Drug price regulation in a nutshell: value based alternatives for personalised drugs in the presence of asymmetry of information

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Abstract

The market for new drugs is changing: personalised drugs are deemed to increase heterogeneity in patients’ responses and, possibly, uncertainty on the outcomes. In this context, price regulation is going to play an increasingly important role. Value based prices are replacing cost based schemes, but their implementation is still controversial. In this article we argue that personalised medicine opens new scenarios as concerns the relationship between pricing, industry listing strategies and research. We suggest that more research should be devoted to study the effects of alternative pricing schemes on competition and innovation in a dynamic perspective.

1 Introduction

Pharmaceuticals account for almost a sixth of health spending across OECD countries and are one of the main factors contributing to the increase of the health care bill. In Europe, where health care is mostly financed by public providers (OECD, 2012), the price dynamics has put budgetary pressure on Governments, that are responding with more stringent price regulations (Carone et al., 2012; Panos et al., 2010; OECD, 2011), whose desirability is controversial.¹ Opponents argue that it may adversely affect innovation by preventing adequate returns to R&D. (Danzon and Chao, 2000). This argument may explain the sharp decrease in the productivity of R&D spending, which in turn makes the price for new drugs increase (Kleinke, 2001; DiMasi et al., 2003, 2016).

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¹For a review see (Wettermark et al., 2009).
However, other authors (Yu et al., 2017; Walton et al., 2017) show that the costs for R&D may not be fully justified the current level of prices.

Against this backdrop, the market for new drugs is changing; according to Schork (2015) more than 20% of NME’s approved by FDA can be considered personalized medicine; in oncology, by 2020 75% of new products will be listed for multiple indications ((Aitken et al., 2015)). This trend is deemed to increase heterogeneity in patients’ responses and possibly uncertainty on the outcomes (Davis et al. 2009); in this context, price regulation is going to play an increasingly important role. (Eichler et al. 2011).

Gravelle (Gravelle (1998)) has shifted drug price regulation from traditional cost-based formulas to value based ones. This shift was the natural consequence of the peculiar characteristics of innovative drugs that make costs an inappropriate base for pricing rules. Value-based prices have received significant attention since the Office of Fair Trading recommended their adoption (Office of Fair Trading, 2007). However, the precise implementation is still uncertain (Sussex et al., 2013). To date, most of the attention has been on marginal value-based prices (MVBP), primarily because they may allow the payer to retain part of the rent (Claxton, 2007). However, average value based rules (AVBP) may be superior, especially when the population is very heterogeneous ((Levaggi and Pertile, 2016)). Finally, Chandra and Garthwaite (2017); Kaltenboeck and Bach (2018) propose to use indication based prices (IVBP) where the price may be indication-specific, i.e. the price depends on the different effectiveness across treatments. In this article we argue that if the industry is better informed than the regulator on heterogeneity in patients responses most of these formulas would produce the same result in a static, short run context. Their use make instead a big difference in a dynamic, long run setting where their alternative use may boost or dampen incentive to R&D in new drugs, a scenario where surprisingly little research has been produced so far.

2 Methods/The model

Let us assume that a new drug is about to be launched in the market for an eligible population \( N \) equal to one. The response to treatment is herogeneous: for a first group \( n \) of patients effectiveness (in terms of QALY gained) is equal to \( E_1 \) while for a second group \( (1 - n) \) it is equal to \( E_2 \) with \( E_1 > E_2 \). The two groups could be distinguished by some observable element, such as the indication for which the drug is used or some specific characteristic.\(^2\) The regulator may use three alternative

\(^2\)For example, for patients with metastatic squamous NSCLC, Pembrolizumab has been listed only for patients with PD-L1 immunohistochemistry (IHC) 22C3
definition of value based prices:

- **marginal value based** (MVBP): the price is set according to the effectiveness of the marginal patient. i.e. it will be equal to $\lambda E_1$ if the firm asks for listing for the indication for which the drug is most effective (target population $n$) or it will be equal to $\lambda E_2$ if listing is asked for both types of patients:

  \[
  p^M(n) = \lambda E_1 \\
  p^M(1) = \lambda E_2
  \]

  where $\lambda$ is the shadow value of health.

- **average value based** (AVBP) prices where the price is set according to the average effectiveness (across groups of patients) of the new drug. The price will be equal to $\lambda E_1$ if the firm asks for listing for the most effective indication (target population $n$). If they ask for both types, since for the first group the effectiveness is $E_1$ while for the second it is $E_2$, the weighted average will be equal to $E_A = nE_1 + (1 - n)E_2$ and on this average effectiveness the price will be set:

  \[
  p^A(n) = \lambda E_1 \\
  p^A(1) = \lambda E_A = \lambda (nE_1 + (1 - n)E_2)
  \]

- **indication based prices** (IVBP). The drug will be marketed under two different prices $\lambda E_1$ for the first group of patients and $\lambda E_2$ for the second group:

  \[
  p^I(n) = \lambda E_1 \\
  p^I(1 - n) = \lambda E_2
  \]

Let a representative profit-maximising firm decide on the target of patients for new drug. Conditional on a successful development process whose sunk cost $I$ has already be borne by the industry, the firm maximises profits, defined as:

\[
\Pi(p, N) = (p(N) - c)N, \quad (1)
\]

pharmDx while Nivolumab can be used for all the patients. See (Shu and Rizvi, 2016)
For each scheme we will consider the choice in terms of listing of a profit maximising firm in two environments: the first one where information on the differential effectiveness can be observed by the industry and the regulator (symmetric information) and a different context where the difference in the effectiveness is private information to the industry. The timing of the game is defined as follows:

1. the regulator defines a pricing rule such that the price equals the monetary value of the benefit of the treatment.

\[ p(N) = \lambda f(E) \]  

(2)

It is assumed that the regulator can commit to this rule.

2. Knowing the pricing rule defined in Eq. 2, the firm decides for which patients to apply for listing. The choice of the industry depends on a profit maximising strategy.

3 Results

Let us first consider the case in which information is symmetric, i.e. the regulator can observe the differential level of effectiveness on the two groups of patients. The profit maximising strategies of the industry are derived in the Appendix and presented in table 1.

For marginal value based prices, the decision depends on the relative difference in effectiveness and on the size of the two groups as shown in Figure 1. On the horizontal axis we measure the number of patients while on the vertical axis we measure price, net of the running cost \( c \). The firm chooses between two alternatives: a) selling only to first group of patients \( n \) enjoying a profit equal to the area \( 0ABn \); b) asking listing for both indications for a profit equal to \( 0CE1 \). The choice depends on the relative size of the two areas.

For average value based, the choice is between listing only for the first group with a profit equal to \( 0ABn \) or to sell to both groups with a profit equal to \( 0FG1 \) which is always greater than the area \( 0ABn \). For indication based, the industry will sell on both markets for profit equal to \( 0ABn + nDE1 \) which is equal to \( 0FG1 \), i.e. average value based and indication based prices bring to the same solution: in both cases, the industry will sell the drug for both indications for the same profit.

Let us now turn to case where the differential effectiveness of the drug can be observed only by the industry (asymmetry of information). This is especially relevant when effectiveness depends on some specific characteristics of the patient rather than the ailment he/she may suffer.
### Table 1: Listing strategy under alternative Value Based Pricing schemes

<table>
<thead>
<tr>
<th></th>
<th>MVBP</th>
<th>AVBP</th>
<th>IVBP</th>
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<tbody>
<tr>
<td>price</td>
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| patients | $\begin{align*}
    a \quad E_H & \geq \frac{E_L}{n} - \frac{c(1-n)}{\lambda} \\
    b \quad E_H & < \frac{E_L}{n} - \frac{c(1-n)}{\lambda}
    \end{align*}$ | $1$                                       | $1$                                       |
| profit | $\begin{align*}
    (\lambda E_H - c) n & \quad if \\
    E_H & \geq \frac{E_L}{n} - \frac{c(1-n)}{\lambda} \\
    \lambda E_L - c & \quad if \\
    E_H & < \frac{E_L}{n} - \frac{c(1-n)}{\lambda}
    \end{align*}$ | $n (\lambda E_H - c) + (1-n) (\lambda E_L - c)$ | $n (\lambda E_H - c) + (1-n) (\lambda E_L - c)$ |
| C/E    | $\begin{align*}
    a \quad 1-n & \quad n.a \\
    b \quad n & \lambda \frac{E_2}{E_1} < \lambda \\
    1-n & \lambda \frac{E_2}{E_1} > \lambda
    \end{align*}$ | $n \lambda \frac{E_2}{E_1} < \lambda$ | $n \lambda \frac{E_2}{E_1} > \lambda$ |

**Table 1:** Listing strategy under alternative Value Based Pricing schemes

**Figure 1:** Profit for different VB definitions
from. Let us also consider a static, one period game where it is impossible for the regulator to find out, even ex post, that the drug effectiveness is patient-dependent. In this case it is easy to show that listing strategies for marginal value based and average value based are going to be the same. Under marginal value based, the industry has no interest in revealing that the drug is highly effective only for the first \( n \) patients. Since the difference in effectiveness is private information, the industry has to choose between two strategies a) selling only to first group of patients \((n)\) at a price \(\lambda E_H\); b) ask for listing for both indications without revealing its private information. In this case the average observed effectiveness will be equal to \(E_A = nE_1 + (1-n)E_2\) and the price will be equal to \(\lambda E_A\), i.e. the same price for AVBP. For average value based, the strategic revelation of information has no effect on the profit of the firm as well as for Indication Based Prices. In a context of asymmetry of information it does not seem to be relevant the scheme chosen; in any case the industry is able to make a profit equal to \(0ABn + nDE_1\).

4 Discussion and Conclusions

The model presented above shows that in a static framework most of the common definitions for value based pricing are surprisingly similar and their different outcome depends on the information structure. If heterogeneity in patients response is observable, only under marginal value based prices the outcome in terms of listing, profit for the industry and drug availability may be different. In this case the industry may choose to list for both indications or just the most effective one depending on the effectiveness differential and in the target population. Average value based and indication based prices are equivalent, even though the implications from a policy point of view may be different.

Average value based explicitly pools effectiveness among the two groups of patients; in this way value for money is higher for those with a higher effectiveness. Pooling may be easier to implement in public health care systems which are informed by equity and risk pooling objectives. For a private health care systems AVBP may be viable only if the two indications are not mutually exclusive (i.e. each patient has a similar probability of having to be treated for both indications). When the difference in effectiveness depends on some genic characteristics, this is not clearly the case, unless this information is not known by the insurance company.

Indications based prices do not foresee pooling among individuals, but they may be difficult to be sustained from a political point of view: it may seem unfair that, if the industry has a profit by selling the drug at price \(\lambda E_2\), the regulator should allow the latter to sell at an higher price
simply because for another indication the willingness to pay is higher. Its implementation may however be viable also in this context by combining several instruments (HTA, risk sharing, payback) as shown by (Towse et al., 2018; Neri et al., 2018).

From the regulator point of view, MVBP are better value for money; if the industry decides to sell for both indications, the expenditure is equal to $\lambda E_2$, while expenditure under AVBP and IVBP is equal to $\lambda (nE_1 + (1 - n)E_2)$. In other words, only MVBP allows to extract the maximum of the producer rent. If the industry decides to sell only for one indication value for money is preserved, but a group of patients will not benefit form its use. This is one of the reason why WHO has recently criticized value based prices.

Let us turn to a context of asymmetry of information: in this setting, in a static context, the results in terms of profit and expenditure are the same because the industry may not reveal the difference in effectiveness. Under MVBP the best strategy for the industry is to present results that pools the effectiveness across the two groups of patients. In this way, it would infact obtain a price equal to AVBP, hence a profit equal to AVBP and IVBP. The case of an industry not revealing the differential information on effectiveness may be questioned on ethical and legal grounds; from a policy point of view this scenario may be interpreted in terms of incentives that the industry has in promoting research aimed at assessing a differential in effectiveness across patients. In a static framework, the industry has an incentive not to invest in research aimed at assessing a differential level of effectiveness under MVBP and it is indifferent in the other two cases.

Let us now turn to the implications of price setting and information disclosure on entry decisions by competitors. In a dynamic setting the industry should also consider the implications that its choice of listing has on its profit in the long run, an essential conditions to recover R&D costs.

To show this let us consider a scenario where a new drug with the same characteristics in terms of differential effectiveness may be developed and launched by a competitor. The probability of this occurrence depends on the expected profit for the new drug which in turn depends on the price of the available alternatives. Let us consider the choice of an industry under marginal value based regulation and asymmetry of information. In a static framework the winning strategy is to sell the drug for both indications without revealing the effectiveness differential. In a dynamic setting, this strategy may not be winning. If the firm reveals the effectiveness differential and lists for both types of patients, the market price $\lambda E_2$ is set and the ICER that a competitor has to
meet to be competitive is quite high\textsuperscript{3}. The strategy of not revealing the effectiveness differential may not offer a sufficient protection on the market where the drug is more effective. A competitor could in fact be able to get this market by listing its product only for the first subgroup of patients\textsuperscript{4}. On the other hand, the investment in R&D to prove this differential may not be recovered if this lead to a reduction in the price.

Let us consider again the example of Nivolumab and Pembrolizumab. Nivolumab was approved in March 2015 for treatment of patients with metastatic squamous NSCLC after progression on platinum-based therapy. Seven months later, the the drug for patients with nonsquamous NSCLC in the same setting.

In theory also Nivolumab could be more effective on the subgroup of patients with PD-L1 immunohistochemistry (IHC) 22C3 pharmDx, but the industry may have decided not to invest in research to discover this information. This may have allowed Pembrolizumab to be listed for this group for which they could show their drug to be more efficient.

In spite of the rich environment and the questions on board, very little research exists on the dynamic implications of different value based price schemes. We think that this avenue may set the agenda for the future of price regulation.

References


\textsuperscript{3}The cost per unit of effectiveness is in fact quite low for the first n patients.

\textsuperscript{4}Ex-post the industry could reveal the differential in effectiveness, but this may not be viable or credible and the industry may end up losing both markets.


A Appendix

A.1 Marginal value based prices

If the firm decides to list only for the patients with the highest effectiveness, the price will be equal to $\lambda E_1$ and the profit will be equal to $\Pi_n = (\lambda E_H - c) n - I$. On the other hand, if the firm asks for listing for both types of patients the price will be equal to $\lambda E_1$ and the profit will be equal to $\Pi_1 = \lambda E_L - c - I$.

The firm chooses the alternative that allows to maximise the profit by comparing $\Pi_1 = \lambda E_L - c - I$ with $\Pi_n = (\lambda E_H - c) n - I$. In particular, if

$$\Pi_n = (\lambda E_H - c) n - I > \Pi_1 = \lambda E_L - c - I$$

the firm will ask for listing only for the first type of patients.

We can write this conditions in terms of $E_H$:

$(\lambda E_H - c) n - I - (\lambda E_L - c - I) > 0$

$(E_H n - E_L) \lambda + c (1 - n) > 0$

$$E_H > \frac{E_L n - c(1 - n)}{\lambda}$$

$(\lambda E_H - c) n - I$ if $E_H \geq \frac{E_L n - c(1 - n)}{\lambda}$

$(\lambda E_L - c - I)$ if $E_H < \frac{E_L n - c(1 - n)}{\lambda}$

If $c=0$ we can write
A.2 Average value based

If the firm decides to list only for the patients with the highest effectiveness, the price will be equal to $\lambda E_2$ and the profit will be equal to $\Pi_n = (\lambda E_H - c) n - I$. On the other hand, if the firm asks for listing for both types of patients the price will be equal to $\lambda E_A$ and the profit will be equal to $\Pi_1 = \lambda E_A - c - I$.

The firm chooses the alternative that allows to maximise the profit by comparing $\Pi_1 = \lambda E_A - c - I$ with $\Pi_n = (\lambda E_H - c) n - I$.

In this case $E_A = (nE_1 + (1 - n)E_2)$ so that

$\Pi_1 = \lambda (nE_1 + (1 - n)E_2) - c - I$

which can be written as

$\Pi_1 = n (\lambda E_H - c) + (1 - n) (\lambda E_L - c)$

$\Pi_1 = \Pi_H + (1 - n) (\lambda E_L - c)$