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ScienceDirect
Health Policy 84 (2007) 14–29
HEALTH policy
www.elsevier.com/locate/healthpol

The impact of generic reference pricing interventions in the statin market

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Abstract

Objectives: The objective of this study was to evaluate the intended and unintended impact on pharmaceutical use and sales of three public reimbursement reforms applied to the prescription of statins: a Spanish generic reference pricing system, and two competing policies introduced by the Andalusian Public Health Service.
Methods: This study is designed as an interrupted time series analysis with comparison series of 46 monthly drug use and sales figures from January 2001 to October 2004 for each active ingredient.
Results: The mean monthly saving for the year after the introduction of reference pricing was 16.7% of total lovastatin sales, representing only 1.1% of total statins sales. Mean monthly savings for the 10 months after reference pricing being applied to simvastatin were 51.8% of simvastatin sales, and 13.9% of statin sales. Over the 46 months of the study, all analysed public interventions resulted in a 2.2% average monthly decrease in statin sales in the rest of Spain and savings non-significantly different from zero in Andalusia.
Conclusion: RP has been effective at reducing the volume of sales growth of the off-patent statins, yet its overall impact on sales of all statins has been relatively modest.

Keywords: Drug costs; Pharmaceutical economics; Generic drugs

1. Introduction

With 43.2 million inhabitants, Spain is the fifth largest market in Europe for pharmaceuticals. Public drug expenditures in Spain set an unprecedented trend in the 1990s and the first years of this century. Per capita public spending on prescription drugs, adjusted for general inflation, more than doubled from 1989 to 2003, from €96 (0.8% of the gross domestic product, GDP) to €194 (1.2% of the GDP) [1].

Reference pricing (RP) is a reimbursement policy that sets a maximum allowable cost that will be covered [2,3]. RP systems can be grouped into different levels according to drug interchangeability [2,4–6]: chemical equivalence (level 1), pharmacological equivalence (level 2), and therapeutic equivalence (level 3). A generic RP system was effectively introduced into

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doi:10.1016/j.healthpol.2007.02.010

the Spanish National Public Health System (henceforth NPHS) in December 2000. This system is applied to off-patent drugs with the same active ingredient (level 1). All the pharmaceutical products included in the same homogeneous group are bio-equivalent (quality and reliability of products in the same group differ little, being nearly perfect substitutes), and at least one of them has to be a generic product. For each homogeneous set of products a reference price is calculated on the basis of the weighted average (year on year) of the lowest-priced products that account for at least 20% of the market volume of sales [7].

A notable change in this generic RP system was introduced in January 2004. Since then the RP has been calculated as the average of the three lowest costs per day of treatment for each form of administration of an active ingredient, according to its defined daily dose. If the prescription price exceeds the reference price and there are other generic products in the same group, the pharmacist has to dispense the lowest-priced generic in that group.

The regional devolution of health services management to the autonomous communities (ACs) completed in January 2002 allowed all these regional authorities to introduce their own procurement mechanisms. In September 2001 the Andalusian Public Health Service (henceforth APHS) (a regional subsystem with 7.7 million inhabitants insured) introduced a new pharmaceutical procurement mechanism based on a more "intensive" RP system, which is additional to the RP system applied by the rest of the NPHS and competes with it. In this regional RP system, product coverage is defined by all those active ingredients with more than two products on the market (originator or licensed brand names, copies or generics) which are being sold at different consumer prices. In the APHS the reference price level is set at the level of the higher price of the two lowest-priced products for each active ingredient with the same package size and dose strength. The main feature of this regional RP system is that it requires prescriptions to be made out using the name of the active ingredient and not the commercial name of the product (International Nonproprietary Name, INN). This RP system only works when and if physicians prescribe the active ingredient of the product. The pharmacies agreed with the regional government to dispense the lowest-priced product for each active ingredient, independently of its generic status. In addition, economic incentives were introduced for physicians to prescribe using the non-commercial name of the active ingredient. This prescribing incentive consists of an additional salary positively related to the proportion of prescriptions using the INN and negatively related to the excess drug cost, defined as the cost above the regional reference price level.

We focused the study on HMG-CoA reductase inhibitors (i.e., statins), which lessen the risk of coronary events. Since the introduction of statins into the market as effective lipid-lowering agents in the early 1990s, they have become blockbusters in many developed countries. Statins accounted for 6.86% of prescription sales in Spain in 2004 [8]. Atorvastatin ranked as the first active ingredient in terms of sales volume (€344 million), and pravastatin as the sixth (€148 million).

A doctor prescribing a statin first faces a choice among the alternative active ingredients in this therapeutic group, and then a choice among brands (the originator's brand name, or those brands resulting from licensing agreements) and generics after patent expiration. However, which statin is prescribed clearly matters in terms of cost [9] (in the absence of solid evidence of differences in clinical benefits/outcomes).

In this paper we look at six particular compounds (statins) sold primarily in oral dosage forms (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, and cerivastatin), which are close therapeutic substitutes, i.e., they can be prescribed for many of the same conditions, but with significant price differences. Three of these drugs (lovastatin, simvastatin, and pravastatin) lost patent protection and experienced generic entry during or before the period under review. Cerivastatin was withdrawn from the market in August 2001.

During the study period the results of several important clinical trials were published which provided evidence of a notable improvement and extension of the efficacy of statins in cholesterol management [10]. These clinical trials had major implications for cholesterol management that resulted in an increase in the number of patients for whom statins may be considered clinically appropriate.

The purpose of this study was to evaluate the intended and unintended impact on pharmaceutical use and volume of sales of three public financing reforms applied to the prescription of the six commercially available statins from January 2001 to October 2004:

a Spanish generic RP system for lovastatin and simvastatin, and two competing policies introduced by the APHS for all statins, first a maximum consumer price (MCP) and then a so called quality prescribing incentive for general practitioners (MCP plus PI), similar to a generic prescribing incentive.

Spain provides an excellent setting to study the impact of several gradual and competing generic reference pricing measures on public expenditure, in the context of a heavily regulated pharmaceutical market and a small generic share. The present study adds to and improves on the current body of literature evaluating reference pricing policies in three ways: by combining a conventional before-and-after time series design with a comparison of aggregate time series for the same time period; by taking into account other simultaneous supply and demand-side interventions; and also by estimating the impact of public financing measures on therapeutic substitutes.

In this paper we chose to examine statins for several reasons. First, three out of the six compounds (lovastatin, simvastatin, and pravastatin) lost patent protection and experienced significant generic entry. Second, two of these three off-patent compounds, allowing a choice between brands and generics, were included under the NPHS reference pricing system, undergoing only one official revision of the reference price during the study period. This enables us to study the impact of reference pricing coverage and price revision on the active ingredients included under this system, and also to analyse the impact on close therapeutic substitutes not included under the RP system. Third, statins have been the subject of several regional procurement innovations by the APHS (a second RP system and economic incentives for primary physicians).

Potential out-of-pocket expenses implicit in the RP system may effectively disappear if all brand and generic statin producers with prices above the reference price immediately reduce them to the reference level after RP introduction, and if many patients have nearly free access to prescribed medicines (only a small fraction of the costs are borne directly by the patients). Notwithstanding, even though this is the case in Spain, the widespread price reduction observed in brand-name products and some generics under RP (a change in the relative price between active ingredients under and not under the RP system) may affect the use and volume of sales of statins subject to RP (own price elasticity), and also that of those not subject to RP (cross-price elasticity).

Pavcnik [11] observed that the overall quantity of product sold is, on average, unaffected by RP, that is, overall quantity is not sensitive to prices. In the present paper it is hypothesized that the effect of lower prices for products under RP may be amplified or compensated by an increase in the number of prescriptions (quantity). Lower prices for some statins following RP introduction may result in an increase in prescriptions in the wake of substantial price reduction, depending on the price sensitivity of patients and doctors.

From the supply perspective, two opposing potential trends may be hypothesized for the use of statins under RP. First, substantial brand-name price reductions will probably result in a reduction in commercial and promotional effort by brand producers among physicians, and a corresponding decline in sales. But, second, the increasing number of generic entrants may exert greater commercial pressure from generic firms on prescribing decisions.

The number of prescriptions of statins not included in the RP system can also undergo changes as a result of the introduction of RP. This substitution effect on consumption of substitute therapies may reflect decisions taken by the patient, the prescriber and/or the influence exerted by the pharmaceutical industry on prescribing decisions.

2. Methods

The data for this paper come initially from IMS Spain, a firm that does marketing research for the pharmaceutical industry.

The data are in the form of a monthly time series from January 2001 to October 2004 (46 monthly periods) of quantity and volume of sales valued at regulated ex-factory prices (not including potential producer discounts to wholesale distribution firms or to pharmacies) at the level of each active ingredient for the six statins available in the Spanish market during that period, separated into Andalusia and the rest of Spain. An observation is equal to an active ingredient-month. Quantity is measured as the aggregate number of prescribed units for each active ingredient, which may differ in dosages. Thus, this variable only represents a proxy of quantity, given that it allows us neither to calculate the quan-

tity of the active ingredient or the number of defined daily doses (DDD), nor to calculate meaningful average prices. Additional consumer price information was obtained from the centralized National Health System pharmaceutical consumption database of the Spanish Ministry of Health and Consumer Affairs.

2.1. The empirical model

This section proposes an empirical approach to identify the effect of RP measures on quantity and volume of sales for statins. Outcome variables of interest are monthly volume of sales (in euros) and number of prescriptions dispensed per person for each of the six active ingredients in the therapeutic group of statins. Volume of sales and quantity are measured as monthly sales and quantity ratios between the per capita value in each period and the per capita value of the initial period. Outcome variables are observed before and after the public insurer interventions.

The following specifications are used for each active ingredient:

$$y_{it} = \beta_0 + \beta_1 \text{time} + \sum \beta_{2j} \text{adopt}_{jit} + \sum \beta_{3j} \text{post}_{jit} + \sum \beta_{4j} \text{post}_{jit} \times \text{time}_j + \varepsilon_{it} \quad (1)$$

where y_{it} is the outcome variable of interest for region i (Andalusia, and rest of Spain) at time t ($t = 0, 1, \ldots, 45$); *time* is a secular trend before insurer interventions for each time period t, being 0 in the first period; $adopt_{jit}$ is a design variable that identifies the time period t when the insurance intervention j is adopted for the first time ($adopt_{jit}$ is 1 if intervention j is adopted in region i at time t, and 0 otherwise); $post_{jit}$ is a design variable indicating whether region i at period t is affected by insurer intervention j ($post_{jit}$ is an indicator that is 1 if the active ingredient at time t is covered by insurer intervention j in region i, and 0 otherwise); the interaction terms between $post_{jit}$ and $time_j$ denote changes in time trend after the implementation of intervention j; and ε_{it} could represent a measurement error in the outcome variable or unobserved factors that affect it. Note that the variable $adopt_{jit}$ is 0 both before and after the initiation of the intervention, while the variable $post_{jit}$ is 1 for all time periods after intervention.

In the absence of any uncontrolled factors or other interventions affecting the outcome variables in Eq. (1), the intercept coefficient β_0 represents the initial level of the outcome variable; the coefficient β_1 on the time trend reflects the monthly trend change (linear slope) in the outcome variable; coefficients β_{2j} on the first period of adoption of the insurance intervention j depict the one-time transitory level effect of the month of intervention activation; coefficients β_{3j} on the indicator *post* of each insurer intervention j depict the permanent impact of changes in insurer interventions on the initial level of the outcome variable; and coefficients β_{4j} on the interaction terms between $post_j$ and $time_j$ depict the impact of insurer interventions on the monthly trend change of the outcome variable (baseline trend changes). Insurer interventions could thus be evaluated for one-time effect of the month of activation, permanent changes in the trend and/or instantaneous permanent changes in magnitude.

The coefficient estimates in Eq. (1) might be biased by intertemporal variation unrelated to insurer interventions, such as changes in technology or demand. The time trend may partially account for technology changes. To mitigate this, the paper compares outcome variables for statins in the APHS with outcome variables in the rest of the NPHS for which it may be assumed that there are no differences in technology changes.

Table 1 provides a detailed summary of nine supply-side or demand-side interventions observed in the Spanish statin market during the study period. The previous situation was characterized by the absence of incentives to prescribe lower-cost drugs with the same active ingredient, and by the absence of incentives for brand firms to lower prices even in the presence of lower-priced generics.

For research purposes, the interventions evaluated in the empirical model may be classified into three groups. First, three Spanish reference pricing interventions adopted by the NPHS: lovastatin under reference pricing (RP) in May 2002; simvastatin under reference pricing (RP) in January 2004; and a revision of the reference price for lovastatin in January 2004. Second, two regional procurement interventions adopted by the APHS: maximum consumer price (MCP) for all statins in September 2001; and MCP plus economic prescribing incentives (PI) for off-patent statins in March 2003. And third, four other concomitant interventions occurred simultaneously during the study period which could also exert a notable influence

Table 1
Main demand-side and supply-side interventions in the Spanish statin market during the study period

Month/year	Intervention
September 2001	Maximum consumer price (MCP) potentially for all statins in the APHS
August 2001	Cerivastatin withdrawal from the market
January 2002	First generic entry for simvastatin
May 2002	Lovastatin under reference pricing (RP)
October 2002	Entry of an extended release form of fluvastatin
January 2003	MCP plus economic prescribing incentives (MCP plus PI) for off-patent statins in the APHS
January 2004	Simvastatin under reference pricing (RP)
January 2004	Substantial decrease in lovastatin reference price (RP)
January 2004	First generic entry for pravastatin

on outcome variables: cerivastatin withdrawal from the market in August 2001; first generic entry for simvastatin in January 2002; entry of an extended release form (a *line extension*) of fluvastatin in October 2002; and first generic entry for pravastatin in January 2004. Thus, *j* interventions considered in the empirical implementation of Eq. (1) include the nine events described in Table 1.

Regional random effects are added to Eq. (1) in order to control for the time-invariant region-specific characteristics. Anticipation effects for the months before the insurer intervention were also considered in the empirical specification of Eq. (1). Eq. (1) assumes linearity in the relation between the explanatory variables and the outcome variables, but after empirically testing non-linear patterns, linearity was maintained in the preferred model. Seasonal fluctuations were controlled by including a term for August in the regression model. Seasonal variation is observed in the monthly periods resulting in a significant decrease during summer holidays (August).

The design of this study is an observational, retrospective, interrupted time series analysis with comparison series of 46 monthly drug use and volume of sales ratios from January 2001 to October 2004. These types of studies represent the strongest quasi-experimental designs for estimating intervention effects in non-randomized settings [12,13]. It should be noted that in a recent review of the research design of studies evaluating pharmaceutical policy outcomes of administrative interventions, only two papers out of 18 in the literature were found to use time series with appropriate comparison series, and only one was a before-and-after design including a comparison group [14].

As time is an explanatory variable in the regression analysis of Eq. (1), error terms of consecutive observations are probably correlated. For each active ingredient, Eq. (1) is estimated using generalized least squares (GLS) and the Prais–Winsten method was used to correct for serial correlation [15]. Robust standard errors were estimated, adjusting for clustering at a regional level. These standard errors are robust to the presence of general forms of heteroskedasticity and they also take into account general forms of serial correlation within each active ingredient over time. The Durbin–Watson statistic was used as a test for serial autocorrelation of the error terms in the regression model. Eq. (1) was estimated using the linear and log-linear empirical specification.

Prediction models were constructed in order to obtain a measure of savings that might result from insurer intervention analysed in this paper after policies were enacted. Potential savings were estimated by comparing volume of sales patterns before implementation of the reform and after it, according to the empirical estimation of Eq. (1), and confidence intervals for potential savings were reported. Volume of sales before implementation of the RP interventions were extrapolated for 12 months, when data permitted, using the estimated linear model to estimate savings accrued by consumers and the public insurer (or losses incurred by pharmaceutical firms).

3. Results

3.1. Descriptive statistics

Table 2 presents a comparison of the average cost per defined daily dose (DDD) for whole tablets or capsules of statins dispensed in Spain in October 2004.

Table 2
Average cost per defined daily dose (DDD) for originator brand-name and lowest-priced generic statins dispensed in Spain

Generic (*brand name*)	Dose (28 tablets) (mg)	DDD cost for brand name, €[a]	DDD cost for lowest-priced generic[a]
Atorvastatin (*Cardyl*, *Zarator*)	10	1.05	–
	20	0.89	–
	40	0.54	–
	80	0.26	–
Fluvastatin (*Lescol*)	20	1.18	–
	40	0.86	–
	80	0.68	–
Lovastatin (*Mevacor*)	20	0.57	0.45
	40	0.57	0.43
Pravastatin (*Lipemol*)	10	1.77	1.28
	20	1.22	0.91
	40	1.09	0.82
Simvastatin (*Zocor*)	10	0.39	0.32
	20	0.39	0.29
	40	0.39	0.20

[a] Average cost per whole tablet or capsule in October 2004. Source: Spanish Ministry of Health and Consumer Affairs database and author's calculations.

For whole pills and most commonly used doses, simvastatin is the least costly.

Fig. 1 plots the prices of the brand-name product, the first generic to enter the market and the lowest-priced generic for the most frequently dispensed presentations of lovastatin and simvastatin from January 2001 until October 2004. Descriptive data on consumer price trends confirm previous price trends observed for other active ingredients in Spain [7]. First, brand-name lovastatin and simvastatin and their generic substitutes, with a price higher than the centralized reference price, immediately reduced their price to the reference level when RP was introduced. The introduction of the RP system tends to decrease the price of the original relative to the price of generics, as observed in other countries [16].

Second, the price of new generic entrants for lovastatin and simvastatin in the period after RP introduction was in all cases lower than the lowest preceding price, usually corresponding to the lowest-priced generic in each period of time.

And third, the price of all products already on the market before the introduction of RP with a price equal to or lower than the reference level remained absolutely constant during the period after, and did not experience any consumer price competition effect because of RP or because of the lower price of new generic entrants. At the same time, the data suggest that RP has not been effective in reducing the consumer price of products with a price initially below the reference level. Zweifel and Crivelli [17] also observed that RP had little impact on generic prices, which were already below the reimbursement ceiling. The number of generics firms in the market does not affect the prices of brands or generics in the market when their previous price was not above the reference level. That is, price decline for brand-name and generic products is not clearly explained by variation in their exposure to competition: it only depends on arbitrary regulatory decisions as to the period for which the product is covered by the RP system and the moment at which the reference price is revised (Fig. 1).

In January 2001, average volume of sales valued at regulated ex-factory prices per 1000 inhabitants was €696.9 in the rest of Spain and 20.7% lower in the APHS (€552.7). Per capita volume of sales in the initial period was lower in the APHS for all active ingredients. At the end of the study period, October 2004, monthly volume of sales per capita was significantly higher than at the beginning (€943.9 in the rest of the Spanish Health System, and €772.8 in the APHS), but the average difference between the two regions had narrowed slightly (18.1%). Trends in per capita volume of

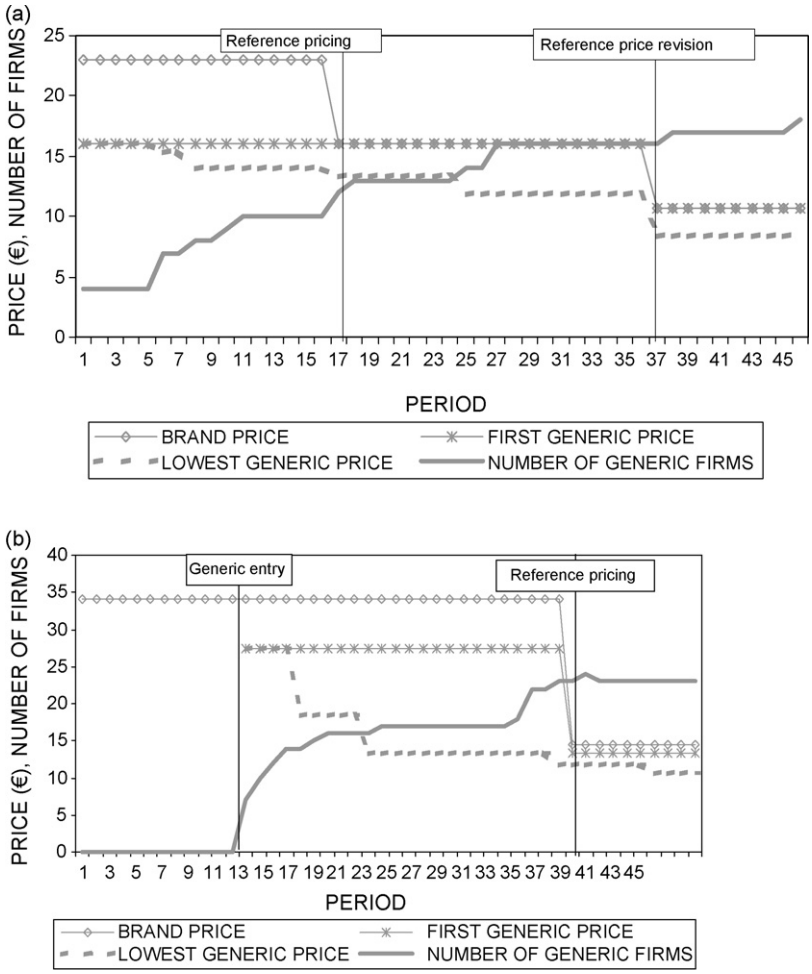

Fig. 1. Price of brands and generics, and number of generic firms from January 2001 to October 2004. (a) Lovastatin 20 mg 28 tablets; (b) simvastatin 20 mg 28 tablets.

sales for each active ingredient in the APHS and in the rest of the Spanish Health System are depicted in Fig. 2.

Quantity and volume of sales ratios for each active ingredient show that the largest increase for volume of sales and number of prescriptions per 1000 inhabitants was observed for the two on-patent statins, fluvastatin and atorvastatin. For fluvastatin, volume of sales per capita was 4.8 times greater in October 2004 than in January 2001 in the rest of Spain, and 5.8 times in the APHS (number of prescriptions per capita was 3.1 and 3.8 times greater, respectively). For atorvastatin, volume of sales experienced a 139.3% increase in the rest of Spain during the period, and a 155% increase in the APHS. Volume of sales ratio trends for each active ingredient is also depicted in Fig. 3. A higher sales trend can be observed for on-patent and highest-priced statins (atorvastatin and fluvastatin) than for off-patent and lowest-priced statins (lovastatin, simvastatin and pravastatin).

At the other extreme, the greatest volume of sales decline was observed for lovastatin and simvastatin, both off patent at the end of the period. Lovastatin, the first statin to reach patent expiration, underwent a pronounced decline in volume of sales (48.6% in the rest of Spain, and 58.4% in the APHS), but also in the number of prescriptions (6.5% in the rest of Spain, and 24.3% in the APHS). Simvastatin, the lowest-cost statin per DDD, experienced an increase in quantity (86.4% in the

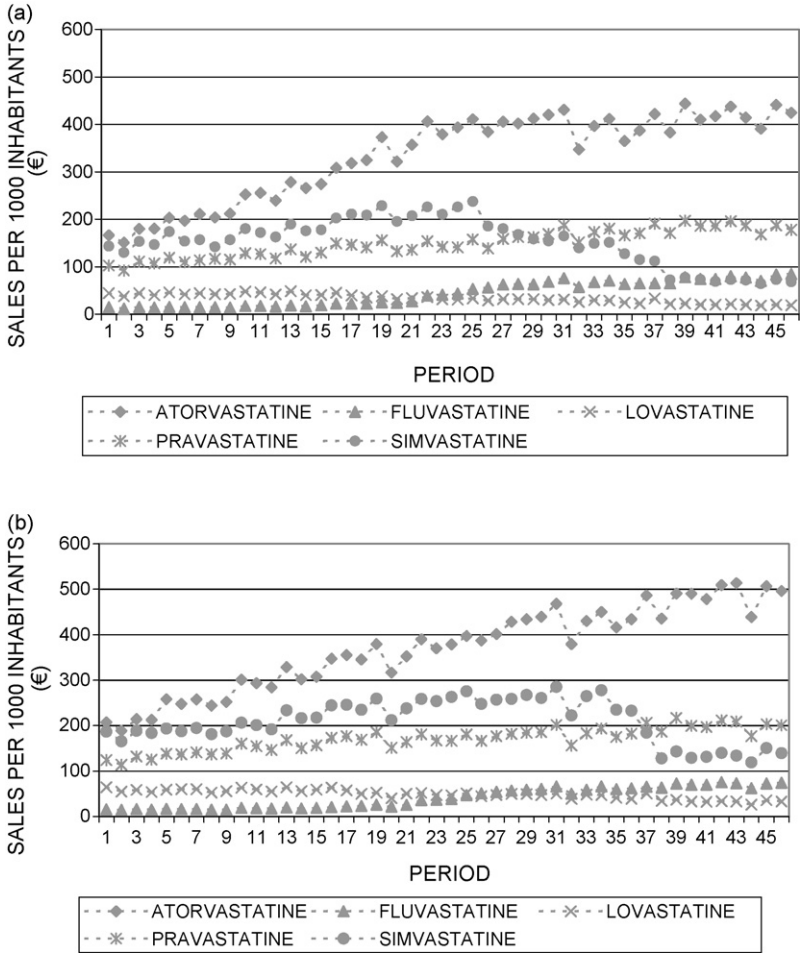

Fig. 2. Volume of sales per 1000 inhabitants. (a) APHS; (b) rest of Spain.

rest of Spain, and 21.5% in the APHS) that was partially offset by price reductions, resulting in a 25.3% volume of sales decline in the rest of Spain and a 52.7% decline in the APHS. The more pronounced sales reduction observed in the APHS region may be related to a higher substitution rate for simvastatin, which experienced a larger increase in this region.

For statins as a whole, volume of sales increased during this period by 35.4% in the rest of Spain, and a fairly similar rate in the APHS (39.8%). Notwithstanding, pattern trends in quantity and volume of sales ratios during this period present significant differences between the two regions. Compared with the rest of Spain, the APHS displayed higher growth rates for quantities and volume of sales for both on-patent statins (fluvastatin and atorvastatin), and also for pravastatin. On the other hand, the APHS also showed a steeper decline or more moderate increase for off-patent and lower-priced statins, resulting in a clearly more pronounced volume of sales reduction for lovastatin and simvastatin.

3.2. Pre-reform series trends

Results of the estimation of Eq. (1) for quantity and volume of sales ratios are presented in Tables 3 and 4. The results depicted in these tables give the best-fitting version of the models. Residuals are assumed to be nor-

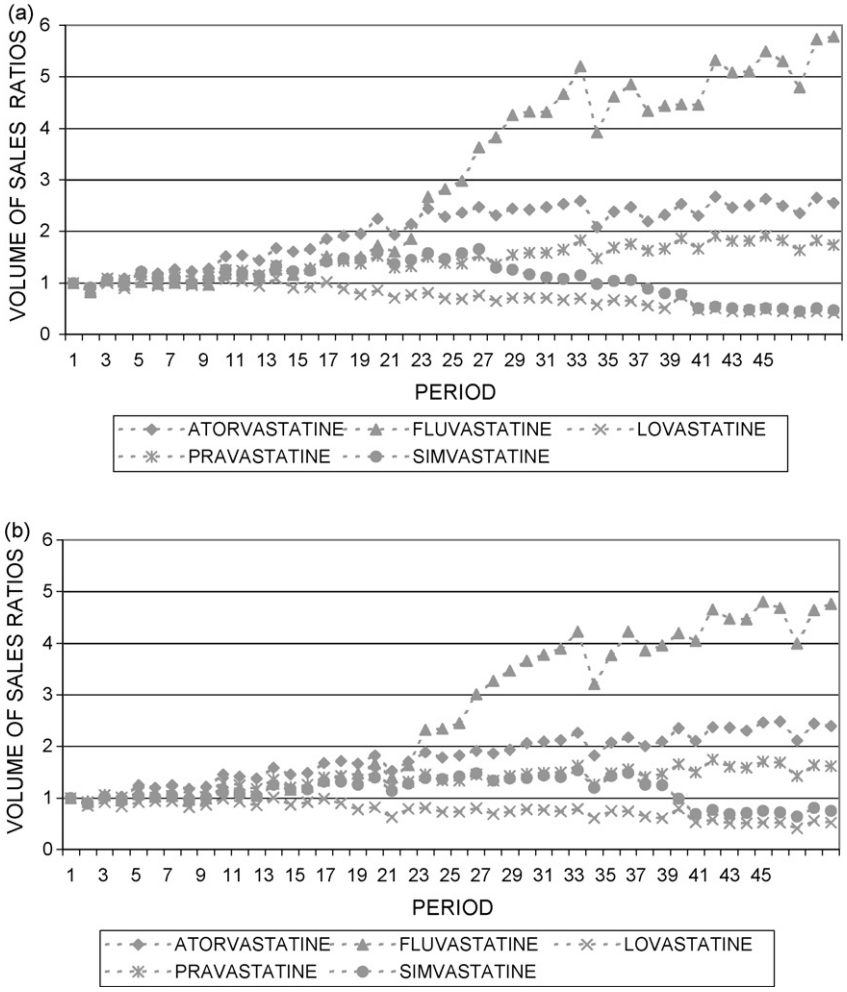

Fig. 3. Volume of sales ratio (January 2000 = 1). (a) APHS; (b) Rest of Spain.

mally distributed, we corrected for heterogeneity, and the Durbin–Watson statistic values indicate no serious autocorrelation of the error terms. No statistically significant anticipatory effects were detected. The linear model, rather than the log-linear model, was the one that best fit the data during the study period.

Pre-reform series trends indicate that the initial level of the outcome variables (quantity and volume of sales ratios) were, as expected by the definition of these variables, not significantly different from one, being slightly higher in the APHS for lovastatin in comparison with the rest of Spain.

The baseline time trend for volume of sales ratio, equivalent to the average monthly trend change in the absence of reforms, was positive for all active ingredients, being higher for on-patent statins and very low for the first off-patent statin: fluvastatin (4.1%; 95% CI 2.8 to 5.5), atorvastatin (3.4%; 95% CI 1.1 to 5.7), pravastatin (0.6%; 95% CI 0.5 to 2.4), simvastatin (1.4%; 95% CI 1.3 to 1.5), and lovastatin (0.1%; 95% CI −0.8 to 1.1). Similar trends were observed for quantity ratios. The rise in the baseline trend of pravastatin for volume of sales ratio in the APHS compared to the rest of Spain was slight but statistically significant, indicating

Table 3
Parameters estimated for quantity ratio models

Coefficients	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Initial level (intercept)	1.0305[a]	0.8440[a]	0.9208[a]	1.0484[a]	0.9521[a]
APHS initial level	–	–	0.0924[a]	−0.0284[a]	–
Baseline trend	0.0217[b]	0.0347[b]	0.0063[c]	0.0125[b]	0.0182[b]
APHS baseline trend	–	–	–	0.0059[a]	–
August	−0.1737[c]	−0.2960[a]	−0.1193	−0.1528[c]	−0.1617
Centralized reference pricing system					
Trend change after lovastatin RP	–	–	−0.0058[c]	–	–
Trend change after lovastatin RP in the APHS	–	–	−0.0042[a]	–	–
Level change for only one period after lovastatin RP revision	–	–	0.4648[b]	–	–
Level change for only one period after simvastatin RP	–	–	–	–	0.6315[c]
Trend change after simvastatin RP	–	–	–	–	0.0023[c]
Trend change after simvastatin RP in the APHS	0.0036[b]	–	–	–	–
Andalusian reforms					
Trend change after MCP	0.0198[a]	0.0076[b]	–	–	0.0138[a]
Level change after MCP plus PI	1.2377[a]	0.5500[a]	–	–	0.9144[a]
Trend change after MCP plus PI	−0.0319[b]	–	–	–	−0.0348[b]
Other interventions					
Level change after cerivastatin withdrawal (one trimester)	–	–	–	0.0556[b]	–
Level change after the introduction of a new form of fluvastatin	–	0.6833[b]	–	–	–
R-squared	0.9291	0.9349	0.7263	0.8819	0.9121
Number of observations	92	92	92	92	92

a: *P*-value < 0.01; b: *P*-value < 0.05; c: *P*-value < 0.10.

a larger monthly trend increase in the volume of sales for this active ingredient.

3.3. Impact of the general Spanish RP system

The impact of including lovastatin under the RP system in May 2002 was a permanent reduction in the previous monthly trend of 0.76% (95% CI −1.4% to −0.2%) for the volume of sales in the rest of Spain, this reduction being greater for the APHS (−1.2%; 95% CI −1.8 to −0.60). However, volume of sales reduction cannot be attributed solely to price reduction forced by the RP system, but also to a quantity reduction after the introduction of RP. A shift in the drug use within each active ingredient could contribute to a reduction in volume of sales. In the case of the statin whose patent first expired, lovastatin, RP coverage and price decline was also accompanied by a negative quantity effect that reinforced the volume of sales reduction. The monthly trend of quantity ratio after RP introduction declined by 0.6% in the rest of Spain (95% CI −1.5 to 0.0) and by 1% in the APHS (95% CI −1.9 to −0.4). All the additional volume of sales reduction observed in the APHS corresponds to an additional regional negative quantity effect. The quantity reduction of the lowest-priced statin in May 2002 observed in this case, as a response to RP coverage, may indicate a potential transfer of prescriptions to statins not under RP, which, however, was not detected in the models presented in Table 3. As a related effect of including lovastatin under RP, pravastatin experienced a one-time increase of 2.4% (95% CI 0.7 to 4.0) in its volume of sales level in the rest of Spain.

The revision of the reference price of lovastatin in January 2004 resulted in a permanent decrease in the initial volume of sales level of 12.3% (95% CI −17.5 to −7.1), without any statistically significant effect on the number of prescriptions such as was observed when lovastatin was included under RP for the first time.

Although the first generic entry for simvastatin occurred in January 2002, it was not covered by the RP system until 2 years later. The monthly trend for volume of sales of simvastatin decreased nearly 2% (95% CI −2.0 to −1.9) after RP introduction. In contrast with the decline in quantity of lovastatin after RP was intro-

Table 4
Parameters estimated for volume of sales ratio models

Coefficients	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Initial level (intercept)	1.0320[b]	0.8594[a]	0.9022[a]	1.0622[b]	0.9762[a]
APHS initial level	–	–	0.0635[a]	−0.0456[a]	–
Baseline trend	0.0339[b]	0.0417[b]	0.0014	0.0135[b]	0.0146[a]
APHS baseline trend	–	–	–	0.0059[a]	0.0115[b]
August	−0.2026[c]	−0.4360[a]	−0.0704	−0.1611[c]	−0.1202
Centralized reference pricing system					
Level change after lovastatin RP	–	–	–	0.0235[b]	–
Trend change after lovastatin RP	–	–	−0.0076[b]	–	–
Trend change after lovastatin RP in the APHS	–	–	−0.0041[a]	–	–
Level change for only one period after lovastatin RP revision	–	–	0.2065[a]	–	–
Level change after lovastatin RP revision	–	–	−0.1229[b]	–	–
Level change after lovastatin RP revision in the APHS	–	–	0.0427[a]	–	–
Trend change after simvastatin RP	–	–	–	–	−0.0198[a]
Trend change after simvastatin RP in the APHS	0.0043[b]	–	–	–	0.0144[a]
Andalusian reforms					
Trend change after MCP	0.0225[a]	–	–	–	–
Level change after MCP plus PI	1.4654[a]	0.7267[a]	–	–	1.0112[b]
Trend change after MCP plus PI	−0.0372[b]	–	–	–	−0.0564[b]
Other interventions					
Level change after cerivastatin withdrawal (one trimester)	–	–	–	0.0509[b]	–
Level change after the introduction of a new form of fluvastatin	–	0.0499[b]	–	–	–
R-squared	0.9506	0.9484	0.9548	0.9006	0.9176
Number of observations	92	92	92	92	92

a: *P*-value < 0.01; b: *P*-value < 0.05; *c*: *P*-value < 0.10.

duced, simvastatin showed a permanent increase in the monthly trend in the number of prescriptions equivalent to 0.2% after RP introduction (95% CI −0.0 to −0.5). The inclusion of simvastatin under RP, and its corresponding price decline, produced a negative cross-effect on the monthly trend for quantity and volume of sales of atorvastatin in the rest of Spain, but not in the APHS, where the monthly trend for atorvastatin actually increased. Neither the volume of sales impact nor the quantity impact of simvastatin inclusion under RP was observed in the APHS, probably due to the impact of prior Andalusian reforms that affected this active ingredient.

In the rest of Spain, the mean monthly saving for the 12 months after intervention attributed to the initial application of RP to lovastatin (May 2002–April 2003) was 16.7% of total lovastatin sales (95% CI −20.4 to −13.0), representing 1.1% (95% CI −1.3 to −0.9) of the total volume of sales of statins. In the APHS, savings attributed to this intervention in the 12 months after RP introduction were larger than in the rest of Spain, being equivalent to 23.7% of the volume of sales of lovastatin (95% CI −29.0 to −18.3), but only 1.3% of total statin sales (95% CI −1.0 to −0.4).

In the rest of Spain, the mean monthly saving for the 10 months after intervention attributed to the reference price revision applied to lovastatin (January 2004–October 2004) was 16.3% of total lovastatin sales (95% CI −23.4 to −9.1), but a mere 0.7% (95% CI −1.0 to −0.4) of the total volume of sales of statins. These figures represent the impact of reference price revision in addition to the previous inclusion of this active ingredient under RP. In the APHS, the additional impact of reference price revision was equivalent to an 11.5% (95% CI −19.5 to −3.5) reduction in the volume of sales of lovastatin for the 10 months after intervention, yet a reduction of only 0.3% (95% CI −0.6 to −0.1) in total statin sales.

In the rest of Spain, the mean monthly savings for the 10 months after RP first being applied to simvastatin (January 2004–October 2004) was 51.8% of total simvastatin sales (95% CI −54.6 to −48.9), and a notable 13.9% (95% CI −14.7 to −13.0) of the total volume of sales of statins. Taking into consideration regional ran-

dom effects and the regional interventions previously adopted in the APHS, the impact of simvastatin under RP was notably more modest than in the rest of Spain: a reduction of 29.7% (95% CI −32.6 to −26.8) in simvastatin sales in the APHS, and a 3.9% reduction (95% CI −4.1 to −3.6) of the total volume of sales of statins.

3.4. Impact of the Andalusian reforms

The introduction in September 2001 of maximum consumer prices (MCP) for all statins in the APHS, complemented by an economic incentive for physicians to prescribe using the non-commercial name in order to allow lower-priced equivalent dispensing substitution, did not contribute, contrary to policy objectives, to reduce the volume of sales of statins. Despite the inclusion of regional fixed effects for the APHS in the model, the impact of this measure was a notable increase in the monthly sales ratio trend of atorvastatin (2.3%; 95% CI 0.8 to 3.7).

The mean monthly change for the 12 months after intervention attributed to MCP (September 2001–August 2002) was an unexpected 21.4% (95% CI −23.7 to −19.0) increase in volume of sales for total statins in the APHS, as a result of quantity increases of atorvastatin (substitution of statins under RP for atorvastatin, not under RP coverage). This sales increase was equivalent to an 8.1% increase (95% CI −9.2 to 7.1) in total statin sales.

Early in 2003, the APHS added to the economic incentive system an indicator considering the proportion of off-patent statin prescriptions (MCP plus PI). This intervention resulted in a reduction in quantity (3.2%; 95% CI −5.6 to −0.8) and volume of sales (3.7%; 95% CI −6.7 to −0.8) in the monthly trend for atorvastatin, one of the two on-patent statins. However, the main unintended impact of this intervention was a decline in the initial level and the monthly trend in the volume of sales (5.6%; 95% CI −7.8 to −3.5) and the quantity ratio (3.5%; 95% CI −3.8 to −3.2) of simvastatin, which was precisely the lowest-priced statin at the end of the period, and one that contributed positively to the economic incentive.

The mean monthly saving for the 12 months after intervention attributed to MCP plus PI was a slight decrease of −3.0% (95% CI −6.5 to 0.5) in volume of sales for total statins in the APHS; the main factors in this change were a notable reduction of 35.4% (95% CI −44.6 to 26.2) in simvastatin sales and an increase of 16.6% (95% CI 10.6 to 21.3) in the volume of sales of atorvastatin.

3.5. Impact of cerivastatin withdrawal

Cerivastatin withdrawal occurred in August 2001 as a result of internationally reported safety problems. This withdrawal produced a temporary increase in the following trimester in the number of prescriptions of pravastatin.

3.6. Impact of a supply-side policy

Probably the most successful intervention in the statin market during the study period was a supply-side policy, the introduction of an innovative extended release form of fluvastatin. The introduction of new forms of active ingredients still under patent protection is often used in the pharmaceutical market by originators as a way to effectively reduce the impact of future generic competition. The introduction of this new form of fluvastatin, with a higher price than previous forms still in the market, may also be considered a government policy in the sense that its impact has been allowed by its inclusion under public insurance coverage.

This supply-side measure led to a major permanent increase of 68% in the initial number of prescriptions, and also an additional increase of 5% (95% CI 4.2 to 5.8) in the monthly volume of sales trend. The magnitude of the volume of sales impact of this measure was greater than the effects produced by any of the public financing reforms analysed in this paper.

In the rest of Spain, the mean monthly increase in volume of sales for the 12 months after the market entry of the extended release form of fluvastatin (October 2002–September 2003) was 70.2% of the total volume of sales of fluvastatin (95% CI 61.3 to 79.1), and 2.2% (95% CI 2.1 to 2.4) of total statin sales. In the APHS, the impact of this measure was equivalent to 52.4% of total fluvastatin sales (95% CI 46.6 to 58.2), and 2.4% (95% CI 2.1 to 2.7) of the total volume of sales of statins.

3.7. Overall impact of the interventions

Over the 46 months of the study period, all the progressively introduced public financing interventions

reported in Table 2 resulted in a 2.2% (95% CI −3.8 to −0.6) average monthly decrease in the volume of sales of statins in the rest of Spain.

The year 2004 was the only year in which the accumulated impact of the interventions was an average monthly decrease of 12.2% in the volume of sales (95% CI −12.9 to −11.5), as a direct result of the inclusion of simvastatin under RP and the revision of the reference price of lovastatin, which appears as the only intervention with a significant impact on the volume of sales in the rest of Spain.

In the APHS, the aggregate effect of all the interventions considered during the overall study period was a change in the monthly volume of sales that was non-significantly different from zero. However, as was observed in the rest of Spain, in 2004 the accumulated effect of all interventions in this market resulted in a 15.3% average decrease in the monthly volume of sales (95% CI −18.3 to −12.3), which may also be attributed mainly to the inclusion of simvastatin under RP.

4. Discussion

The results of the impact evaluation model presented in this paper lead to the following basic conclusions for the statin market in Spain during the study period.

First, in a heavily regulated market such as the Spanish one, the decline in the consumer price of brand-name and generic off-patent products was not associated with potential competition from lower-priced new entrants, but with arbitrary regulatory decisions as to the period for which the product is covered by RP or the moment at which its reference price is revised.

Second, the results confirm that prices of off-patent brand-name drugs and generics with a price higher than the reference price tend to drop to this level immediately when RP is introduced, but RP was not effective in reducing the price of products initially below the reference level.

Third, RP coverage of the first off-patent statin, lovastatin, was the only intervention that was observed to be effective in reducing its volume of sales growth, despite previous entry of lower-priced generics, while the impact of the delayed revision of its reference price was of similar importance. This indicates that the moment (number of generic firms in the market at that time) at which the reference price is fixed, when it is updated, and the method of calculation of the reference price are key determinants of the impact of RP on the volume of sales. In fact, however, the importance of the welfare contribution of the impact of interventions on this statin may be diminished when we take into consideration that they may have contributed to reinforce the shift to more expensive on-patent statins.

Fourth, including simvastatin under RP 2 years after the entry of generics, when more than 20 generic firms had entered the market, resulted in a delayed but substantial price reduction and therefore a substantial decrease in the volume of sales equivalent to a reduction of nearly 14% in overall statins sales in the 10 months after RP introduction in the rest of Spain.

Fifth, dispensed quantities of statins are not inelastic to price variations: price reductions of lovastatin forced or induced by RP interventions were accompanied by a reduction in the number of prescriptions of this first off-patent statin, although the other statins maintained their time trend growth as observed before RP; in contrast, price reduction of simvastatin was accompanied by a slight increase in its growth rate, and also a slight decrease in the number of prescriptions of atorvastatin, the top-selling on-patent statin.

Sixth, the regional public financing reforms adopted in the APHS only resulted in a slight volume of sales decrease in the case of simvastatin and atorvastatin. In the first year after MCP there was even a differential increase in atorvastatin, an on-patent statin uncovered by RP, possibly as a result of an unobserved marketing effort to shift drug use to higher-priced statins in order to counteract more intensive regional policies.

And seventh, the intervention occurring in the study period that had the greatest impact on the volume of sales was the marketing of an extended release form of fluvastatin, a still on-patent statin.

This study presents several limitations that merit consideration. First, public expenditure data on dispensed statins are proxied in this paper by overall volume of sales, including publicly financed but also out-of-pocket sales, valued at regulated ex-factory prices. Several potential problems could arise from this data set, in view of the purpose of this paper. In order to evaluate public financing reforms, public procurement data should be used. However, in the Spanish market, most dispensed prescription drugs are publicly financed, out-of-pocket prescription sales rep-

resenting a very small market share. Furthermore, the public financing reforms established the reimbursement limits at the level of the consumer price, therefore volume of sales valued at consumer prices would be more appropriate for evaluating the impact of these reforms. Notwithstanding, in this case price regulation establishes consumer prices by adding proportional distribution margins to the regulated ex-factory price, so this ex-factory price presents a perfect correlation with consumer prices. And lastly, the quantity data do not allow the calculation of defined daily doses, which would have provided a more precise quantity measure than is possible by simply using the number of prescriptions.

Second, a key feature of the method employed in this paper is that the difference between the observed value for the outcome variable in the period before the intervention and the value that would have been obtained in the absence of the intervention in the after period depends only on past trends. However, when controlled prospective randomized trials are not possible, the quasi-experimental techniques used in this paper are a recommended method of assessing impacts of interventions [12,13].

Third, the impact of the interventions under evaluation on other health services and on health status is not considered in this paper. Although these factors are important, this paper restricts its attention to quantity and volume of sales changes attributable to public financing reforms in the statin market, as all the interventions examined here involve pharmaceutical treatment substitution for patients using the same bioequivalent active ingredient, and therefore the impact on other health services and health status is expected to be very low. Furthermore, the impact of administration costs and time spent (by government, physicians, etc.) as a result of the policies are not included in the analysis.

A fourth limitation inherent in all policy evaluations applied to a class of drugs is that results cannot be easily generalized to all drug categories or to other health systems or pharmaceutical markets.

And, finally, a fifth limitation of this paper is that some potential confounding factors such as marketing expenditure have not been considered because of lack of reliable data.

Despite some data and method limitations, the results of this paper can be regarded as important for a number of reasons, at least relative to the case under analysis but also for the design of similar interventions in the pharmaceutical market. The observed persistent expenditure inelasticity to potential price competition even after RP introduction is probably the result of the widespread absence of cost-consciousness and proper efficiency incentives for the patient and the prescriber. Incentives on the patient and prescriber side remained nearly unchanged during the study period, at least in the rest of Spain; notwithstanding, their price inelasticity was substituted by potential co-payments under RP, which were effective at changing the pricing behaviour of producers. However, the sensitivity of pricing decisions to potential co-payments has not been able to take advantage of decentralized market decisions after patent expiry, but instead has been associated with a highly demanding and detailed regulation through RP, which may have intended but also unintended consequences on market performance. As an example, it would be of great interest, although it is beyond the scope of this paper, to know whether the RP system resulted in a clustering of prices of new generic entrants around the reference price with little variation, or whether RP resulted in a smaller generic market share than would have been expected without RP.

The question that still remains to be answered is to what extent long-term welfare effects of other alternative interventions more directed towards introducing cost incentives for patient and prescriber behaviour (e.g., generic substitution by the cheapest equivalent, differential co-payments for lower-priced cost-effective products in order to make patients more cost-conscious, transferring financial responsibility for prescription drugs to physicians, etc.) could have been more effective to curb the rise in drug spending and achieve a more cost-effective use of drugs than the short-term regulatory interventions under evaluation. Even when the evaluation is restricted to quantity and expenditure impact, it is important to note that the results obtained in this paper are only indicative of the impact of the interventions on quantity and volume of sales ratios compared with the status quo or simply compared to doing nothing different from before the interventions (used as a counterfactual).

The magnitude of the impact of interventions on quantity and volume of sales ratios is highly dependent on RP regulatory details. The RP systems employed by each insurer differ greatly in details and scope.

In fact, we should think of RP as a family of many different pharmaceutical insurance coverage policies. In the case analysed in this paper, the impact of RP interventions on price and volume of sales ratios was dependent on the moment at which RP was introduced as of the first generic entry (and the number of entrants at that time), the reference price calculation method and the updating frequency. Arbitrary regulatory decisions in the Spanish statin market led lovastatin to come under RP 17 months later than the introduction of RP (with 12 generic products in the market). The reference price of lovastatin was maintained 34% higher than the lowest-priced generic until its price revision 20 months after being covered by RP. And, after lovastatin price revision, in October 2004 the reference price was maintained 27% higher than the lowest-priced generic with significant sales in the market. In the same way, simvastatin was included under the centralized RP scheme only after 23 generic firms had effectively entered the market, and with a reference price that in October 2004 still remained 36% higher than the lowest-priced generic. The comparison between a policy of generic substitution by the cheapest equivalent, with free generic pricing, and the centralized Spanish RP system would probably provide an approximation to the distance between a genuine cost-minimization perspective and the present RP system.

The results of this paper show that the market demand for a given drug (i.e., the combined demand for the original drug and its generic substitutes) is not perfectly inelastic in relation to its own price change induced by RP. Pavcnik [11] observed that for oral antidiabetics and antiulcerants in Germany, the quantity of products sold was unaffected after RP introduction. However, in this paper it has been observed that when the first off-patent statin, lovastatin, was covered by RP, the quantity ratio after RP introduction was lower than before RP. Thus, the 0.76% monthly decline in lovastatin volume of sales is not only a proxy of expenditure savings for the public insurer, but also a proxy of a transfer of consumption to other higher-priced therapeutic alternatives, especially when the other active ingredients in this group maintained the larger monthly trend increases in the number of prescriptions. Market behaviour was different, at least in the rest of Spain, when simvastatin, the second off-patent statin, was covered by the RP system. In this case, pharmaceutical management by regions in the rest of Spain was probably able to control the quantity reduction of this active ingredient, contrary to the market reaction to lovastatin price reduction, and the observed outcome was not only a quantity increase in simvastatin but also a quantity decline in atorvastatin, a higher-price and top-selling statin. Depending on the degree to which clinical decision makers believe that different active ingredients in the group of statins are close substitutes in a therapeutic sense, these results could point to possible scope for RP equivalence criteria reforms.

Furthermore, the unexpected results obtained for the regional public financing reforms adopted in the APHS serve to underline the need for close attention to intervention design and details by policy makers. First, the only significant reduction in volume of sales attributed to the regional reforms was observed for simvastatin, probably as a result of applying a reference price as of the entry of the first generics and not waiting until the arbitrarily delayed coverage of simvastatin under the centralized RP system. Second, the introduction of a physician incentive to prescribe statins without using the commercial name cannot be automatically expected to generate cost-effective behaviour: in fact, the regional public insurer could be fostering statin prescription generally, independently of price and patent status. And third, according to the results of this paper, the physician incentive to increase the proportion of off-patent prescribed statins has not been enough to counteract industry pressure in favour of on-patent statin prescriptions.

Acknowledgements

The author is grateful to Paloma Fernández-Cano, Ricard Meneu and Salvador Peiró, who generously provided helpful suggestions and comments in preparing this paper. Ivan Planas and Anna Tur, from CRES, provided assistance in the management of the data set used in this research. Pilar García, also from CRES, provided valuable and efficient assistance in the statistical analysis. Financial support is acknowledged from Merck, Sharp and Dohme de España S.A. and the Spanish Ministry of Education and Science under grant SEC2003-00036. The author also benefited from support by an unrestricted educational grant from the Merck Company Foundation, the philanthropic arm of

Merck & Co. Inc., Whitehouse Station, New Jersey, USA.

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