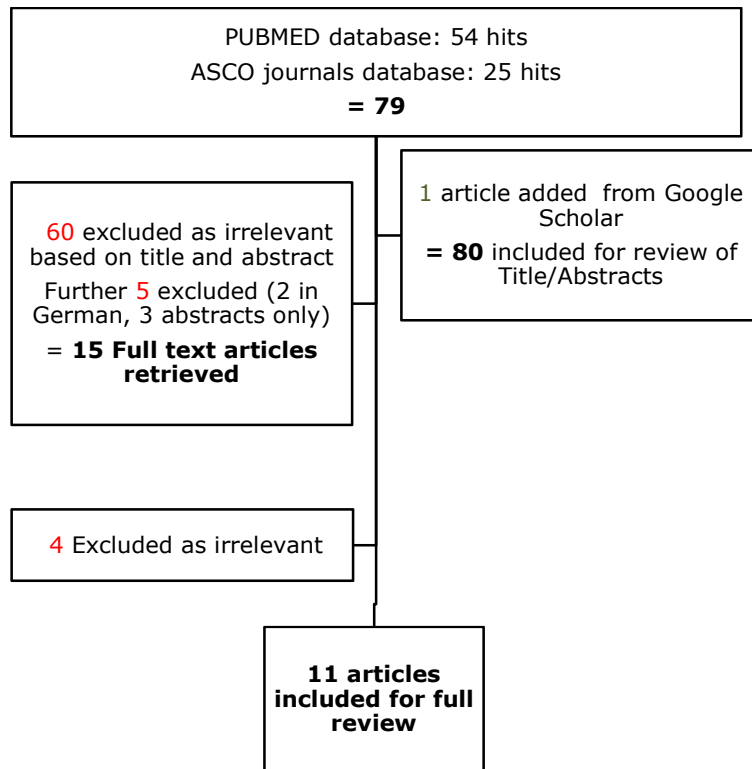
**Table 1: Search Strategy**

Search strategy	Query	Number of results	Number selected (based on title/abstract)
PUBMED main search	(indication-specific[All Fields] OR indication-based[All Fields] OR multi-indication[All Fields]) AND (value[All Fields] OR ("costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields] OR "pricing"[All Fields]) OR ("commerce"[MeSH Terms] OR "commerce"[All Fields] OR "price"[All Fields]) OR ("costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields] OR "costs"[All Fields]) OR ("economics"[Subheading] OR "economics"[All Fields] OR "cost"[All Fields] OR "costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields]) OR ("cost-benefit analysis"[MeSH Terms] OR ("cost-benefit"[All Fields] AND "analysis"[All Fields]) OR "cost-benefit analysis"[All Fields] OR ("cost"[All Fields] AND "effectiveness"[All Fields]) OR "cost effectiveness"[All Fields]))	54	11, of which 2 in German
ASCO main search	"indication-based/ indication-specific/ multi-indication/ pricing"	25	8, of which 2 only abstracts

In addition, we performed cross-comparisons of citations and new searches were performed in Google Scholar, to ensure that we did not miss any key papers: we obtained one further paper from this exercise.



**Figure 1: Numbers of Articles Identified**



## 2.2 Yeung, Meng and Carlson (2017)

Yeung K, Li M, Carlson JJ. Using Performance-Based Risk-Sharing Arrangements to Address Uncertainty in Indication-Based Pricing. *J Manag Care Spec Pharm.* 2017; 3(10):1010-1015

The authors argue that IBP “allows payers to consistently pay for value across indications” but that “a limitation of IBP as originally conceived is that efficacy estimates are typically based on clinical trial data, which may differ from real-world effectiveness.” Their paper seeks to “illustrate the potential of an outcomes guarantee to achieve indication-based prices aligned with real-world value..” as opposed to the “expected value” derived from RCT data. Using trastuzumab indications for metastatic breast cancer and for advanced gastric cancer, they construct a “stylised example.” They adjust an average current uniform sale price before IBP of \$9.17 per mg to achieve a target ICER of \$150,000 per QALY under the two IBP scenarios.

For the *expected-value* scenario based on efficacy data from pivotal trials, trastuzumab was calculated to achieve \$3.50 per mg for breast cancer (BC) and \$0.93 per mg for gastric cancer (GC). For the simulated *outcomes guarantee* scenario based on data from observational cohorts, trastuzumab was calculated to achieve \$8.66 for BC and \$0.20 for GC. Incremental observed overall survival over expected increased from 4.8 months for MBC to 15.1 months and for GC from 2.7 months to 5.1 months, partially offset in the cost-per-QALY calculation by longer treatment periods as a result of longer survival. Note that none of the calculations suggest that trastuzumab is cost-effective in either of these indications at its current \$9.17 per mg price assuming a target ICER of \$150,000 per QALY. However, the authors make the point that “if a health plan had used an expected value IBP, it would have overpaid in gastric cancer and underpaid in breast cancer according to the actual value that was realised.” It may seem odd that the price paid for the drug’s use in GC should go down when patients are observed to live longer. This almost certainly reflects the fact that the other drugs in the extended treatment regimen are so expensive that the reward available for trastuzumab goes down when it extends life at a threshold of \$150,000 per QALY.

The authors conclude that “IBP should not be perceived primarily as a method for reducing health care expenditures outright (few health care innovations do) but primarily as a method of aligning payment with value.” They note the R&D incentive benefits of doing this “IBP can encourage development for high value-indication populations, even if the population is relatively small.” They note some of practical challenges to outcomes guarantee models but note the success of the Italian Medicines Agency (AIFA) in doing this.

## 2.3 Pearson et al. (2017)

Pearson SD, Dreitlein WB, Henshall C, Towse A. Indication-specific pricing of pharmaceuticals in the US healthcare system. *J Comp Eff Res.* 2017 Jul; 6(5):397-404.

The authors<sup>1</sup> note that “two national pharmacy benefit managers, Express Scripts and CVS Caremark will launch an ISP initiative in 2016 for certain cancer drugs; and the announcement by the Centers for Medicare and Medicaid Services (CMS) that it will

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<sup>1</sup> Note that Towse, a co-author of the current report, is also a co-author of this paper.

implement a Medicare Part B Demonstration Project which aims to change the way provider-administered drugs are reimbursed and includes ISP as a value-based strategy that could be used by payers.” They note that comparative effectiveness research is an important input into ISP. The authors are clear that use of ISP to better align drug price with clinical value will be of value to the US health care system, if it can be done.

They also note the possibility of launching separate brands to enable ISP, but argue that “for similar indications, however, such as treatment of different forms of cancer, multiple brands may be too burdensome or contribute unnecessary confusion.” A weighted average price is possible with retrospective adjustments to reflect actual patient volumes for the different indications. However “it may be best suited for organisations with robust data capabilities.”

They set out a number of challenges to the implementation of IBP in the US and potential solutions. These are summarised in Table 1 from the paper, set out below.

Table 1. Summary of challenges and potential solutions for indication-specific pricing programs in the US market.	
Challenges	Potential solutions
Insufficient data systems and analytic capabilities	Use claims data and improve data systems to capture the indication for each prescription use
Limitations of drug formulary tier structure and difficulty linking ISP to differential patient cost-sharing	Select drugs for which pricing can vary by indication but formulary tier can remain consistent
Potential misalignment with Medicare provider reimbursement for office-administered drugs	Focus ISP pilots on oral drugs with indications across different conditions and use a single weighted-average price approach Request that federal policy makers include ISP in Medicare Demonstration projects
Unintended pricing effects related to Medicaid best price provisions	Focus ISP pilots on oral drugs with indications across different conditions and use a single weighted-average price approach Request that federal policy makers include ISP in Medicare Demonstration projects that include exemptions from Medicare and Medicaid pricing provisions Request changes to Medicaid best price provisions so that best prices are linked to specific indications
Restrictions on negotiations related to off-label indications	Select drugs for ISP that have minimal off-label use, apply price adjustments only to labeled indications, and use a weighted-average approach to ISP
Anti-kickback statutes create legal concerns	Both payers and manufacturers should be mindful of anti-kickback laws forbidding certain kinds of contractual promotion of products that are reimbursable by federal healthcare programs
ISP: Indication-specific pricing	

Source: Pearson et al. (2017). Reproduced with permission from Future Medicine Ltd.

They conclude that ISP has potential to support efforts “for better patient access to innovative medicines at prices that achieve the twin goals of affordable health care system and a sustainable business model.” However, it was “but one of many possible policy tools...payers were clear that ISP, by itself, does not meet challenges to affordability. ” They note that “Manufacturers, although encouraged by successful ISP contracts in non-US markets, were also realistic in acknowledging the many barriers to

this approach in the US. ..Many will be watching how ISP pilots undertaken by Express Scripts and CVS Caremark will fare...”

## 2.4 Chandra and Garthwaite (2017)

Chandra A, Garthwaite C. The Economics of Indication-Based Drug Pricing. *N Engl J Med*. 2017 Jul 13; 377(2):103-106.

This paper argues 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”. The authors argue this is not true by constructing two examples which both show prices for high value indications increasing as a result of introducing IBP.

However, the authors do not explain that this arises from the fact that they have constructed the examples as ones in which the profit maximizing uniform price is *not* to charge the price of the highest value indication. In one scenario the profit maximizing uniform price is to charge the price of the lowest value indication because the volume of sales is so high relative to the higher value indications such that it is the most profitable market. In the other case the profit maximizing price is to set price equal to the value of the middle value indication. By definition, in these circumstances allowing IBP will lead to a higher price for the high-value indication.

Chandra and Garthwaite recognize that IBP “expands access” but argue that “the same access-expanding pricing flexibility also allows manufacturers to increase prices for high-value indications.” This statement is correct, 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 manufacturers to seek to use “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.

## 2.5 Sachs, Bagley & Lakdawalla (2017):

Sachs R, Bagley N, Lakdawalla DN. Innovative Contracting for Pharmaceuticals and Medicaid's Best-Price Rule. *J Health Polit Policy Law*. 2017 Sep 28.

The authors note a number of obstacles to “sever the link between sales volume and revenue” including legal barriers, of which “Medicaid’s best-price rule may be the pharmaceutical industry’s most commonly invoked objection.” Under novel pricing models “manufacturers may charge less when their drugs perform poorly – implying that the drug’s “best price” is quite low.” However, they argue that no article has examined the rule in detail.

“Medicaid is entitled to a minimum rebate of 23.1 percent off the average manufacturer price. However, if the lowest price available from the manufacturer is lower even than the post-rebate price, Medicaid is entitled to that “best price””. They note that prices charged to the Veterans Administration or through Medicare Part D including Medicare Advantage plans are exempt. Moreover, the rule is not triggered by discounts that are less than 23.1 per cent. “The rule is also more likely to deter or reduce discounts on drugs with large Medicaid-eligible populations.”

They put forward possible solutions including:

1. companies using “weighted average pricing for multiple indications, rather than setting an individual price for each indication.”

2. companies seeking a separate National Drug Code (NDC) for each indication. However, this is expensive – in effect creating a separate brand.

3. CMS defining a “drug” as an “indication”, which the authors think may be legally possible and consistent with FDA definitions.

They find that outcomes-based pricing presents the biggest challenge as there is no difference in indication, only in patient response. Solutions to this problem could include:

- Congress excluding these from the “best-price” rule; and
- rebates for non-performance being linked across populations “instead of granting a rebate if a drug fails to work for a particular patient.” This is another form of blended average price.

“Manufacturers could further cap the amount of any population-wide rebate, thus setting a floor on the possible discount.” CMS could perhaps state that “best price must be determined on a unit basis” so requiring use of a weighted average price. CMS could also offer guidance to companies as to how to calculate “average manufacturer price” to reduce the risk of a miscalculation leading to penalties.

Finally, the authors note that the Center for Medicare and Medicaid Innovation (CMMI), set up by the Affordable Care Act, could potentially relax the best price rule for drugs purchased through Medicare Parts A and B if it determines that such an approach might reduce expenditures or increase quality. CMMI has indicated a wish to experiment with indication-based and outcome-based pricing for Medicare. This would not however impact on private sector arrangements.

## 2.6 Hui et al. (2017)

Hui L, von Keudell G, Wang R, Zeidan AM, Gore SD, Ma X, Davidoff AJ, Huntington SF. Cost-effectiveness analysis of consolidation with brentuximab vedotin for high-risk Hodgkin lymphoma after autologous stem cell transplantation. *Cancer*. 2017 Oct 1;123(19):3763-3771.

This paper presents a theoretical example of how IBP could facilitate expansion into new indications. The authors develop a markov decision-analytic model of the cost-effectiveness of brentuximab vedotin (BV) in different treatment indications.

BV is usually used as a salvage therapy for high-risk Hodgkin lymphoma (HL) after autologous stem cell transplantation (ASCT), an indication for which it is cost-effective. The authors present the cost-effectiveness of BV when used as a consolidation therapy (i.e. provided routinely after ASCT). BV improves QALY gain, but at a high cost (“the ICER for BV consolidation compared with active surveillance was estimated at \$148,664/QALY”). The authors assume “a willingness to pay threshold of \$100,000 per QALY gained.” They find that “under indication-specific pricing, BV in the consolidation setting would be priced lower than BV used for post-ASCT salvage; ultimately our model indicated that price reductions for BV in the consolidative setting from 18%-38% produced more reasonable ICERs of \$100,000 per QALY and \$50,000 per QALY respectively.” CV as consolidation therapy would be cost-effective. They conclude that

“value-based and indication-specific pricing has the potential to align drug prices with their underlying clinical utility and continue to reward highly effective cancer therapy.”

## 2.7 Bradley (2017)

Bradley, J. (2017) Cancer, Financial Burden, and Medicare Beneficiaries. *Journal of Clinical Oncology* 35, no. 22 (August 2017) 2461-2462.

IBP is discussed as a proposed Medicare reform to counteract the high level of cancer drug prices. The Medicare drug coverage has two parts: the Part B program provides payments for drugs administered in a physician’s office or outpatient clinic; the Part D covers prescription drugs dispensed in pharmacies.

“In the absence of altering price negotiation and mandatory coverage policies, the Centers for Medicare and Medicaid Services proposed reforms to counteract high prescription drug prices.” Reforms proposed include “incentivizing best clinical care (meaning choosing lower-cost, clinically equivalent or better treatment options), indication-based pricing, reference pricing, and risk sharing on the basis of outcomes. A common feature of the reforms proposed is to shift the pressure to reduce costs to physicians, by asking them to make value-based prescribing decisions.” The authors suggest that “a much more accelerated effort to bring more evidence about comparative cost-effectiveness of alternative treatments to providers and patients is needed. Without this evidence the Part D reforms will not have the intended reduction on prescribing low-value therapies, but instead, may result in other unintended consequences that negatively affect patients.”

## 2.8 Bach (2016)

Bach, P.B. Walking the Tightrope Between Treatment Efficacy and Price. *Journal of Clinical Oncology*. 2016; 34(9): 889-891.

The paper discusses a paper from Durkee et al. (2016) on how to handle the pricing of pertuzumab and, by extension, of highly effective (but not cost-effective) cancer medicines in the metastatic setting. Bach notes the authors cite “commonly banded-about thresholds of \$50,000 per quality-adjusted life year (QALY) for cost-effectiveness and an alternative threshold of three times the gross domestic product per capita, which is currently approximately \$160,000 per QALY” but find that “these thresholds have little bearing on much of anything.” The National Comprehensive Cancer Network (NCCN) recommends the use of pertuzumab due to high clinical effectiveness. Bach asks “How did we get ourselves into a situation where a highly effective, new treatment like pertuzumab in the metastatic setting can cost so much that the cost per QALY approaches \$1 million?”

He points to “the paradox that highly expensive pertuzumab costs the same in adjuvant and metastatic settings although its efficacy is so different in each.” He reiterates the case for “indication specific pricing.” He also makes the case for “relative, not absolute” benefit, i.e. “a month of life gained for someone with a life expectancy of a few months has higher value than a month gained for someone with a life expectancy of several years.”

## 2.9 Flume et al. (2016)

Flume M, Bardou M, Capri S, Sola-Morales O, Cunningham D, Levin L-A, et al. Feasibility and attractiveness of indication value-based pricing in key EU countries. *Journal of Market Access & Health Policy*. 2016; 4(1):30970.

The authors contrast interest in implementing IBP in the US as with Europe, where “no major country has experimented with IBP or is seriously discussing it.” In the case of the US, they cite Bach and Express Scripts as promoting IBP to get better value by linking cost to clinical benefit.

They note the risk without IBP that “products may never be developed in an indication for which they could represent a major therapeutic advance, simply because this would lead to lower price than that achieved or achievable in other indications.” They hypothesise that in this situation “the product will likely be used off-label at a much higher price than it would deserve.” They also note that “payment by results” “do not allow payers to fully capture the difference in value found across indications.”

The paper finds that “both use of and interest in IBP are limited in Europe”. IBP could develop in the UK (although this reflects the authors’ view as they recognise that “in theory there is no option for differential price per indication, at least from drugs that are reviewed by NICE”), and Sweden (although “in the current reimbursement system of prescription drugs, there is no role for IBP...”). Even in Italy, where AIFA “de facto obtains different net prices for different indications... through managed entry agreements ..[which] ..often include pay for performance beyond discounting and price volume agreement” it may not be “true” IBP as “differences in price do not necessarily represent differences in value”. No prospects are seen for changes in the current price setting system in France (where there is “an average price that already represents the value across indications weighted by expected volumes”) or Germany (where there is “a single price representing a volume-weighted average price per indication”), and Spain (where it “has no real advocates, probably because of the legal framework”) to accommodate IBP. As a result they expect to see:

- “1) Continued use of a volume-weighted average price..in France and Germany mostly.
- 2) Increased or continued use of managed entry agreements in Italy, the United Kingdom, and Sweden..net price may depend on the indication but without full correlation to value.”

## 2.10 Mestre-Ferrandiz et al. (2015)

Mestre-Ferrandiz, J., Towse, A., Dellamano, R., and Pistollato, M. *Multi-indication Pricing: Pros, Cons and Applicability to the UK*. Seminar Briefing 56. Office of Health Economics. 2015.

The authors<sup>2</sup> note estimates that, by 2020, 75% of major cancer medicines will be for multiple indications. They argue that “a single, uniform, price across indications has negative consequences.” These are “restricted access” with some lower value indications not being reimbursed if the uniform price is based on a high value indication, and discouraging the development of high value indications if the uniform price is based on a

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<sup>2</sup> Note that Towse, a co-author of the current report, is also a co-author of this paper.

low value indication. They note possible solutions include having the uniform price be a “blended price” of high and low volume uses “weighted by expected patient volumes.” However, they point out that a blended price risks local budget holders not facing the correct price when they make a decision about which treatment to give a patient. They also note that separate brands can be created, but that if the price difference is large and the dose forms are similar, this may not be possible. The incentives for arbitrage may be too large. They give the example of alemtuzumab, where the manufacturer withdrew the indication in onco-haematology to protect its pricing of the product in a higher value (more health gain per patient) multiple sclerosis indication.

The authors argue that IBP should be explored as an efficient solution to the challenges of different value in different uses for products. They note the success of the Italian Agency, AIFA, in implementing discounts by indication for some oncology drugs. The main changes needed in the UK NHS to implement IBP as a differential net price (i.e. list price minus discount) per indication are to:

- use current data capabilities, notably the potential for the Systematic Anti-Cancer Therapy (SACT) dataset to track use per indication at hospital level, and extend these to prescription systems including those used in community pharmacies.
- introduce flexible pricing models other than the current Patient Access Schemes (PAS) discounts which are only applied at a medicine level, not an indication level.

The authors note that the Department of Health is currently unlikely to agree to multiple PAS schemes in England for a single medicine with several indications. This is partly to do with the ability of the NHS to manage the complexity of the arrangements needed, but the authors also show in an illustrative example that, whilst there are scenarios in which new indications are not developed under uniform pricing there are also scenarios in which they are, and in which a uniform price means payer expenditure to achieve the health gain is lower than in the case of IBP.

## 2.11 Bach (2014)

Bach PB. Indication-specific pricing for cancer drugs. *JAMA*. 2014 Oct 22-29;312(16):1629-30.

This paper seeks to explore “what changes in drug pricing might result from ...moving towards paying for drugs at prices that better match the benefits they will deliver..”

By describing the survival gains and costs associated with different indications for four drugs, Bach demonstrates the impact of IBP obtained by basing price on a value threshold of \$150,000 per life year gained, and by anchoring price to that of the highest value indication. The results are set out in the Table below. We can see that differences in cost per year of life gained arise from both differences in median survival gain and in median treatment duration. The final three columns of the paper are key. They compare current monthly price of treatment with (i) monthly price using the current monthly price for the highest value treatment (i.e. that offering the greatest median survival gain) as an anchor and (ii) a theoretical monthly price using a cost per life year gained threshold value of \$150,000.

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.”

We can note that 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 currently monthly price. This comparison is, presumably, one of the drivers for Chandra and Garthwaite to write their paper. Perhaps of more interest is the use of the \$150,000 as a threshold to generate value-based prices. We see four of the nine prices rise and five of the nine prices fall. If \$150,000 is the appropriate threshold and these nine indications are typical then his analysis does not suggest US oncology prices are too high per se, but rather that they are very inefficient, with price in any particular indication bearing little relation to value.

Table. Comparison of Incremental Survival Improvement and Cost of Treatment for Several Cancer Drugs Across Different Approved Indications, Plus a Hypothetical Scenario in Which Price Is Set per Indication to Yield the Same Total Treatment Cost per Median Benefit (Indication-Specific Pricing)<sup>a</sup>

Drug and Indication	2014 US\$						
	Median Survival Gain, y <sup>b</sup>	Typical Treatment Duration, mo	Typical Treatment Cost <sup>c</sup>	Cost per Year of Life Gained (Median)	Current Monthly Price	Monthly Price Based on Indication With Most Value <sup>d</sup>	Monthly Price Based on Achieving Value of \$150 000 per Year of Life Gained
<b>nab-Paclitaxel (Abraxane)</b>							
Metastatic breast cancer	0.18 <sup>5</sup>	4.16 <sup>7</sup>	25 990	145 288	6255	6255	6458
Non-small-cell lung cancer	0.08	4.16	29 988	399 840	7217	2622	2708
Pancreatic cancer	0.15	4.00	27 065	180 433	6766	5448	5625
<b>Erlotinib (Tarceva)</b>							
First line treatment of metastatic non small-cell lung cancer	0.28	8.20	51 596	182 104	6292	6292	5183
Pancreatic cancer	0.03	3.90 <sup>6</sup>	21 696	650 885	5563	1556	1282
<b>Cetuximab (Erbiximab)</b>							
Locally advanced squamous cell carcinoma of the head and neck	1.64	1.39 <sup>7</sup>	14 292	8706	10 319	10 319	177 798
First-line treatment of recurrent or metastatic squamous cell carcinoma of the head and neck	0.23	4.16	42 875	190 556	10 319	471	8123
<b>Trastuzumab (Herceptin)</b>							
Adjuvant treatment of breast cancer	1.99 <sup>8</sup>	12.0	64 941	32 645	5412	5412	24 867
Metastatic breast cancer	0.40	10.0	54 118	135 294	5412	905	6000

<sup>a</sup> Data on survival gain and median treatment duration from the FDA label<sup>9</sup> and publications accompanying those studies.

<sup>c</sup> Only includes direct cost of the drug, as per <http://www.mskcc.org/research/health-policy-outcomes/cost-drugs>.

<sup>b</sup> As per FDA package inserts or studies summarized therein (unless otherwise noted). Package inserts are available via [drugs@FDA](mailto:drugs@FDA).<sup>9</sup>

<sup>d</sup> Assumes the price of the drug in its most effective setting is the appropriate reference price.

Source: Bach (2014). Reproduced with permission from Journal of Clinical Oncology. 2014. 34(9): 889-891. Copyright© (2014) American Medical Association. All rights reserved.

Bach also addresses some of the practical challenges. Oral treatments are distributed via pharmacies and “manufacturers do not know which patients are receiving their drugs for which indications. Infusion treatments are administered in a physician’s office and paid for “at a set price per milligram in a process not linked with the intended indication.” Both arrangements could, he argues, be changed. Prices could be agreed by indication and “ordering, prescribing, price tracking, and reimbursement would be based on the drug with its indication, rather than the drug alone.” He concludes it is “technically feasible” but notes that political challenges “may be more substantial”, although he does not elaborate on that statement. Finally he notes that the technical moves to implement IBP would “create an infrastructure for real-world outcomes analysis as relevant information about indication could be captured as part of the clinician’s workflow.”

There was a letter response to this paper from Andrea Messori, Mauro De Rosa, Luca Pani. Alternative Pricing Strategies for Cancer Drugs. JAMA. 2015;313(8):857.

doi:10.1001/jama.2014.17814 – available at  
<http://jamanetwork.com/journals/jama/article-abstract/2130306> .

Messori et al. describes the Italian experience where payment by outcomes is achieved through the collection of data about each individual patient including use by indication, and associated outcome. Value-based reimbursement is operationalised through a system of pay-backs when a drug is not effective.

Bach replied in:

Peter B. Bach. Alternative Pricing Strategies for Cancer Drugs—Reply. *JAMA*. 2015; 313(8):858-858. doi: 10.1001/jama.2014.17817.

He said that whilst both approaches seek to pay for value, his proposal is based on setting differential prices based on evidence around average effect in a particular patient group, rather than tracking actual outcomes on a per patient basis. He argued that the second option (as used in Italy) could be more difficult to operationalise in the US and also would present higher uncertainty for industry.

## 2.12 Garrison and Veenstra (2010)

Garrison LP Jr, Veenstra DL. The economic value of innovative treatments over the product life cycle: the case of targeted trastuzumab therapy for breast cancer. *Value Health*. 2009 Nov-Dec; 12(8):1118-23.

The authors note that if a unitary price is set for a molecule based on its “initial indication, manufacturers will set the price by which cost-effectiveness is judged.” However, “the aggregate economic value delivered by a new medicine will ultimately be determined by the different types and numbers of patients using it over its life cycle, and this may include totally new indications (often at different doses).” They note that differences in value may occur particularly when an oncology drug is approved first for a metastatic indication and then for an adjuvant indication. Using the example of Herceptin (trastuzimab) they estimate that the ICER in the US for metastatic breast cancer (MBC) was \$85,676 per QALY and for the treatment of early breast cancer (EBC) was \$26,417. Using estimates of patient numbers for these two indications they estimate an overall life cycle ICER of \$35,590 per QALY. They contrast this with estimates of societal willingness to pay for QALYs in the US ranging from \$50,000 to \$150,000 indicating that the innovator is getting between 24% and 71% of the economic value of the drug, depending on the threshold used. They conclude that “Reimbursement systems that do not account for changing value across indications or over time may produce suboptimal long-term societal outcomes.” If companies have to set price based on the initial indication and it is a relatively low value one, then fewer socially valuable drugs will get developed as the rewards to the innovator are less than economic value. They note that their analysis ignores factors such as off-label use that may increase the economic value and competition which may reduce it. They do not indicate how much of the economic value it is appropriate for the innovator to have. The model appears to cover the patent period as there is no consideration of the post-patent expiry biosimilar period as the overall life-cycle ICER is based on the initial MBC indication, approved in 1998, and a 10-year horizon after the approval of the adjuvant EBC indication in 2006.

### **3 INDICATION BASED PRICING IN EUROPE AND THE U.S.**

#### **3.1 The potential for IBP in France**

The CEPS negotiates the price of new medicines according to a framework agreement negotiated with the French association of pharmaceutical industry (les entreprises du médicament, LEEM). The latest version of this agreement, currently used for these price negotiations, is the "Accord cadre du 31/12/2015 entre le comité économique des produits de santé et les entreprises du médicament" (CEPS and LEEM). Price negotiations depend on several factors. Firstly, they depend on the ASMR granted by the HAS to the new technology. When a product has several indications, ASMR ratings are given separately for each indication and an average volume weighted price is negotiated. Secondly, medicinal products which provide high ASMRs (ASMR I-III) are guaranteed a certain price for their medicine compared with the prices in four reference EU countries: Germany, Italy, Spain and the United Kingdom. This price is guaranteed for a duration of five years following the date of official marketing. The duration of the price guarantee can be extended by 1 year for products which have obtained an ASMR I-III for an extension of indication. Therefore, the added therapeutic value of an extension of indication allows higher prices to be maintained for longer periods.

New innovative and expensive medicines are mostly used in a hospital setting. There are possibilities for a differential reimbursement per indication of hospital medicines. If they provide an important added therapeutic value (ASMR I-III) they benefit from a preferential reimbursement mechanism in French hospitals. The legal basis for this is the "liste en sus" i.e. a reimbursement in accordance with Article L.162-22-7 of the social security code. A new decree establishing the procedure to include or remove medicines from the L.162-22-7 list was published last year on 24 March 2016. The "liste en sus" is a list of medicines which are provided and reimbursed as part of hospital costs (T2A or groups homogènes de séjour) GHS for given indications, i.e. not all the indications of a medicine will be listed in this list, only those that provide an important added therapeutic value characterised by the ASMR. Before 2014 a medicinal product was included on this list for all of its indications. Since 2014, only indications associated with an important ASMR are included on the list, and only then when the budget impact associated with the use of this medicine in that indication is high, opening access to this separate funding arrangement. The price of "liste en sus" medicines are negotiated by the CEPS.

Although there is currently no provision in the French social security law allowing for different prices for the same medicinal product for different therapeutic indications, both (i) the extension of the period of a price premium for new indications with important ASMR and (ii) the "liste en sus" arrangements for indications of a particular status can provide opportunities to increase revenues for medicines with important added therapeutic value and, conversely, exclude from reimbursement low-value indications.

Another way to achieve an indication based price, sometimes used in France, is via the authorisation of a given active substance under different trade names.

A report to the French government by the constitutional consultative assembly Economic, Social and Environmental Council put forward several proposals to improve the current system of pricing and reimbursement of innovative medicines in France. Indication based pricing was part of these proposals (Pajares y Sanchez and Saout, 2017). Two types of risk sharing agreements were included in the agreement signed between CEPS and LEEM on 31/12/2015: coverage with evidence development ("payer

pour voir”) and outcomes-based payments (“satisfait ou remboursé”). These types of contracts have been used for innovative high cost medicines requiring real world evidence. These have been applied to Solvadi and Harvoni for Hepatitis C, and to Imnovid for multiple myeloma. In the case of Solvadi, CEPS undertook price negotiations with Gilead on the basis of performance relative to “viral eradication” with a follow up real world study on 12,000 patients (“Hépater” cohort). These types of contract potentially allow for differential net prices - via differential discounts - for different indications. However, we are not aware of the application of these contracts in a multi-indication context, and no legislative proposal has been drafted yet to support such an approach. It is possible that there remains one blended or average price for all indications which is adjusted or renegotiated as evidence on volumes of use and on real world effectiveness becomes available.

### 3.2 The potential for IBP in Germany

Different prices per indication have not been implemented in Germany. Nevertheless, IQWiG methodology for estimating the additional benefit of a new drug is based on randomized controlled trial (RCT) evidence of indication-based outcomes and different outcomes for patient sub-groups within indication. A single pharmaceutical product can obtain more than one level of additional benefit depending on patient subpopulations and indications. These different levels of benefits are used in price negotiations (Lauenroth and Stargardt, 2017).

A drug that receives different levels of added benefit assessment for different subpopulations will ultimately receive only a single price that takes into account these various levels. This is called a mixed price. Mixed prices apply to the drug across all patient groups, no matter what additional benefit has been reported in individual patient groups. For the manufacturer, this means getting too little money for the population with proven added value and too much (in the view of the SHI) for the patient group with less added benefit. Exactly how each indication is weighted in the negotiation to arrive at the mixed price is unknown.

Renegotiation of the price of a particular drug can happen due to the assessment of new indications. One year after the publication of the resolution on benefit assessment, the manufacturer can request, or the GBA can decide, that a new benefit assessment needs to be performed in view of new scientific findings. This can trigger a new set of negotiations between the SHI and the manufacturers.

Currently, price differentiation by indication is possible only through individual contracts between pharmaceutical manufacturers and regional SHIs providing discounts on top of the AMNOG-negotiated price. In addition to a published national fixed rebate on all prices, further rebates can be negotiated in this way between manufacturers and the SHIs. It is not clear how frequently additional individual contracts are agreed or if multiple indications might provide a rationale for such an agreement. The critical issue is likely to be if the SHI is able to shift market share towards the product that is subject to the agreement.

Whilst the SHIs are interested in IBP in order to manage costs, other stakeholders, particularly physicians, cite the significant bureaucratic burden that could be placed on them, and that this burden would most likely not be remunerated. An important barrier to the implementation of IBP is the current data structure, whereby payers receive only

high-level ICD-10 data. This does not include the level of detail needed to implement IBP. Due to data protection regulations for patients, the indication for which a pharmaceutical was prescribed are not reported.

Although the price negotiation process is unpredictable, particularly as it is not clear how benefit levels are reflected in the final price, it is not likely that there will be any major modifications in the near term, although greater transparency about the method of calculation may be needed. We can note that after a dispute over the price of the medicines Eperzan® (albiglutide) and Zydelig® (idelalisib) the responsible arbitration board set a mixed price. The arbitration decision was taken to court, and judges from the Landessozialgericht (LSG) Berlin-Brandenburg, found that the rationale for the calculation of the mixed price was not clear. The court therefore annulled both arbitration awards.

There was discussion about including a modification to permit differential pricing in multiple indications and subpopulations prior to publishing the Gesetz zur Stärkung der Arzneimittelversorgung in der GKV (AMVSG; Act to Strengthen Pharmaceutical Supply in the Statutory Health Insurance System) (Bundesgesetzblatt (Federal Law Gazette) on 12th May 2017. The expectation was to have a more flexible procedure that would allow manufacturers to apply for an exclusion of reimbursement for certain subpopulations, but also differentiate in the price negotiations by conducting price/volume agreement per indication and subpopulation. In the event, it was not included.

### 3.3 The potential for IBP in Italy

In Italy, prices for pharmaceuticals are negotiated centrally between companies and the Italian Medicines Agency's (AIFA) Committee for Prices and Reimbursement (AIFA, 2016). The negotiation of prices takes place after a positive opinion on reimbursement has been expressed by the AIFA's Technical and Scientific Committee. Prices for reimbursable drugs are negotiated at the ex-factory level and are usually valid for at least two years (Jommi and Minghetti, 2015). As a consequence of recent cost-containment policies, a system of mandatory discounts applies to all drugs reimbursed by the Italian National Health System (NHS).

When a marketed drug obtains additional indications and the number of patients treated increases considerably, AIFA asks the manufacturer for an additional price reduction. In principle, it may appear that prices are independent of different therapeutic indications, but are volume related. However, Managed Entry Agreements (MEAs) can be used to vary net prices (i.e. list prices minus any agreed discounts) across indications. Whilst a fixed nominal price is assigned to the drug regardless of indication, different MEA schemes can be agreed on for each indication. In other words, AIFA is *de facto* able to set different net prices (the price paid by the hospital) for different indications (Flume et al., 2016). In Italy, MEAs are implemented on top of mandatory discounts: while information on the drugs subject to MEAs is publicly available, financial details on discounts are confidential. MEAs in Italy are classified as either 'financial based' or as 'performance based' (AIFA, 2017). Schemes of the first group aim to monitor the budget impact of drugs and include:

- a) Cost-sharing - discount given on the price of the first course of therapy for all patients eligible to treatment;

- b) Budget cap – payback equivalent to the value of sales that exceeded the pre-allocated pharmaceutical budget.

'Performance-based' MEAs have been designed to deal with uncertain evidence on clinical benefit and cost effectiveness at the time of the assessment. They are:

- a) Risk-sharing - discount on the first course of therapy for all non-responders;
- b) Payment by results - full refund for all non-responders based on outcome evaluation;
- c) Success fee – free distribution of the medicine followed by retrospective payment to the manufacturer based on successfully observed patient outcomes. We explain this scheme in further detail below.

The crucial factor for the wide scale implementation of MEAs in Italy since 2006 has been the availability of nationwide web-based registries for each product indication or line of treatment, depending on the nature of the pricing agreement. The registries are owned by AIFA and collect information on patient eligibility, supply, dispensing and follow-up. Each pharmaceutical company has to pay a yearly €30,000 fee for each registry that includes its products (Mestre-Ferrandiz et al., 2015). For drugs included in the registries, prescribers need to create a patient file and upload relevant clinical data. Once the patient file is submitted to the hospital pharmacy, the drug can be dispensed.

The patient file is updated when the re-evaluation of the outcome takes place and is closed and sent to AIFA at the end of the course of treatment. AIFA checks the quality of the data and whether use is appropriate according to the indication. In the case AIFA is able to confirm the reimbursement to the hospital, any refund due can be claimed in the form of free goods or a credit on future purchases (Mestre-Ferrandiz et al., 2015). In practice, the automated flow of data transmission from the web-based registries on patient outcomes, costs and eligibility, means the correct prescriptions are traceable (Montilla et al., 2015).

The Italian approach to the implementation of IBP has intuitive appeal because, not only does it recognise the possibility that drugs have different indications, but also that they may work differently in clinical studies and in the real world, making payment conditional on a drug's effectiveness (Bach, 2014). Nonetheless, there are a number of challenges associated with the infrastructure required to operationalise indication-based MEAs and to maintain the web-based monitoring registries. Outcome-based MEAs require a definition of 'non-responders', which may be difficult to derive on the basis of clinical trials results alone (Navarria et al., 2015; Garattini et al., 2015). In general, the management costs of MEAs are also high: since 2012, AIFA has contracted the management of MEAs to an international consulting company on a 3-year tender for €8.7 million (Garattini et al., 2015). Finally, as a result of the weak incentives for prescribers to undertake the necessary administrative and reporting work once authorisation to use the drug has been achieved, the savings accrued to the healthcare system in the form of reimbursement from MEAs have reduced (Navarria et al., 2015).

### **3.4 The potential for IBP in Spain**

The national regulation on pricing and reimbursement of medicines is the Law of Guarantees and Rational Use of Medicaments RD 1/2015 of 24 July 2015. The law incorporates previous legislation establishing criteria of therapeutic, social, clinical value and cost-effectiveness, budget impact, and therapeutic innovation in medicines

reimbursement decisions. The combined effect of these regulations opened the way to value-based pricing. Since incremental clinical benefit is, in theory, demonstrated for a particular indication, this could lead to IBP. However, this has not, to date, led to IBP.

There are no examples of IBP being implemented nationally but value-based pricing, usually a pre-condition for the implementation of IBP, is being introduced through risk-sharing agreements. The autonomous region of Catalonia has been a pioneer in the use of risk-sharing agreements. In 2013, a risk-sharing agreement was signed in Catalonia with Astra Zeneca for gefitinib (Iressa) for lung cancer (UIMP 2013). By October 2015, Catalonia had 16 risk-sharing agreements in place (EIU 2015).

Most of the new medicines authorised by the AEMPS are distributed directly to hospitals and dispensed by hospital pharmacies (Organización Médica Colegial, 2014), but little is known about the net price paid by hospitals. Direct purchases by hospitals, frequently centralised at regional level, are likely to include rebates. A regulation attempted to introduce transparency in the pharmaceutical expenditure of public hospitals (R.D. 177/2014 of 21 March 2014) by requiring them to report monthly data on number of doses dispensed by the hospital pharmacies, although not on prices per unit.

The collection of real-world data and patient registries has been implemented for several diseases, and is potentially available from Electronic Health Records (EHRs) and from electronic prescription data. Since 2012, the CIPM identified the need for tracking new high priced medicines indicated for “niche” indications. A registry has been created for Hepatitis C patients treated with the most recent and innovative medicines, which includes payment agreements based on invoice reconciliation regarding the number of treatments and patients treated. It is not clear outside of the Hepatitis C case, how much registry and/or EHR data can be made available to support agreements between manufacturers and payers.

Several bodies have proposed further change to the Spanish system. The Organización Médica Colegial proposed value-based pricing, with new financing models like risk-sharing agreements, financed according to indication or therapeutic value. The Competition Commission (Comisión Nacional de los Mercados y la Competencia, CNMC) considered law RD 1/2015 and recommended implementation of the cost-effectiveness criterion which is in the law but not yet systematically used. The CNMC also recommended the use of the cost-effectiveness criterion for the follow-up and revision of prices. This could include a revision with a new indication, although this was not explicitly mentioned by the CNMC.

### **3.5 The potential for IBP in the UK**

In the UK, some arrangements operate at the UK level, i.e. across all four nations (England, Scotland, Wales and Northern Ireland) and others at the devolved nation level. Manufacturers are free to set launch prices in the UK. In England and Wales, The National Institute for Health and Care Excellence (NICE) recommends whether a medicine should or should not be funded based on an assessment of its clinical and cost-effectiveness at this given price, in the context of a specific indication. In Scotland, the Scottish Medicines Consortium (SMC) does the same thing.

In the UK, there is no current facility to implement IBP at the visible list price level. Net prices could however differ, based on discounts and/or rebates provided by the manufacturer.

Arrangements which can alter the net price for products were set out in the 2009 Pharmaceutical Price Regulation Scheme (PPRS). It introduced the concept of Patient Access Schemes (PAS) in England and Wales for the first time. Similar arrangements were put in place by the Scottish government. A PAS has the objective of facilitating earlier patient access for medicines that are not in the first instance found to be cost and/or clinically effective by NICE, within a framework that preserves the independence of NICE. These include:

- Financial-based schemes: List price is not altered but discounts or rebates are offered, linked to various parameters;
- Outcomes-based schemes: prices increased or rebates provided based on further evidence collection, or risk-sharing arrangements.

In the 2014 PPRS, a typology for PAS was introduced, categorizing them as 'simple discount schemes' (no significant burden or data collection) or 'complex schemes' (e.g. involving rebates, dose capping and outcomes-based schemes).

Such schemes could in theory offer flexibility in pricing arrangements. However, the 2014 PPRS states that: "*In contrast to simple discount PAS, complex PAS may be specific to one or more indications of a medicine. However, a PAS should only modify the cost of a single product. Further, the Department is unlikely to agree to more than one PAS for a single medicine, because of the complexity this would introduce for the NHS. In view of this, PAS proposals should be designed so that the same PAS could apply across all relevant indications*". By extension, the arrangement currently in place to facilitate flexible pricing does not support indication-based pricing. Whilst PAS arrangements have been in place for a number of years, there is a trend towards simple discounts rather than anything more sophisticated.

The shift in the English NHS of specialised commissioning to NHS England has led to the introduction of Managed Access Agreements (MAAs) as an alternative mechanism to the PAS for managing price and patient access. These have been used to date in two contexts: (i) as part of the revised arrangements for the Cancer Drugs Fund where two drugs and three indications have been subject to MAAs and (ii) in the Highly Specialised Treatment programme, where two drugs have been approved with MAAs as well as PASs. It is not clear if any of these arrangements amount to de facto indication-based pricing as the detailed contractual arrangements are commercially confidential.

It is also possible for large hospitals – for example those specialising in cancer treatment – to negotiate additional agreements with manufacturers. Increasingly NHSE as the commissioner of specialist services, including oncology, is seeking to drive all contracting arrangements. The terms of NHSE and hospital level agreements are not made public. However, NHSE has run a competitive tendering process for drugs to treat Hepatitis C separating tenders by genotype – in effect by indication. It has done this because there are competing drugs for some genotypes but not for others and thus it sees this as a way of getting lower prices for some genotypes. This appears to be a unique arrangement for this particular group of drugs.

There are a number of operational challenges that need to be overcome in order to support IBP in the UK (Mestre-Ferrandiz et al., 2015). The first is around the ability of the NHS to undertake financial reconciliation and to administer rebates. The second is the availability of data to monitor usage by indication. Data collection is most advanced in oncology. For example, the NHS Systemic Anti-Cancer Therapy (SACT) dataset is a



mandatory chemotherapy dataset which captures treatment for all solid tumours and haematological malignancies funded by the NHS in England.

The views of decision-makers around the desirability of IBP in the UK are not clear. There is a view from senior NHSE officials that it makes more sense for the NHS to use its bargaining power to drive prices down to the price of the indication which has least additional value and so the lowest price. However, companies can choose price, and may seek a higher price accepting that this is for a more restricted set of indications. Attendees at an expert workshop (representing payers, clinicians, pharmacists, HTA and academics) showed an interest in using a 'blended' single list price, with discounts calculated retrospectively based on utilisation for different indications (Mestre-Ferrandiz et al., 2015). In October 2016, the Government set out recommendations to speed up access to innovative healthcare and technologies and to improve efficiency and outcomes for NHS patients, through the Accelerated Access Review. Discussion of IBP did not feature in the final report, but in a Forward, Simon Stevens – CEO of NHS England – stated that *"...where it makes sense, we'll increasingly be open to agreeing innovative win/win product-specific reimbursement models, incorporating a mix of outcomes-based, annuity-based and volume-based pricing deals"* (AAR, 2016).

### 3.6 The potential for IBP in the U.S.

The debate on the potential for implementation of Indication-Based Pricing started in 2012 with the new pricing models proposed by Roche for Avastin (bevacizumab) (The Pink Sheet Jun. 11, 2012) and with the input of independent thought leaders such as Dr. Peter Bach, Director, Center for Health Policy and Outcomes at Memorial Sloan Kettering, and Dr. Steven Pearson, Founder and President of the Institute for Clinical and Economic Review (ICER). In December 2015, ICER held a Policy Summit with 44 health care leaders from the 22 payer and life sciences organizations that comprise the ICER membership group. The discussions and analysis from this Policy Summit (Pearson et al. 2017) describe the barriers and potential solutions for efforts to implement ISP initiatives in the U.S.

Manufacturers must sell drugs to Medicaid at the lowest price they have offered to any private insurer (the "best price rule"). The ICER Policy Summit (Pearson et al. 2017) suggested that IBP could potentially be implemented through a number of different routes including using a single weighted average price for oral drugs with different indications, which reduces the risks of being caught by the "best price rule" as a low value / low price indication is averaged with a higher value, higher priced indication.

Prices charged for pharmaceuticals covered by Medicare Part D, including through Medicare Advantage plans, do not trigger the best price rule, meaning that discounts obtained by these purchasers need not be passed on to Medicaid (Sachs et al. 2017).

Both CMS and commercial health plans in the US are currently piloting implementation of IBP methods with the objective to better manage expenditure. Initiatives include:

- Anthem (previously WellPoint) initiated a cancer pathway programme providing information that would enable contracting based on indication. It is linked with reimbursement incentives to oncologists contingent on the use of evidence-based treatments which provide greater value.

- UnitedHealthcare completed in 2014 a cancer pathway pilot which separated oncologist's income from drug sales, which could also facilitate a move toward IBP. United also started a process of data collection, matching clinical conditions or indications with prescribing data and outcomes (The Pink Sheet, 20 Oct, 2014).
- In 2016, Express Scripts launched an Oncology Care Value Program (OCV) focusing oral and self-administered drugs for prostate cancer, lung cancer, and renal cell carcinoma. The OCV Program leverages Express Scripts' Oncology Therapeutic Resource Center (TRC) through exclusive dispensing of all oncology medications through its Accredo specialty pharmacy. The intention is to target clinically appropriate and cost-effective medication for each specific indication (Express Scripts, 15 Jun., 2015). We note that CVS entered an IBP programme in 2016 for different indications of Herceptin (trastuzumab). (The Pink Sheet, 4 Mar., 2016).
- An IBP for Anti-inflammatories programme was launched by Express-Scripts in 2017 by redesigning the formulary, initially defined for a broad class of anti-inflammatory drugs, to a classification allowing for competition at indication level, in particular for psoriasis and psoriatic arthristis. This change in the formulary allowed the entry of new medicines such as Cosentyx (interleukin inhibitor) to compete with the broader spectrum drugs such as Humira (TNF-inhibitors) (The Pink Sheet, 13 Sep 2016; 19 Jul., 2016).
- CMS has indicated its intention to introduce IBP to explore the reimbursement of the breakthrough CAR-T therapy commercialised by Novartis as Kymriah (tisagenlecleucel). The list price of Kymriah is \$475,000 and there are 600 patients expected to be treated per year in its initial indication of paediatric leukemia, about half covered by Medicare. For this initial indication CMS agreed an outcomes-based reimbursement contract with Novartis, which excludes payment for non-responders. The contract has been structured such that it does not invoke "best price" nor trigger further rebates or the "anti-kickback" statute.

Other aspects which may hinder the implementation of IBP in the US are related to regulations. The Anti-Kickback Statute, applying to both private and public payers, could restrict the implementation of outcome-based agreements on the grounds that they are a source of income to induce or reward use of a manufacturer's product. Medicaid "best price" provisions are identified as a major implementation barrier. However, the pilot implementation of outcomes-based contract between Novartis and CMS for CAR-T appears to have been arranged without triggering best price rules. Sach et al. (2017) suggest that Medicaid best price rule could be mitigated through using a weighted average price, product differentiation, and rebates based on average effect.

## 4. DISCUSSION

In Section 1.2 we identified a number of issues. We revisit these in the light of the material set out in Sections 2 and 3.

**Who benefits and who loses?** Differences of opinion remain as to whether IBP is in the interests of payers. It increases the potential number of patients who can benefit from a medicine and thus most economists regard it as efficient. However, IBP may lead to some prices being higher than with a uniform price, as well as some prices being lower. A number of US payers see the potential for IBP to increase price competition in some indications.

As was seen in some of the papers we reviewed, the value at which prices are currently set in a single-price system will impact on the consequences of a move to a multiple-price system. A pharmaceutical company's strategy will be one of profit maximisation. In some cases, this could correspond with setting a high price to reflect benefits in a high-value indication. Where this is the case, a move to IBP would permit lower prices to serve lower value, including new, indications, so reaching more patients. If, on the other hand, the current single price corresponds with the value achieved in the higher-volume lower-value indication then, from the payer's perspective, a move to IBP would serve only to raise prices for the high value indications, and the number of patients treated would not be impacted. Chandra and Garthwaite (2017) assume the latter, whilst Mestre-Ferrandiz et al (2015) develop static and dynamic scenarios exploring the implications of the former. Both approaches ignore any potential impact of IBP on competition, as anticipated by some US payers, and as used by the NHSE in England, in its use of contracting by genotype in Hep C drug procurement.

**Can it be implemented in practice and at an affordable cost?** In the US and Europe, with the possible exception of Italy, practical obstacles remain to implementing IBP in all three of the areas identified:

- legal or regulatory hurdles;
- data collection problems;
- contractual or financial flow issues.

In France and Germany an average, blended or mixed price can be set ex ante. However, there are challenges in collecting data that can support a reassessment of the price. There are challenges in enabling differential discounts by indication being offered at hospital (in France) or SHI (in Germany) level, which means that the average price may not reflect value in a particular setting.

In Spain, only one national price can be set, but more flexibility is possible at the level of the autonomous regions. Here, however, data collection and availability is an issue.

In the UK, progress has been made in England with the potential to use the SACT database to support IBP in oncology. However, NHS England has resisted moves towards complex pricing arrangements because of the potential burden on hospitals and clinicians in managing data collection and financial flows.

In Italy de facto IBP arrangements are in place through Managed Entry Agreements using the national registries managed by AIFA. Questions have been raised about cost

and about ensuring rebates and discounts are claimed. However, a system is in place that can deliver IBP.

In the US the legislative barriers are of concern, notably “anti-kickback” provisions and the Medicaid “best price rule.” There are also data collection and payment issues. However, as noted, private payers are experimenting with IBP, and CMS is also exploring the use of IBP.

### **Additional issues**

Additional points of note are:

- continued differences of view as to the case for using (i) evidence-based prices, based on expected value using RCT and other evidence to identify ex ante what additional benefits a drug may bring in a particular indication or (ii) outcomes-based reimbursement, based on realised value, i.e. identifying ex post what value was delivered to a patient. The main challenge with outcomes based agreements is ensuring they can practically be implemented.
- how IBP is operationalized? The moves to date towards IBP (with the exception of Italy) seem to involve an average weighted price or a “blended” price reflecting the prices appropriate to the different indications, and the volumes associated with each indication. Volume data and price will, however, need to be periodically updated. One challenge to this approach is that the prescriber and budget holder faces an average price and not the price that is relevant for the indication for which they plan to use the product. This is raising issues in France, Germany and the UK.
- are there incentives for payers and providers to accurately report usage? To implement IBP, data that accurately capture use are essential. Depending on the contractual arrangements, there may be incentives for prescribers to report a high-priced use of a drug (they receive a percentage of the price), or where they have a fixed budget, to record that the drug has been used for a low-value low-priced indication. Where the differences between indications are relatively nuanced (e.g. line of therapy, dosing regimens, combination with other drugs, etc.), and clinical governance and audit procedures limited, then any inaccurate reporting would be difficult to detect. Mestre-Ferrandiz et al (2015) provide an example where an indication was withdrawn as a result of the risk of “arbitrage”.

In summary, the case for IBP and the practicalities of implementation continue to be debated. In principle it can be both efficient – increasing the numbers of patients using a medicine – and potentially promote competition. However, a number of barriers need to be overcome to enable benefits to be realised for patients, payers and pharmaceutical companies.

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