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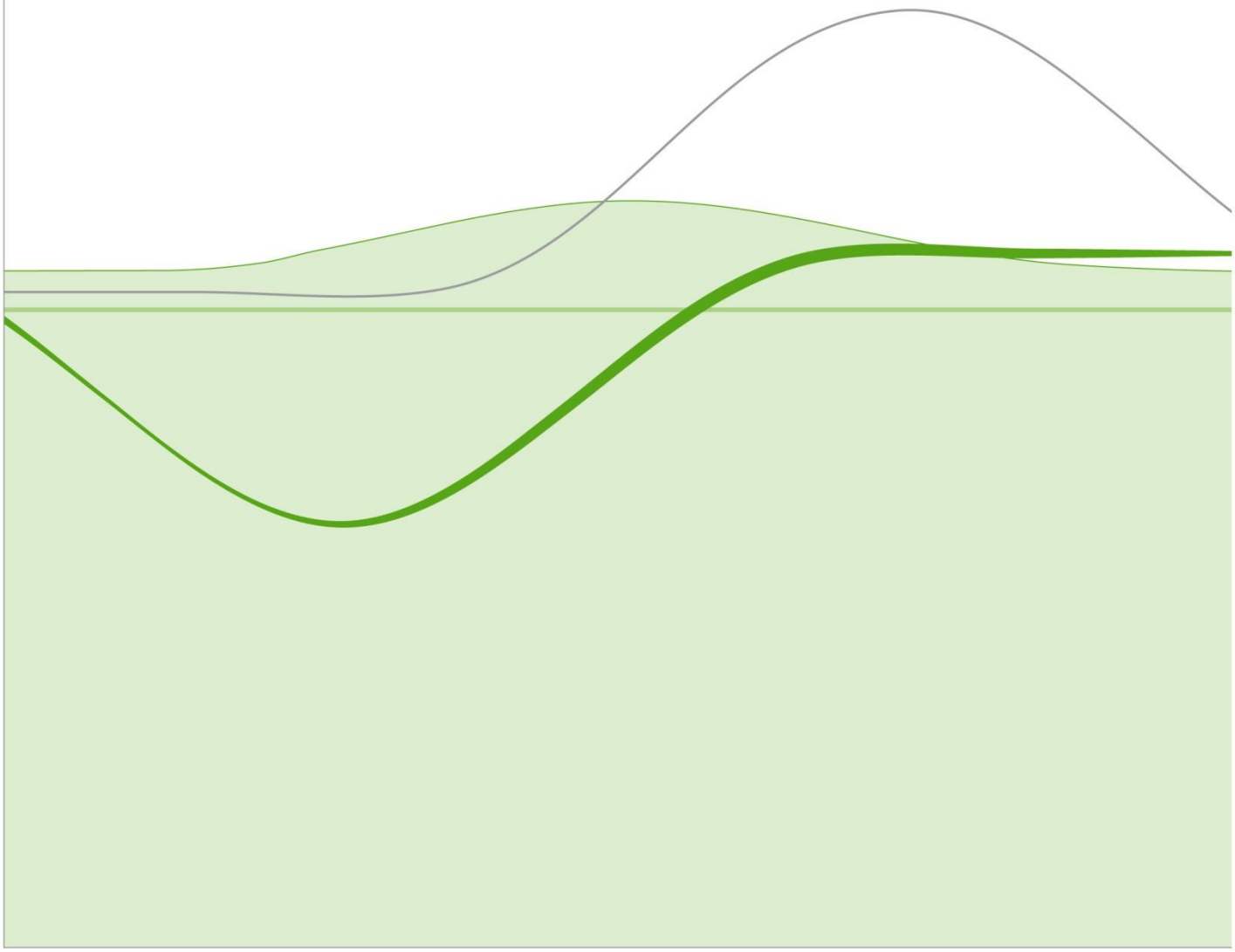

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Incorporating life-cycle price modelling into pharmaceutical cost-effectiveness evaluations

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August 2, 2015

Abstract

Why might the launch price of a new drug be a poor indicator of future expenditure for a drug? Which are the factors that determine the future prices and market shares of a drug? Understanding the answers to these questions can be crucial when conducting cost-effectiveness analyses, i.e. when studying if it is desirable to publicly fund/reimburse a new drug. This paper models and studies the price of a new drug along its life-cycle, from launch to discontinuation, to understand how the price of the drug evolves and to help inform cost-effectiveness evaluations.

JEL classification: I10, I11, I18, L11, L13, L51, L65

Keywords: Pharmaceuticals; Life-cycle price; Drugs competition; Cost-effectiveness analysis

1 Introduction

The health care budget and the impact of pharmaceutical expenditure on it have always been of major interest for all the policy makers in markets where social health insurance provides universal coverage. The need to control pharmaceutical expenditure has become even more urgent in recent years, due to

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financial and political pressures to contain health care spending. Pressure to contain pharmaceutical expenditure coincides with increasing prices of pharmaceuticals, which in turn reflect the growing cost of pharmaceutical R&D, and the increasing demand for health services. To achieve allocative efficiency in drug spending, national pricing and reimbursement (P&R) agencies are increasingly adopting price control policies and making use of health technology assessment (HTA) to decide which new drugs are cost-effective for public provision and funding.

The cost-effectiveness (CE) and the reimbursability, or otherwise, of a new drug can be assessed through the incremental cost-effectiveness ratio (ICER), which compares the incremental cost of funding a new drug with the incremental benefits it provides to patients. As, usually, the benefits of a medicine last also into the future and, similarly, the treatment may need to be provided over the years (possibly for the patient's lifetime), a health sector decision maker needs to assess the present value of future costs and benefits when evaluating the CE of a new drug. In particular, when discounting future costs, the price of a drug is typically assumed to be constant in real terms (i.e. the price increases at the same rate as inflation) and it is discounted at a real interest rate reflecting the time preferences of society. However, this approach does not account for drug life cycle pricing, i.e. the evolution of a drug price throughout its life. The drug launch price (which is considered in cost-effectiveness analysis, CEA) is likely to decrease in both nominal and real terms when other drugs with similar therapeutic effects enter the market. More importantly, when the patent of the drug expires, generic versions are launched and sold at substantially lower prices.

Although the assumption that the real price of a drug stays constant along its life has widely been recognised as not being realistic, the difficulty of predicting a drug price evolution and the lack of theoretical modelling to support policy recommendations have made it difficult for policy makers to account for a drug life-cycle pricing in CEA. To cover this gap, in this paper

we provide a theoretical model to support policy recommendations related to the evolution of a drug life-cycle price and its impact on pharmaceutical expenditure. In particular, the objective of this work is to analyse how a drug price evolves along the drug life cycle, and to show how different factors affect drug pricing and implications for CEA.

We find that when the launch price of a drug is also determined taking into account the future (after patent expiry) evolution of the market, this can have some important implications on how the cost-effectiveness of a drug varies along its life-cycle. In addition, we show that, under specific circumstances, the way in which the ICER is traditionally computed can systematically fail to capture future changes in cost-effectiveness. In these cases, if it is not practical to adopt an adjusted version of the ICER to account for the future, it is recommendable to identify which types of drugs can be systematically favoured or hindered under the traditional ICER and to design a specific corrective policy to deal with misjudged drugs.

We provide the background for the theoretical analysis in Section 2. Our model will be presented and solved for equilibrium values in Section 3. In Section 4 we analyse the equilibrium and in Section 5 we show the impact of life-cycle prices on the ICER. Section 6 concludes.

2 Background

Although almost all the HTA bodies do not account for the future evolution of drug prices in CEA, a notable exception is Pharmac, the New Zealand agency that manages Government spending on medicines. Pharmac clearly recognises that the future costs of using a drug should take into account the lower price of a future generic medicines, as it is very likely that the price of a new drug will drop substantially after generic entry. Therefore, in its economic analysis guidelines Pharmac allows for a one-off drop in price when

the patent of the new drug expires.[1]

The need for life-cycle pricing considerations in CEA is also highlighted by academic research. Hoyle (2008) conducted a statistical study to analyse the historical change in price of individual drugs in the UK, finding that the real price of drugs has fallen over time. For this reason the author recommends that a methodology accounting for the decreasing true cost of a drug should be introduced in all UK drug-related CEAs. Hoyle (2011) also observes that the real price of drugs does not stay constant over the time and develops a 'life-cycle correction factor' to account for future price reductions in CEA. Similarly, Refoios Camejo et al. (2012) and Refoios Camejo et al. (2013a) observe that drugs' prices decrease over time due to market competition and loss of exclusivity. Although these works provide an excellent contribution to study the policy implications of including the drug life-cycle prices into CEA, they do not address the issue of how the prices are determined, i.e. how prices evolve along the drugs life depending on the characteristics of a market. We aim to study how prices are set and their impact on CEA by considering two main aspects of a drug life: launch and patent expiry.

Contrary to many beliefs, the launch price of a drug is not set at the monopoly level even if a patent protects the manufacturer from direct competition. Especially in countries where HTA bodies decide about the reimbursement of new drugs, launch prices are normally a function of var-

[1] More in detail, Pharmac's guidelines for pharmacoeconomic analysis (Pharmac, 2012) say:
"When calculating the cost of a pharmaceutical intervention and comparator pharmaceutical(s), consideration should also be given to the length of the pharmaceutical patent and time until a generic pharmaceutical is likely to become available. It is recommended that in cases where the patent expiry is within 10 years from expected date of pharmaceutical funding, the expected time and price reduction from a likely generic pharmaceutical should be included in the analysis. If the patent expiry is after 10 years from expected date of funding, a conservative proxy should be used for the estimated time until the introduction of a generic pharmaceutical and subsequent price reduction (e.g. 25 years until expiry and 70% price reduction with introduction of generic)."

ious factors such as the price and the quality of therapeutic alternatives (Refoios Camejo et al., 2011, 2013b). We will therefore model horizontal and vertical competition between the new drug and existing therapeutic alternatives to include therapeutic competition aspects into the determination of the launch price. A similar model of therapeutic competition has been considered, for instance, in Brekke et al. (2007).

Moreover, it is also documented that, when patent expires, instead of engaging a price competition with the generic version of the off-patent drug which enters the market, a manufacturer prefers to exploit brand-loyalty and to charge a relatively high price to the consumers who prefer the branded originator to the generic version (Berndt and Aitken, 2011; Kanavos et al., 2008; Lu and Comanor, 1998). Brand-loyalty can be profitable to manufacturers to the extent it can be sustained in the long run. From the payer's perspective, to achieve budget savings, policies can be implemented to affect the degree to what consumers stay loyal to a brand and encourage switching to generic versions when they become available. We will model vertical differentiation between the branded and generic version to capture the different perceptions of the consumers over the quality of generics.[2] In particular, an exogenous parameter will measure the magnitude of brand-loyalty and inform how equilibrium values would change when policy makers implement policies to limit brand-loyalty.

The present work is close to Brekke et al. (2007), who analyse the market structure and the pricing of a new drug competing with a branded incumbent and the generic version of the latter. The branded incumbent and the entrant are assumed to be horizontally differentiated à la Hotelling and to provide the same level of therapeutic benefit/quality. The branded incumbent and generic version are supposed to be vertically differentiated. The competition between between the two branded drugs and the generic is simultaneous.

[2]A similar approach has been used in Antoñanzas et al. (2011), Cabrales (2003), Frank and Salkever (1992, 1997) and Koenigbauer (2007) among the others.

Brekke et al. study the impact of different price regulation policies on the entry and pricing decision of the new entrant drug to explore which policy has the best impact on total welfare and pharmaceutical expenditure. Our model builds on a similar structure but in addition we assume that there are two different periods, one with between-brand (i.e. between branded alternatives) competition only, and one with between-brand and intra-brand (i.e. branded originator vs. generic) competition after patent expiry. We also allow for the two branded drugs to be vertically differentiated, i.e. the new drug can provide a superior therapeutic effect with respect to the existing drug. And to focus this study on how the price of a new drug evolves along its life-cycle, we consider the branded alternative as an exogenous competitor. This is not necessarily a strong assumption, as the pharmaceutical market is usually characterised by examples where the price of an incumbent competitor does not change in response to the entry of a new drug. For instance, if the competitor is a generic drug, its price is already close to the marginal cost so it cannot be adjusted downward. Even in the case of an on-patent incumbent drug the manufacturer usually prefers to adopt non-pricing strategies to react to the new entry (Ellery and Hansen, 2012). Or it can also be the case where the current standard of care is not even a drug but, for instance, a medical device or a surgical intervention. In this case the price of the intervention is often regulated and very unlikely to vary.

3 The model

We consider the market for a therapeutic indication in two different periods, $\tau = 1, 2$ (time is discrete). In the first period, a new drug B is launched to treat patients with the indication. It is assumed that, under the current standard of care, all these patients are treated with drug C from a different manufacturer. Patients are heterogenous and differentiated in one characteristic (e.g. genetic structure, age, physical status) so they can be represented

in the Hotelling unit segment, where a given patient is denoted by $x \in [0,1]$. Drugs B and C are exogenously located at $x = 0$ and $x = 1$, respectively,[3] and their therapeutic effect varies across different patients diminishing at a constant rate $\varepsilon > 0$. In the second period, the patent of drug B expires and a generic drug G enters the market. Drug G is produced by a third manufacturer and is not horizontally differentiated from B (i.e. it is located at $x = 0$). However, some patients (or their GPs who prescribe a specific treatment) might have different perceptions of the efficacy of generic drugs and in general they would tend to attribute an inferior efficacy to the generic version of drug B (brand-loyalty). We represent the fraction of these patients/GPs by parameter $\lambda \in (0,1)$. In this case, the perceived quality of G is captured by the random variable $\theta \in [0,1)$, where a patient (or a prescribing GP) characterised by $\theta = 0$ does not perceive any quality in generic drugs. The other fraction of patients/GPs, $1 - \lambda$, does not distinguish between the branded originator and the generic version so the efficacy of the two versions of the drugs is considered the same (i.e. $\theta = 1$).

We also assume that B (and G) will be discontinued at the end of period 2 (either because the drug becomes obsolete or because the patients do not need it anymore). For the sake of simplicity, and to keep the analysis brief, there is no uncertainty over the future.[4] All the manufacturers incur a constant marginal cost $c_i > 0$, with $i = \{B, C, G\}$, to produce a unit of their drug. Moreover, it is assumed that the branded and the generic companies have

[3]The present analysis does not address the issue of location in the characteristic space, which is instead taken as exogenous. As pointed out by one reviewer, this is an acceptable assumption when approaching the issue for the first time. However, this assumption should be relaxed and the choice of location should be allowed to cover all the set of relevant cases. For the sake of brevity and to keep this paper readable, we do not cover this issue here but we recognise that this may provide a worthwhile extension of our basic model.

[4]As pointed out by one reviewer, introducing uncertainty would not change the main argument in this analysis: changes of the pharmaceutical prices over the time affect the cost-effectiveness at launch of a new medicine. Uncertainty can be introduced in an extension to this model to study how it can affect the decisions of an HTA body and to suggest possible solutions to deal with it.

reached the same efficiency levels in manufacturing, so they face the same marginal cost: $c_g = c_b$. In addition, we assume that the market for generic drugs is perfectly competitive and other generic competitors would kick G off the market by charging a lower price if manufacturer G would set a positive markup above the marginal cost of manufacturing. Therefore, the price of the generic version is considered to be equal to its marginal cost c_b. The R&D costs of B and C are sunk as incurred before launch and G does not have any fixed cost as it uses the off-patent technology of B.

We analyse a simple model where the choices of the comparator C are taken as exogenous. Manufacturer B maximises its intertemporal profits by setting a price $p_{b,\tau} > 0$ in each period.[5] We first describe the market structure in the two periods and then fully characterise the pricing choice of B.

3.1 Market structure under patent protection

In the first period, the brand drug B is launched and competes against the comparator C. Each drug provides a therapeutic benefit, whose quality is measured by a value parameter $e_i > 0$, with $i = \{B, C\}$. It is assumed that the value of each drug is always larger than its marginal cost, i.e. $e_i > c_i$. Given a drug price $p_{i,1}$ and the different efficacy of drugs for different patients, patient's x net benefit $u_{i,t,x}$ is:

$$u_{i,1,x} = \begin{cases} e_b - p_{b,1} - x\varepsilon, & \text{if } i = B \quad (1a) \\ e_c - p_{c,1} - (1-x)\varepsilon, & \text{if } i = C \quad (1b) \end{cases}$$

[5]The equilibrium is therefore determined by the solution of the manufacturer's optimisation problem. The model can be expanded to consider the comparator's manufacturer is also a player: in this case the equilibrium concept would be subgame perfect equilibrium.

In this case, the indifferent patient is[6]

$$\tilde{x}_1 = \frac{1}{2} + \frac{e_b - e_c}{2\varepsilon} - \frac{p_{b,1} - p_{c,1}}{2\varepsilon}$$

If we define $\sigma \equiv \frac{1}{2\varepsilon}$, σ would denote the degree of competition in the market and the indifferent patient between B and C can be expressed as[7]

$$\tilde{x}_1 = \frac{1}{2} + \sigma(e_b - e_c) - \sigma(p_{b,1} - p_{c,1}) \tag{2}$$

Let $d_{i,\tau}$ denote the market share of manufacturer i, then $d_{b,1} = \tilde{x}_1$ and $d_{b,2} = 1 - \tilde{x}_1$, as represented in Figure 1.

3.2 Market structure after patent expiry

After the patent of B has expired, the generic drug G enters the market at price $p_{g,2}$ providing the same therapeutic benefit, e_b, as B. Now competition can happen intra-brand (i.e. branded originator vs. generic version) or between brands (branded originator and generic version vs. comparator).

[6] An implicit assumption of the model is the absence of health insurance: usually patients do not pay the full price and there is a difference between what the patient pays and what the manufacturer receives. We do not consider the issue here as it would imply adding more variables to the model, reducing its tractability. However, as correctly pointed out by one reviewer, the moral hazard problem is not only a matter of higher consumption, it also changes the sensitivity of demand to prices, which affects the equilibrium values. If both drugs receive the same co-insurance rate to patients/consumers, then prices will be higher in equilibrium as demand will be less sensitive, even if total demand is constant. Under symmetry the indifferent patients will be the same, and the co-insurance rate will just be an adjustment in transport cost. However, in case of asymmetries in costs or co-insurance rates this will not be true. Similarly, the co-insurance rate of generics would affect the equilibrium if asymmetric. We leave the inclusion of (asymmetric) health insurance in the analysis as a possible future extension of the model.

[7] We focus on interior solutions, i.e. when both the new drug manufacturer and the current standard of care compete in the market. We provide the details for interior solutions to hold in Appendix B.

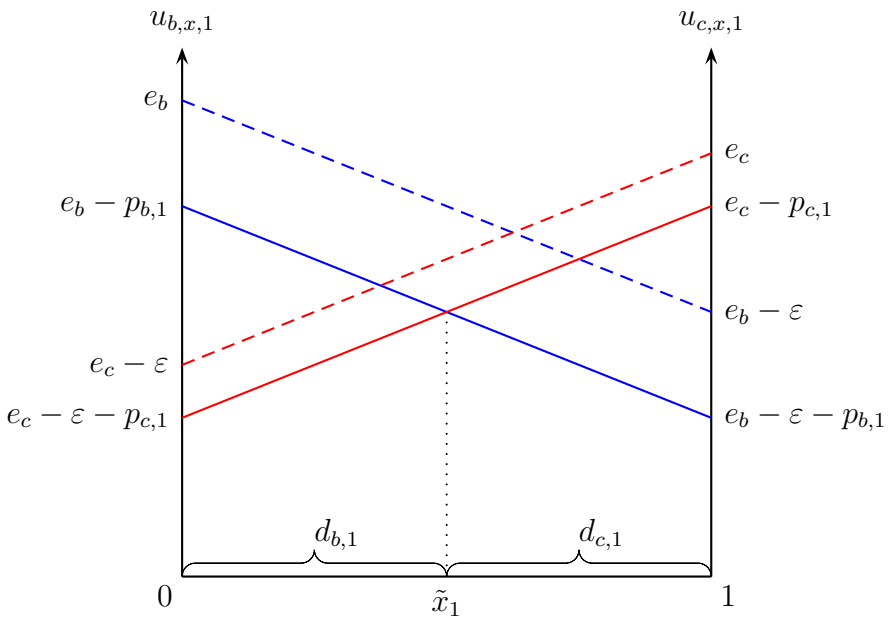


Figure 1: Market shares in period 1 (B in blue and C in red).

3.2.1 Intra-brand competition

When the patients have used the branded version in the previous period, they can be brand-loyal (fraction λ), and perceive a lower quality for the generic version, or brand-indifferent (fraction $1-\lambda$), and attribute the same efficacy to generic and originator.[8] In case of brand-loyal patients, the perceived efficacy of G is θe_b when compared to B (so the expected patient's net benefit

[8]Notice that brand loyalty introduces strategic dependence between the two periods from the perspective of the branded originator: the potential size of the market of brand-loyal GPs/patients depends on the size of the market for the new drug in the first period, which ultimately depends on the launch price (i.e. the manufacturer chooses the price at launch, which determines the market share in the first period that in turn, affects the share of loyal consumers in the second period).

varies across the two drugs depending on parameter θ):

$$u_{i,2,\theta} = \begin{cases} e_b - p_{b,2} - x\varepsilon, & \text{if } i = B \\ \theta e_b - c_b - x\varepsilon, & \text{if } i = G \end{cases}$$

and the indifferent patient is[9]

$$\tilde{\theta}_2 = 1 - \frac{p_{b,2} - c_b}{e_b} \tag{3}$$

In case of brand-indifferent patients, competition is à la Bertrand, i.e. the patients always receive the cheapest drug. For the branded manufacturer B is not profitable to set a price below the marginal cost c_b (i.e. the price charged by the generic manufacturer) because it would incur in losses. It could match the price of the generic version ($p_{b,2} = c_b$) but in this case it would make zero profits in both the loyal and brand-indifferent segments of the market. Therefore, the best strategy for B is to set a positive markup so it can make positive profits in the loyal segment. This implies that all the brand-indifferent patients will receive drug G as it is the cheapest.

3.2.2 Between-brand competition

Given the availability of a cheapest variant of drug B, some patient subpopulations will switch from the old comparator to the new drug.[10] In addition, we allow for the price of the comparator to decrease in the second period, i.e. $p_{c,2} \leq p_{c,1}$. This possibility is introduced to cover the case where regulator cuts the price of the comparator. If so, it could be the case where the comparator gains a larger market share with respect to the previous period to the detriment of the branded drug and its generic version. To keep the analysis

[9] In this case, it can be shown that there is always an interior solution.

[10] No switching costs from migrating from one medicine to another are assumed in the model and consumption decisions are based only on comparison between prices and effectiveness.

relatively concise, we rule out this possibility by assuming that the decrease in the comparator price is not larger than the markup of the branded drug in the first period ($p_{b,1} - c_b$).

Assumption 1. *We assume that the markup of the branded originator in the first period is larger than the price decrease of the comparator drug between the first and the second period:* $p_{b,1} - c_b > p_{c,1} - p_{c,2}$.

This assumption implies that $\tilde{x}_2 > \tilde{x}_1$ (i.e. the new drug expands its market share in the second period) and also excludes the possibility of a corner solution where the comparator serves all the market in the second period.

When a patient has not used the branded version B in the previous period the brand-loyalty effect would be ruled out and, therefore, the switching patients will all be prescribed the cheapest drug, i.e. the generic version.[11] In this case, a patient's net benefit is

$$u_{i,2,x} = \begin{cases} e_b - c_b - x\varepsilon, & \text{if } i = G \quad (4a) \\ e_c - p_{c,2} - (1-x)\varepsilon, & \text{if } i = C \quad (4b) \end{cases}$$

The indifferent patient is[12]

$$\tilde{x}_2 = \frac{1}{2} + \sigma(e_b - e_c) - \sigma(c_b - p_{c,2}) \quad (5)$$

We represent the market structure in the off-patent period in Figure 2. In

[11] This means that patients' or GPs' preferences loyalty only operates within the brand, i.e. some patients/GPs might think that the branded version of a medicine is better than the generic. However, when comparing two different brands (no matter if the originator or the generic version), consumers' choice depends on prices and effectiveness only, and no loyalty effect is in place. For instance, this could be due to a revision of the prescription guidelines, which might recommend the new drug to a subgroup population who were using the comparator before the patent expiry.

[12] The conditions for an interior solution to hold are provided in Appendix B.

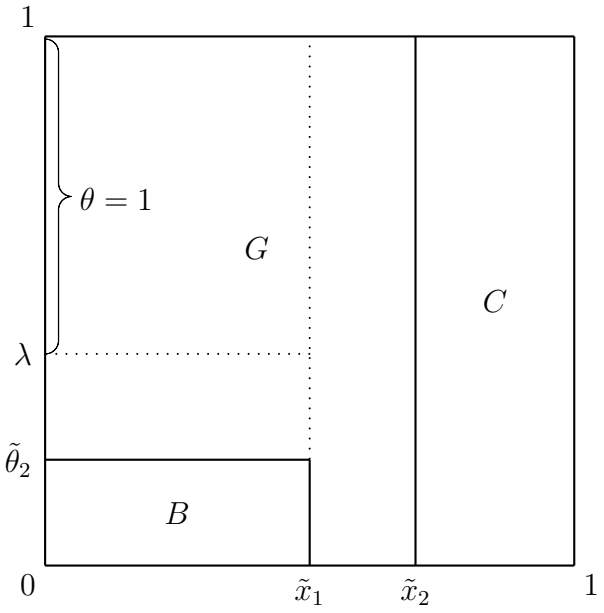


Figure 2: Market shares in period 2

particular, the market share of B is

$$d_{b,2} = \lambda \tilde{x}_1 \tilde{\theta}_2 = \lambda \tilde{x}_1 \left(1 - \frac{p_{b,2} - c_b}{e_b}\right) = \frac{\lambda \tilde{x}_1 (e_b - p_{b,2} + c_b)}{e_b} \tag{6}$$

while the demand for the generic drug is $d_{g,2} = \tilde{x}_2 - \lambda \tilde{x}_1 \tilde{\theta}_2$.

3.3 Branded drug pricing and equilibrium market shares

Given the marginal cost c_b, the profits in each period for manufacturer B are

$$\pi_{b,t} = \begin{cases} (p_{b,1} - c_b)\tilde{x}_1 & \text{if } \tau = 1 \\ (p_{b,2} - c_b)\frac{\lambda \tilde{x}_1 (e_b - p_{b,2} - c_b)}{e_b} & \text{if } \tau = 2 \end{cases} \tag{7}$$

We assume a discount factor $\beta \in (0,1)$ is used to represent the current value at period 1 of the profits the branded manufacturer makes in period 2, so the present value of total profits of B is $\Pi_b = \pi_{b,1} + \beta\pi_{b,2}$. The equilibrium prices are characterised by the first order conditions $\frac{\partial \Pi_b}{\partial p_{b,1}} = 0$ and $\frac{\partial \Pi_b}{\partial p_{b,2}} = 0$ and are[13]

$$p^*_{b,1} = \frac{1}{4\sigma} + \frac{p_{c,1} + c_b + e_b - e_c}{2} - \frac{\beta\lambda e_b}{8} \tag{8}$$

$$p^*_{b,2} = \frac{e_b}{2} + c_b \tag{9}$$

In the first period, with market exclusivity, the main competitor of the new drug is the current standard of care C. Notice that the optimal price $p^*_{b,1}$ is lower than the price that would be expected if the manufacturer would not consider future profits when deciding prices, i.e. if $\beta = 0$, and if there were no brand-loyalty, i.e. $\lambda = 0$. The reason is that manufacturer B anticipates the impact of the current price on current and future market shares. In particular, a relatively low launch price implies a higher market share in the first period and, because of brand loyalty, a higher market share in the second period. Therefore, increasing market penetration through a lower price allows exploiting the benefits from the loyal market in the second period. As it should be expected, the current price is increasing in the efficacy of the treatment, e_b the marginal cost of producing the drug c_b, and in the price of the competitor $p_{c,1}$. Moreover, it is decreasing in the degree of competition σ, in the discounting factor β and in the size of the brand-loyal segment of the market.

[13] Further details on the first order conditions are provided in Appendix A.

3.3.1 Equilibrium market shares

Given the optimal prices, the equilibrium market shares of B are

$$d^*_{b,1} = \frac{1}{4} + \frac{\sigma(e_b - e_c + p_{c,1} - c_b)}{2} + \frac{\beta\sigma\lambda e_b}{8}$$
$$d^*_{b,2} = \lambda\tilde{\theta}_2 d^*_{b,1} = \frac{\lambda}{2}\left(\frac{1}{4} + \frac{\sigma(e_b - e_c + p_{c,1} - c_b)}{2} + \frac{\beta\sigma\lambda e_b}{8}\right)$$

Recall that the total market covered by the new drug, either by the branded originator B or by the its generic version G, is $\tilde{x}_2$ as defined in (5), which is larger than the total market covered by the new drug in the first period, $\tilde{x}_1$. We denote by

$$s_{b,2} \equiv \frac{d^*_{b,2}}{\tilde{x}_2} = \frac{\frac{\lambda}{2}\left(\frac{1}{4} + \frac{\sigma(e_b - e_c + p_{c,1} - c_b)}{2} + \frac{\beta\sigma\lambda e_b}{8}\right)}{\frac{1}{2} + \sigma(e_b - e_c) - \sigma(c_b - p_{c,2})}$$

the share of B over the generic version for the market of the new drug only. Similarly,

$$s_{g,2} \equiv 1 - \frac{d^*_{b,2}}{\tilde{x}_2} = 1 - \frac{\frac{\lambda}{2}\left(\frac{1}{4} + \frac{\sigma(e_b - e_c + p_{c,1} - c_b)}{2} + \frac{\beta\sigma\lambda e_b}{8}\right)}{\frac{1}{2} + \sigma(e_b - e_c) - \sigma(c_b - p_{c,2})}$$

is the share of the generic in the market of the new drug only. We can therefore express the average price of the new drug weighted by market shares as

$$\bar{p}_2 \equiv s_{b,2} p^*_{b,2} + s_{g,2} c_b \tag{10}$$

4 Equilibrium analysis

In this section we compare the patient surplus provided by the new drug (either in the branded version and in the generic version when this is available) and the pharmaceutical expenditure with the case where the new drug is not

launched and C is the only available therapy.

4.1 Patient surplus

In period 1, the total patient benefit when treated with drug B is

$$B_{b,1} = \int_0^{\tilde{x}_1} u_{b,x,1} dx = \left(e_b - \frac{\tilde{x}_1}{4\sigma} \right) \tilde{x}_1$$

Similarly, if treated with the standard of care, the total patient benefit would be

$$B_{c,1} = \int_0^{\tilde{x}_1} u_{c,x,1} dx = \left(e_c - \frac{2 - \tilde{x}_1}{4\sigma} \right) \tilde{x}_1$$

Therefore, the total health gain for the patients treated with the new drug B, represented in Figure 3(a), is the difference between the two total health gains:

$$\Delta B_1 = B_{b,1} - B_{c,1} = \left(e_b - e_c - \frac{1}{2\sigma} \right) \tilde{x}_1$$

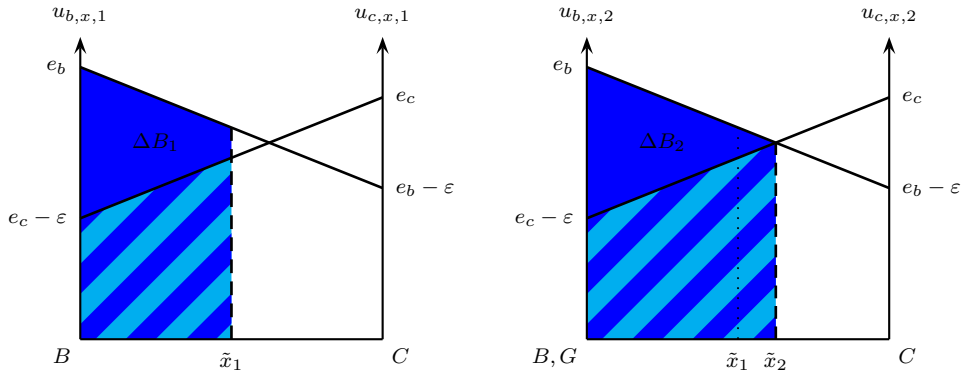
On average, the health gain for a patient treated with the new drug is

$$\Delta \bar{B}_1 = \frac{\Delta B_1}{\tilde{x}_1} = e_b - e_c - \frac{1}{2\sigma} = e_b - e_c - \varepsilon \tag{11}$$

The average health gain as in (11) is the incremental benefit an HTA body considers when performing CEA. The average health in period 2, illustrated in Figure 3(b), is the same as in period 1 (see Appendix C for details).

Assumption 2. *We assume that the average health gain from the new drug is positive, that is, we assume that* $e_b - e_c - \varepsilon > 0$.

Notice that Assumption 2 requires that the new drug performs better than the existing standard of care for at least one patient. In principle, new drugs providing lower benefits could be introduced in the market if at a significantly lower price compared to the existing standard. However there is only a limited number of cases where this has happened, and the



(a) Period 1 (b) Period 2

Figure 3: Health gain from the new drug (solid blue area). The striped area shows where the health benefit from B (or G) and C is the same.

vast majority of cost-effectiveness evaluations involves drugs that represent therapeutic improvements with respect to the current standard of care.

4.2 Pharmaceuticals expenditure

The new medicine B implies an increment in the pharmaceutical expenditure if the price of the new drug is larger than the price of the existing standard of care. However, when the generic version becomes available, the price of the generic can be lower than the price of the comparator, so the incremental pharmaceutical expenditure could be negative in the second period. To establish the net impact of the introduction of the new drug, we analyse how the total pharmaceutical expenditure changes over the two periods.

4.2.1 Period 1

In the first period a share $d^*_{b,1}$ of patients receive the new drug at price $p^*_{b,1}$ instead of the comparator at price $p_{c,1}$, therefore the incremental price to

provide the new drug to these patients is

$$\Delta p_1 \equiv p^*_{b,1} - p_{c,1} = \frac{1}{4\sigma} + \frac{e_b - e_c - p_{c,1} + c_b}{2} - \frac{\beta\lambda e_b}{8}$$

The total incremental pharmaceutical expenditure, $\Delta P_1 \equiv \Delta p_1 d^*_{b,1}$, is the additional expenditure to provide medicine B:

$$\Delta P_1 = \frac{\sigma}{4}\left((1 + 2(e_b - e_c))^2 - \frac{(4(p_{c,1} - c_b) + \beta\lambda e_b)^2}{4}\right) \tag{12}$$

4.2.2 Period 2

In the second period a share $\tilde{x}_2$ of patients receive the new drug, either in the branded or in the generic format, and the average price is $\bar{p}_2$. In this case, the total incremental expenditure, $\Delta P_2 = (\bar{p}_2 - p_{c,2})\tilde{x}_2$, is

$$\Delta P_2 = \frac{\lambda e_b}{4}\left(\frac{1}{4} + \frac{\sigma(e_b - e_c + p_{c,1} - c_b)}{2} + \frac{\beta\sigma\lambda e_b}{8}\right) + \\ - (p_{c,2} - c_b)\left(\frac{1}{2} + \sigma(e_b - e_c) - \sigma(c_b - p_{c,2})\right) \tag{13}$$

The incremental expenditure in Equation (13) consists of two terms. In the second line we have the incremental expenditure (if $p_{c,2} \leq c_b$) assuming that all the patients who are prescribed the new drug in the second period receive the generic version. Notice that if the price of the generic version is lower than the price of the comparator, i.e. if $p_{c,2} > c_b$, this term would represent the incremental saving in the second period due to the introduction of the new drug. However, given the brand-loyalty and the fact that the branded manufacturer charges a positive markup, the incremental expenditure also includes the positive markup over the marginal cost, represented in the first line of Equation (13) by the profits of B.[14]

[14]Further details about the derivation of the incremental pharmaceutical expenditure in the two periods are provided in Appendix D.

4.3 Interior solutions

The equilibrium prices and market shares are consistent with the model where both the new drug and the comparator have positive market shares in the first and in the second period if there exists at least one indifferent patient between the new drug and the comparator. This requires the degree of competition to be smaller than a given threshold in both periods.[15] In particular, in the first period it is necessary that $\sigma < \sigma_1$, where

$$\sigma_1 \equiv \frac{2}{-4(e_b - e_c - p_{c,1} - c_b) + \beta\lambda e_b - 8p_{c,2}} \tag{14}$$

in case that $\xi_1 \equiv -4(e_b - e_c - p_{c,1} - c_b) + \beta\lambda e_b - 8p_{c,2} > 0$. In the second period, the condition is that $\sigma < \sigma_2$, where

$$\sigma_2 \equiv \frac{1}{2(e_b - e_c + p_{c,2} - c_b)} \tag{15}$$

in case $\xi_2 \equiv e_b - e_c + p_{c,2} - c_b > 0$.

5 Effects of change in future drug price on cost effectiveness

The price and the effectiveness of the new medicine are the input used by the HTA to decide about its reimbursement. In this analysis, we do not consider the outcome of the HTA process: the reimbursement decision stage would be a sub-game of a larger game, and price setting would depend on it. Instead, we are interested in analysing how the incremental cost-effectiveness ratio (ICER), one of the instruments that can be used by an HTA body to inform its decisions, varies depending on whether the life-cycle price is taken into account or not.

[15] See Appendix B for further details.

In particular, in this section we analyse how the ICER should be determined to account for the future price change due to the generic entry. We first consider the benchmark case where cost-effectiveness is evaluated at the launch price only, as typically occurs in traditional CEA. We will then compare it to the adjusted version of the ICER where future costs account for the generic entry. When comparing the two ICERs, one might be interested in understanding whether under specific policy measures the traditional ICER might favour (vs. hinder) certain types of drugs with respect to the adjusted ICER; the last part of this section will analyse if this is the case.

5.1 Benchmark

Let us denoted by δ_τ the discounting factor for prices for period τ and by δ_T the total discounting factor for all the drug life. Similarly, we denote by ρ_τ the discounting factor for health gains for period τ and by ρ_T the total discounting factor for all the drug life. In this case, the ICER for the new drug B compared to the existing standard of care C is

$$R_b = \frac{\delta_T \left(p^*_{b,1} - p_{c,1}\right)}{\rho_T \Delta \bar{B}} = \frac{\delta_T \left(\frac{1}{4\sigma} + \frac{e_b - e_c + c_b - p_{c,1}}{2} - \frac{\beta \lambda e_b}{8}\right)}{\rho_T \left(e_b - e_c - \varepsilon\right)} \tag{16}$$

It is easy to observe that the standard ICER is an increasing function of the marginal cost of the new drug c_b: a higher production cost is translated into a higher launch price, which ultimately leads to a higher incremental cost. Moreover, the standard ICER is a decreasing function of the current price of the comparator $p_{c,1}$ (as it should be expected), of the discount factor for future profits β and of the size of the loyal segment of the market λ. Notice that the larger is β, the more important are future profits compared to current profits. This can be due to the fact that the patent of the drug is close to expiry when the new drug is launched, so profits (and the drug price) after patent expiry have a more relevant impact on the current pricing decision of the manufacturer. This effect is emphasised by the brand-loyalty:

the larger is the loyal segment of the market, the larger can be the future profits. For these reasons, a manufacturer can decide to charge a relatively lower price in the first period (implying a lower ICER) so it can gain a larger market share on which to exploit the loyalty advantage in the second period. Finally, as the standard ICER does not focus on the future price changes, a variation of the price of the current standard of care $p_{c,2}$ has no impact on it.

5.2 Adjusted ICER

The adjusted ICER needs to account for the impact of the generic entry on the price of the new drug. We therefore consider the weighted average price for the new drug in second period as defined in (10).[16] In this case, the ICER adjusted for accounting the life-cycle pricing of the new drug should be computed as follows:[17]

$$\begin{aligned}\hat{R}_b &= \frac{\delta_1}{\delta_T}R_b + \frac{\delta_2}{\rho_T}\frac{\bar{p}_2 - p_{c,2}}{\Delta\bar{B}} \\ &= \frac{\delta_1}{\delta_T}R_b + \frac{\delta_2}{\rho_T}\frac{\frac{\lambda e_b}{4}\left(\frac{1}{4}+\frac{\sigma(e_b-e_c+p_{c,1}-c_b)}{4}+\frac{\beta\sigma\lambda e_b}{8}\right)}{\frac{1}{2}+\sigma(e_b-e_c)-\sigma(c_b-p_{c,2})} + c_b - p_{c,2}}{\Delta\bar{B}}\end{aligned} \tag{17}$$

[16] If we take the price of the generic as the cost of the therapy in the second period, the ICER adjusted for future price variations is:

$$\hat{R}_b = \frac{\delta_1\left(p^*_{b,1} - p_{c,1}\right) + \delta_2\left(c_b - p_{c,2}\right)}{\rho_1\Delta\bar{B} + \rho_2\Delta\bar{B}} = \frac{\delta_1}{\delta_T}R_b + \frac{\delta_2}{\rho_T}\frac{c_b - p_{c,2}}{\Delta\bar{B}}$$

This formula would represent the adjusted ICER if the future price would be assumed to be the generic price only, i.e. ignoring brand loyalty and the fact that the new drug can be sold at a higher price with respect to the generic when off-patent. However, although HTA bodies usually consider the price of generics in CEAs if there is a generic alternative available, the adjusted ICER should account for both the branded originator and generic prices.

[17] Further details about the derivation of the adjusted ICER are provided in Appendix E.

where it is considered that in the second period the drug will be sold at a lower price.[18] If we denote by $\hat{R}_2 \equiv \frac{\delta_2(\bar{p}_2 - p_{c,2})}{\rho_2 \Delta B}$ the future ICER adjusted to account for the average price, the life-cycle adjusted ICER can be expressed as

$$\hat{R}_b = \frac{\delta_1}{\delta_T} R_b + \frac{\rho_2}{\rho_T} \hat{R}_2 \tag{18}$$

Expression (18) shows that the life-cycle adjusted ICER is a weighted average between the ICER as currently computed, R_b, and the future ICER computed when patent expires, $\hat{R}_2$. The weight of R_b is the ratio between the discounting factor for prices for the on-patent period and the total discounting factor along the drug life. The weight of $\hat{R}_2$ is the ratio between the discounting factor for health gains for the off-patent period and the total discounting factor along the drug life. The closer is the patent expiry to the end of the useful life of the drug, i.e. as $\bar{t}$ approaches T, the closer is the first ratio/weight to 1 and the second to 0, meaning that if the patent does not expiry during the time period considered, the adjusted ICER is the same as the traditional ICER.

5.3 Comparison between the standard and the adjusted ICERs

Equation (18) shows how the adjusted ICER is a weighted sum of the standard and the future ICER. It is easy to see that the future ICER, $\hat{R}_2$, depends positively on the first period price of the comparator $p_{c,1}$, the discount factor β and the size of the loyal market segment λ. Parameters $p_{c,1}$ and λ contribute to increase the market share of the branded drug in the second period

[18] This would still be the case in a different modelisation where manufacturers are myopic, i.e. they do not account for future profits when setting the launch price. In this case, where $\beta = 0$, the launch price would be higher and the generic market share in the second period would be larger. This would not change the qualitative findings discussed here but would amplify their magnitude, implying that the errors in the assessment associated with using the traditional ICER would have a larger impact.

to the detriment of the share of the generic version, so the average price paid for the new drug is larger. Parameter β emphasises this effect. Moreover, $\hat{R}_2$ depends negatively on the period 2 price of the comparator $p_{c,2}$: the larger is this price, the more patients switch to the new drug in second period paying the generic price c_b.

Given that changes in these parameters have opposite impacts on the standard ICER R_b and the future ICER $\hat{R}_2$, the overall impact on the adjusted ICER can be different from the impact on the standard ICER (see Table 1). Therefore the standard and the adjusted ICER could move in opposite direction when a given parameter changes. This can have important implications for the assessment of different drugs with different characteristics, as the standard ICER might favour some types drugs that the adjusted ICER might hinder, and vice versa. We conclude this analysis by examining

Parameter:	$p_{c,1}$	$p_{c,2}$	β	λ
R_b	$-$	0	$-$	$-$
$\hat{R}_2$	$+$	$-$	$+$	$+$
$\hat{R}_b$	?	$-$	?	?

Table 1: Impact of different parameters on the standard (R_b), the future ($\hat{R}_2$) and the adjusted ($\hat{R}_b$) ICERs.

when these parameters have an opposite impact on the two ICERs.

5.3.1 The impact of the current price of the comparator $p_{c,1}$

The current price of the comparator has a negative impact on the traditional ICER: the bigger is the price of the current standard of care, the lower is the incremental cost of adopting the new drug, implying a lower incremental cost-effectiveness ratio. After the patent expiry, the fact that the new drug

has gained a larger market share in the first period, due to a relatively large price of the comparator, implies that the branded manufacturer can exert the brand-loyalty advantage on a relatively larger segment of the market, reducing the benefits from the lower price of the generic. This latter effect can prevail on the former, implying the current price of the comparator has a positive effect on the adjusted ICER, under given circumstances.

Proposition 1. *A change in the current price of the comparator has opposite impacts on the traditional and the adjusted ICER when the degree of competition is large enough and the HTA body considers relatively important the future value of the drug. That is, if*

$$\begin{cases} \sigma > \dfrac{2\delta_1}{\lambda e_b \delta_2 - 4(e_b - e_c + p_{c,2} - c_b)\delta_1} & \text{(19a)} \\ \dfrac{\delta_2}{\delta_1} > \dfrac{4(e_b - e_c + p_{c,2} - c_b)}{\lambda e_b} & \text{(19b)} \end{cases}$$

Proof. See Appendix F.1. □

The above proposition states that the positive impact of an increment in $p_{c,1}$ on the future ICER can prevail on the negative impact on the traditional ICER, implying that $p_{c,1}$ has an overall positive impact on the adjusted ICER when two conditions occur.

First, when the differentiation between the new drug and the comparator is small enough, implying that the degree of competition in the market is large enough (Condition (19a)). Higher competition implies that the new drug is launched at a relatively lower price (vs. the launch price in case of low competition). The lower launch price of B has a twofold effect: (1) the new drug obtains a larger market share in the first period, which allows the manufacturer to exploit the brand-loyalty effect on a wider market share in the second period; and (2) since the new drug is relatively cheaper under high market competition, there is less room for the generic version to gain the market of the comparator. The overall effect is that the average price in

the second period is relatively higher (i.e. the average price decrease due to generic entry is lower when the degree of competition is higher).

Second, when the ratio $\frac{\delta_2}{\delta_1}$ is sufficiently large, i.e. when the importance of benefits and costs of the new drug before patent expiry is relatively small compared to the importance after patent expiry, either because patent expiry is close enough to the date of launch or because patients will use the new treatment for many years after patent expiry (Condition (19b)).

5.3.2 The impact of the future price of the comparator $p_{c,2}$

A change in the future price of the current standard of care has no impact on the traditional ICER as changes in future prices are not accounted for. On the contrary, $p_{c,2}$ has always a negative impact on the adjusted ICER: the larger the future price of the comparator is, the lower the future ICER is.

5.3.3 The impact of the discount factor of the private profits β

A change in the discount factor of the future profits has a negative impact on the traditional ICER: the higher the importance of the future profits is, the lower the traditional ICER is. In order to increase its future profits, the branded manufacturer may be willing to set a relatively lower launch price so the market share increases. This implies that the manufacturer will be able to serve a larger market segment of loyal consumers in the future. The ultimate effect is a higher share of the branded version with respect to the generic, leading to a higher average price of the new drug in the second period. Because an increase in the future average price of the new drug will increase the future ICER, the discount factor of the future profits can have an opposite impact on the adjusted ICER under given circumstances.

Proposition 2. *A change in the discount factor of the future profits has opposite impacts on the traditional and the adjusted ICER if the degree of*

competition is large enough and the future value of the drug is relatively important. That is, when

$$\begin{cases} \sigma > \dfrac{2\delta_1}{\lambda e_b \delta_2 - 4(e_b - e_c + p_{c,2} - c_b)\delta_1} & \text{(20a)} \\ \dfrac{\delta_2}{\delta_1} > \dfrac{4(e_b - e_c + p_{c,2} - c_b)}{\lambda e_b} & \text{(20b)} \end{cases}$$

Proof. See Appendix F.2. □

Notice that the above conditions are the same as in Proposition 1 and the reasons why the positive impact of β on the future ICER can prevail on the negative impact on the traditional ICER, implying that β has an overall positive impact on the adjusted ICER, are similar.

5.3.4 The impact of the brand loyalty effect λ

A change in the brand loyalty effect has a negative impact on the traditional ICER: the larger the loyal market segment the branded manufacturer can retain in the second period is, the lower the incremental cost of adopting the new drug is, implying a lower incremental cost-effectiveness ratio. After the patent expiry, the fact that the branded version of the drug has a larger market share, due to the loyalty effect, implies a higher the average price of the new drug. This latter effect can prevail on the former, implying the brand loyalty effect has a positive impact on the adjusted ICER, under given circumstances.

Proposition 3. *A change in the magnitude of the brand loyalty effect has opposite impacts on the traditional and the adjusted ICER if:*

(i) the HTA body assigns a higher value than the branded manufacturer to the future costs and benefits and:

a) the degree of competition is low enough when the HTA body's evaluation of the future is slightly higher than that of the brand manu-

facturer, that is if

$$\sigma \leq \frac{\beta\delta_1 - \delta_2}{(\xi_2 + p_{c,1} - p_{c,2} + \beta\lambda e_b)\delta_2 - 2\xi_2\beta\delta_1} \tag{21}$$

when $\beta \leq \frac{\delta_2}{\delta_1} < \frac{2\xi_2}{\xi_2 + p_{c,1} - p_{c,2} + \beta\lambda e_b}\beta$

b) for any degree of competition when the HTA body assigns a sufficiently larger value to the future compared to the branded manufacturer, that is if $\frac{\delta_2}{\delta_1} \geq \frac{2\xi_2}{\xi_2 + p_{c,1} - p_{c,2} + \beta\lambda e_b}\beta$

(ii) the HTA body assigns a lower value than the branded manufacturer to the future costs and benefits and the degree of competition is high enough. That is, if

$$\sigma > \frac{\beta\delta_1 - \delta_2}{(\xi_2 + p_{c,1} - p_{c,2} + \beta\lambda e_b)\delta_2 - 2\xi_2\beta\delta_1} \tag{22}$$

provided that:

a) $\frac{4(p_{c,1} - p_{c,2}) + \beta\lambda e_b}{3(2(p_{c,1} - p_{c,2}) + \beta\lambda e_b) - 2\xi_2}\beta \leq \frac{\delta_2}{\delta_1} < \beta$ *and* $3(2(p_{c,1} - p_{c,2}) + \beta\lambda e_b) - 2\xi_2 \geq 0$ *when:* $\xi_1 > 0$ *and* $\xi_2 \leq 0$

b) $\frac{4(e_b - e_c + p_{c,2} - c_b)}{3e_b - 3e_c + p_{c,1} + 2p_{c,2} - 3c_b + \beta\lambda e_b}\beta \leq \frac{\delta_2}{\delta_1} < \beta$ *when:* $\xi_1 \leq 0$ *and* $\xi_2 > 0$

c) $\max\left\{\frac{4(p_{c,1} - p_{c,2}) + \beta\lambda e_b}{3(2(p_{c,1} - p_{c,2}) + \beta\lambda e_b) - 2\xi_2}\beta, \frac{4(e_b - e_c + p_{c,2} - c_b)}{3e_b - 3e_c + p_{c,1} + 2p_{c,2} - 3c_b + \beta\lambda e_b}\beta\right\} \leq \frac{\delta_2}{\delta_1} < \beta$ *and* $3(2(p_{c,1} - p_{c,2}) + \beta\lambda e_b) - 2\xi_2 \geq 0$ *when:* $\xi_1 > 0$ *and* $\xi_2 > 0$

d) $\frac{\delta_2}{\delta_1} < \beta$ *when:* $\xi_1 \leq 0$ *and* $\xi_2 \leq 0$

Proof. See Appendix F.3. □

The above proposition states that the positive impact of λ on the future ICER can prevail on the negative impact on the traditional ICER, implying that λ has an overall positive impact on the adjusted ICER in two cases. First, when the HTA body values the future more than the branded manufacturer does. In this case, if the HTA body's evaluation of the future is

sufficiently high compared with the manufacturer's evaluation, the brand-loyalty has always a positive impact on the adjusted ICER. Or, if the HTA body's evaluation is slightly higher than that of the manufacturer and the degree of competition is sufficiently low, the brand loyalty has still a positive impact on the adjusted ICER because the future average price is relatively higher due to a relatively small generic market share. Second, when the HTA body assigns a lower value to the future than the branded manufacturer and the degree of competition is large enough.

6 Conclusions

The analysis in this paper considers how manufacturers take into account the future profitability of the market when deciding the launch price of a new drug. Probably, one of the most important events in a drug life that affects pricing decisions is the patent expiry, as it changes the model of competition. Before patent expiry, a new drug faces no direct (perfect) competition, although other therapeutic alternatives can compete with it. In this case, the market is configured as a model of horizontal (therapeutic) differentiation, although there is also vertical differentiation because the new drug can provide a better quality (efficacy) than the rivals. After patent expiry, the generic entry implies that bio-equivalent drugs enter the market without any form of horizontal differentiation between the generic and the branded originator. However, the generic and the originator can be vertically differentiated because some patients (or prescribing GPs) might prefer the branded version over the generic even if both provide the same therapeutic effect. The loyalty to the brand allows the originator to achieve a positive market share after patent expiry even if its price is above the generic price. In particular, the higher is the brand-loyalty effect after patent expiry, the higher is the importance of achieving a larger market share during patent protection where the loyalty effect can be built on after patent expiry. Therefore, launch price

decisions are also influenced by brand loyalty considerations after patent expiry.

Because the launch price also depends on future considerations, to some extent the traditional ICER (which only looks at the launch price) indirectly incorporates future prices into the analysis. However the launch price reflects the manufacturer's perception of the future only, which does not necessarily corresponds to the cost-effectiveness needs of an HTA body. Since the manufacturer could prefer to set a relatively lower launch price because this allows achieving a larger market share on which exploit brand loyalty in the future charging higher-than-the-generic prices, the traditional ICER can deem as cost-effective a drug that could be cost-ineffective in the future. We verified that an adjusted ICER (which also considers future cost-effectiveness) can provide different cost-effectiveness indications with respect to the traditional ICER. In particular, some parameters that affects the traditional ICER in one direction can affect the adjusted ICER in the opposite. For instance, while traditionally cost-effectiveness is always increasing in the current price of the comparator, future cost-effectiveness might decrease in it because a higher price of the comparator/competitor today might imply a higher market share for the branded originator in the future and less room for the generic.

The key message from this analysis is that the traditional ICER can fail to consider the life cycle cost-effectiveness under some circumstances, leading to the recommendation (or not) of drugs that will be no longer (or that will be) cost-effective in the future. Even if a policy maker might not want to adopt an "adjusted" ICER because this could be considered impractical to compute, it is important to understand if any particular class of drugs is systematically favoured or hindered under the traditional ICER. In the present paper we have suggested some of the characteristics of the market for these misjudged drugs: a high degree of therapeutic competition, a long after-patent useful life and a high importance of the brand-loyalty. From a policy-maker perspective it is therefore recommended to identify which types

of drugs meet the characterisation and verify whether their cost-effectiveness could have been misjudged. Then, a specific corrective policy could be designed to remedy for faulty uses of the traditional ICER.

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A Profit maximisation

The branded drug maximisation problem is

$$\max_{p_{b,1},p_{b,2}} \Pi_b \quad \text{s.t. } p_{b,1}, p_{b,2} \geq 0$$

where

$$\begin{aligned}
\Pi_b &= \pi_{b,1} + \beta\pi_{b,2} \\
&= (p_{b,1} - c_b)\tilde{x}_1 + \beta\lambda\tilde{x}_1\frac{(p_{b,2} - c_b)(e_b - p_{b,2} + c_b)}{e_b} \\
&= \tilde{x}_1\left(p_{b,1} - c_b + \beta\lambda\frac{(p_{b,2} - c_b)(e_b - p_{b,2} + c_b)}{e_b}\right) \\
&= \left(\frac{1}{2} + \sigma(e_b - e_c) - \sigma(p_{b,1} - p_{c,1})\right)\left(p_{b,1} - c_b + \beta\lambda\frac{(p_{b,2} - c_b)(e_b - p_{b,2} + c_b)}{e_b}\right)
\end{aligned}$$

The first order conditions for a maximum are

$$\begin{aligned}
\frac{\Pi_b}{\partial p_{b,1}} = 0 \;&\Rightarrow p_{b,1} = \frac{1}{4\sigma} + \frac{p_{c,1} + c_b + e_b - e_c}{2} - \frac{\beta\lambda(p_{b,2} - c_b)(e_b - p_{b,2} + c_b)}{2e_b} \\
\frac{\Pi_b}{\partial p_{b,2}} = 0 \;&\Rightarrow p_{b,2} = \frac{e_b + 2c_b}{2}
\end{aligned}$$

B Conditions for interior solutions

In order to have an interior solution in both the first and the second period, it is required that $\tilde{x}_1, \tilde{x}_2 \in (0, 1)$. Moreover, to satisfy Assumption 1, we require $\tilde{x}_1 < \tilde{x}_2$. Therefore we need to define which region of the parameters satisfy $0 < \tilde{x}_1 < \tilde{x}_2 < 1$.

In order to have an interior solution in the first period, we need that $\tilde{x}_1$, as defined in Equation (2), is larger than 0 (Assumption 1 automatically

implies $\tilde{x}_1 < 1$ when $\tilde{x}_2 < 1$). This requires

$$p^*_{b,1} < e_b - e_c + p_{c,1} + \frac{1}{2\sigma} \implies \sigma > -\frac{2}{4(e_b - e_c + p_{c,1} - c_b) + \beta\lambda e_b}$$

Given Assumption 2, $e_b > e_c$, implying that the denominator of the above inequality is always positive. Therefore, because $\sigma > 0$, the equilibrium price always satisfies the condition for an interior solution in the first period.

Assumption 1 requires that the total market share of the new drug (both the branded and the generic versions) increases from the first to the second period. The assumption is satisfied when $\tilde{x}_1 < \tilde{x}_2$, requiring that $\sigma < \sigma_1$, where

$$\sigma_1 \equiv \frac{2}{-4(e_b - e_c - p_{c,1} - c_b) + \beta\lambda e_b - 8p_{c,2}}$$

in case that $\xi_1 \equiv -4(e_b - e_c - p_{c,1} - c_b) + \beta\lambda e_b - 8p_{c,2} > 0$. Otherwise, Assumption 1 is always satisfied for any positive value of σ.

In the second period the total market share of the new drug is defined by equation (5). An interior solution is guaranteed if $0 < \tilde{x}_2 < 1$. However, given Assumption 1, we only require $\tilde{x}_2 < 1$, which is satisfied if $\sigma < \sigma_2$, where

$$\sigma_2 \equiv \frac{1}{2(e_b - e_c + p_{c,2} - c_b)}$$

in case $\xi_2 \equiv e_b - e_c + p_{c,2} - c_b > 0$. Otherwise, if $\xi_2 \leq 0$, we always have an interior solution in the second period.

To summarise, in order to have interior solutions to the model, the degree of competition parameter $\sigma > 0$ has to satisfy the following:

$$\sigma < \begin{cases} \min\{\sigma_1, \sigma_2\} & \text{if } \xi_1 > 0 \text{ and } \xi_2 > 0 \\ \sigma_1 & \text{if } \xi_1 > 0 \text{ and } \xi_2 \leq 0 \\ \sigma_2 & \text{if } \xi_1 \leq 0 \text{ and } \xi_2 > 0 \end{cases}$$

Otherwise, if $\xi_1, \xi_2 \leq 0$, any positive value of σ guarantees the existence of

interior solutions.

C Average health gain in period 2

In period 2 the total patient benefit when treated with drug B, or its generic equivalent G, is

$$B_{b,2} = \int_0^{\tilde{x}_2} u_{b,x,2} dx = \left(e_b - \frac{\tilde{x}_2}{4\sigma} \right) \tilde{x}_2$$

Notice that, although if to the eyes of the patients/GPs the branded originator may seem superior to the generic version, from the perspective of the HTA body, and by regulatory requirement, the generic drug is identical to the brand-name counterpart with respect to pharmacological properties. Therefore CEA does not assume any difference between branded originator and generic version in terms of health benefits to the patients.

If treated with the standard of care, the total patient benefit would be

$$B_{c,2} = \int_0^{\tilde{x}_2} u_{c,x,2} dx = \left(e_c - \frac{2 - \tilde{x}_2}{4\sigma} \right) \tilde{x}_2$$

Therefore, the total health gain for the patients treated with the new drug B, represented in Figure 3(b), is

$$\Delta B_2 = B_{b,2} - B_{c,2} = \left(e_b - e_c - \frac{1}{2\sigma} \right) \tilde{x}_2$$

Again, the health gain for a patient treated with the new drug is

$$\Delta \bar{B}_2 = \frac{\Delta B_2}{\tilde{x}_2} = e_b - e_c - \frac{1}{2\sigma} = e_b - e_c - \varepsilon = \Delta \bar{B}_1 \equiv \Delta \bar{B}$$

D Pharmaceutical expenditure

The total incremental pharmaceutical expenditure in the first period is

$$\begin{aligned}\Delta P_1 &= \left(\frac{1}{4\sigma} + \frac{e_b - e_c - p_{c,1} + c_b}{2} - \frac{\beta\lambda e_b}{8}\right)\left(\frac{1}{4} + \frac{\sigma(e_b - e_c + p_{c,1} - c_b)}{2} + \frac{\beta\sigma\lambda e_b}{8}\right) \\ &= \frac{\sigma}{4}\left((1 + 2(e_b - e_c))^2 - \frac{(4(p_{c,1} - c_b) + \beta\lambda e_b)^2}{4}\right)\end{aligned}$$

In the second period, the total incremental expenditure is

$$\begin{aligned}\Delta P_2 &= p^*_{b,2} d^*_{b,2} + c_b d^*_{g,2} - p_{c,2}\tilde{x}_2 \\ &= p^*_{b,2} d^*_{b,2} + c_b(\tilde{x}_2 - d^*_{b,2}) - p_{c,2}\tilde{x}_2 \\ &= (p^*_{b,2} - c_b) d^*_{b,2} - (p_{c,2} - c_b)\tilde{x}_2 \\ &= \pi^*_{b,2} - (p_{c,2} - c_b)\tilde{x}_2 \\ &= \frac{\lambda e_b}{4}\left(\frac{1}{4} + \frac{\sigma(e_b - e_c + p_{c,1} - c_b)}{2} + \frac{\beta\sigma\lambda e_b}{8}\right) - (p_{c,2} - c_b)\tilde{x}_2\end{aligned}$$

E Adjusted ICER

The adjusted ICER is calculated as the ratio between the present value of the flow of future costs (i.e. prices) and the discounted value of future benefits:[19]

$$\begin{aligned}
\hat{R}_b &= \frac{\delta_1\left(p^*_{b,1} - p_{c,1}\right) + \delta_2\left(\bar{p}_2 - p_{c,2}\right)}{\rho_1\Delta\bar{B} + \rho_2\Delta\bar{B}} \\
&= \frac{\delta_1}{\delta_T}R_b + \frac{\delta_2}{\rho_T}\frac{\bar{p}_2 - p_{c,2}}{\Delta\bar{B}} \\
&= \frac{\delta_1}{\delta_T}R_b + \frac{\delta_2}{\rho_T}\frac{\frac{s_{b,2}p^*_{b,2}+s_{g,2}c_b}{\tilde{x}_2} - p_{c,2}}{\Delta\bar{B}} \\
&= \frac{\delta_1}{\delta_T}R_b + \frac{\delta_2}{\rho_T}\frac{\frac{d^*_{b,2}p^*_{b,2}}{\tilde{x}_2} + \frac{(\tilde{x}_2 - d^*_{b,2})c_b}{\tilde{x}_2} - p_{c,2}}{\Delta\bar{B}} \\
&= \frac{\delta_1}{\delta_T}R_b + \frac{\delta_2}{\rho_T}\frac{\frac{d^*_{b,2}}{\tilde{x}_2}(p^*_{b,2} - c_b) + c_b - p_{c,2}}{\Delta\bar{B}} \\
&= \frac{\delta_1}{\delta_T}R_b + \frac{\delta_2}{\rho_T}\frac{\frac{\frac{\lambda e_b}{4}\left(\frac{1}{4} + \frac{\sigma(e_b - e_c + p_{c,1} - c_b)}{2} + \frac{\beta\sigma\lambda e_b}{8}\right)}{\frac{1}{2} + \sigma(e_b - e_c) - \sigma(c_b - p_{c,2})} + c_b - p_{c,2}}{\Delta\bar{B}}
\end{aligned}$$

F Comparison between traditional and adjusted ICER

We analyse the impact of parameters $p_{c,1}$, $p_{c,2}$, β and λ on the adjusted ICER.

F.1 Impact of $p_{c,1}$ on the adjusted ICER

The impact of $p_{c,1}$ is given by the sign of

$$\frac{\partial\hat{R}_b}{\partial p_{c,1}} = \frac{\delta_1}{\delta_T}\frac{\partial R_b}{\partial p_{c,1}} + \frac{\delta_2}{\rho_T}\frac{\partial\hat{R}_2}{\partial p_{c,1}}$$

[19] To avoid any doubt, the adjusted ICER is the ratio of the present values and not the present value of the ratios between costs and benefits.

where:

$$\frac{\partial R_b}{\partial p_{c,1}} = -\frac{\delta_T}{2\rho_T \Delta\bar{B}} \quad \text{and} \quad \frac{\partial \hat{R}_2}{\partial p_{c,1}} = \frac{\sigma\lambda e_b}{8\tilde{x}_2 \Delta\bar{B}}$$

Therefore:

$$\begin{aligned}\frac{\partial \hat{R}_b}{\partial p_{c,1}} &= -\frac{\delta_1}{2\rho_T \Delta\bar{B}} + \frac{\delta_2 \sigma\lambda e_b}{8\rho_T \tilde{x}_2 \Delta\bar{B}} \\ &= \frac{-4\tilde{x}_2\delta_1 + \delta_2\sigma\lambda e_b}{8\rho_T\tilde{x}_2\Delta\bar{B}}\end{aligned}$$

Given that by Assumption 2 $\Delta\bar{B} > 0$, the sign of the above fraction is given by the sign of the numerator, which is positive when

$$\begin{aligned} -4\tilde{x}_2\delta_1 + \delta_2\sigma\lambda e_b > 0 \quad &\iff \\ -\left(2 + 4\sigma(e_b - e_c + p_{c,2} - c_b)\right)\delta_1 + \sigma\lambda e_b\delta_2 > 0 \quad &\iff \\ \sigma(\lambda e_b\delta_2 - 4(e_b - e_c + p_{c,2} - c_b)\delta_1) > 2\delta_1 \end{aligned}$$

The above inequality is satisfied, implying that $\frac{\partial \hat{R}_b}{\partial p_{c,1}} > 0$, when

$$\begin{cases} \sigma > \sigma_{p_{c,1}} \equiv \dfrac{2\delta_1}{\lambda e_b\delta_2 - 4(e_b - e_c + p_{c,2} - c_b)\delta_1} & \text{(23a)} \\ \dfrac{\delta_2}{\delta_1} > \dfrac{4(e_b - e_c + p_{c,2} - c_b)}{\lambda e_b} & \text{(23b)} \end{cases}$$

If $\frac{\delta_2}{\delta_1} = \frac{4(e_b - e_c + p_{c,2} - c_b)}{\lambda e_b}$, $p_{c,1}$ has no impact on the adjusted ICER. Otherwise, in all the remaining cases, $p_{c,1}$ has a negative impact on the adjusted ICER, as on the traditional ICER.

F.1.1 Condition $\sigma < \sigma_1$

Condition (23a) requires that $\sigma > \sigma_{p_{c,1}}$. This is consistent with condition $\sigma < \sigma_1$, which can be binding only if $\xi_1 > 0$, when:

$$\begin{aligned}\sigma_{p_{c,1}} = \frac{2\delta_1}{\lambda e_b \delta_2 - 4(e_b - e_c + p_{c,2} - c_b)\delta_1} < \frac{2}{\lambda e_b \beta - 4(e_b - e_c - p_{c,1} - c_b) - 8p_{c,2}} = \sigma_1 \quad \Longleftrightarrow \\ \delta_1(\lambda e_b \beta - 4(e_b - e_c - p_{c,1} - c_b) - 8p_{c,2}) < \lambda e_b \delta_2 - 4(e_b - e_c + p_{c,2} - c_b)\delta_1 \quad \Longleftrightarrow \\ \delta_1(\lambda e_b \beta + 4p_{c,1} - 4p_{c,2}) < \lambda e_b \delta_2\end{aligned}$$

The last inequality is satisfied for

$$\frac{\delta_2}{\delta_1} > \beta + \frac{4(p_{c,1} - p_{c,2})}{\lambda e_b}$$

Notice that

$$\xi_1 > 0 \Longrightarrow \beta + \frac{4(p_{c,1} - p_{c,2})}{\lambda e_b} > \frac{4(e_b - e_c + p_{c,2} - c_b)}{\lambda e_b}$$

and therefore Condition (23b) also guarantees that there always exists a value of σ compatible with the condition for an interior solution to hold and that implies that the impact of $p_{c,1}$ on the adjusted ICER is opposite to the impact on the traditional ICER.

F.1.2 Condition $\sigma < \sigma_2$

To be consistent with the condition for an interior solution $\sigma < \sigma_2$, which can be binding only if $\xi_2 > 0$, Condition (23a) needs to satisfy

$$\begin{aligned}\sigma_{p_{c,1}} \equiv \frac{2\delta_1}{\lambda e_b \delta_2 - 4(e_b - e_c + p_{c,2} - c_b)\delta_1} < \frac{1}{2(e_b - e_c + p_{c,2} - c_b)} \equiv \sigma_2 \quad \Longleftrightarrow \\ 8(e_b - e_c + p_{c,2} - c_b)\delta_1 < \lambda e_b \delta_2\end{aligned}$$

The last inequality is satisfied for

$$\frac{\delta_2}{\delta_1} > \frac{8(e_b - e_c + p_{c,2} - c_b)}{\lambda e_b}$$

Notice that Condition (23b) implies that the above inequality is always satisfied, hence there always exists a value of σ compatible for an interior solution in this case.

F.2 Impact of β on the adjusted ICER

The impact of β is given by the sign of

$$\frac{\partial \hat{R}_b}{\partial \beta} = \frac{\delta_1}{\delta_T}\frac{\partial R_b}{\partial \beta} + \frac{\delta_2}{\rho_T}\frac{\partial \hat{R}_2}{\partial \beta}$$

where:

$$\frac{\partial R_b}{\partial \beta} = -\frac{\delta_T \lambda e_b}{8\rho_T \Delta\bar{B}} \qquad \text{and} \qquad \frac{\partial \hat{R}_2}{\partial \beta} = \frac{\sigma\lambda^2 e_b^2}{32\tilde{x}_2 \Delta\bar{B}}$$

Therefore:

$$\begin{aligned}\frac{\partial \hat{R}_b}{\partial \beta} &= -\frac{\delta_1 \lambda e_b}{8\rho_T \Delta\bar{B}} + \frac{\delta_2 \sigma\lambda^2 e_b^2}{32\rho_T \tilde{x}_2 \Delta\bar{B}} \\ &= \frac{-4\tilde{x}_2\delta_1\lambda e_b + \delta_2\sigma\lambda^2 e_b^2}{32\rho_T\tilde{x}_2\Delta\bar{B}}\end{aligned}$$

Given that by Assumption 2 $\Delta\bar{B} > 0$, the sign of the above fraction is given by the sign of the numerator, which is positive when

$$-4\tilde{x}_2\delta_1\lambda e_b + \delta_2\sigma\lambda^2 e_b^2 > 0 \quad \iff \quad -4\tilde{x}_2\delta_1 + \delta_2\sigma\lambda e_b > 0$$

Notice that the above condition is the same required for the proof of Proposition 1, therefore the same demonstration as in Section F.1 applies.

F.3 Impact of λ on the adjusted ICER

The impact of λ is given by the sign of

$$\frac{\partial \hat{R}_b}{\partial \lambda} = \frac{\delta_1}{\delta_T}\frac{\partial R_b}{\partial \lambda} + \frac{\delta_2}{\rho_T}\frac{\partial \hat{R}_2}{\partial \lambda}$$

where:

$$\frac{\partial R_b}{\partial \lambda} = -\frac{\delta_T \beta e_b}{8\rho_T \Delta \bar{B}} \quad \text{and} \quad \frac{\partial \hat{R}_2}{\partial \lambda} = \frac{e_b\left(1 + (e_b - e_c + p_{c,1} - c_b + \beta\lambda e_b)\sigma\right)}{16\tilde{x}_2 \Delta \bar{B}}$$

Therefore:

$$\begin{aligned}\frac{\partial \hat{R}_b}{\partial \lambda} &= -\frac{\delta_1 \beta e_b}{8\rho_T \Delta \bar{B}} + \frac{\delta_2 e_b\left(1 + (e_b - e_c + p_{c,1} - c_b + \beta\lambda e_b)\sigma\right)}{16\rho_T \tilde{x}_2 \Delta \bar{B}} \\ &= \frac{-2\tilde{x}_2\delta_1\beta e_b + \delta_2 e_b\left(1 + (e_b - e_c + p_{c,1} - c_b + \beta\lambda e_b)\sigma\right)}{16\rho_T \tilde{x}_2 \Delta \bar{B}}\end{aligned}$$

Given that by Assumption 2 $\Delta \bar{B} > 0$, the sign of the above fraction is given by the sign of the numerator, which is positive when

$$\begin{aligned}-2\tilde{x}_2\delta_1\beta e_b + \delta_2 e_b\left(1 + (e_b - e_c + p_{c,1} - c_b + \beta\lambda e_b)\sigma\right) > 0 \quad &\iff \\ -2\tilde{x}_2\delta_1\beta + \delta_2\left(1 + (e_b - e_c + p_{c,1} - c_b + \beta\lambda e_b)\sigma\right) > 0 \quad &\iff \\ -\left(1 + 2\sigma(e_b - e_c + p_{c,2} - c_b)\right)\delta_1\beta + & \\ \delta_2\left(1 + (e_b - e_c + p_{c,1} - c_b + \beta\lambda e_b)\sigma\right) > 0 \quad &\iff \\ \left((e_b - e_c + p_{c,1} - c_b + \beta\lambda e_b)\delta_2 - 2(e_b - e_c + p_{c,2} - c_b)\beta\delta_1\right)\sigma > \beta\delta_1 - \delta_2 &\end{aligned}$$

The last inequality can be written as

$$\left(\left(\xi_2 + p_{c,1} - p_{c,2} + \beta\lambda e_b\right)\delta_2 - 2\xi_2\beta\delta_1\right)\sigma > \beta\delta_1 - \delta_2$$

The parameter λ has a negative impact on the adjusted ICER only if

$$\sigma_\lambda \equiv \sigma \begin{cases} > \dfrac{\beta\delta_1 - \delta_2}{(\xi_2 + p_{c,1} - p_{c,2} + \beta\lambda e_b)\,\delta_2 - 2\xi_2\beta\delta_1} & \text{if } \eta > 0 \quad (24a) \\ < \dfrac{\beta\delta_1 - \delta_2}{(\xi_2 + p_{c,1} - p_{c,2} + \beta\lambda e_b)\,\delta_2 - 2\xi_2\beta\delta_1} & \text{if } \eta < 0 \text{ and } \frac{\delta_2}{\delta_1} > \beta \quad (24b) \end{cases}$$

where $\eta \equiv (\xi_2 + p_{c,1} - p_{c,2} + \beta\lambda e_b)\,\delta_2 - 2\xi_2\beta\delta_1$. If $\eta < 0$ and $\frac{\delta_2}{\delta_1} \leq \beta$, λ has a negative impact on both the adjusted and on the traditional ICER. Otherwise, if $\eta = 0$, parameter λ has no impact on the adjusted ICER.

F.3.1 Condition $\sigma < \sigma_1$

To be consistent with the condition for an interior solution $\sigma < \sigma_1$, which can be binding only if $\xi_1 > 0$, Condition (24a) requires

$$\begin{aligned} \frac{\beta\delta_1 - \delta_2}{(e_b - e_c + p_{c,1} - c_b + \beta\lambda e_b)\delta_2 - 2(e_b - e_c + p_{c,2} - c_b)\beta\delta_1} < \\ \frac{2}{-4(e_b - e_c - p_{c,1} - c_b) + \beta\lambda e_b - 8p_{c,2}} = \sigma_1 \quad \Longleftrightarrow \\ (-2(e_b - e_c - 3p_{c,1} + 4p_{c,2} - c_b) + 3\beta\lambda e_b)\delta_2 > \\ (4(p_{c,1} - p_{c,2}) + \beta\lambda e_b)\beta\delta_1 \quad \Longleftrightarrow \\ (-2\xi_2 + 3(2(p_{c,1} - p_{c,2}) + \beta\lambda e_b))\delta_2 > (4(p_{c,1} - p_{c,2}) + \beta\lambda e_b)\beta\delta_1 \end{aligned}$$

Notice that the above term $-2\xi_2 + 3(2(p_{c,1} - p_{c,2}) + \beta\lambda e_b)$ can also be written as $\frac{\xi_1}{2} + 4(p_{c,1} - p_{c,2}) + \frac{5\beta\lambda e_b}{2} > 0$, given the assumption that $p_{c,1} \geq p_{c,2}$.[20] Therefore, the above last inequality is satisfied for

$$\frac{\delta_2}{\delta_1} > \frac{4(p_{c,1} - p_{c,2}) + \beta\lambda e_b}{3(2(p_{c,1} - p_{c,2}) + \beta\lambda e_b) - 2\xi_2}\beta$$

Condition (24b) requires that $\sigma < \frac{\beta\delta_1 - \delta_2}{\eta}$ when $\beta\delta_1 - \delta_2 < 0$ and $\eta < 0$.

[20] Otherwise, if $-2\xi_2 + 3(2(p_{c,1} - p_{c,2}) + \beta\lambda e_b) < 0$, there is no value of σ compatible with the requirement of interior solution in this case.

Notice that this is always verified in the region for interior solution if $\frac{\delta_2}{\delta_1} \geq \frac{4(p_{c,1}-p_{c,2})+\beta\lambda e_b}{3(2(p_{c,1}-p_{c,2})+\beta\lambda e_b)-2\xi_2}\beta$ and $3(2(p_{c,1}-p_{c,2})+\beta\lambda e_b)-2\xi_2 > 0$, which implies that $\sigma_\lambda > \sigma_1$.[21]

F.3.2 Condition $\sigma < \sigma_2$

To be consistent with the condition for an interior solution $\sigma < \sigma_2$, which can be binding only if $\xi_2 > 0$, Condition (24a) requires

$$\frac{\beta\delta_1 - \delta_2}{(e_b - e_c + p_{c,1} - c_b + \beta\lambda e_b)\delta_2 - 2(e_b - e_c + p_{c,2} - c_b)\beta\delta_1} < \frac{1}{2(e_b - e_c + p_{c,2} - c_b)} = \sigma_2 \iff$$

$$2(e_b - e_c + p_{c,2} - c_b)\beta\delta_1 - 2(e_b - e_c + p_{c,2} - c_b)\delta_2 < (e_b - e_c + p_{c,1} - c_b + \beta\lambda e_b)\delta_2 - 2(e_b - e_c + p_{c,2} - c_b)\beta\delta_1$$

The last inequality is satisfied for[22]

$$\frac{\delta_2}{\delta_1} > \frac{4(e_b - e_c + p_{c,2} - c_b)}{3e_b - 3e_c + p_{c,1} + 2p_{c,2} - 3c_b + \beta\lambda e_b}\beta$$

Condition (24b) requires that $\sigma < \frac{\beta\delta_1 - \delta_2}{\eta}$ when $\beta\delta_1 - \delta_2 < 0$ and $\eta < 0$. Notice that this is always verified in the region for interior solution if $\frac{\delta_2}{\delta_1} \geq \frac{4(e_b-e_c+p_{c,2}-c_b)}{3e_b-3e_c+p_{c,1}+2p_{c,2}-3c_b+\beta\lambda e_b}\beta$, which implies that $\sigma_\lambda > \sigma_2$.

F.3.3 Effect of λ on the adjusted ICER

Given the above analysis, λ has an opposite effect on the traditional and the adjusted ICER, which is compatible with the conditions for an interior solution to hold, if:

[21] Otherwise, if $3(2(p_{c,1}-p_{c,2})+\beta\lambda e_b)-2\xi_2 > 0$ and $\frac{\delta_2}{\delta_1} < \frac{4(p_{c,1}-p_{c,2})+\beta\lambda e_b}{3(2(p_{c,1}-p_{c,2})+\beta\lambda e_b)-2\xi_2}\beta$, then $\sigma_\lambda \leq \sigma_1$.

[22] Notice that the denominator is always positive when $\xi_2 > 0$ holds.

1. $\sigma > \frac{\beta\delta_1 - \delta_2}{\eta}$ and $\eta > 0$ and one of the following occurs:
   a) $\xi_1, \xi_2 < 0$
   b) $\xi_1 > 0$, $\xi_2 < 0$ and $\frac{\delta_2}{\delta_1} > \frac{4p_{c,1} - 4p_{c,2} + \beta\lambda e_b}{8p_{c,1} - 8p_{c,2} + 3\beta\lambda e_b}\beta$
   c) $\xi_1 < 0$, $\xi_2 > 0$ and $\frac{\delta_2}{\delta_1} > \frac{e_b - e_c + p_{c,2} - c_b}{4(e_b - e_c - c_b) + 2(p_{c,1} + p_{c,2})\beta\lambda e_b}\beta$
   d) $\xi_1, \xi_2 > 0$ and: $\frac{\delta_2}{\delta_1} > \frac{4p_{c,1} - 4p_{c,2} + \beta\lambda e_b}{8p_{c,1} - 8p_{c,2} + 3\beta\lambda e_b}\beta$ if $\sigma_1 < \sigma_2$ or $\frac{\delta_2}{\delta_1} > \frac{e_b - e_c + p_{c,2} - c_b}{4(e_b - e_c - c_b) + 2(p_{c,1} + p_{c,2})\beta\lambda e_b}\beta$ if $\sigma_2 < \sigma_1$
2. $\sigma < \min\left\{\frac{\beta\delta_1 - \delta_2}{\eta}, \sigma_1, \sigma_2\right\}$ and $\eta < 0$ and $\beta\delta_1 - \delta_2 < 0$

In all the remaining cases, λ has the same impact on the traditional and the adjusted ICER.