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Review of the literature on reference pricing

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Abstract

This paper reviews the literature on reference pricing (RP) in pharmaceutical markets. The RP strategy for cost containment of expenditure on drugs is analyzed as part of the procurement mechanism. We review the existing literature and the state-of-the-art regarding RP by focusing on its economic effects. In particular, we consider: (1) the institutional context and problem-related factors which appear to underline the need to implement an RP strategy; i.e. its nature, characteristics and the sort of health care problems commonly addressed; (2) how RP operates in practice; that is, how third party-payers (the insurers/buyers) have established the RP systems existing on the international scene (i.e. information methods, monitoring procedures and legislative provisions); (3) the range of effects resulting from particular RP strategies (including effects on choice of appropriate pharmaceuticals, insurer savings, total drug expenditures, prices of referenced and non-referenced products and dynamic efficiency; (4) the market failures which an RP policy is supposed to address and the main advantages and drawbacks which emerge from an analysis of its effects. Results suggest that RP systems achieve better their postulated goals (1) if cost inflation in pharmaceuticals is due to high prices rather than to the excess of prescription rates, (2) when the larger is the existing difference in prices among equivalent drugs, and (3) more important is the actual market for generics.

Keywords: Reference pricing; Pharmaceutical expenditure; Generic drugs; Drug patents

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1. Introduction

The purpose of this paper is to assess the status of the literature on reference pricing (henceforth referred to as RP). We identify several studies, either published in the health and economics Journals or under the Working Paper format, since the introduction of RP in 1989 till the end of 1998. Studies were found searching different computerized databases, and examining partial review papers, as well as from personal bibliographies and contacts. The review also includes papers published in Journals, book chapters, as some working papers and technical reports. Short papers only expressing author's views without any evidence and short paper news (such as that appeared in Scrip magazine) were excluded of the study. A total of 45 studies have been identified according to the inclusion criteria [1–45].

1.1. Classification of the literature

The papers are classified using four descriptive criteria. First, the type of journal in which the study has been published, or any other identification on the publication source (chapter books, academic working papers and private or governmental technical reports).

Second, the country the RP system is referring to. We limit our attention to those countries, which introduced a RP system during the period.

Third, the type of study, according to three different categories:

(a) studies which provide descriptive, institutional and policy details on the country's implementation strategy of RP;

(b) studies which include some sort of modelling of the pharmaceutical and health services market on which RP effects can be observed and tested; and

(c) empirical studies which describe the results from the introduction of the RP policy once in place.

Of course, many papers may involve a non-proportional mix of these three approaches too.

And, fourth, we consider the particular area of the empirical studies:

(a) expenditure, volume and prices of pharmaceuticals,

(b) health outcomes and other related effects; and

(c) dynamic effects and others.

Studies have been grouped according to journal types. Half of the total number of studies: [22] were published in scientific journals: six in clinical journals, five in health policy journals, ten in health economics journals, and only one in economic (non-health) journals[1].

[1] This the case despite the fact that RP can be understood as a procurement measure. Clinical journals: Canadian Journal of Cardiology (3), Canadian Medical Association Journal (2), and New Zealand Journal of Medicine (1). Health policy journals: Health Policy (5). Health Economics: Health Care Financing Review (1), Pharma Pricing Review (2), and PharmacoEconomics (7). Economic (non health) journals: Journal of Regulatory Economics (1).

Another important part of the RP literature comes from academic working papers and papers presented at conferences[2]. The remaining are technical reports financed by governments and private firms. With regard to their contents, more than half of the studies consist of institutional descriptions and limited reviews of country specific RP strategies (26 studies), and only five examine RP in the grounds of some sort of theoretical model. Twenty one empirical studies identify the impacts of RP, but none of them explore the dynamic effects of RP, say on I & D. Most part of the empirical studies (18 over 21) analyze the effects on expenditure, prices and consumption; few (7) intend to quantify health outcome and related effects.

1.2. The focus of the analysis

As explained above, the first thing one should notice is that the bulk of the RP literature is mainly descriptive[3]. This is an important limitation of the existing research on RP, since its empirical effects cannot be universally applied, thereafter, in absence of a common theoretical framework. Although dual pricing economics may provide this basic framework for RP modelling, few papers seem to base their research on this approach[4], with the notable exception of Danzon and Liu's contribution [10][5]. Only this paper, and those of Zweifel and Crivelli [45] and Woodfield et al., [42], estimate the effects of RP and the behavior of the agents using a theoretical model of the pharmaceutical and the health services market[6]. One of the possible difficulties in order to fully incorporate RP in the optimal health insurance literature may be the fact that quality and information problems are here crucial in order to capture the nature and the effects of several RP schemes.

[2] They represent a 27% of all studies. These papers may end in journals too.

[3] Descriptive status, the quasi absence of theoretical models and limitations derived from the 'before and after' methodology are, probably, the main reason to explain why only few RP papers have appeared till now in leading international journals.

[4] The most favoured-customer rule also may provide some useful insights on the industrial economics effects of RP. See F. Scott Morton [46,47].

[5] Their theoretical analysis uses a model of physician decision-making under assumptions of imperfect agency. This is the case despite the fact that its results are not fully taken into account in the empirical estimation on the effects of the German regulatory initiatives to control pharmaceutical expenditure.

[6] Danzon and Liu [10] predict price responses to RP according to a kinked demand model in the context of a model of physcian decision-making under the assumption of imperfect agency. Zweifel and Crivelli [45] concentrate their analysis on market reactions to RP by pharmaceutical firms in the context of a Bertrand duopoly model (in which each producer chooses its price, instead of quanity, and assumes that the other will not change the price level). And Woodfield et al. [42] discuss RP impact adapting a simple model of an oligopolistic pharmaceutical market developed by Johnston and Zeckhauser [48], where the firms engage in Bertrand price competition (the market determines quantities). In their model exist differentiated products, firms have identical costs and face demand functions.

The second important limitation of the RP empirical literature is that it does not allow for a clear-cut identification of the effects of RP in isolation from other regulatory policies or influential factors. Most of the empirical studies often-present simple after and before comparisons, which are not much useful to obtain valid conclusions on the effects of RP[7]. The difficulty to isolate RP effects from other regulatory measures or external factors is mainly due to the following features: [1] at any given point in time, it is very hard to isolate RP effects of the results derived from other policies on health expenditure control; (ii) RP strategies in health care overlap with changes in the social and economic scenario. This makes particularly implausible the 'ceteris paribus' assumption in assessing the long-term effects of the RP policy; (iii) finally, the lack of measurement of some indirect effects (both complementary and substitutive to the drug expenditure effect) produced by RP (on primary care, pharmaceutical employment, etc.) may bias the estimation of RP policies. Consequently, observation of changes before and after the introduction of RP policies does not provide enough evidence from which to draw conclusions as to the effects of RP.

In fact, from a methodological point of view, and with regard to RP's impact on pharmaceutical expenditure, one can draw a further distinction for the purpose of the analysis (i) changes which affect the average rate of expenditure increase (for instance, before and after the introduction of RP); (ii) changes which produce a one-off saving, with a shift, say, in the expenditure line without affecting the rate of increase (i.e. gradient); (iii) perverse changes, when the expenditure, after a once-for-all saving, rises even at a higher rate; and (iv) successful reforms with a one-off saving and a reduction of the expenditure growth once RP is implemented.

Descriptive and empirical literature has concentrated in the experience of the European countries which first introduced RP. It is the case of Germany, Netherlands and Denmark. Amongst them, the German case offers a more accurate arena, since the introduction in 1989, for evidence on RP (44.4% of the empirical studies are devoted to this German experience), although an increasing number of bibliographical references related to the other countries are there too[8].

1.3. The main topics

The subject of the literature has mainly focused on the impact of RP on the following topics: (a) pharmaceutical expenditure, drug consumption and prices; (b) health effects and other related impacts, (c) physician choice; (d) dynamic efficiency; and (e) overall welfare effects. However, in assessing RP as a whole from a health policy point of view, and not just as a health expenditure mechanism, we have to consider which sort of drug market is substituting: was there a pre-existing market

[7] As Roberts [29] states: 'Such studies can attribute all changes in dependent variables to policy, changes, when they can equally well be due to other short or long run social and economic trends'.

[8] Complementary bibliographic references, classified by country and author, are included at the end of the paper.

of generics working on a competitive basis? Do exist 'basic packages' for health care in a social insurance mechanism where RP may fit in?. Is there an already existing consumer's culture on willingness to pay for additional amenities?. In our view, the answer of these questions may provide the relevant k-factors to understand the success or failure in the implementations of RP policies.

We plan to offer to the reader in the following Section 2 a review of the international experience on the market responses to RP We will assess its overall impact on pharmaceutical expenditure, drug consumption and prices, on the innovator's price, dynamic efficiency, on physician choice, competition and welfare. However, in doing so we will take a broad view of the pharmaceutical sector. In this sense, the role of drugs will be seen in the context of the health care sector, bearing in mind the relevance of innovation for the long-term productivity and efficiency of the entire health care system.

2. Reference pricing in context

We outline here the major features of RP systems, and the institutional background, which seems to favor RP as one of the preferred strategies for drug expenditure control.

2.1. Definition and objectives

What does reference pricing mean in pharmaceutical markets? Despite the basic feature (a system where a buying agent decides on a reimbursement price and then the user/patient or insurer pays the difference if the chosen medicine is more expensive), reference pricing differs in details and scope [10,11,26,44]. Since the introduction of RP in Germany in 1989, reference pricing schemes have been applied in some other countries such as The Netherlands, Sweden, Denmark, New Zealand, Poland, Slovenia, Spain, USA, British Columbia (Canada), Italy and Australia. However, these schemes reveal significant differences.

The goal of RP seems to be the control of third-party expenditure on prescription drugs, not the limitation of overall pharmaceutical expenditure. By limiting the level of public reimbursement, RP aims to reduce the price of referenced products, either through (i) a relative decrease in the demand for highly-priced products (a demand-side approach) or (ii) cutting drug prices by encouraging self restraint (a supply side approach) once manufacturers face the threat of losing markets. Other issues may also be involved, such as the concern about the appropriate use of drugs, but in a less explicit way.

Two related conditions are important here. The first has to do with the possibility of promoting price competition in the drug market[9]: this is, as a result of RP, firms should price products around the reference price. The second relates to the chances

[9] 'When circumstances allow, reference prices should be preferred to price controls, to the extent that they spur, rather than stifle, competition', [page 17, European Commision 49].

to achieve a more cost-effective approach to prescription by increasing cost consciousness in putting financial pressure on consumers and/or drug prescribers.

2.2. International experience

At any rate, a common factor leading to the introduction of RP has been the concern of these countries about the relative impact of pharmaceutical expenditure on public funds. However, the factors explaining this situation differ. For instance, Germany, with the highest European per capita level of drug expenses in 1989 (the RP implementation year), seems to show a problem with prices of drugs more than with consumption. In fact, German expenditure captures the impact of a very high weighted average price for drugs[10], but a middle of the range prescription rates (per capita and per year). The Netherlands offers a similar profile on prices (very high pharmaceutical prices), but has a relatively low prescription rate (one third of the German level). Northern European countries do not currently reveal a clear trend in pharmaceutical cost inflation: the pressure on public funds at an age of economic stagflation seems to be the problem.

In addition, a different public versus private share of expenditure, and financing mix of prices and taxation (see Table 1), make a different impact, at least in welfare terms, from the resulting cost shifting towards consumers.

Most of the countries first to introduce reference pricing share three significant features. First, before introducing RP, these countries did not directly regulate the price of medicines (free pricing prevailed). This was the case of Germany, Denmark and New Zealand. Second, generic products in these countries already accounted for a significant share of the market: in Germany they represented 16.1% of the total retail pharmaceutical market in 1995 [26]. The comparable figure for Denmark was 22, and 12.6% for The Netherlands. Third, as can be seen in Table 1, public purchasing accounted for more than half of the pharmaceutical sales: 64.2% in The Netherlands, 71.4% in Germany, 71.2% in Sweden, 58.8% in New Zealand, and 50.5% in Denmark.

The main features of the international experience of reference pricing policies are descriptively summarized in Tables 2–10 for Australia, British Columbia, Denmark, Germany, The Netherlands, New Zealand and Sweden. The descriptive aspects reviewed include[11]:

- the main supply conditions for medicines,
- the date of introduction of each scheme,
- the types of drugs covered by the initial and subsequent versions of each scheme,
- the method of calculating the reference price and the method for grouping each class of drug,
- how often the list of drugs included in each system is updated, and how frequently the reference price for each class of drug is revised;

[10] With a high VAT incidence (around 13%).

[11] This Section updates [17], Section 2.

Table 1
Public pharmaceutical expenditure in countries applying reference pricing systems in 1997[a]

Country	Public pharmaceutical expenditure as a (%) of GNP	Public pharmaceutical expenditure as a (%) of public health expenditure	Public pharmaceutical expenditure as a (%) of total pharmaceutical expenditure	Public pharmaceutical expenditure per capita ($ purchasing power parity
Australia ([a])	0.5	8.2	49.7	100
Canada	0.4	7.0	38.4	101
Denmark	0.4	7.3	50.5	88
Germany	0.9	11.6	71.4	210
Italy	0.6	11.3	40.6	125
Netherlands	0.6	9.9	64.2	131
New Zealand	0.7	12.1	58.8	127
Norway ([a])	0.6	8.6	79.2	137
Sweden	0.8	10.9	71.2	156

[a] Data refer to 1996. Source: [49].

- the measured impact of each scheme on prices and on the use of generic drugs,
- the measured impact of each scheme in the mix of innovative (patented) drugs and generic drugs in each market,
- the expected savings to the government drug budget identified by government at the announcement or launch of each scheme, and
- the actual impact of each system on total government expenditures on drugs.

Reference systems reviewed show significant differences in their product coverage: level of equivalence (chemical, pharmacological and therapeutic) and inclusion or exclusion of patented drugs. A simple characterization of existing reference price systems according to product coverage is presented in Table 2. Sweden and Denmark apply the reference system only to identical products with the same active substance (level 1). British Columbia and Australia reference systems cluster drugs from a group of related but different drugs, regardless of indication, including

Table 2
A simple classification of existing reference pricing schemes according to product coverage

Interchangeability level	Off-patent drugs	Patented and off-patent drugs
Chemical equivalence	Sweden Denmark Norway	
Chemical and pharmacological equivalence	British Columbia	Australia
Chemical, pharmacological and therapeutic equivalence	Germany	New Zealand The Netherlands

Table 3
Evolution of public pharmaceutical expenditure as a proportion of public health expenditure[a]

Year	Denmark	Germany	Netherlands	New Zealand	Norway	Sweden
1985	3.7	12.8	7.5	n/a	4.6	5.4
1986	3.8	13.0	7.9	17.6	4.4	5.6
1987	3.8	13.4	8.1	16.2	4.2	5.9
1988	4.0	13.6	8.3	13.8	6.0	5.1
1989	3.7	13.7	7.9	14.0	6.3	6.3
1990	3.1	13.6	8.8	12.5	6.8	6.4
1991	4.8	13.7	8.6	12.6	6.9	7.0
1992	5.1	13.7	12.2	12.7	7.2	7.9
1993	5.1	11.4	12.6	13.3	6.9	8.6
1994	5.3	11.4	12.5	13.5	6.1	9.7
1995	5.5	11.4	12.7	13.4	8.3	10.6
1996	7.1	11.8	9.7	13.0	8.6	11.2
1997	7.3	11.6	9.9	12.1	n/a	10.9

[a] Source: [49].

Table 4
The reference pricing system in Australia[a]

Factor	Description
1. Supply conditions for medicines	Price control and generic substitution.
2. Date of introduction	February 1, 1998.
3. Product coverage	1. Six therapeutic groups, mainly drugs affecting heart disease and ulcer disease: H2 receptor antagonists (ulcer), statins (lipid lowering drugs), calcium channel blockers (CVD), ACE inhibitors (CVD), beta blockers (CVD). 2. Phone exemption system. Amnesty for people with existing prescriptions.
4. Reference price level	Lowest price for each therapeutic group.
5. Updating	Lists: quarterly. Reference system: annually, but can be quarterly.
6. Immediate impact on prices and generic product market	
7. Impact on total market shares	1. Total 140 drug products. 2. 1/3 of pharmaceutical benefits scheme (PBS) expenditures. 3. Generic market: 12–19%.
8. Expected third party savings	1. A $561 million over 4 years, reduced to A $460 m after [17] report. 2. If all products priced to reference, it would be expected a 18% reduction in dispensed costs of the medicines covered under reference pricing [17].
9. Actual impact on total unknown drug expenditures	Unknown, current growth rate: 8% per year.

[a] Source: [17].

patented drugs. However, other countries like Germany, New Zealand and The Netherlands have extended product coverage to all classes used to treat a particular condition. Germany excluded patented drugs from the reference coverage in January 1996. Exceptions at the patient level have been put forward in British Columbia, Denmark and Sweden, in order to manage the problem of heterogeneity at the individual level.

3. Economics of reference pricing

3.1. Justification

What distinguishes the market for pharmaceutical products and creates the need for establishing reimbursement ceilings such as those implied by a RP scheme? The pharmaceutical industry differs from other industries in several important respects [50]. Some of the most important ones are agency imperfections, information

Table 5
The reference pricing system in British Columbia[a]

Factor	Description
1. Supply conditions for medicines	1. Price control (excessive price guidelines for new products). 2. Negative list of products not available for reimbursement 3. Generic substitution 4. Low cost alternative (April 1994): limits reimbursement to the lowest priced drug when there are alternatives available.
2. Date of introduction	October 1995
3. Product coverage	1. Drugs composed of different active ingredients from the same therapeutic category are grouped together: - H2 Antagonists - Oral and transdennal states (excluded in April 1996) - Non-steroidal anti-inflammatory - Angiotensin converting enzyme (ACE) inhibitors (included in January 1997) - Dihydropyridine calcium channel blockers (CCB), (included in January 1997). 2. Physicians can complete a special authorization form on behalf of the patient to be reimbursed for a non-referenced product
4. Reference price level	1. Full price is paid for one drug in each therapeutic group and this is the maximum price that will be reimbursed for any drugs in that group. 2. Usually the reference for reimbursement is the least expensive product: Average price of 30 day supply of referenced drug
5. Updating	On going and ad hoc.
6. Immediate impact on prices and generic product market	1. British Columbia had the highest generic substitution rate in Canada before implementing reference pricing. 2. The effect on generics has been minimal. 3. There are indications of greater price competition into the market.
7. Impact on total market shares	1. Increased market share for referenced products. 2. Increased number of prescriptions. 3. December 1995: generics = 45% of all prescribed drugs.
8. Expected third party savings	Government claims to have saved $30 million in the first year and $44 million in the second year. However, - $15 million additional funding given to Gps and an extra $250 million to pharmacists. - Administrative costs in just 7 months for special authorizations estimated at $3.7m

Table 5 (*Continued*)

Factor	Description
9. Actual impact on total drug expenditures	1. Total drug expenditures: 1995/96: C $406 m 1996/97: C $396 m 1997/98: C$430 m 2. RP is saving the province about $44 million per year, according to data from the Minister of Health.

[a] Source: [4,39,3,17].

imperfections, moral hazard, and global, sunk, fixed costs. In short, pharmaceutical market imperfections create: (i) reduced price sensitivity on the demand side; (ii) a certain degree of market power on the supply side; and, (iii) demand curves that do not reflect true social benefits. Pharmaceutical demand is stronger and less price-elastic than it might otherwise be. The reasons are the price insensitivity of consumers, especially when public or private insurers reimburse their drug expenditures. Insurance tends to encourage over-use, higher prices and therefore welfare losses.

On the supply side, patents allow for substantial price discretion to the innovator firms producing new drugs. However, new products can be complements or substitutes for rival's products. Firms face competition, first via R & D to discover new products and then after their discovery, via pricing and marketing strategies for gaining market share. In fact, drug companies are in an oligopolistic market typified by a limited number of competitors (especially in sub-markets such as the cardio-vascular or the gastricduodenal ulcer markets), differentiated products and strong innovation strategies, etc. [50]. In such a context, demand curves may not reflect the social benefits.

In addition, agency and imperfect information issues, together with supply side problems, may result in pricing power, even when patent protection has expired. Indeed, after patent expiration, the expected outcome from generic entry is an increase in price competition and lower prices for brand name drugs. In the long run, it may be reasonable to expect that competition will push generic drug prices down to a level approaching the marginal cost of production[12]. In practice, the so-called 'generic paradox' expounded by Scherer [50] hold true: average prices for brand name products have tended to increase following entry by generics[13]. Evidence shows a high degree of brand loyalty for pioneering brands: the result is that brand names are able to retain large market shares relative to lower-priced

[12] Genetic drug producers complete largely with one another on the basis of price: 'Prices follow a Cournot-like path, approaching marginal cost as more firms enter' (P.Termin, 1991, in Comments and Discussion to [52]).

[13] 'The most common scenario, then, is for the incumbent to maintain or increase its price, while ceding a substantial share of the market to much lower-priced generic rivals' [50,p.101].

generic entrants after the patent expires[14]. Despite high rates of lower-priced generics, in some cases brand producers have continued to increase prices at an average rate that exceeds general inflation. Several authors observed that 'several firms' products had prices more than 50 percent greater than the minimum and still had a significant share of the generic market. Frank and Salkever [54] also

Table 6
The reference pricing system in Denmark[a]

Factor	Description
1. Supply conditions for medicines	1. Co-payment mechanism varies by type of preparation. 2. Free pricing. 3. Incentives for generic competition and parallel import.
2. Date of introduction	June 21, 1993
3. Product coverage	1. Substances that are patent expired and contain generic substitutes. 2. Products are grouped on the basis of type of pack. 3. All products, which have at least one, copy version, including generics and parallel imports, are included. 4. Generic substitution possible. 5. Exceptions: doctors could, by special application on medical grounds, have specific patients exempt from the system.
4. Reference price level	The average of the two cheapest products in a given group.
5. Updating	
6. Immediate impact on prices and generic product market	1. Any single pattern (in pricing) was very difficult to discern and it seems clear that individual firms were optimizing their own position given the specific market conditions surrounding their own products [44]. 2. There is no doubt that the introduction of reference prices has resulted in lower drug prices generally [6].
7. Impact on total market shares	The reference price system covers 20% of total sales.
8. Expected third party savings	An expected saving of 1% of overall drug sales (including OTC).
9. Actual impact on total drug expenditures	1. In the first year, growth in pharmaceutical expenditure was lower than at any point in the previous six years.

[a] Source: [1,44,6,17].

[14] 'Pharmaceuticals represent an extreme on two of these dimensions — the difficulty of judging quality in advance of consumption, and the risk of bad choices — and as a result, first-mover brand image advantages significantly supplement patent protection as barriers to rapid imitation' [53, p. 372].

Table 7
The reference pricing system in Germany[a]

Factor	Description
1. Supply conditions for medicines	1. Free pricing, 2. Co-payments for drugs. 3. Prescription drug budgets for office-based physicians.
2. Date of introduction	1. September 1, 1989 2. January 1, 1993: patented products are exempt from reference pricing as long as the first substance of a group is under patent. 3. January 1, 1994: co-payments by pack size. 4. No reference price for patented products registered after 31.12.1995.
3. Product coverage	1. Three stages for the introduction of reference pricing: Products with identical active compound (1989). Products with pharmaceutical/therapeutical equivalence (1991). Products with therapeutically equivalent effects (1992). 2. In July 1997: 60% of the market under reference pricing system.
4. Reference price level	1. Econometric model regressing manufacturer's prices in some therapeutic group 2 on dosage strength and pack size. 2. Standard prices then converted to reference price by multiplying price per standard unit by relative standard price. 3. Result: price = statistically derived median price.
5. Updating	1, Lists: quarterly for new pack sizes and dose strengths. 2. The system: annually (as of 1997).
6. Immediate impact on prices and generic product market	1. Reduction in total number of prescribed drugs 1991–1995: −4. 1%. 2. Increased share of generics.
7. Impact on total market shares	1. Share volume of generic increased from 34.0% in 1991 to 38.6% in 1995. 2, Share volume of patent protected prescribed drugs increased from 11.7% in 1991 to 20.0% in 1995. 3. In 1995 referenced products represents 66% of the total sickness funds expenditure on medicines for the 1988 basket of available drugs. 4. Most firms choose to reduce their prices to the reference level (an average 1.6% reduction in 1989). 5. The gap between the original product and its generics has practically disappeared. 6. Some generic firms increased their prices in response to reference pricing.

Table 7 (*Continued*)

Factor	Description
	7. Pharmaceutical firms increased the prices of products not yet affected by the reference system: between 1991 and 1992 prices of drugs subjected to reference prices decreased by 1.5% whereas the prices of those that were not increased by 4.1%.
8. Expected third-party savings	1. Expected savings from reference pricing: DM 2.5 billion p.a. 2. Expected total savings 1993–1995: DM 10.85 billion. 3. With 75–80% market coverage, estimated average price decrease = 20%.
9. Actual impact on total drug expenditures	1. Total savings in 1992–1994 of: DM 5 billion. - altered prescribing behavior of doctors (DM 3 billion). - lower prices and extended reference pricing (DM 1 billion). - increased patient charges (DM 1 billion). 2. Net effect on total insurers expenditures for drugs in 1993 compared to 1992: 19.5% decrease. 3. Public expenditure on drugs subjected to reference pricing showed a steady increase after an initial reduction.

[a] Source: [10,12,14,17,21,32,33,37,44,45].

concluded that 'increased competition from generics was not accompanied by lower prices of brand name drugs,- on the contrary, evidence suggests small price rises tied to expanded competition'. This may be the case despite the fact that a positive correlation is not always found between generic entry and brand-name price levels.

The 'generic paradox' may be observed as an expression of brand loyalty. According to the Schmalensee model of first-mover pricing advantages, 'the image advantage that comes from consumer recognition as the first mover in some product category may permit its possessor to hold prices above costs for significant periods of time while retaining a large share of the relevant market' [55, page 585]. Thus first-mover advantages confer pricing power in the pharmaceutical market. The first mover advantage also appears to hold true for the first generic entrant, which is able to retain a substantial market share with a higher price than later generic entrants. The relative quality of the product of the first mover is more a consumer perception than an objective standard (product image); higher perceived quality may lead to prices above those of competitors and allow the company to hold on to a substantial share of the market.

Frank and Salkever [51] provided a market segmentation model to explain the price response to generic entry of brand-name products. Their price discrimination model suggests that entry of generics lead price-sensitive buyers to shift to generics, leaving only price-insensitive buyers to purchase brand-name products. Thus brand-

Table 8
The reference pricing system in The Netherlands[a]

Factor	Description
1. Supply conditions for medicines	1. Maximum prices based on international comparisons (July 1, 1996: price regulation law on drugs).
2. Date of introduction	2. Financial incentives to substitute expensive drugs. 1. July 1, 1991: reference pricing based on four criteria (Medicines Reimbursement System -MRS-). 2. July 1, 1993: new drugs that cannot be clustered will be fully reimbursed if they are used to treat conditions for which there are no therapeutic interventions. 3 July 1 1996: Price Regulation Law on Drugs.
3. Product coverage	1. All prescription drugs. 2. Reference price system: - Clusters of therapeutical equivalent products - Unique products (there are no comparable pharmaceuticals products on the market) 3. Products could be classified into the same group if. - they had the same therapeutic action, - they were used in the same range of indications, - there were no differences in desirable/undesirable effects, - they were administered by the same route, - they were given to the same age groups,
4. Reference price level	1. Clusters 1-5: price = product below average cluster. Price per day of therapy for a given class is based on January 1990 prices and DDDs. 2. Cluster 6 (unique drugs): fully reimbursed. Due to budget constraints, the list has been closed since July 1993.
5. Updating	1. Lists-, monthly. 2. The system: twice yearly for maximum price.
6. Immediate impact on prices and generic product market	1, The system has had the initial effect of lowering the prices of drugs that were clustered and reimbursed (5% in 1991–1993). 2. Increase in the price of those drugs, which could not be clustered. 3. Market shares of cheaper generic and parallel import drugs increased 40% in period 1993–1995.
7. Impact on total market shares	1. The system initially covered 90% of the market, including patented drugs. 2. Some drugs have been marketed outside the reference system.
8. Expected third-party savings	1. June 1, 1996 legislation: prices will drop 20%, leading to savings of DG 700 million. 2. Reduction of growth from 8 to 3.5%.

Table 8 (*Continued*)

Factor	Description
9. Actual impact on total drug expenditures	I. Pre-MRS: expenditure increased by 11.2% from 1989 to 1990 and 8.3% from 1990 to 1991. 2. Expenditure increased a 11.7% in 1992. 3. Expenditure increased a 11.2% in 1993.

[a] Source: [28,40,26,17].

name producer's demand becomes less elastic, 'allowing the profit-maximizing brand-name firm to raise its price' [54, page 77].

Reasons that confer pricing power on the innovating firm are: (i) imperfect agency between the physician (the agent) and the insurer (the principal). The prescriber may prefer the brand name product in which, he has gained experience during the period of patent protection (risk averse physicians); (ii) the patient, and sometimes the physician, may have imperfect information as to whether a lower priced product meets the quality of the extensively tested pioneering drug; and (iii) lack of incentives to change prescription habits (moral hazard). Hellerstein [56] observed that there are potentially large social costs from prescription of trade-name drugs after patent expire which cannot be explained by patient- specific characteristics. This is, 'when physicians make prescription decisions based on incomplete information combined with agency problems, they do not make cost-effective decisions' [56, page 130].

Public expenditure control efforts to reduce pricing power after patent expire therefore seem to require incentives to prescribers and dispensers in order to substitute lower priced generics for brands. Managed care organizations, as well as more price sensitive buyers in the market may help to achieve this purpose too. In this context, RP may be justified on the grounds of reducing the welfare losses involved in choosing more expensive drugs when appropriate low-priced substitutes are available.

3.2. Reference pricing as a procurement mechanism

One should first note that five features characterize RP strategy

1. The third-party payer (public or private insurer) directly sets a ceiling for the amount reimbursable to the manufacturer for a prescribed pharmaceutical product. In this sense, RP success requires the exercise of a relative purchasing power from the insurer's side.
2. RP is equivalent to setting a co-payment which: (i) implies a variable amount depending on the price of the selected drug; and (ii) may be avoided if the drug does not exceed the reference price,
3. Identical reimbursement ceilings are defined for groups of pharmaceutical products. 'Clusters' of pharmaceuticals are defined in terms of their interchangeability. This may be interpreted more strictly or loosely depending on chemical, pharmacological or therapeutic equivalence. Clusters may or may not include patented products.

Table 9
The reference pricing system in New Zealand[a]

Factor	Description
1. Supply conditions for medicines	A positive list of medicines and related products reimbursed by the government.
2. Date of introduction	1993
3. Product coverage	1. At least one subsidized drug in each subgroup, although not all subgroups is reference-priced. A sub-group is defined as a set of pharmaceuticals, which produce the same or similar therapeutic effects in treating the same or similar condition. 2. Pharmacy can decide to opt out of funding particular subgroups at any time and delist all products concerned. Similarly new medicines in a new class may not be subsidized.
4. Reference price level	1. Full subsidy at the historically lowest price to cheapest products in each therapeutic sub-groups or at the price of a newly admitted product if its price is lower than the current subsidy. 2. It is required to a new product having to enter its class at a lower or equal price to the reference-priced product. Then, new products may effectively be kept out of the subsidized market.
5. Updating	1. Lists: monthly. 2. The system: at any time including a new product and via therapeutic group or sub-group review.
6. Immediate impact on prices and generic product market	1. Firms have been known to set the prices above the subsidy level (the anti-inflamatory Naprosyn of Roche rose 20%). 2. There is evidence of a downward trend in the real price of subsidized pharmaceuticals prior to the inception of reference pricing, raising the issue of the extent to which reference pricing policy was able to reduce the price of subsidized medicines relative to the general price level in addition to any reductions that would have occurred in its absence. 3. Small average differentials in prices between generics and pioneering brands. But reference pricing is not effective keeping generic price levels low by international standards.

Table 9 (*Continued*)

Factor	Description
	4. Generics not considered for a subsidy unless price offered is significantly below the reference price.
7. Impact on total market shares	Low market penetration of generics, consistent. with their low favorable price differential.
8. Expected third-party savings	1. Reference price component: unclear 2. Pharmacy claims: 10% 3. Pharmacy expected successive generic entrants to cut their prices by 30, 20 and 10% below the currently reference-priced product, for successive generic entry.
9. Actual impact on total drug expenditures	1. Unable to separate effects of reference pricing, generic substitution and other policy measures. 2. Pharmacy's reference-pricing system may, on average, be reasonably effective in reducing both subsidy levels and subsidy payments for existing drugs relative to the previous system. 3. From June 1993 to June 1994 the subsidy per head corrected for population aged >60 years increased a 11%, and only a -0.6% from June 1994 to June 1995.

[a] Source: [4,42,17].

4. For the reimbursement ceilings the insurer usually applies the observed domestic prices of the products included in the same cluster or group as a benchmark[15].
5. These reimbursement ceilings are adjusted periodically by an adjustment factor, which may or may not be previously announced. In many cases this factor is not exogenous to the price behavior of the benchmark product(s) or to the price of new products included in the same group. The concept of interchangeability and the selection criteria for setting the select the reference price are reviewed every few years and changed where necessary.

A second point well worth noting is that RP implies a reimbursement limit, not a final market price. Reference pricing is not, strictly speaking, and a pricing system. Rather it is only a reimbursement or procurement mechanism the third-

[15] Thus, in a restricted sense, reference pricing would be similar to a yardstick competition mechanism, without considering the existence of the avoidable co-payment. The yardstick competition is a regulatory pricing policy in which the average cost of all competing firms is used to determine the price level in order to induce the firms to engage in cost-cutting innovations. The Prospective Payment System to hospital in the United States is an application of yardstick competition.

Table 10
The reference pricing system in Sweden[a1]

Factor	Description
1. Supply conditions for medicines	1. Direct price control was abandoned in January 1, 1993 (free pricing versus negotiated prices). 2. A positive list for reimbursement. 3. No one pays more than SEK 1.300 for prescribed drugs per year. Variable proportion of co-payment according to the price level.
2. Date of introduction	January 1, 1993
3. Product coverage	1. Products with expired patents and generic equivalents (same form, same active substance and same quality). 2. To be included under RP a product must have been on the market for at least 6 months and have at least 20% of sales in outpatient care. 3. It is possible to grant a certain patient exemption from the system. 4. Restricted generic substitution is possible.
4. Reference price level	10% above the price of the cheapest product (based on pack size, dosage and method of administration).
5. Updating	1. List reviewed quarterly. 2. The system is re-evaluated every 2 years.
6. Immediate impact on prices and generic product market	1. For original products within the RP system, the price, with few exceptions, dropped to the reimbursement price. 2. Market share for generic products increased. 3. Generic prices were reduced to the price of the lowest generic. 4. There is no incentive to set a price lower than that reimbursed. 5. Some products were effectively delisted of the reimbursement system and their prices increased.
7. Impact on total market shares	1. Total market for all products in the reference price system in the first 6 months of 1993 compared to 1992 dropped from SEK 474 million (−27%). 2. Market shares changes in the reference price segment during the first 6 months of 1993 compared to 1992: - Original products 1992: 65% 1993: 51% - Generic products 1992: 35% 1993: 49% 3. It was mainly an effect between 1993 and 1994. The selling of drugs with reference pricing system in 1993 compared with 1996 (same drug, form and package):

Table 10 (*Continued*)

Factor	Description
	- The volume increased by 4.6%, and - The cost decreased by 16.9%. 4. In 1996, 70 substances were included and accounted for about 8% of total sales.
8. Expected third party savings	Expected savings of SEK 400 million annually (about 5% of the total expenditure).
9. Actual impact on total expenditures	1. total change in public expenditure in 1993; SEK −485 million. 1.1. Factors contributing to changes: price reductions (−305), cost over reference pricing paid by the consumer (−30), switch to less expensive drugs (−80), drugs outside the reimbursement system (−70). 1.2. Changes in financing: reduced revenue for industry (−300), reduced revenue for pharmacies (−85), increased expenditure for patients (+100). 2. The total reimbursement saving for the period 1993–1996 (calculating costs in 1996 if the RP system had not been introduced) can be estimated at SEK 1 billion. 3. In 1993 sales growth in the non-reference price segment was 18.3%, and the overall growth in the Swedish market was 12.6%.

[a] Source [18,44,18] Andersson (1998) [17].

party payer establishes the maximum 'reasonable' price he is willing to pay. The supplier is allowed to set a market price above the reference price if he believes that the patient will be willing to pay the difference. In spite of this, as noted by Drummond et al., [12], pricing and reimbursement decisions are conceptually linked: reimbursement decisions (inclusion or exclusion, or the extent of reimbursement) are dependent on the price, but price changes or the introductory price of a new product are also dependent on the reimbursement. However, in practice, the influence of RP on firm pricing may be very strong if firms are led to set market prices at the reference level. In this case, it is not only a reimbursement control but, some authors argue, also a price cap in all but name.

The influence of RP on market prices depends on the power of the buyer, the own price demand elasticity, cross-price elasticity for pharmaceutical products, and how wide the system's coverage is. The most favorable circumstances under which the reference price would virtually constitute a price cap are where there is a large buyer, wide product coverage and high demand elasticity.

Differences in existing RP schemes may obscure, however, the difference between a pricing and a reimbursement system. Reference pricing may become a

pricing system when the decision to include or exclude a product from public reimbursement depends on its price level. The use of reference pricing in Italy and New Zealand may illustrate this situation. Italy introduced a stringent reference pricing system in July 1996. This was a special case because the reimbursement ceiling immediately set the maximum price since patients had to pay the full amount for drugs, which were priced above the reference price rather than simply the difference[16]. Only the cheapest product in the group of identical drugs is reimbursed. Products with prices above the reference (cheapest) value are delisted (i.e. receive no public reimbursement). However, practically all companies have now agreed to cut prices, to avoid de-listing. Thus Italian reference pricing policy effectively excludes patient co-payment and the possibility of selecting a drug priced above the RP since there are very few patients around who are prepared to meet the whole cost out of their own pockets. In New Zealand, Woodfield et al., [42] report that reference pricing appears to involve listing a new drug in a given cluster only if its price is set below that of the currently reference-priced product.

The basics of the RP approach are as follows:

We call Pr the reference price, Pc the price faced by the consumer, Pl the price charged by laboratories and k the existing co-payment percentage[17]. Two cases are possible:

Case 1: If $Pl_1, < Pr$, Pc is set at kPl.

Case 2: If $Pl_2, > Pr$, Pc is set at $P1 - Pr + KP_r$.

The implicit subsidy in each case is $T_1 = (1 - k)$ and $T_2 = (Pl_2 - Pc)/Pl_2 = Pr(1 - k)/Pl_2$. Since $Pl_1 < Pl_2$ and $Pl_2 > Pr$, T will compare with T_2 according to k and Pr. That is, the per product net subsidy is larger the lower the difference between Pr and Pl[17], and the lower co-payment k.

From a welfare point of view, at an equal amount of public subsidy, it will be noted that reference pricing replaces an ad valorem subsidy. Before this, the amount of the public subsidy depended on commercial prices, whereas in RP the subsidy is bounded by $(1 - k)Pr$, a limited amount that does not depend on the Pl. However, this new approach still can be considered Pareto inferior to a lump sum voucher system.

Notice, in addition, that RP will have the desired effects on drug expenditure control depending on the exact level of the set prices. When Pr is the lowest price in the therapeutical subgroup and no interchangeability between subgroups occurs (say through a different treatment or condition classification), savings will appear.

This may be the case of the new Spanish RP Bill: For each homogeneous set of products, Pr is calculated on the weighted average (year on year) of the lowest-

[16] According to our definition of reference pricing, the Italian systern is not a pure reference pricing system.

[17] Although a k parameter depending on $(Pl - Pr)$ might be postulated too.

priced products which account for at least 20% of the market sales. If the difference of this calculated price and the highest price for the group is less than 10%, P*r* will be the result of applying a 10% reduction to the highest price (thus achieving at least a 10% saving). If the difference between the calculated price and the highest priced product is more than 50% *Pr* is recalculated as exactly 50% of the highest priced product (thus foregoing some potential savings). In all cases, P*r* never will be less than the generic with the lowest price.

Otherwise, products already priced at below benchmark prices may take advantage of increasing their prices at no consumer cost. This increase may or may not be offset by potential savings arising from greater pressure on drug companies pricing over reference price levels. This ultimately depends on the price elasticity of demand for their products and the prevailing product differentiation policy[18]. This issue may affect which companies enter the market since only low cost (and perhaps poor quality) products involving low R&D overheads may prove commercially attractive under such a scheme.

In addition, if savings have to be shared by some other agents, as is the case in The Netherlands for drug dispensers, this will further reduce the amount of savings. In Norway reform is being considered to strengthen incentives to prescribe the cheapest drug available. This is done through a central electronic database. Therefore, the pharmacist should provide the cheapest brand or a parallel imported version of the prescribed brand unless the prescription states otherwise. This reform can usefully complement the RP system introduced in 1993, which uses the price of the cheapest brand available. Moreover, the system is to be extended from March 1998 to patent protected drugs but parallel imported or manufactured under license at a lower price [38].

A third relevant feature is that of RP as an avoidable co-payment. In contrast with positive or negative lists, the choice of medicines available to the patients and their physicians is not restricted. If a doctor prescribes a product that is more expensive than the fixed payment level, then the patient will pay the difference.

In the case of differential co-payments, doctors must tell the patient if he wishes to prescribe a product that requires the co-payment [58]. Since doctors dislike discussing this, they frequently choose a product at or below the fixed level. If there is a discussion with the patient, the patient often selects a product which does not involve co-payment [57]. This reimbursement mechanism is intended to make patients more aware of costs and to promote the rational use of 'similar' or interchangeable medicines.

In the context of a public decision maker with the objective of maximizing health returns (e.g. quality adjusted life years, -QALYs-), the ceiling on the drug reimbursement level could be interpreted as the use of a decision rule based on the

[18] Another alternative co-payment scheme may be based on a fixed price per item and a percentage co-payment which decreases according the distance between *Pl* and *Pr*. In addition, whenever there is a stop-loss co-payment, the deterrent effect of *Pr* will depend not just on the prices but also on the amount of drugs (full bill). In this sense, holding the fixed per item price may avoid the perverse incentives which would otherwise exist.

maximum price the insurer is prepared to pay to gain one unit of 'health' and thus lead to budgeting decisions. However, this equivalence of reference pricing with a social decision rule depends heavily on the appropriateness of treatment and measurement of effectiveness implied in drug interchangeability. At the same time, avoidable co-payments can sometimes become unavoidable if drugs clustered in the same group are not 'perfectly' interchangeable for a specific patient and depending on the pricing strategies adopted by the companies marketing these products [41].

A fourth basic aspect is that of the concept of interchangeability- Reference price systems observed in the international arena present remarkable differences in the proportion of the pharmaceutical market or sub-markets covered, according to the equivalence criteria selected, and the exclusion/inclusion of patented drugs. In Section 2 we review reference price systems according to the equivalence criteria used and the policy in relation to patented drugs.

There are three levels or criteria of interchangeability (equivalence) observed in the use of reference price schemes: chemical, pharmacological and therapeutic equivalence [12,21]. The first level corresponds to establishing groups with the same active ingredient. All products included here are patent-expired drugs, usually clustering generics and branded products after the patent ends. The second level clusters products in the same therapeutic category (drugs with pharmacological and therapeutically comparable active ingredients), for instance, angiotensin-converting enzyme (ACE) inhibitors. The third level clusters products with the same therapeutic function, such as, for instance, all antihypertensives. Level two and three may include or exclude products under patent protection.

The issue of lack of equivalence or interchangeability between drugs included in the same group (heterogeneous clusters) probably constitutes the most controversial issue in the literature on reference pricing. Zammit-Lucia and Dasgupta [44] stated that the concept of interchangeability between drugs cannot always be objectively defined, and as a result it varies from country to country, and can be considered a bureaucratic concept, not a medical one. If the groups include drugs with different dosages, as it is the case in Italy, it imposes a penalty on low dose drugs because their price, expressed in cost per mg. of therapeutic agent will be higher than that of higher dose products [26].

Three questions arise in relation to heterogeneity in the same group of medicines[19]. First, what are the main forms of potential heterogeneity between medicines grouped with one single common and uniform reference price? Secondly, does the degree of potential heterogeneity differ between levels of interchangeability? Thirdly, what are the expected effects of heterogeneity in the same group of medicines?

We may distinguish, therefore, different cases:[1] Individual patients have physiologically different responses to the administered drugs. Heterogeneity between medicines with the same level and price reference group may stem from [21]:

[19] This section is mainly based on Massen [21].

- differences in drug quality (e.g. the presence of impurities);-performance (speed of absorption, indications, effects);
- differences in the chemical preparation of drugs (e.g. structural formula, molecular weight and dissociation constant, which may result in different indications);
- differences in application form (e.g. oral, topical, rectal or parental, which may imply significant differences in production costs);
- differences in power/dosage form (weak, medium, strong dosage);-differences in bio-availability (fast/slow action, retard; half life);
- differences in the number and type of admitted indications;
- differences in the type and frequency of unwanted effects;
- differences in side-effects (contra-indications);
- differences in additional services provided by the pharmaceutical entrepreneur (breadth of range, therapy- supporting services provided).

If not adequately considered, these sources of heterogeneity between groups of medicines in the same category and price may lead to differences in effectiveness and in the cost of products as a result of applying uniform reimbursement.

The degree of potential heterogeneity differs between levels of interchangeability. As described, the first level is the more homogeneous group. In this sense, for instance, the Canadian Cardiovascular Society [5] considers reference pricing appropriate ('in situations of constrained resources') for drugs which have identical active ingredients and are therapeutically interchangeable for a specific disease. However, no significant differences in absorption, bioavailability, efficacy, safety or tolerance are expected in generic and non-generic products with identical bioactive ingredient and formulation. But even when the active ingredient, can be the same, Maassen [21] has reported the possible wide variations stemming from differences in chemical preparation, bioavailability and performance.

Diversity among patients is always a complex issue, particularly when the unit of analysis is a broad patient category, as it usually the case of second and third levels of equivalence.

Differences between medicines are greater at the much less homogeneous second and third levels. Medicines with different active ingredients may differ in performance, effects, absorption, contra-indications, undesired effects and all other sources of heterogeneity[20,21].

[20] The Canadian Cardiovascular Society [5] only accepted the application of reference price systems at these levels if supported by level 1 medical evidence (Sackett criteria). Maassen [21] observed further heterogeneity problems in Germany at levels 1 and 2 arising from: (i) from the inadequacy of the average daily dose (ADD) concept (different opinions on the ADD, existence of ADD ranges, differences between initial and maintenance ADD, varying ADDs according to indications); and (ii) from the co existence of level 1 and level 2–3 reference price groups with different price levels.

[21] 'If the active ingredient in a level I reference price group on the one hand and the active ingredients in the level II or III reference price group on the other hand are therapeutically comparable, different reference prices will apply in spite of a comparable performance of the active ingredients which should be rewarded with the same reference price' [21, p. 10].

What are the expected effects of heterogeneity in the same group of medicines? Three different kinds of arguments have been highlighted in the literature. First, if there is no interchangeability at the level of the individual patient, as commented, then the co-payment may become not avoidable and the reference price system may discriminate against some patients[22]. Second, selection of a drug under a RP category may result in a lower level of effectiveness and potentially harmful side effects for the patient because the drug is chosen simply with a view to avoiding the co-payment. This in turn may involve increased expenditure on other complementary health care services or even additional drugs. Third, the adoption of a single price for drugs with reduced interchangeability may distort competition between products and discriminate against particular firms[23]. In particular this may prove to be the case at levels 2 and 3 since the patient's willingness to pay may not adequately reflect a fully informed preference for the additional benefits obtainable by choosing a product priced above the reference benchmark.

In addition, using a single reimbursement level may also imply that even where significant therapeutic differences exist, the insurer may place greater importance on his budget constraints than on the potential additional health benefits conferred by choosing a more expensive drug. This does not distort competition by itself, but it recognizes a sort of buyer's right to limit willingness to pay and to establish priorities as a resource allocation mechanism in order to improve efficiency. Thus, in theory, the patient -or the physician acting on their behalf- has to decide if he is willing to face a co-payment in order to obtain additional health benefits. In the case of perfect information about effectiveness, costs borne by the patient would be the measure of the willingness to pay for extra benefits above those of the benchmark product of the group. This will happen when the expressed insurer's marginal willingness to pay is lower than that of the least effective financed service. However it should be noted that patients are not privy to perfect information regarding therapeutic effectiveness. Indeed, perceptions may be distorted since RP encourages the belief that all products clustered in the same group are perfectly interchangeable[24] and hence equally effective. Providing information about additional benefits and co-payments impose costs on the physician side. As a result, price demand elasticity would be higher than in the case of perfect information as additional benefits above the reference benchmark are assigned little importance. Furthermore, the price elasticity of a pharmaceutical product faced by the manufacturer depends on the difference between the market price and the reference price, which only represents an arbitrary proportion of the whole price if there is no perfect interchangeability. In general, RP systems have responded to these problems

[22] As an example, Zammit-Lucia and Dasgupta [44] cite the case of patient suffering intolerable adverse effects from one calcium antagonist, but tolerating another, both being included in the same group.

[23] 'The basic principle of equal treatment-like price for like performance- is violated' [21].

[24] Note that the argument applies to additional imperfect information induced by the reference pricing system.

by increasing the number of groups (trying to reduce heterogeneity in the same group) or by considering special safeguards to the mechanism at the patient level[25].

In brief, we have identified two sorts of problems arising from heterogeneity among clustered drugs ('the costly consequences of assuming all patients are the same', in Looney's words, 1997), particularly important in level 2 and 3 groups. First, cluster heterogeneity may produce unjustified inequalities between patients if the reference system falls to accommodate differentiation at the individual patient level. Second, heterogeneity may lead to inefficiencies when there is additional imperfect information involved in considering differences with respect to the benchmark product in the group. This may increase other health care costs, lower health and distort competition in the pharmaceutical market. Health policy, and not just health expenditure control, matters.

A fifth relevant aspect of RP is the treatment of drugs under patent protection. Initially Germany included patented drugs, but later on (January 1996) they were exempted from RP. In other countries like Denmark and Sweden the system covers only products with expired patents and generic equivalents. Maassen [21] points out that RP applied to patented drugs produces an economic erosion of patent rights by lower performing in the same reference price group[26].

The literature unanimously agrees on the potential negative incentives for pharmaceutical innovation when patented products are covered by RP. If this is the case, companies will have reduced financial incentives to develop: (i) incremental improvements in alreadyestablished drugs that are subject to reference prices[27]; (ii) new drugs which fall into a class of drugs subject to a reference price; and (iii) additional indications for an active ingredient that is already covered by a reference price. In order to maximize profits, firms will invest more in the development of new, innovative drugs, which are not classified under RP. The bias against innovative new drugs will be higher if a market price ceiling for the new product is imposed when old and newer products are clustered in the same group and when a larger share of profits is obtained before the patent expires.

The welfare effects of these disincentives to innovate will depend, however, on how complete information plays when selecting a drug. Under perfect information, if the patient's willingness to pay for an incremental improvement is very low the

[25] For example, in British Columbia a special authorization permits full reimbursement above the refence price if the doctor provides the insurer with convincing medical reasons for his prescription choice.

[26] However, the erosion of patented drugs may not only be attributed to reference pricing given that patent protection does not guarantee isolation from competition in any pharmaceutical sub-market. 'Erosion' also occurs because the patented drug has to compete with older and newer products in the same therapeutic group.

[27] 'Why should a pharmaceutical manufacturer have an interest in incremental improvements in already-established drugs that are subject to reference prices? There would be no point, for example, in developing an innovative benzodiazepine tranquilizer that it-as non-addictive and did not interact with alcohol, when it would immediately be reference-priced alongside the older compounds of the same class.' [21, p. 8].

disincentive to invest in innovation would be maximized. It follows that the risk of adverse effects resulting from imperfect information increases when the potential differences between drugs clustered in the same RP group are greater, as may be the case for levels 2 and 3.

Does the exemption of patented drug from RP solve the negative effects on research and development capacity of the pharmaceutical industry? The exclusion of patented drugs from the system may reduce the economic erosion of patent rights and the disincentive to invest in research and development. However, the negative effects on innovation will not fully disappear because: (i) reference pricing increases uncertainty about the expected return on a given investment, (ii) innovation incentives will be reduced because of the joint aspects of research and development given the decrease in overall profitability implied by reference pricing; and (iii) exclusion of patented drugs has proven to be incomplete in some cases (e.g. drugs with a process patent, with a patented new galenic form and with a patent for a further indication). The impact on investment R&D decisions of RP applied to off-patent drugs is also limited because of the very long time lag between investment and sales (because of discounting, the existence of RP for off patent products should have a little impact on R&D).

4. Impact of reference pricing policies

4.1. Descriptive observations

As commented in the first section of the paper, a wider range of reforms affecting both supply and demand has accompanied RP in most countries. In this case it is unreasonable to attribute all changes in expenditure and market prices to reference pricing alone. From a descriptive point of view, the implementation of RP since 1989 may be roughly summarized by considering its impact on drug expenditures, prices and market shares (see Tables 4–10, and their references). However, descriptive observations are unable to separate the effects of reference pricing from the results of other policy measures applied at the same time.

1. It appears that RP produced *short-term* reductions in insurer's expenditure. Its global impact of the reduction seems to depend on product coverage. This shows a large range of market coverage: from 8% in Sweden (1996) up to 90% in The Netherlands (1991). Short term savings require changes in the prescribing behavior of doctors (switch to less expensive drugs), lower market prices, changes in the extension of the reference price mechanism, and increased focus on patient charges (i.e. cost over the RP being paid by the consumer). In Germany, the net effect on total insurers expenditures for drugs in 1993 compared to 1992 was a one off 19.5% decrease. In Denmark, the first year produced slower growth in pharmaceutical expenditure than at any time during the previous 6 years.
2. The experience proves that RP does not result in important long-term savings. Following the initial impact, expenditure growth resumes, partly due to new and

more expensive drugs. In Germany, the share of patent protected prescribed drugs increased from 11.7% in 1991 to 20.0% in 1995. Generally speaking, there is a increase in prescriptions, prices and expenditure of non-referenced products over time[28]. In the following years after the introduction of RP, countries need to implement further controls on the drugs bill. As the case of Denmark or Germany shows, results suggest that RP are not likely to affect the trend in insurer drug costs in a meaningful, ongoing way. Table 3 shows the evolution of public pharmaceutical expenditure as a proportion of public health expenditure since 1985 in those countries which first introduced RP. Only Germany showed a significant decline in the proportion of pharmaceuticals health expenditure (for which the contribution of complementary regulatory measures needs to be borne in mind). In other countries this proportion continued to increase despite RP introduction.

3. The price of products covered by RP tends to decrease. Initial price reductions are reported in all countries, which introduced this mechanism. In Sweden, the price for products within RP, with some few exceptions, dropped to the reimbursement level, also generic prices lowered to the price of the lowest generic. In Germany most firms chose to reduce their prices to the reference level; according to Danzon and Liu [10]. There was an immediate price cut of about 13% in the first year and an additional 2% to 10% thereafter. In New Zealand there is evidence of a downward trend in the real price of subsidized pharmaceuticals prior to RP. In The Netherlands, the system showed an initial effect with lower prices (5% between 1991 and 1993) for those drugs that were clustered and reimbursed under RP.

In general, no incentives to set a price lower than the reference prices were observed in Germany it has been reported that some generic producers increased their prices to the reference level, the benchmark being set through a statistically derived median price. If market prices decrease, the difference between brand name drugs and generics is consequently reduced. Even so, it has to be said that RP in New Zealand has failed to deliver low prices for generics by international standards.

Price and market share of non-covered products increased notably. Generally, pharmaceutical firms increased the prices of products not directly affected by RP. In Germany, prices of drugs subjected to reference prices decreased by 1.5% between 1991 and 1992 whereas the prices of those under the RP scheme increased by 4.1%. In The Netherlands the price increased of those drugs, which could not be clustered. In some cases, products have been de-listed from the reimbursement system, as in Sweden and New Zealand, and their prices have increased. Not surprisingly, in Italy many pharmaceutical companies reduced prices to maintain their products under public coverage (given that Italian patients are forced to meet the full cost of drugs priced above the reference level). However, some other

[28] The result was that in 1995 referenced products represent 66% of the total sickness funds expenditure on medicines for the 1988 basket of available drugs; but because of the addition of new products to the list, the share for the actual drug expenditure is only about 37%.

companies decided not to reduce prices and their drugs were consequently delisted. As a result, more than 400 products were delisted and more than 150 had their prices reduced by an average 7% [13]. In Sweden, sales growth in the non-referenced price segment was 18.3% in 1993 while overall growth in the Swedish market was 12.6%.

When the generic substitution rate was higher before implementing reference pricing, as was the case in British Columbia, the effect of RP on generic market share was minimal. A low penetration of generics is also observed in New Zealand due to small price differences. However, in some countries such as Germany, a moderate increase in the share of generics is observed: share volume of generics increased from 34% in 1991 to 38.6% in 1995. An increase in market share for generic products is also observed in Sweden. In the Netherlands, market share of generics (and parallel imports) increased from 18% by volume in 1990 to about 30% in 1993.

4.1.1. Advantages and disadvantages

Briefly, the main arguments for reference pricing, are three-fold. First, from the company's point of view [26], manufacturers remain free to set any price they wish in order to increase their market share in a fully transparent context. Second, in contrast with positive and negative lists, RP does not set legal limitations on the freedom of the doctor to prescribe drugs since all drugs are available.

And third, potential reductions in pharmaceutical expenditure (the cost containment effect) may be achieved without any sacrifice in effectiveness (i.e. RP promotes an ongoing improvement in cost-effectiveness) by increasing cost-conscious drug consumption. The conditions for success of RP as a reimbursement mechanism rely basically on the existence of important price differentials between products clustered in the same group and the scope of the previously existing generic market.

The main arguments against the incentive and efficiency postulated effects of RP may be summarized as follows. The desired cost-containment of pharmaceutical and health services expenditure is not always achieved and when it is, it is less than expected and short-lived. Reference pricing falls to contain pharmaceutical spending [26,44]. This limited cost containment effect of RP can be explained by several factors:

1. RP can only be applied to a small proportion of the pharmaceutical market and is usually not the driving factor behind the growth in spending on drugs (limited scope).
2. Firms may minimize the effect of RP on total pharmaceutical revenues: firms attempt to recover losses in the referenced product market by increasing the prices of those pharmaceuticals not covered by RP [12]. RP stimulates the industry to make a major effort in order to promote drugs that do not fall under the scheme.
3. RP only addresses the price component driving growth in pharmaceutical expenditure. Growth in volume and prescribing composition is not affected. Under the assumption of low demand elasticity, RP would only be useful in situations where pharmaceutical expenditure growth is mainly price driven.

4. Savings in pharmaceutical expenditure under RP are basically achieved at the expense of increased expenditures in the utilization of other health care services in the form of higher hospital admission rates or higher rates of referral to other physicians[29]. (higher costs faced by some other agents in the health system).

RP is also questioned because of its insensitivity to differences in the clinical profile of drugs [28]. As has been observed, the heterogeneity problem is present at equivalence levels 2 and 3. The result is that RP: (a) may discriminate against individual patients, and individual health outcomes may be adversely affected; (b) product differentiation may not be adequately rewarded and may bias the system against innovative new drugs whenever they are grouped with existing products and therefore reimbursed at the same price; and (c) competition between products may be distorted.

Finally, RP is also controversial because of the possible negative effects on efficiency. Inefficiency may arise from: (1) increased uncertainty about payback of R&D costs (patent rights may be additionally eroded when the system clusters patented and off patent products in the same group). This may result in a cut in R&D expenditure leading to less pharmaceutical innovation (dynamic efficiency problems); (ii) it imposes an important administrative regulatory burden on authorities and firms; and, (iii) it distorts competition: RP does not supply incentives to price a product below the reference level if savings are accrued by the insurer[30].

As commented on earlier, it is difficult to isolate RP effects from those related to other cost containment measures applied at the same time such as, for instance, the introduction of a global budget for pharmaceutical expenditure funded by insurers. In this sense, it should be noted that the term 'reference prices' is something of a misnomer. Reimbursement level would be a much more accurate description[31]. In addition, reference pricing, when exclusively applied to off-patent drugs, may be interpreted as a tool which improves information in the pharmaceutical market so that generic products become more efficient substitutes when patents expire.

4.2. The impact of RP

4.2.1. The impact on pharmaceutical expenditure, drug consumption and prices

Giuliani et al., [15] investigated the effects of introducing RP in Germany in order to assess whether the system has been effective in containing public spending on pharmaceuticals during the period 1990–1996. They observed that average price per Defined Daily Dose (DDD) declined after the introduction of RP, but that the decrease in unit cost failed to fully offset the increase in expenditure, except in the

[29] This would be a consequence of considering prescription drugs, physician services, and perhaps other medical services as bundled goods, as previous studies on the effects of co-payment and prescription drug use suggest.

[30] The same agruement applies if there is competition but a cost saving process innovation is introduced by the manufacturer.

[31] Selke [35, p. 149].

case of NSAIDs and (to a lesser extent) analgesics. Savings were offset by the growth in spending on those products not subject to RP. An obvious limitation of RP is that it cannot be applied to innovative drugs.

Danzon and Liu [10] show how the short-run effect of RP is to put a kink in the manufacturer's demand curve at the reference price, assuming that physicians have perfect price information. The pure kinked demand model implies that brand prices fall and generic prices increase in response to RP (those price priced at or below the reference level). According to these authors, in a kinked demand curve model, it is never optimal to price below the kink. The optimal pricing strategy for a manufacturer of non-RP drugs may be to pursue a market segmentation strategy. By abandoning the more price sensitive market segment to RP drugs, the manufacturer faces a less price-elastic demand in the non RP market of brand-loyal consumers. The profit maximizing 'non referenced' price therefore increases. Empirical evidence from Germany quoted by Danzon and Liu seems to be consistent with the convergence hypothesis of the kinked demand model amongst prices for brand and generic products.

The effect of RP schemes on price changes may also be heavily dependent on factors such as the proportion of over the counter (OTC) sales of the product, and may be also influenced by the inclusion of the product price in one country in cross border pricing mechanisms.

4.2.2. Health effects and other health related impacts

Schneeweiss et al. [31] argued that the effect of RP on health or overall resource use has never been validly evaluated. Given that level one is not expected to show a systematic difference in health outcomes and resource utilization, they focus on level 2 clusters. These authors point out two broad categories of limitations to explain why there no valid conclusions can be drawn regarding the effect of RP in Germany: (1) the lack of studies using time series analysis to individual level data over a reasonable length of time before and after the introduction of RP and with a suitable time trend control group; and (2) the difficulty of monitoring simultaneous changes in the health care system.

Schulenburg and Schöffski [33] observed substitution processes and economic losses in other areas as a result of implementing limits on prescription drugs in Germany. The rate of referral to other physicians rose by almost 9% in the first 7 months of 1993 compared with the same period the year earlier. The hospital admission rate rose by 10%. However, McGregor [24] reports that in British Columbia, 'there has been no increase in physician's office visits or in the rates of hospitalization of seniors associated with any of the sentinel illnesses' since the introduction of RP in 1995.

Finally, in relation to pharmacists substituting generic equivalents, the potential health risk to consumers is assumed to be small given the regulatory bio-equivalency requirements. However, a recent survey of 254 doctors in 1997 in British Columbia identified some of these problems: (a) 90% of physicians reported at least one or more problems experienced by their patients as a result of RP, and (b) 75% of physicians who had changed prescriptions reported that some of their patients experienced a worsening of symptoms [22].

Comparison of health effects on patients switching from drug A to drug B as a result of the introduction of RP could be a more appropriate way to observe health effects. The only study of this type is Thomas et al. [36], which assess the impact in-patients switching from simvastatin to fluvastatin following the introduction of RP in New Zealand. These authors observed a significant increase in total cholesterol, low density lipoprotein (LDL) cholesterol and triglyceride levels. Thomas et al., [36] concluded that the lipid elevations observed in their study were related both to the lesser potency of fluvastatin and underdosing. However, note that drug underdosing may be attributed to inadequate clinical management, which is independent of the introduction of RP.

4.2.3. The effects of RP on physician choice

If the innovator firm sets prices at the reference level, the introduction of RP does not affect the physician's choice. It the innovator's price is higher than the reference level, physicians who are highly aware of adverse drug reactions may continue to exclusively prescribe the original brand, albeit in smaller amounts. Otherwise, physicians may prescribe a smaller quantity of branded products, possibly substituting generics instead. As far as we know, there is no empirical evidence of this.

4.2.4. The effect of RP on the innovator's price

The optimal seller response to the introduction of RP depends on the characteristics of the physician [45]. Drugs prescribed by physicians with a strong interest in the unique proper-ties of the original drug are predicted to be priced above RP, while others should be priced at the RP level. By assuming that the patient is fully informed, with no influence exerted by his physician, Zweifel and Breyer [59] conclude that suppliers will react to the introduction of RP by accepting the reference level for drugs with large (absolute) price elasticity of demand and small sales, while requiring co-payment for drugs having small price elasticity and large sales (this was the case in Germany). In this sense, manufacturers with prices higher than the reference level lowered prices to maintain their market shares.

4.2.5. Dynamic efficiency

The welfare effects of the exercise of purchasing power in the pharmaceutical sector differ from the standard monopsony analysis because of the role of sunk costs [60]. In markets where the innovator faces competition from entrants after patent expiration, the monopsonist can force prices down to short run marginal cost. The welfare distortion is not the sub-optimal consumption of drugs which is argued in the traditional monopsony model. The welfare loss occurs because the monopsonist's price does not cover the sunk R&D costs, leading to a sub-optimal rate of investment and a decrease in the supply of new products in the long run. Note that if off-patent products are excluded from RP, and if the patent system is appropriately designed, dynamic inefficiency does not necessarily result. This will occur when innovative and generic drugs are clustered in the same group, or when patented drugs with specific therapeutic advantages are combined with other patented drugs that do not possess such advantages [17,21].

4.2.6. Welfare effects

Welfare effects will depend on the following considerations:

On the one hand, reference prices can make the demand for prescription drugs more elastic than would otherwise be the case, although they may prove ineffective in preventing inefficient extension of the use of a pharmaceutical product to new indications for which much cheaper alternatives are available.

On the other hand, welfare losses may arise from RP with regard to transaction costs. Gross and Fortescue [17] identified the following costs associated with a reference pricing system:

1. Costs to government: (a) administrative costs related to the RP system (design of the mechanism, updating the scheme for new drugs, litigation, the cost of managing exemptions, etc.); and (b) increased costs to other parts of the health sector.
2. Costs to patients: (a) social costs (derived from new regulation on access, or just convenience); (b) economic costs of changing prescriptions (prescription costs and extra visits to doctors); (c) costs of extra medical visits as a result of complications from changed prescriptions.
3. Costs to physicians: time and costs of counselling.
4. Costs to manufacturers: (a) policy delays or non-listing; (b) reduced investment and innovation.

4.2.7. Effects on competition

RP increase the de facto degree of substitutability between the drugs. However, by emphasizing competition based on product differentiation, drug manufacturers were able to attenuate price competition. Promotional information to physicians is intended to convince them of the therapeutic superiority of their drugs over alternative drugs..

5. Concluding remarks

In assessing the policy implications of RP some conclusions may be raised:

1. From a theoretical and health policy view, without going into the practical details of RP, it is very difficult to be against a RP strategy, Indeed, RP shows a great capacity to raise political support across different government's ideologies. Its principles look sound: medical equivalence, consumer's cost consciousness, limited reimbursement and cost control of the drug bill. However, if we look at the details, we will find the k-elements to assess the actual RP effects.
2. Regarding reality, a first issue is that of the definition of'equivalence' a direct relationship exists between broadening the groups affected by RP (relaxing the bioequivalence principle) and the relevance of RP in terms of its impact on drug expenditure control. However, an indirect relationship seems to be also present between enlarging the field of RP and causing medical and social disagreement on RP. In this sense, a potential marginal impact on cost savings comes out at a very high price in terms of transaction costs and other related problems (for

instance, on the lack of incentives in I & D if patented products are covered by RP).

3. RP systems achieve better their postulated goals (1) if cost inflation in pharmaceuticals is due to high prices rather than to the excess of prescription rates, (ii) when the larger is the existing difference in prices among equivalent drugs, and (iii) more important is the actual market for generics.
4. In order to appraise each individual RP strategy, it is very important to identify pre-existing alternatives: for instance, whether a competitive market on generics exists or whether drug prescribers or dispensers may have compatible incentives to third party reimbursers and consumers (given the cost-shifting nature of the RP effects).
5. In fact, this is the case since the generalization of RP policies among different countries, economic context, and social insurance schemes have distorted RP initial purposes. RP today is not any more a control device of pharmaceuticals reimbursement in markets with free prices for drugs, but a quasi universal complement of the country's general pricing policy on drugs.
6. RP has thus become one more of a set of policy measures for drug expenditure control. This loss of focus has the danger of further eroding the whole spectrum of the drug policy, with health expenditure control substituting health policy, promoting undesirable side effects on I & D, raising new issues on medical equivalence or partial -views on consumer's responsiveness to changing financial environments in health care systems.

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