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Assessing the Impact of Global Price Interdependencies

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Abstract

Documented launch delays and the ensuing debate over their underlying causes have focused on assessment from the individual country's perspective. Seen in a larger game theoretical framework this may cause problems, because although the countries see an individual game, the pharmaceutical firm sees a repeated linked game. The links are due to external reference pricing and parallel trade. Behaviours that are optimal in the single, individual game (for either the country or the pharmaceutical firm) may no longer be optimal when considering the global repeated game.

A theoretical mixed integer linear model of the firm's launch and pricing decisions is presented along with examples wherein international price dependencies most likely played a role. This model can help countries understand the implication of their external reference pricing policies on the global repeated pricing game. Understanding the behaviour of the pharmaceutical firm in this global context aids countries in designing policies to maximize the welfare of their citizens.

Several recent studies have documented the phenomenon of delayed or non launch of pharmaceutical products,[1-3] but there remains questions as to whether it is due to the external reference pricing (setting the maximum in-country price based on a review of prices charged in other countries) and parallel trade as the studies claim. In the ongoing debate, the primary arguments have centred on the tenets of welfare economics and whether or not the delays represent a country's 'best' utilitarian decision or the pharmaceutical firm's response to market structures.[4,5] As required for pharmacoeconomic studies, the societal point of view is used.[6] In these cases, 'societal' typically refers to the viewpoint of the individual country. Therefore, these analyses do not capture the pharmaceutical firm's perspective and expected behaviours.

However, if the problem is viewed in a game theoretical framework where the negotiations for price and/or reimbursement between the country and the pharmaceutical firm is seen as a game, only examining one side of the game may produce poor outcomes. This is especially important in these decisions because countries view the issue as a single, one-time game; however, the pharmaceutical firm views it as a repeated game, where the games and their outcomes are linked through external reference pricing and parallel trade. Each country wishes to obtain the medication at the lowest possible price and plays the individual game accordingly. The firm wishes to maximize its revenue across all of the games with all of the countries in which the product is launched. By only studying the perspective of the individual country, the influence of the repeated games is not explored and this puts the individual country at an informational disadvantage in their negotiations.

Although there has been much written about reference pricing in general, most articles refer to internal reference pricing (setting maximum prices

for all drugs deemed to be equivalent[7,8] [1]) policies and the extent to which they have (or have not) been successful.[7,9,10] Almost all of the analyses have been done from the perspective of the country, with the following exceptions. Brekke et al.[8] examined the theoretical impact of three different internal reference pricing regulations from both the perspective of the country and the pharmaceutical firm. This model did not look at external reference pricing or other multicountry issues. Ridley[11] examined a model to demonstrate the impact of differential pricing between countries, taking into account the pharmaceutical firm's point of view. This model did not explicitly account for external reference pricing either, focusing instead on the case of a uniform price in lieu of a differentiated price. Stargardt and Schreyogg[12] conducted an analysis of the interrelationship between European countries using their published external reference pricing regulations. They show how a change in the reimbursement price of a pharmaceutical in Germany causes changes in the maximum reimbursement prices in six other European countries. Although this calculation is highly informative, it does not address the notion of how a country or pharmaceutical firm would use or respond to this information.

This article examines the issue of external reference pricing and product launch decisions from a pharmaceutical firm's perspective and discusses how these results may be useful to individual countries in their price/reimbursement negotiations. A model is designed to examine the launch of an innovative, first-in-class medication for outpatient use in a collection of countries implementing a variety of external reference pricing regulations. Since the medication is first in class, these drugs are more likely to be affected by external reference pricing as there may not be sufficient comparators for internal reference pricing to be done.[1] Model solutions are developed for revenue maximization of the pharmaceutical firm, and their impact on the individual countries is discussed. By understanding how external reference pricing, parallel trade and market size influence potential global profits, countries may be better prepared when developing their pricing and reimbursement regulations, and in their individual pricing and reimbursement negotiations, to counter potentially undesirable manifestations of pharmaceutical firms' decision making in the face of the repeated game, such as delayed or non-launch of a product in their country.

1. Pricing Regulation

There are many different tools countries can use to regulate the price of medications, including internal reference pricing, control of pharmaceutical company profits, direct price controls and external reference pricing.[8,10,13,14] Most countries use multiple different competing regulations to control pharmaceutical expenditures.[12-14]

Regulations affect different drugs to varying degrees. A drug that is entering a therapeutic area with an established cadre of options will face strict internal reference pricing controls if they exist within a country. These will be the strongest regulations since the country has already established its reimbursement levels for the therapeutic area. An innovative drug may not have sufficient comparative treatments to permit a country to use internal reference pricing. In these cases, external reference pricing regulations and other forms of price control may become the primary means for establishing a maximum price. The exact determination of the final, actual reimbursement price is usually the outcome of a series of negotiations between the reimbursement authority of a country and the pharmaceutical firm. Although it is not possible to detail the exact interplay of the different regulations, each of the price regulation techniques can be seen as creating a maximum allowable price,[12] which will serve a basis in the negotiations.

External reference pricing is currently implemented by many countries, including Ireland, Belgium, France, the Netherlands, Spain, Austria, Denmark, Finland, Greece, Norway, Portugal, Sweden, Croatia, Taiwan and New Zealand.[13-19] Although geographical reference pricing originated in Europe, it is now practiced by many countries worldwide.[20]

1 There are many different ways of determining the groupings of 'equivalent' drugs. Some countries only look at classifications with drugs that have the same chemical compound, whereas other countries consider all the medications that are available to treat a certain therapeutic group.

The practice of external reference pricing implies that the pharmaceutical firm's pricing decisions for countries, either using reference pricing or being referenced by other countries using reference pricing, is linked (i.e. the choice of a price in one country may affect the potential prices in a number of other countries).

Parallel trade, the parallel importing of drugs across national boundaries, is another pricing link influencing a global pricing strategy. Parallel trade arises when a third party can purchase the pharmaceutical product in countries with lower prices and resell them to countries with higher prices. The European Court of Justice has upheld the free transport of goods, including pharmaceutical products and services, among member nations.[21,22] Parallel importing among these nations is growing and often is nationally encouraged in the hopes of lowering national healthcare expenditures.[10,21,23-26] Chaudhry and Walsh[23] found that a differential of 15% was sufficient for parallel trade to occur in countries that are in proximity to each other.

2. Theoretical Model

From a pharmaceutical firm's perspective, they wish to maximize total revenue and hence the return on investment for a new medication across all countries in which it is launched. The firm's decisions are in which countries to launch (and at what points in time) and what prices to set in each country. External reference pricing introduces limits on the prices that can be charged in a given country, and are included in the model as a series of pricing constraints. This model is a classical mixed integer mathematical optimization problem, shown in figure 1.

2.1 Objective Function

The goal of the pharmaceutical company is to maximize the total discounted revenue over all countries and over all time periods. However, parallel trade causes a loss of income in the country into which the goods are brought since the demand in that country is satisfied by a lower priced product from another country. Therefore, the impact of parallel trade is a loss of revenue and must be incorporated in the objective function as a penalty.

If there is a country j whose price is ≤85% of the price in country i, then parallel trade may occur from country j to country i, up to the percent of market share that may be susceptible to loss due to parallel trade in country i, (LM_{it}). If a suitably large price differential exists, y_{it} is equal to one, indicating the presence of parallel trade, or it is zero. Since it is possible that there may be several countries that have the requisite cost differential with country i, we assume that the parallel importer will choose to import the lowest cost product. This lowest cost is Z_t, the minimum price of all the countries in which the product has been launched.

The above discussion can be represented mathematically as shown in equation 1:

$$Z_t \leq P_{jt} + (1 - S_{jt}) \times M \qquad \forall\, i \neq j,\, t$$

(Eq. 1)

where M is an arbitrarily large number (see table I for definitions). For parallel trade to exist, the following equations must hold true (equation 2):

$$\begin{aligned} &Z_t - (0.85 \times P_{it}) \leq M \times (1 - y_{it}) && \forall\, i, t \\ &0.85 \times P_{it} - Z_t \leq M \times y_{it} && \forall\, i, t \\ &y_{it} \in \{0, 1\} && \forall\, i, t \end{aligned}$$

(Eq. 2)

For every individual country, it is now possible to determine whether or not the expected revenue from that country will be diminished by parallel trade, and if so, by how much, Z_{it}. Equation 3 shows this calculation:

$$\begin{aligned} &Z_{it} \leq P_{it} + M \times y_{it} && \forall\, i, t \\ &Z_{it} \leq Z_t + M \times (1 - y_{it}) && \forall\, i, t \end{aligned}$$

(Eq. 3)

Therefore, the parallel importer will purchase the product to meet the demand in country i at time t for parallel imports ($LM_{it} \times Q_{it}$) from the country that has the overall lowest price (Z_t). Combining this information, the objective function is as shown in equation 4:

$$\text{Maximize} \sum_i \left(\sum_t \frac{1}{(1+r)^t} \times (P_{it} \times Q_{it} - LM_{it} \times Q_{it} \times [P_{it} - Z_{it}]) \right)$$

(Eq. 4)

The first term in equation 4 represents the revenue generated by selling a drug in country i and time t. The second term represents the impact of parallel trade.

Max

$$S_{it}P_{it}y_{ijt}$$

$$\sum_{i}\left(\sum_{t}\frac{1}{(1+r)^{t}}\times(P_{it}\times Q_{it}-LM_{it}\times Q_{it}\times[P_{it}-Z_{it}])\right)$$

s.t.

$Z_t - 0.85\times P_{it} \le M\times(1-y_{it})$	$\forall$ i, t
$0.85\times P_{it} - Z_t \le M\times y_{it}$	$\forall$ i, t
$Z_t \le P_{jt} + M\times(1-S_{jt})$	$\forall$ i, t
$Z_{it} \le P_{it} + M\times y_{it}$	$\forall$ i, t
$Z_{it} \le Z_t + M\times(1-y_{it})$	$\forall$ i, t
$P_{it} \le 0.95\times P_{jt} + (1-S_{jt})\times M$	$\forall$ t, j ε {reference countries for country i}
$P_{jt} \le \left(\frac{P_{it}}{PAlt_{it}}\right)\times PAlt_{jt} + (1-S_{it})\times M$	$\forall$ t, i ε {reference countries for country j}
$S_{it} \le S_{it+1}$	$\forall$ i, t
$P_{it} \le P_{it+1}$	$\forall$ i, t
$P_{it} \le Pmax_{it}$	$\forall$ i, t
$P_{it} \le S_{it}\times M$	$\forall$ i, t
$P_{it} \ge 0$	$\forall$ i, t
$y_{it}\ \varepsilon\ \{0, 1\}$	$\forall$ i, t
$S_{it}\ \varepsilon\ \{0, 1\}$	$\forall$ i, t

Fig. 1. Mathematical model formulation. For ease of exposition, external reference constraint types 2 and 3 were not included. Refer to table I for definitions of abbreviations.

2.2 External Reference Pricing Constraints

There are a wide variety of external reference pricing methods that have been employed by countries. Stargardt and Schreyogg[12] provided examples for techniques employed in Europe. Generalizing these to a broader base, there are four basic types of external reference prices.

2.2.1 Type 1

The price of a product in country i must be a given percentage lower, for (e.g. 5%), than the price of the product in a set of reference countries. If the product is not sold in the reference country (S_{it} equals zero), then the constraint is not binding (M is large). Mathematically, this is shown by equation 5:

$$P_{it} \le 0.95\times P_{jt} + (1-S_{jt})\times M$$
$$\forall\ t, j\ \varepsilon\ \{\text{reference countries for country i}\} \quad \text{(Eq. 5)}$$

This type of external reference pricing is used by an individual country to ensure that historical price differentials between itself and its neighbours remain unchanged. Frequently, the percentage reduction is based on the comparative purchasing power parities between the primary country and the referenced countries. This approach has been applied in Spain.[14]

2.2.2 Type 2

The price of a product in country i must be less than or equal to the average price of the product in a set of reference countries. Mathematically, this is shown by equation 6:

$$P_{it} \le \frac{\sum_{k} P_{kt}\times S_{kt}}{\sum_{k} S_{kt}} \quad \text{if } \sum_{k} S_{kt} \ne 0 \text{ for}$$
$$\forall\ t,k\ \varepsilon\ \{\text{reference countries for country j}\} \quad \text{(Eq. 6)}$$

Although this equation is not linear in the decision variables (P_{it}, S_{it}), it can easily be reformulated to preserve linearity. This reformulation is presented in the technical appendix (see the supplementary

material ['ArticlePlus'] at http://pharmacoeconomics.adisonline.com). This type of external reference pricing is used by an individual country to ensure that it does not pay more than the average price in a select set of countries. For example, the Netherlands wish to ensure that they do not pay more than the average price seen in Belgium, France, Germany and the UK.[12]

2.2.3 Type 3

The price of a product in country i must be the lowest price of the product in a set of reference countries. Mathematically, this is shown by equation 7:

$$P_{it} \leq \min \{P_{jt}, \ldots, P_{kt}\}$$
$$\forall\, t, j \in \{\text{reference countries for country i}\} \quad \text{(Eq. 7)}$$

This equation can be rewritten as a linear function by setting P_{it} as less than the price in every referenced country (equation 8).

$$P_{it} \leq P_{jt} + (1 - S_{jt}) \times M$$
$$\forall\, t, j \in \{\text{reference countries for country i}\} \quad \text{(Eq. 8)}$$

This type of external reference pricing is used by an individual country to ensure that it does not pay more than a specific country, e.g. Portugal wishes to ensure that it does not pay more than France, Italy or Spain.[12]

2.2.4 Type 4

The ratio of the price of the product and its closest competitor(s) in country i must be less than or equal to the ratio of the price of the product and its closest competition in the reference countries in which the product is sold. $PAlt_{it}$ represents the price of established alternative therapy in country i. If the product is not sold in the reference country (S_{jt} equals zero), then the constraint is not binding (M is large). Mathematically, this is shown by equation 9:

$$P_{it} \leq \left(\frac{P_{jt}}{PAlt_{jt}}\right) \times PAlt_{it} + (1 - S_{jt}) \times M$$
$$\forall\, t, j \in \{\text{reference countries for country i}\} \quad \text{(Eq. 9)}$$

This type of external reference pricing is used by an individual country to ensure that it provides a fair monetary incentive for an improved medication that is in line with the monetary bonuses offered by other countries.

The different basic types of reference pricing can be combined into more complex regulations, e.g. Ireland employs both type 2 and type 3.[12]

2.3 Other Constraints and Model Assumptions

Several other constraints need to be included in the model. Prices must be positive and may only decrease over time (equation 10):

Table I. Definitions of constants and variables

Constants and variables	Definition
Indices and constants	
t	Year (or other unit of time)
i (j,k)	Country
r	Discount rate applied to cost and revenues
Q_{it}	The amount of (projected) demand in country i during period t
$Pmax_{it}$	Boundary price, i.e. the maximum price that can be charged for the product in country i (regardless of the regulatory mechanisms of country i) at time t
$PAlt_{it}$	Price of established alternative therapy in country i at time t
LM_{it}	The market share that is lost in country i at time t because of parallel trade
M	An arbitrarily large number
Variables	
Z_t	The price in the lowest priced country, which will serve as the source for parallel imports at time t
y_{it}	Indicator of parallel trade in country i in time period t (binary)
Z_{it}	The penalty price for when there is parallel trade
Company choices	
S_{it}	Indicates whether or not the product is launched in country i at time t (binary)
P_{it}	Price of product in country i at time t

$$P_{it} \geq 0 \qquad \forall i, t$$
$$P_{it} \leq P_{it} + 1 \qquad \forall i, t$$

(Eq. 10)

Once a product is launched it is difficult to pull the product from the market. Therefore, (equation 11):

$$S_{it} + 1 \geq S_{it} \qquad \forall i, t$$
$$S_{it} \varepsilon \{0,1\} \qquad \forall i, t$$

(Eq. 11)

The final set of constraints is related to the assumptions made about the demand for an innovative, first-in-class pharmaceutical product. The most basic assumption is that the quantity demanded is fixed at the expected market share of the product. This is not an unreasonable approach since price elasticity in relation to prescription medicines has been found to be very small in absolute value, which indicates that demand is not very sensitive to price.[27,28] This inelasticity is largely because in countries with national healthcare coverage including reimbursement for prescription medications, the patient does not see the true cost of the drugs.[7,8] A relatively common simplification makes use of the fact that demand for a pharmaceutical product, Q_{it}, is mostly inelastic up to a boundary price, $Pmax_i$, after which the product will no longer be purchased.[8,29] In this case, an additional constraint becomes as shown in equation 12:

$$P_{it} \leq Pmax_{it} \qquad \forall i, t$$

(Eq. 12)

It is possible to use other functional forms for the demand function; this will impact the solution technique used to solve the mathematical model.

Taken together, these equations are a mixed integer linear program. The complete mathematical formulation is given in figure 1. Although for small problems it is feasible to examine all possible combinations of launch sequence and price to determine the optimal solution, this approach quickly becomes unmanageable. Considering only two countries (and only two time periods), there are nine possible launch sequences, e.g. A and B simultaneously, A then B, B then A, only A, only B, etc. If three countries (and therefore three time periods) were considered, there would be well over 50 possible launch sequences. Fortunately, solution algorithms and commercial codes for solving mixed integer linear programs have been available for many years (e.g. see Nemhauser and Wolsey[30]) and are available in numerous commercially available software packages.

3. Real-World Examples

In searching for real-world situations wherein global price interdependencies may have been a factor, it is necessary to identify instances where the 'expected' results of a pricing or reimbursement decision did not occur. The situations are not a result of the direct application of the model but serve as examples of the applicability of the methodology discussed. These situations are not being examined with any intent to discuss whether the decisions taken were 'right' or 'wrong' by any of the parties involved. The goal of the assessment is to view, as objectively as possible, the manifestation of the multiplayer repeated game.

Several situations of interest arise in the context of countries that have instituted some form of internal price control, such as internal reference pricing wherein the reimbursement level for a set of 'equivalent' drugs is set to a benchmark level. The theoretical underpinnings of this approach maintain that since the chosen drugs are equivalent and consumers are price sensitive, pharmaceutical firms will lower their prices to the reimbursement level for fear of losing their market share to the fully reimbursed drugs. The country saves money and there are no negative therapeutic implications. Situations where all of these assumptions seem to be met – a price is lowered to a benchmark where at least one product is fully reimbursed and the market share of the fully reimbursed medicines expands to cover almost the entire market – and yet the pharmaceutical firm is willing to lose its original market share rather than lower the price of its drug indicates that there are external considerations to the company's decision. After all, within the one market, the best choice for the firm would be to lower its price to the level necessary to maintain a market share that preserves its revenues. In each of the cases discussed in the following sections, if the country could have anticipated the likely responses of the pharmaceutical companies, it could have used this information to form a more reasonable estimate of savings, con-

templated the likely set of primary therapeutic options, and ascertained whether or not this set would have been likely to cause issues or concerns with physicians.

3.1 Germany

Germany instituted various forms of internal reference pricing from 1989.[31,32] The original round of reimbursement lowering led to price declines in all existing medications in the antiulcer agents (histamine H2 antagonists), oral hypoglycaemics and calcium channel antagonists (CCAs) therapeutic subgroups. In subsequent years, six new CCAs were introduced into the German market. When these in turn were subject to the reimbursement restrictions of the older CCAs, none of the manufacturers of the newer drugs substantially reduced their prices. The prices remained at over twice the reimbursement rate, with an ensuing substantial loss in market share.[31] When HMG-CoA reductase inhibitors (statins) were subject to a therapeutic maximum reimbursement rate, all statins but one had their price lowered. The manufacturer of atorvastatin refused to lower its price and it dropped from being the market leader to having negligible market share.[33]

To understand the refusals of companies to lower prices in Germany, it is important to note that Austria, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal,[12] Spain,[18] Switzerland[13] and Norway[15] all directly use the price in Germany in their external reference pricing. Stargardt and Schreyogg[12] showed that a €1 price reduction in Germany would lead to reductions of up to €0.36 in the other referencing countries. To determine whether the price reduction in Germany is worthwhile given its international ramifications, the pharmaceutical company must solve the objective function of the model. In addition, in the case of atorvastatin, it is important to note that 2 years earlier the pharmaceutical company had applied for and received a special, higher reimbursement rate than all existing statins in New Zealand by claiming drug superiority through improved efficacy. For it to accept Germany's ruling that it is 'equivalent' to the other drugs would have called into question all of its prior global pricing strategy.[34] Again, the global price interdependencies caused the pharmaceutical firm not to follow the optimal single country pricing decision.

3.2 British Columbia, Canada

British Columbia has instituted various forms of internal reference pricing for a number of therapeutic areas. In each area, the province set a reimbursement rate that fully subsidized a few medications. For ACE inhibitors, there were three fully subsidized medications that, after the reimbursement levels were set, more than tripled their market shares. The manufacturers of the five other ACE inhibitors did not change their prices even though enalapril lost approximately 20% of its market share.[35] In fact, a recent study reported that no savings were seen because of changes in drug prices when lower reimbursement levels were set.[36] For analgesic drugs, a similar pattern was seen. Although the prices of many non-benchmarked drugs declined, none came close to the fully reimbursed price. Drugs such as diclofenac, which had been the most widely used NSAID, saw enormous loss of market share. Other medications even preferred to be delisted rather than lower their prices.[37]

British Columbia is automatically referenced by all of the other Canadian provinces since they each implement the lowest price seen in any Canadian province.[38] From the pharmaceutical firm's perspective, the loss in market share in British Columbia is less costly than having its prices lowered in all other provinces, especially the largest provinces of Ontario and Quebec.

However, this decision need not hold true for all therapeutic areas. After British Columbia introduced a reimbursement ceiling for nitrates, the nitroglycerin patch – not originally at the benchmark – chose to lower its price to become fully subsidized. It now completely dominates this market.[39] In this case, even though this lower price was carried over into the other provinces, the market share gained outweighed the loss due to the lower prices on an intra-Canadian scale.

3.3 New Zealand

In New Zealand, both statins and ACE inhibitors were assigned therapeutically referenced reimbursement rates; however, the pharmaceutical firms with

products in these therapeutic areas reacted very differently. In the ACE inhibitor market, most of the drugs had their prices reduced to the benchmark. In the statin market, fluvastatin, the benchmark, went from <1% of the market pre-reference pricing to a high of 47% of the market after reference pricing was instituted. Neither simvastatin nor pravastatin had their price reduced to the reference price. Simvastatin lost half of its market share and pravastatin's market share became negligible. A year later, atorvastatin was introduced on the market, and because of a complex cross-product arrangement, it was fully reimbursed at a higher rate than the other statins. Since it was fully subsidized, atorvastatin took 70% of the market. Although the maker of simvastatin still refused to lower its official price, a bonusing arrangement with wholesalers effectively reduced its cost to the reference level. With this unofficial reduction, simvastatin captured the remaining 30% of the market. The agreement involving atorvastatin had its maker reduce the price of quinapril by 60%, which became the new benchmark price for ACE inhibitors. Although cilazapril dropped to the same level because of another cross-product agreement, none of the other ACE inhibitors lowered their prices, despite the fact that the two new benchmark medications went from a negligible market share to over 80% of the market.[34]

To help understand the companies' refusals to lower ACE inhibitor prices in New Zealand, it is important to note that Australia, Canada and Italy directly reference New Zealand and by extension, Austria, Greece, Portugal,[12] Spain[18] and Norway[15] reference it indirectly in their external reference pricing. Given New Zealand's small market size, companies were more willing to accept losses in that country than have their prices in other, larger markets threatened. It is interesting to note that the maker of simvastatin was willing to accept a lower price for its drug in the small market as long as the officially listed price remained high. This strongly indicates the importance of global price interdependencies on the choice of price in an individual country.

3.4 Other Countries

In the Netherlands, when internal reference pricing was adopted to set reimbursement levels, the official prices of the medications did not change. However, there was price competition in the form of discounts.[9] This indicates that the pharmaceutical firm was willing to accept a lower price for its drug in the small market of the Netherlands, but it was not willing to have this lower price be available to other, necessarily larger, markets in the EU. The Netherlands is referenced either directly or indirectly by at least Austria, Ireland, Greece, Portugal and Italy.[12]

Like Germany, Sweden reported that after introduction of a reference reimbursement level, prices of those products affected dropped to the reimbursement level with few exceptions. Interestingly, products that were delisted saw their prices increase.[40] The only reason for this phenomenon (since the delisted products are no longer sold in Sweden) is to set prices for international comparisons. Like British Columbia, Hungary reported that it saw no overall price reduction in its statin market after the introduction of a reimbursement level, but there was an increased use of generics.[41] Patients could either pay the difference between the reimbursement level and the price of the product or switch to a generic.

As countries consider and evaluate internal pricing schemes, the model and a view of the global game may help them determine whether they are more likely to meet with the results more typical of Germany, Canada or New Zealand. They can assess the likelihood of success at lowering drug prices across the board and this will help them determine which manufacturers will probably not reduce their price or may prefer to withdraw their product from the market.

Another manifestation of the game is that a pharmaceutical firm may be willing to delay the launch of its product in certain countries (or not launch at all). Although this is not an optimal decision from the individual market perspective, when considering the impact of global price interdependencies, it may become the pharmaceutical firm's best option. Examples of this can be seen in the launch delays of up to 4 years within the EU in certain countries, such as Portugal, Greece, Spain, Italy and Belgium.[42] The authors of the cited study feel that these delays are due to parallel trade, since these countries are frequently sources for such trade within the EU.

4. Discussion

The model provides a structured analysis of the global strategic pricing problem faced by pharmaceutical companies at the macro level. It explicitly takes into account the interdependencies that arise during pricing decisions due to geographical reference pricing and parallel trade. This model can help individual countries understand the implications of their individual, external pricing policies on the global, repeated pricing game. Although countries may not be able to influence who references them, knowing that they are being referenced and the size of the markets referencing them can provide insight to the pharmaceutical firm's decisions and negotiation strategies. Individual countries can choose to alter their pricing strategies if they decide that the strategies lead to undesirable outcomes. Understanding how the pharmaceutical firm is likely to act will help countries better prepare to counter potentially unwanted actions by the firm.

Interestingly, the highest drug price is not always the best option for the pharmaceutical firm, nor is a low drug price always the worst option in a given country. What may have been an optimal pricing strategy in a single country is no longer optimal when considering the international ramifications of this price. This result can already be observed in some pharmaceutical firms' current pricing choices. Similarly, an individual country may have a markedly different experience when instituting therapeutic reference prices for different indications. For one indication, in the response to the reference price, the manufacturers of all competing drugs may reduce their prices to their reimbursement level providing the best possible outcome for the country with complete therapeutic choice and lowered economic costs. However, for other indications, the manufacturers may opt not to reduce their prices. Then there are only one or two drugs (typically, the benchmarks) that are fully subsidized and the only cost savings are those seen due to increased use of these drugs. Models such as the one proposed in this article can help in the strategic analysis of these decisions.

The solution method for the mathematical model depends on the assumptions surrounding the demand function for the prescription pharmaceutical product. If we assume that the demand for a prescription pharmaceutical is relatively independent of price, then the problem is a mixed integer linear program and can be solved easily with standard algorithms. If we assume that the demand function is linear, then the problem is a convex optimization. If the demand function has other forms, then the problem is a mixed integer non-linear program because the objective function contains the term $P \times Q = P \times f(P)$. Several new methods and codes have recently become available for this type of problem.[43]

The model currently focuses on revenue and does not incorporate the price of launching a product in a given country, potential interdependencies of launches in different countries or costs of supplying the product to each market. These can easily be incorporated into the model.

In the current formulation, the model views parallel trade as a negative, a loss of potential revenue. However, this need not always be the case. Given the issues of parallel trade and international benchmarking, the model predicts that there may be some countries that may experience long delays until the product is officially launched in their country. Some of the demand in these countries may be serviced through parallel imports. In this case, parallel trade would actually be a boon both to the consumer, who has access to the medicine if they can afford the cost of the medicine privately, and to the pharmaceutical firm, who will realise greater sales of their drug. This facet of sales in a country in which the product has not officially been launched can be readily incorporated into the model objective function. In order to do this, it is necessary to estimate the size of the demand for the privately purchased market that may be serviced by parallel imports. This quantity would then be multiplied by Z_t, the lowest price in the countries that have been launched at time t – assumed to be the source of parallel imports – and added to the objective function.

5. Conclusion

As the barriers to importation across nations of pharmaceutical products are lowered and as more countries consider geographical reference pricing as a means of controlling pharmaceutical costs, the global pricing decision becomes more complicated.

Understanding the behaviour of the pharmaceutical firm in the global context can help countries in designing policies to maximize the welfare of their citizens. Although the model does not cover all possible complexities encountered by a pharmaceutical firm during its global strategic pricing process, it does provide insight into the issues surrounding external reference pricing and parallel trade.

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