Reports of the Ministry of Social Affairs and Health 2009:25

Matteo Galizzi, Simone Ghislandi, Joni Hokkanen, Aki Kangasharju, Ismo Linnosmaa, Marisa Miraldo, Hannu Valtonen

Reference pricing in Finnish pharmaceutical markets:

PRE-POLICY EVALUATION

MINISTRY OF SOCIAL AFFAIRS AND HEALTH, FINLAND

For Health and
Social Protection.

Matteo Galizzi[e,g], Simone Ghislandi[b], Joni Hokkanena,[f] , Aki Kangasharju[c],
Ismo Linnosmaa[a], Marisa Miraldo[d], Hannu Valtonen[a]
[a] = Department of Health Management and Policy, University of Kuopio,
Savilahdentie 6 A, 70211 Kuopio, Finland
[b] = ECONPUBBLICA, Bocconi University, Milan, Italy
[c] = Government Institute for Economic Research (VATT), Arkadiankatu 7,
P.O. Box 1279, 00101 Helsinki, Finland
[d] = Imperial College London, London, United Kingdom
[e] = Queen Mary University of London, London, United Kingdom
[f] = Research Center for Social Economics, Latomo, Kauppakatu 1,
76100 Pieksänmäki, Finland.
[g] = University of Brescia, Italy
Reference pricing in Finnish pharmaceutical markets: pre-policy evaluation.

Reports of the Ministry of Social Affairs and Health 2009:25

ISBN 978-952-00-2835-0 (PDF)
ISSN 1797-9897 (online)

URN:ISBN:978-952-00-2835-0
http://urn.fi/URN:ISBN:978-952-00-2835-0

Summary

Reference price system in the Finnish pharmaceutical markets: ex ante policy evaluation

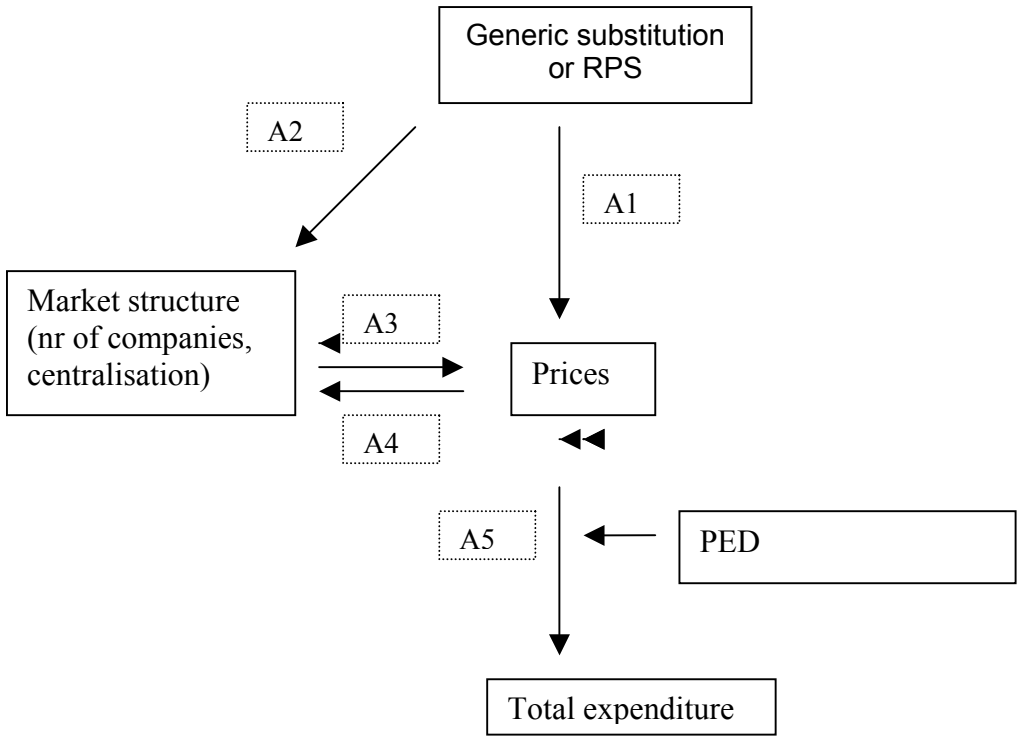
The evaluation assesses the effects the reference price system is expected to have on the pharmaceutical markets. The effects of the reference price system is evaluated with the help of experiences of the generic substitution and the effects of reference price systems in other countries. A framework is designed for the analysis to help in evaluating also the impact of other different kinds of reforms on the pharmaceutical markets, prices, and expenditure.

The reference price system is introduced in Finland in circumstances where the generic substitution has already had significant price, market structure, and competition effects. In principle, the difference between the reference price system and the generic substitution is the incentive for consumers to respond to prices. The generic substitution has already produced some of the effects the reference price system could have produced, and therefore the expected effects should be assessed with relative caution.

The reference price system can be expected to have an impact on the pharmaceutical prices, the market structure, competition, and the pharmaceutical total expenditure (see Analysis framework, Figure 1). The reference price system can influence prices through two routes: directly (arrow A1) or indirectly through the market structure (arrows A2 and A3). Direct impact means that enterprises respond to the reform by revising their pricing, i.e. enterprises respond by changing their prices because they assume that the market works differently as a result of the reform. Also the demand for medicines can change if the public and physicians, as a result of the reform, get more information about the possible alternative drugs and switch to cheaper generic drugs.

The impact through the market structure is based on increasing competition, which leads to lower prices. It follows from the reform that generic competitors see new business opportunities and enter new markets with their own products. The increasing competition in the markets leads, then, to lower prices. The market structure can also depend on the prices, since new producers enter such pharmaceutical markets where the level of prices is high (A4). Such a market structure is endogenous (determined within the system), and the prices and the market structure are inter-dependent.

Figure 1. Analysis framework on the effects of generic substitution



The effect of price changes on the pharmaceutical total expenditure depends on the price and cross elasticity of demand (A5), i.e., on how the demand of a medicinal product changes when the price of that product changes and when the price of a competing medicinal product changes. Normally, a rise in the product price leads to a decrease in the demand for the product, while a rise in the price of a competing product has the opposite effect. The impact on the total expenditure depends on the elasticity. If the demand does not respond easily to changes in prices (a low elasticity), the total expenditure decreases when the prices drop, because the fall in prices does not lead to a corresponding rise in demand. However, if demand responds easily to changes in prices, the total expenditure can increase even though prices decrease.

This study used a variety of statistical methods to analyse the effects of the 2003 generic substitution on the arrows in Figure 1. As of yet there is no data on the effects of the Finnish reference price system. With the help of elasticity, the study assessed the effects the reform has had on the prices, market structure, and total expenditure. Also a thorough literature review was carried out on the effects of reference price systems in other countries.

The research material consisted of the quarterly medicine data for selected ATC groups (A02, C07, C08, C09, C10, N03, N05, N06) in 1997–2007. The medicines are both generic preparations and non-generic preparations. This basic material was used to create divisions of data suitable for various estimations.

The generic substitution has increased competition on the pharmaceutical markets. Even before the generic substitution was introduced, there were more enterprises on the markets for medicines included in the 2003 generic substation scheme than on the markets for medicines excluded from the scheme. It appears that the generic substitution has increased the number of enterprises in the markets for active ingredients included in the scheme with 1–2 companies (in early 2003 the average was 2.5 companies). On the markets for active ingredients excluded from the generic substitution scheme no such changes in the number of companies has taken place.

Before the reform, the average price of medicines included in the generic substitution scheme was higher than the average price of non-generic drugs. The introduction of the generic substitution decreased these prices dramatically. On the basis of the results from the models used in the study, the price reduction was around 60 per cent by the end of 2007. A simultaneous evaluation of the direct effect of the generic substitution, on one hand, and its indirect effect through the market structure, on the other hand, is difficult because the variables measuring these effects correlate with each other, and there is a problem of multicollinearity in the model. When the models are estimated separately, it appears that the majority of the price drops were the results of direct impact and a smaller part of the price changes were due to indirect impact through the market structure.

The medicine price elasticity was studied for statins and antihypertensives. For statins the hypothesis was that the products are substitutes. The price elasticity was mainly as expected. The price elasticity of demand for fluvastatins was to a degree contrary to the hypothesis. The absolute values of price elasticity are so small that a drop in the total expenditure decrease can be expected as the prices decrease.

The evaluation of the effects of the reference price system on the pharmaceutical markets can be summarised as follows:

- According to the literature review, reference price systems have decreased pharmaceutical prices by 10–29 per cent in most countries.
- On the basis of these figures and the empirical results of the study, it can be assessed that the reference price system has some decreasing effect on pharmaceutical prices and total expenditure. The pharmaceutical prices decrease by 10–30 per cent and the total expenditure by 5–16 per cent.

Two factors especially complicate the impact analysis: Prior to the introduction of the reference price system, the generic substitution scheme has generated a large part of the effects the reference price system would have produced without the generic substitution. Secondly, a large part of the effects of the generic substitution are direct effects due to changes in the behaviour of enterprises and consumers instead of indirect effects through the market structure (increased competition). It is difficult to predict changes in behaviour, as there is too little research data on the pricing strategies of pharmaceutical enterprises and the prescription decisions of physicians in order for a proper analysis of this impact.

The division of tasks in the research group was as follows: Aki Kangasharju is the responsible manager of the project. Matteo Galizzi, Simone Ghislandi, and Marisa Miraldo carried out the literature review on the effects of reference price systems in other countries. Hannu Valtonen studied the impact of generic substitution on competition in the pharmaceutical markets and prices (Chapter 4). Ismo Linnosmaa and Joni Hokkanen assessed the elasticity of cholesterol reducers and the impact of medicine prices on the pharmaceutical expenditure (Chapter 5). Aki Kangasharju, Ismo Linnosmaa and Hannu Valtonen wrote the conclusions regarding the empirical analysis and the literature review as well as the summary, the introduction, Chapter 2 on the regulations concerning the Finnish pharmaceutical markets, and the theoretical frame of reference in Chapter 3. The projects was financed by the University of Kuopio, the Ministry of Social Affairs and Health, the Government Institute for Economic Research, and the Yrjö Jahnsson Foundation.

Key words: generic substitution, reference price, competition, prices, medicines, total expenditure

Sammandrag

Referensprissystemet på den finska läkemedelsmarknaden: en förhandsanalys av politiken

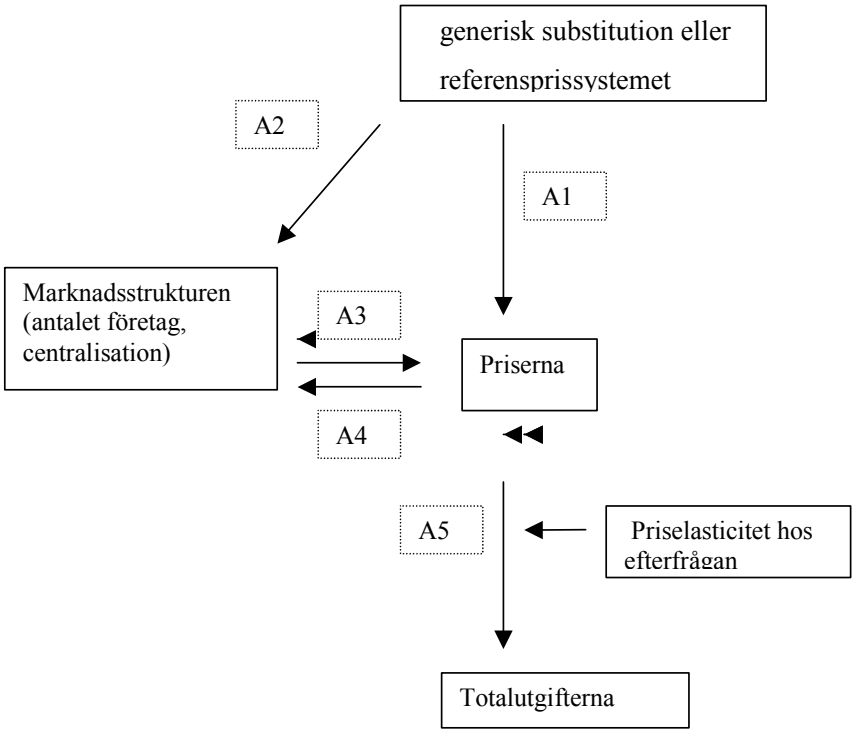
I undersökningen bedöms referensprissystemets förväntade effekter på läkemedelsmarknaden. Referensprissystemets effekter bedöms med hjälp av de erfarenheter som vi har om läkemedelsutbytet och de effekter som referensprissystemet har haft i andra länder. För analysen skapas ett ram som kan också användas för att bedöma hur olika andra reformer påverkar läkemedelsmarknaden, priserna och läkemedelsutgifterna.

Referensprissystemet införs i Finland i en situation där utbytet av läkemedel redan har haft betydande effekter på priserna, marknadsstrukturen och konkurrensen. Den principiella skillnaden mellan referensprissystemet och läkemedelsutbytet är att den förstnämnda sporrar konsumenterna att reagera mot priserna. Läkemedelsutbytet har redan genererat en del av de effekter som referensprissystemet skulle ha kunnat medföra och därför ska man vara relativt försiktigt med att utvärdera de förväntade effekterna.

Referensprissystemet kan förväntas att påverka läkemedelspriserna, marknadsstrukturen, konkurrensen och totalutgifterna för läkemedel (Analysramen, figur 1). Referensprissystemet kan påverka priserna genom två vägar: som en direkt effekt (pilen A1) eller som en effekt genom marknadsstrukturen (pilarna A2 och A3). Den direkta effekten kommer till om företag reagerar mot att reformen träder i kraft genom att ändra på sin prissättning, dvs. företag reagerar genom att justera priserna, eftersom de förväntar att marknaden som en följd av reformen beter sig annorlunda. Också efterfrågan på läkemedel kan förändras när medborgare och läkare i och med att reformen träder i kraft får mer information om möjliga alternativa läkemedel och byter till billigare utbytbara läkemedel.

Den effekt som uppstår genom marknadsstrukturen baserar sig på ökad konkurrens och dess prissänkande verkning. Reformen medför att generiska konkurrenter ser nya affärsmöjligheter och kommer in på marknaden med sina egna produkter. Ökad konkurrens på marknaden leder i sin tur till prissänkningar. Marknadsstrukturen kan påverkas av priserna eftersom det kan hända att mest nya producenter kommer in på marknaden av sådana läkemedel som har en hög prisnivå (A4). I så fall är marknadsstrukturen endogen (bestäms inom systemet), och då är priserna och marknadsstrukturen beroende på varandra.

Figur 1. *Analysramen för effekterna av läkemedelsutbytet*



Prisernas inverkan på totalutgifterna för läkemedel beror i sin tur på pris- och korselasticiteten hos efterfrågan (A5), dvs. på hur efterfrågan på en läkemedelsprodukt förändras i och med priset på produkten eller priset på en konkurrerande produkt förändras. Den normala situationen är att efterfrågan på en produkt avtar om priset på produkten ökar och ökar om priset på en konkurrerande produkt går upp. Effekten på totalutgifterna beror på hur stor elasticiteten är. Om konsumtionen inte är särskilt känslig för prisändringar (dvs. elasticiteten har ett lågt absolut värde), minskar totalutgifterna när priserna sjunker eftersom prisfallet inte medför en jämförbar ökning i konsumtionen. Däremot om konsumtionen är känslig för prisändringar kan totalutgifterna öka även om priserna sjunker.

I undersökningen estimerades med hjälp av olika slags statistiska metoder vilka effekter som kan förknippas med de olika pilarna i figur 1 som följd av utbyte av läkemedel som trädde i kraft år 2003. Uppgifter om effekterna av det finska referensprissystemet är inte ännu tillgängliga. I undersökningen studerades reformens effekter på priserna, marknadsstrukturen och totalutgifterna med hjälp av elasticiteten hos efterfrågan. Därtill genomfördes en genomgripande litteraturöversikt om hurdana effekter referensprissystemet har haft i olika länder. Undersökningsmaterialet består av kvartalsvis läkemedelsstatistik om utvalda ATC-grupper (A02, C07, C08, C09, C10, N03, N05, N06) åren 1997–2007. Läkemedlen i materialet var både utbytbara läkemedel och läkemedel som inte omfattas av läkemedelsutbytet. Ur det här basmaterialet uppbyggdes delmaterial som tillämpar till olika estimeringar.

Läkemedelsutbytet har ökat konkurrens på läkemedelsmarknaden. Även innan utbytet av läkemedel trädde i kraft fanns det mer företag på marknaden för sådana läkemedel som redan år 2003 omfattades av läkemedelsutbytet än på marknaden för sådana läkemedel som uteslutits från läkemedelsutbytet. Det ser ut som att utbytet av läkemedel har ökat antalet företag på marknaden med 1–2 företag när det gäller de verksamma läkemedelssubstanser som omfattas av utbytet (genomsnittet var 2,5 företag vid ingången av 2003). På marknaden för verksamma läkemedelssubstanser som inte omfattas av utbytet skedde inga ändringar i antalet företag.

Medelpriserna på läkemedel som omfattades av läkemedelsutbytet var högre före reformen än priserna på läkemedel som uteslutits från utbytet. Utbytet av läkemedel sänkte således priserna dramatiskt. Enligt resultaten för modellerna i undersökningen sjunker priserna med cirka 60 procent mot slutet av 2007. Det är svårt att samtidigt estimera både de direkta effekterna av läkemedelsutbytet och effekterna genom marknadsstrukturen eftersom de variabler som mäter de här effekterna korrelerar och modellerna har ett s.k. multikollinearitetsproblem. När modellerna estimerades separat verkade det som att den största delen av prissänkningar beror på reformens direkta effekter och en mindre del på ändringar i marknadsstrukturen.

Priselasticiteten hos läkemedel estimerades för statiner och läkemedel mot högt blodtryck. För statiner var den grundläggande hypotesen att de undersökta läkemedlena är varandras substitut. Priselasticiteten beter i huvudsak som förväntad. Elasticiteten hos efterfrågan för fluvastatiner var i fråga om plus- och minustecknen i vissa delar motsatta till de grundläggande hypoteserna. Priselasticiteten har så pass låga absoluta värden att det kan förväntas att totalutgifterna minskar i och med att priserna sjunker.

Uppskattningen om hur referensprissystemet påverkar läkemedelsmarknaden kan sammanfattas som följer:

- Enligt litteraturöversikten har referensprissystemet skurit ned läkemedelspriserna med 10–29 procent i andra länder.
- På basis av dessa siffror och undersökningens empiriska resultat kan det uppskattas att referensprissystemet minskar något läkemedelspriserna och totalutgifterna. Läkemedelspriserna sjunker med 10–30 procent och totalutgifterna med 5–16 procent.

Speciellt två faktorer försvårar bedömningen av effekterna: Innan referensprissystemets ikraftträdande har läkemedelsutbytet redan genererat en del av de effekter som referensprissystemet skulle ha genererat utan läkemedelsutbytet. För det andra skapas den största delen av läkemedelsutbytets effekter direkt genom ändringar i företags och konsumenters beteende och inte genom ändringar i marknadsstrukturen (ökad konkurrens). Det är svårt att förutse ändringar i beteendet eftersom det finns för lite forskningsmaterial om läkemedelsföretags prissättningsstrategier och läkares beslutsfattande i fråga om recept för att man skulle kunna analysera den här effekten på ett hållbart sätt.

Arbetsfördelningen inom forskningsgruppen var som följer: Matteo Gallizzi, Simone Ghislandi och Marisa Miraldo utförde litteraturöversikten om referensprissystemets effekter i andra länder och Joni Hokkanen, Aki Kangasharju, Ismo Linnosmaa och Hannu Valtonen analyserade läkemedelsutbytets effekter på konkurrensen, priserna på och efterfrågan för läkemedel på basis av det finska materialet och sammanfattade den empiriska analysen och litteraturöversikten.

Nyckelord: utbyte av läkemedel, referenspris, konkurrens, priser, läkemedel, totalkostnader

Tiivistelmä

Viitehintajärjestelmä Suomen lääkemarkkinoilla: politiikan etukäteisanalyysi

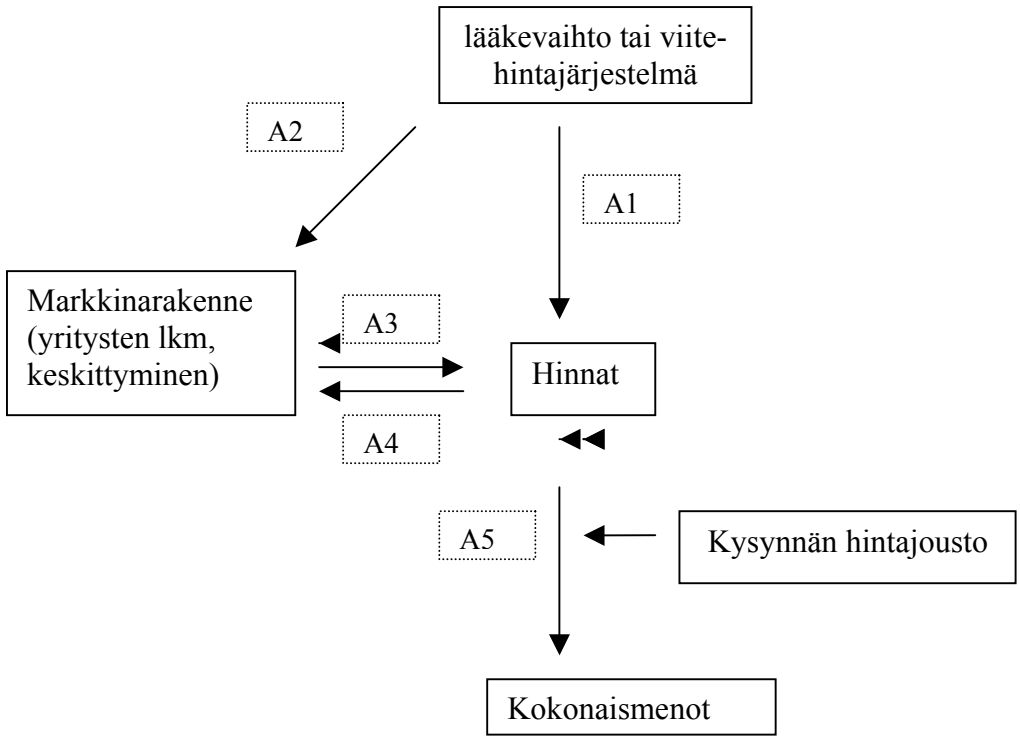
Tutkimuksessa arvioidaan viitehintajärjestelmän odotettavissa olevia vaikutuksia lääkemarkkinoilla. Viitehintajärjestelmän vaikutuksia arvioidaan käyttäen hyväksi kokemuksia lääkevaihdosta ja viitehintajärjestelmän vaikutuksista muissa maissa. Analyysia varten rakennetaan kehikko, jonka avulla voidaan arvioida myös erilaisten muiden reformien vaikutusta lääkemarkkinoihin, hintoihin ja lääkemenoihin.

Viitehintajärjestelmä tulee Suomessa voimaan tilanteessa, jossa lääkevaihto on jo tuottanut merkittäviä hinta-, markkinarakenne- ja kilpailuvaikutuksia. Viitehintajärjestelmän periaatteellinen ero lääkevaihtoon on sen kuluttajille luoma hintareagoinnin kannustin. Lääkevaihto on jo vienyt osan niistä vaikutuksista, jotka viitehintajärjestelmä olisi voinut tuottaa ja siksi odotettavissa olevia vaikutuksia arvioitaessa on syytä olla kohtuullisen varovainen.

Viitehintajärjestelmän voidaan odottaa vaikuttavan lääkkeiden hintoihin, markkinarakenteeseen, kilpailuun ja lääkkeiden kokonaismenoihin (Analyysikehikko, kuvio 1.) Viitehintajärjestelmän vaikutus hintoihin voi kulkea kahta kautta: suorana vaikutuksena (nuoli A1) tai markkinarakenteen välittämänä (A2 ja A3). Suora vaikutus syntyy, jos yritykset reagoivat reformin voimaantuloon muuttamalla hinnoitteluaan, eli yritykset reagoivat muuttamalla hintoja, koska odottavat markkinoiden käyttäytyvän toisin reformin seurauksena. Myös lääkkeiden kysyntä voi muuttua, kun kansalaiset ja lääkärit reformin voimaantullessa saavat lisää informaatiota mahdollisista vaihtoehtoisista lääkkeistä ja siirtyvät halvempiin vaihtokelpoisiin lääkkeisiin.

Markkinarakenteen kautta syntyvä vaikutus perustuu lisääntyneeseen kilpailuun ja sen hintoja alentavaan vaikutukseen. Reformin seurauksena geneeriset kilpailijat näkevät uusia liiketoiminnan mahdollisuuksia ja astuvat markkinoille kilpailemaan omilla valmisteillaan. Lisääntynyt kilpailu markkinoilla puolestaan johtaa hintojen alenemiseen. Markkinarakenne voi riippua myös hinnoista, koska uusia tuottajia voi ilmaantua eniten sellaisten lääkkeiden markkinoille, joilla hintataso on korkea (A4). Tällöin markkinarakenne on endogeeninen (järjestelmän sisällä määräytyvä), ja hinnat ja markkinarakenne riippuvat molemmat toisistaan.

Kuvio 1. *Analyysikehikko lääkevaihdon vaikutuksista*



Hintojen muutoksen vaikutus lääkkeiden kokonaismenoihin puolestaan riippuu kysynnän hinta- ja ristijoustoista (A5), eli siitä miten lääkevalmisteen kysyntä muuttuu sen oman hinnan muuttuessa ja jonkin kilpailevan lääkkeen hinnan muuttuessa. Normaali tilanne on, että oman hinnan noustessa lääkkeen kysyntä alenee ja jonkin kilpailevan lääkkeen hinnan noustessa taas kasvaa. Vaikutus kokonaismenoihin riippuu joustojen suuruudesta. Jos kulutus ei reagoi kovin herkästi hintojen muutoksiin (eli joustojen itseisarvot ovat pienet), kokonaismenot alenevat hintojen laskiessa, koska hinnan lasku ei johda vastaavansuuruiseen kulutuksen kasvun. Jos taas kysyntä reagoi herkästi hinnanmuutoksiin, kokonaismenot voivat kasvaa vaikka hinnat alenevat.

Tässä tutkimuksessa estimoitiin eri tilastollisin menetelmin vuonna 2003 voimaan tulleen lääkevaihdon seurauksena kuvion 1. eri nuoliin liittyvät vaikutukset. Suomalaisen viitehintajärjestelmän vaikutuksia ei ole vielä saatavissa. Tutkimuksessa selvitettiin reformin vaikutuksia hintoihin, markkinarakenteeseen ja kokonaismenoihin kysynnän joustojen avulla. Lisäksi tutkimuksen yhteydessä tehtiin perusteellinen kirjallisuuskatsaus viitehintajärjestelmän vaikutuksista eri maissa.

Tutkimuksen aineisto on neljännesvuosittainen lääkeaineisto valituista ATC-ryhmistä (A02, C07, C08, C09, C10, N03, N05, N06) vuosilta 1997 - 2007. Lääkkeet ovat sekä vaihtokelpoisia että lääkevaihdon ulkopuolella olevia lääkkeitä. Tästä perusaineistosta rakennettiin eri estimointitehtäviin soveltuvia osa-aineistoja.

Lääkevaihto on lisännyt kilpailua lääkemarkkinoilla. Jo ennen lääkevaihdon voimaantuloa yrityksiä oli enemmän sellaisten lääkkeiden markkinoilla, jotka otettiin lääkevaihdon piiriin vuonna 2003, kuin markkinoilla, joilla myytävät lääkkeet jäivät lääkevaihdon ulkopuolelle. Lääkevaihto näyttää lisänneen vaihdon piirissä olevien vaikuttavan aineen markkinoilla kilpailevien yritysten määrää 1-2 yrityksellä (keskiarvo vuoden 2003 alussa oli 2.5 yritystä). Vaihdon ulkopuolella olevien vaikuttavien aineiden markkinoilla ei ole tapahtunut muutosta yritysten määrässä.

Lääkevaihdon piiriin tulleiden lääkkeiden keskihinnat olivat ennen reformia korkeammat kuin vaihdon ulkopuolelle jääneiden lääkkeiden. Lääkevaihto alensi näitä hintoja dramaattisesti. Tämän tutkimuksen mallien tulosten perusteella hintojen aleneminen vuoden 2007 loppuun mennessä on noin 60 prosenttia. Sekä lääkevaihdon suoran vaikutuksen että sen markkinarakenteen kautta kulkevan vaikutuksen yhtaikainen estimointi on hankalaa, koska nämä vaikutuksia mittaavat muuttujat korreloivat ja malleissa on ns. multikollineaarisuusongelma. Kun malleja estimoitiin erikseen, näyttää siltä, että suurin osa hintojen alenemisesta johtuu reformin suorasta vaikutuksesta ja pienempi osa hintojen muutoksesta tulee markkinarakenteen muutoksen kautta.

Lääkkeiden hintajoustoja estimoitiin statiini- ja verenpainelääkkeiden osalta. Statiinien osalta lähtökohtaoletuksena oli, että tutkittavat lääkkeet olisivat substituutteja. Hintajoustot käyttäytyvät pääasiallisesti odotusten mukaisesti. Fluvastatiinien kysynnän joustot olivat joiltakin osin etumerkeiltään lähtökohtaoletusten vastaisia. Saatujen hintajoustojen itseisarvot ovat niin pieniä, että kokonaismenojen voidaan odottaa alenevan hintojen laskiessa.

Yhteenvetona arviosta, kuinka viitehintajärjestelmä vaikuttaa lääkemarkkinoihin, voidaan todeta:

- Kirjallisuuskatsauksen mukaan viitehintajärjestelmä on alentanut lääkkeiden hintoja muissa maissa 10-29 prosenttia.
- Näiden lukujen ja tutkimuksen empiiristen tulosten perusteella voidaan arvioida, että viitehintajärjestelmä alentaa jonkin verran lääkkeiden hintoja ja kokonaismenoja. Lääkkeiden hinnat alenevat 10-30 prosenttia ja kokonaismenot 5-16 prosenttia.

Vaikutusten arviointia vaikeuttaa erityisesti kaksi seikkaa: Ennen viitehintajärjestelmän voimaantuloa lääkevaihto on jo vienyt suuren osan niistä vaikutuksista, jotka viitehintajärjestelmän olisi tuottanut ilman lääkevaihtoa. Toiseksi lääkevaihdon tuottamista vaikutuksista suuri osa syntyy suorana yritysten ja kuluttajien käyttäytymisen muutoksesta syntyvänä vaikutuksena eikä markkinarakenteen muutoksen (kilpailun lisääntymisen) kautta syntyvänä vaikutuksena. Käyttäytymisen muutosten ennakointi on vaikeaa, koska lääkeyritysten hinnoittelun strategioista ja lääkäreiden lääkemääräysten päätöksenteosta on olemassa aivan liian vähän tutkimustietoa, jotta tätä vaikutusta voitaisiin pätevästi analysoida.

Tutkimusryhmän työnjako oli seuraava: Aki Kangasharju on projektin vastuullinen johtaja. Matteo Galizzi, Simone Ghislandi ja Marisa Miraldo tekivät kirjallisuuskatsauksen viitehintajärjestelmän vaikutuksesta muissa maissa. Hannu Valtonen tutki lääkevaihdon vaikutuksia

kilpailuun markkinoilla ja lääkkeiden hintoihin (Kappale 4). Ismo Linnosmaa ja Joni Hokkanen tutkivat kolesterolilääkkeiden joustoja ja lääkkeiden hintojen vaikutuksia lääkemenoihin (Kappale 5). Aki Kangasharju, Ismo Linnosmaa ja Hannu Valtonen kirjoittivat yhteenvedon empiirisestä analyysista ja kirjallisuuskatsauksesta, tiivistelmän, johdannon, Suomen lääkemarkkinoiden sääntelyä koskevan kappaleen 2 ja teoreettisen viitekehyksen (kappale 3). Hankkeen rahoittivat Kuopion yliopisto, sosiaali- ja terveysministeriö, Valtion taloudellinen tutkimuskeskus ja Yrjö Jahnssonin säätiö.

Asiasanat: lääkevaihto, viitehinta, kilpailu, hinnat, lääkkeet, kokonaiskustannukset

Abstract

Finland introduced the reference pricing system to the pharmaceutical market at the beginning of April 2009. This paper evaluates the effects of the reform from the ex-ante perspective. The reform will potentially affect the prices, structure, competition and total expenditure of the market. This study takes all these perspectives into account in making an overall synthesis of the results. Evaluation is based on past Finnish experiences concerning the generic substitution policy, in force since 1 April 2003, and a literature survey of studies evaluating the effects of reference pricing abroad.

The data include information on the number of firms selling as well as the prices and sales volumes of pharmaceuticals in eight ATC groups between 1997–2007, comprising pharmaceuticals both inside and outside the substitution scheme.

The results indicate that generic substitution increased the number of firms in the pharmaceutical market. However, the effect on competition was clearly lower than that on prices. Generic substitution reduced prices by 60 per cent by the end of 2007. The literature survey suggests that reference pricing will reduce pharmaceutical prices by 10-29 per cent. The effects are presumably country-specific, since regulation schemes vary over countries and reference pricing is only one part of the schemes. Since generic substitution has already dramatically reduced prices in Finland, we believe that the effect of reference pricing in Finland will be closer to the conservative estimate. Our results on the demand elasticities of blood pressure medicines (statines) with respect to changes in prices suggest that the total pharmaceutical expenditure can be expected to decline with declining prices. Combining all the results, we expect that the reference pricing will decrease prices by 10 percent and the total pharmaceutical expenditure by 5 percent.

Contents

1 Introduction

Pharmaceuticals have been continuously capturing an increasing part of total health costs internationally. In Finland, pharmaceuticals accounted for less than 10% of the total health care costs in 1990, but this figure increased to 16% by the early 2000s (Stakes 2007). Since then, the trend has levelled off. There are alternative explanations for this. One potential explanation is the system of generic substitution (GS) Finland introduced in April 2003. According to first estimates, generic substitution has generated substantial savings through increased price competition. Further policy tools are also being designed. Finland will adopt reference pricing (RP), where the cost of a pharmaceutical is reimbursed to the customer up to a reference price. Customers pay the costs beyond the reference price themselves. The new Reference Pricing Act will come into effect in April, 2009. The legislator estimates that the reform will reduce the expenditures of customers and taxpayers on pharmaceuticals by €35 million.

The application of reference pricing to prescription drugs is new (Panavos and Reinhardt, 2003). Germany was first to introduce RP for prescription drugs in 1989, and was followed in Europe by the Netherlands (1991), Denmark and Sweden (1993), Spain (2000), and Belgium and Italy (2001). Norway adopted RP in 1993 but abandoned it in 2001 because the expected cost savings did not materialize. Australia, the Canadian province of British Columbia, and New Zealand have also implemented RP.

This study evaluates how the reference pricing is likely to affect both prices and expenditures of pharmaceuticals in the Finnish pharmaceutical market. The assessment is based on two approaches. First, a review of the existing literature on reference pricing and pharmaceutical policies sheds light on the issue from the perspective of other countries mentioned above. Second, an analysis of empirical data on Finnish pharmaceutical markets provides a more detailed picture of the Finnish case. Because the study was conducted before the reference pricing policy was introduced in Finland, our assessment of the policy effects is based on the economic consequences of the generic substitution policy.

In the empirical part of study we construct a framework that can be used to evaluate the impact of the reference pricing or generic substitution policy (or, in fact, any policy aiming to affect pharmaceutical expenditures through price changes) on pharmaceutical expenditures. This framework is based on the following two-stage concept. In the first stage, the policy affects the prices of pharmaceutical either directly (via changes in firms', consumers' and prescribing doctors' behaviour as a direct consequence of the GS reform) or indirectly through market structure (via increased competition). In the second stage, the resulting price change affects pharmaceutical expenditures, the magnitude of this effect depending on the magnitude of demand elasticities. The goal of the first stage is to determine whether the price impact of a policy is direct or indirect,

and the goal of the second stage is to estimate relevant demand elasticities and compute corresponding expenditure effects.

The rest of our report is organized as follows. Section 2 describes how the prices and entry of pharmaceuticals are regulated in Finland. In particular, we discuss the policy of generic substitution and reference pricing. Section 3 develops a model that is used to analyze the interaction between the market structure and pricing in Finnish pharmaceutical markets. Sections 4 to 6 analyze the effects of a price change on pharmaceutical expenditures. The literature review is extensive. It is therefore located in an Appendix, and the major conclusions from it are drawn in the Conclusion section.

The distribution of labour within the research group was as follows: Aki Kangasharju is the responsible director for the project. Matteo Gallizzi, Simone Ghislandi and Marisa Miraldo prepared the literature survey on the effects of reference pricing systems in other countries. Hannu Valtonen examined the effects of the generic substitution policy on the market structure and prices in Finnish pharmaceutical markets (Section 4). Ismo Linnosmaa and Joni Hokkanen estimated demand elasticities and examined the effect of the generic substitution policy on pharmaceutical expenditures (Section 5). Aki Kangasharju, Hannu Valtonen and Ismo Linnosmaa were responsible for writing the summary of the empirical analysis and literature review, abstract, Section 2 concerning the regulation of the Finnish pharmaceutical market and the theoretical framework (Section 3).

2 Regulation of the Finnish pharmaceutical market

2.1 The generic substitution scheme in Finland

Finland adopted generic substitution on 1April 2003. The aim of the generic substitution policy is to promote cost-effective drug therapies. According to the scheme, the prescribed medicinal product can be replaced in a pharmacy by the cheapest, or close to the cheapest, generic alternative. The price of the prescribed medicine is considered to be close to the cheapest when the price difference to the cheapest generic alternative is less than €2 (for products costing less than €40) or when the price difference to the cheapest is less than €3 (for those costing at least €40). Substitution with a cheaper alternative and increased competition between pharmaceutical companies will lead to cost savings. The National Agency for Medicines maintains the list of substitutable medicinal products. Interchangeable products must contain the same active substance in equal amounts and pharmaceutical form and be biologically equivalent. A group of interchangeable products includes all generic and parallel imported products with the

same active ingredient (Paldan et al., 2004). Both the prescribing physician and the purchasing individual can forbid the substitution.

2.2 Reference pricing

Panavos and Reinhardt (2003) list three alternative ways patients may pay for prescribed drugs. First, patients may pay a fixed copayment per prescription. Secondly, patients may pay a fixed coinsurance of the retail price charged at the pharmacy. The third method is reference pricing, in which patients are responsible for the full price difference between the retail price and a reference price. The reference price is the price of a low-cost drug in a group of drugs with similar health effects.

According to Danzon (2001), reference pricing is a reimbursement rule that sets the maximum reimbursement for one product by reference to the price of other "comparable" product(s) in the same market. Specific features that reference pricing systems have are:

1. classifications of pharmaceuticals into subgroups according to therapeutic effects,
2. the reference price as the maximum reimbursement in a subgroup,
3. the reference price is defined using information about the price distribution of pharmaceuticals in each subgroup,
4. manufacturers are free to set their prices, and
5. patients pay the difference between the price of the drug and the reference price, if such difference exists.

Germany was the first country to introduce a reference pricing policy in 1989. Other countries that have introduced the policy since Germany include the Netherlands, Sweden, Denmark, New Zealand, Poland, Slovenia, British Columbia, Australia, Italy and Spain (Lopez-Casasnovas and Puig-Junoy, 2000). Danzon (2001) suggested that reference pricing has informally existed in generic substitution programs in the United Kingdom, Medicaid and managed care programmes in the US and in some Canadian provincial programmes, because these programmes share some of the features of the reference pricing system.

A reference pricing policy may be internal or external (Danzon, 2001). An internal reference pricing system compares the prices of pharmaceuticals within a single country. External reference pricing sets the maximum reimbursement for a pharmaceutical by comparing the price of a pharmaceutical product in one country with the price of the same product in another country. Internal referencing is based on the comparison of prices of competing pharmaceuticals in one country, whereas external referencing utilizes information about the prices of the same pharmaceutical in different countries.

Finland adopted the internal reference pricing policy on 1 April 2009. The subgroups of pharmaceuticals in the Finnish reference pricing system are the groups of interchangeable products created at the time generic substitution scheme was introduced. The reference price in a subgroup of substitutable products is the minimum price + €1.5 if the minimum price is less than €40, and the minimum price + €2 if the minimum price exceeds €40. If the retail price exceeds the reference price, a patient must pay the difference between the retail price and the reference price, and the insurance reimbursement will be based on the reference price. If the retail price is lower than the reference price, the insurance reimbursement is based on the retail price charged at the pharmacy.

In Finland, the price of a pharmaceutical with market authorization is not regulated if the price of the pharmaceutical is not reimbursed from the social insurance scheme. Authorities fix a reasonable wholesale price for all reimbursed pharmaceuticals. A reasonable wholesale price is the maximum price at which a pharmaceutical can be sold to pharmacies or hospitals. In other words, reimbursable pharmaceuticals are subject to price-cap regulation (Viscusi et al., 2005). In this respect, the Finnish system differs from general features of the reference pricing systems listed by Danzon (2001).

3 Identifying the effects of a policy

Both the generic substitution policy (GSP) and reference pricing policy (RP) aim at influencing pharmaceutical expenditures by fostering substitution and price competition among equally effective pharmaceuticals. Neither policy regulates the use or prices of pharmaceuticals directly, but they affect both the prices and the demand for pharmaceuticals indirectly through changes in market incentives.

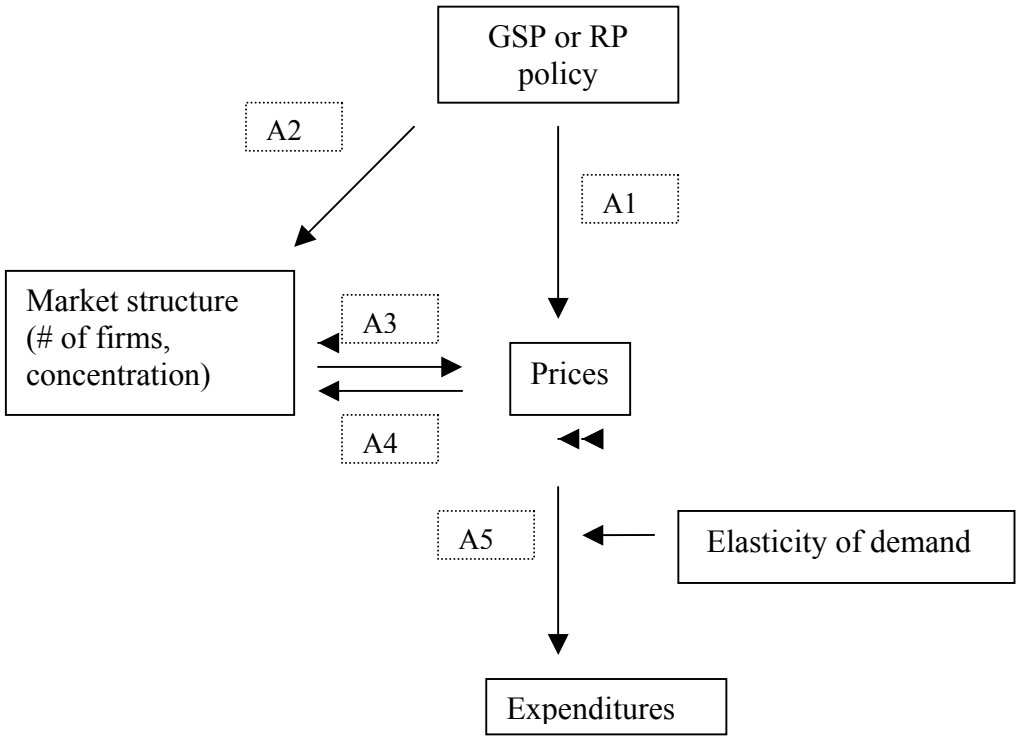
Direct price effects

Figure 1 depicts the potential ways in which GSP or RP may influence pharmaceutical expenditures. A policy may influence the prices of pharmaceuticals either directly or indirectly. The price effect is direct (Arrow A1) if the pricing behaviour of firms and the behaviour of doctors and consumers in prescribing and buying pharmaceuticals changes as a result of the policy implementation. The generic substitution policy (or reference pricing policy) may have such an effect on prices of pharmaceuticals if it succeeds in fostering substitution among equally effective pharmaceuticals. Economic theory (e.g. Bertrand price competition model, model of perfect competition) suggests that the more responsive consumers are to price differences, the more fierce price competition is in the market (see e.g. Tirole, 1988).

Indirect price effects

Price effects may also occur indirectly through a change in the market structure. If the GSP increases the profitability of generic entry, the policy may also affect the entry of new generic pharmaceuticals (Arrow 2). If the generic substitution policy increases price awareness and induces patients to switch from an expensive branded pharmaceutical to inexpensive generic drugs, the implementation of the policy may make generic entry more lucrative and the policy may increase generic entry.

Figure 1. *Policy effects*



The case in which GSP decreases the likelihood of entry can also be theoretically justified. In the literature on the determinants of market entry (see Berry and Reiss, 2008, Scott Morton, 2000), the likelihood of entry depends on profitability: the higher (lower) the economic profit of an industry is, the more (less) likely it is that new entrants enter the industry. Therefore, any policy promoting substitution and price competition in the market may also reduce the likelihood of entry (or increase the likelihood of exit from a market). Potential entrants may simply consider a competitive market to be an unprofitable place of business. In conclusion, any policy promoting substitution and price competition in the market may either increase or decrease the likelihood of entry.

Given the effect of a policy on market structure, one can then explore the impact of a change in market structure on the prices of pharmaceuticals (Arrow A3). Several models examining the impact of competition on the prices of goods (e.g. Cournot model, Model of perfect competition, Salop's circle model on price competition) have concluded that the more competitive the market is, the lower are the prices of goods. A typical conclusion in the theoretical literature is that new entrants increase the supply of goods on the market, which tends to reduce prices.

However, it is worth pointing out that the way competition affects prices depends on how sensitive consumers' decisions are to price differences in the market. The Bertrand price competition model and the model of perfect competition both assume that firms sell perfect substitutes. In such circumstances we should expect that informed consumers do respond to price differences and consume only the lowest-priced good in the market. For various reasons, however, consumers may be less price-sensitive. The model developed by Salop and Stiglitz (1977) suggests that incomplete information about the prices of goods may be one such reason. In the literature examining pharmaceutical markets, Frank and Salkever (1992) analyzed a market consisting of price-sensitive and loyal consumers. Price-sensitive consumers respond to price differences in the market. Loyal consumers, on the other hand, are insensitive to price differences and consume only the branded pharmaceutical. The authors demonstrated that in such markets the entry of generic pharmaceuticals (or generic competition in general) may also increase the price of the branded pharmaceutical.

One should accordingly observe that market structure may be endogenously determined by prices and the profitability of a market. As discussed above, the likelihood of entry is high in industries that earn high economic profits. High prices often imply high economic profits, which should increase the likelihood of entry (Arrow A4). This also means that the market structure in such industries may become more competitive in the long term.

Prices and expenditures

Once the impact of a policy on the prices of pharmaceuticals has been implemented, expenditure effects arise by the interaction between price changes and changes in the consumption of pharmaceuticals (Arrow A5). In the simplest case of one good, a reduction in the price of the good reduces expenditures on that particular good only if the demand for the good is inelastic with respect to a change in the price of that good. A good may also have substitutes and complements on the market and, hence, the change in the price may also influence the demand for other pharmaceuticals on the market. To fully examine the expenditure effects of a price change, such interconnections should be taken into account. This is done in Section 5 of this report.

4 Policy of generic substitution and prices of pharmaceuticals

Our objective in this part of the study is to examine the link between pharmaceutical policy and the prices of pharmaceuticals. Ideally, we would like to analyse the impact of the Finnish reference pricing policy on the prices of pharmaceuticals using data from Finnish pharmaceutical markets. This, however, is currently an impossible task. Therefore, we utilize Finnish experiences on the effects of the generic substitution policy on the prices of pharmaceuticals. We fully acknowledge that the policy measures implemented in the generic substitution reform in 2003 differ from those measures intended to be implemented after the introduction of the reference pricing policy in Finland. We take these differences into account when drawing final conclusions about the effects of the policy on the prices of pharmaceuticals.

4.1 Description of the data

The original data were provided by the National Agency for Medicines. They consist of disaggregated 'packet' data, i.e. the information in the data concerns single drug packets with varying size and strength, and each packet of the same brand name and pharmacological substance appears as separate observations. In the original data we had more than 50 000 observations, and they comprised all pharmaceuticals in 8 three-digit ATC groups (see Table 1).

For the various estimation tasks in this study, we created three different types of data set from the original data:

1) Disaggregated packet data to analyse the effect of GSP reform and competition on prices.
2) Aggregated (pharmacological substance level) data to analyse the effect of GSP reform on the market structure and competition.
3) Selected data sets for the price elasticity estimations for selected pharmacological substances.

1) Disaggregated packet data

This set of data was used to examine the effect of competition and the GSP reform on prices (Arrows A3 and A1 in Figure 1).

For the analysis, we removed some of the observations in order to create quasi-experimental data. After the observation removal, the data included two different groups of observations: only such pharmacological substances that were

- non-substitutable (the 'control' or non-substitutable group) during the whole observation period (1997-2007), and
- included in generic substitution from the implementation of the GSP reform, from the 2nd quarter of 2003, and that had not been excluded from the substitution since then (the 'intervention' or substitutable group).

The pharmacological substances not fulfilling these selection criteria were removed from data. After the removal, we had 27 771 observations in the data. In some of the later analyses, there are some missing observations.

Table 1. The ATC groups in the data, 44 quarters over 11 years from 1997 to 2007

ATC		Substitutable, N	Non-substitutable, N	Total, N
A02	DRUGS FOR ACID RELATED DISORDERS	790	961	1751
C07	BETA BLOCKING AGENTS;	958	1651	2609
C08	CALCIUM CHANNEL BLOCKERS;	3104	777	3881
C09	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM;	883	3685	4568
C10	LIPID MODIFYING AGENTS;	531	2717	3248
N03	ANTIEPILEPTICS;		2354	2354
N05	PSYCHOLEPTICS;	4349	478	4827
N06	PSYCHOANALEPTICS;	1620	2913	4533
Total		14589	13182	27771

The data contain 325 different branded drugs, 121 pharmacological substances over 44 time periods (quarters, i.e. 11 years) from the 1st quarter of 1997 to the 4th quarter of 2007, from eight (three-digit) ATC groups (A02, C07, C08, C09, C10, N03, N05, N06), and 79 different firms. The panel is unbalanced, since some new substances have entered the market and some have left (see Appendix 2.). Most of the drugs (75% in the 4th quarter of 2007) are prescription drugs.

2) Aggregated (pharmacological substance level) data

This data set was used to analyze the impact of the GSP reform on market structure and competition. The measure for competition is the number of firms in the market.

For the analysis of the effect of the GSP reform on market structure and competition (Arrow A2 in Figure 1), the previous data set was aggregated over pharmacological substances. This was done because the 'markets' were defined in this part of the study as a pharmacological substance market. The firms were assumed to compete with each other within markets defined by pharmacological substances. After the aggregation, the data for market structure evaluation were panel data comprising 3543 observations, and same 121 pharmacological substances over 44 time periods (quarters, i.e. 11 years) from the 1st quarter of 1997 to the 4th quarter of 2007, from eight (three-digit) ATC groups (A02, C07, C08, C09, C10, N03, N05, N06).

3) Selected data sets for the price elasticity estimations

The third type of data set was formulated from the original data by choosing selected pharmacological substances (separate data sets for both statins and beta-blockers) for the analysis. From these selected substances, brand name (original or market leaders with large markets shares in the 1st period in our data) drugs and generic competitors were identified, where this was feasible. If the original drug could not be identified, a market leader was identified instead. The generic competitors (prices and quantities) were aggregated as one 'generic competitor'. The DDD prices for each time period were calculated as weighted averages (market shares as weights). In the price elasticity analyses, data from several time periods are needed for original and generic competitors, and thus drugs that either had no generic competition or were in the data only for some time periods were excluded from the data. From these data, the variables needed in the analysis, the market share of the original drug and the relative prices were calculated.

4.2 Empirical models

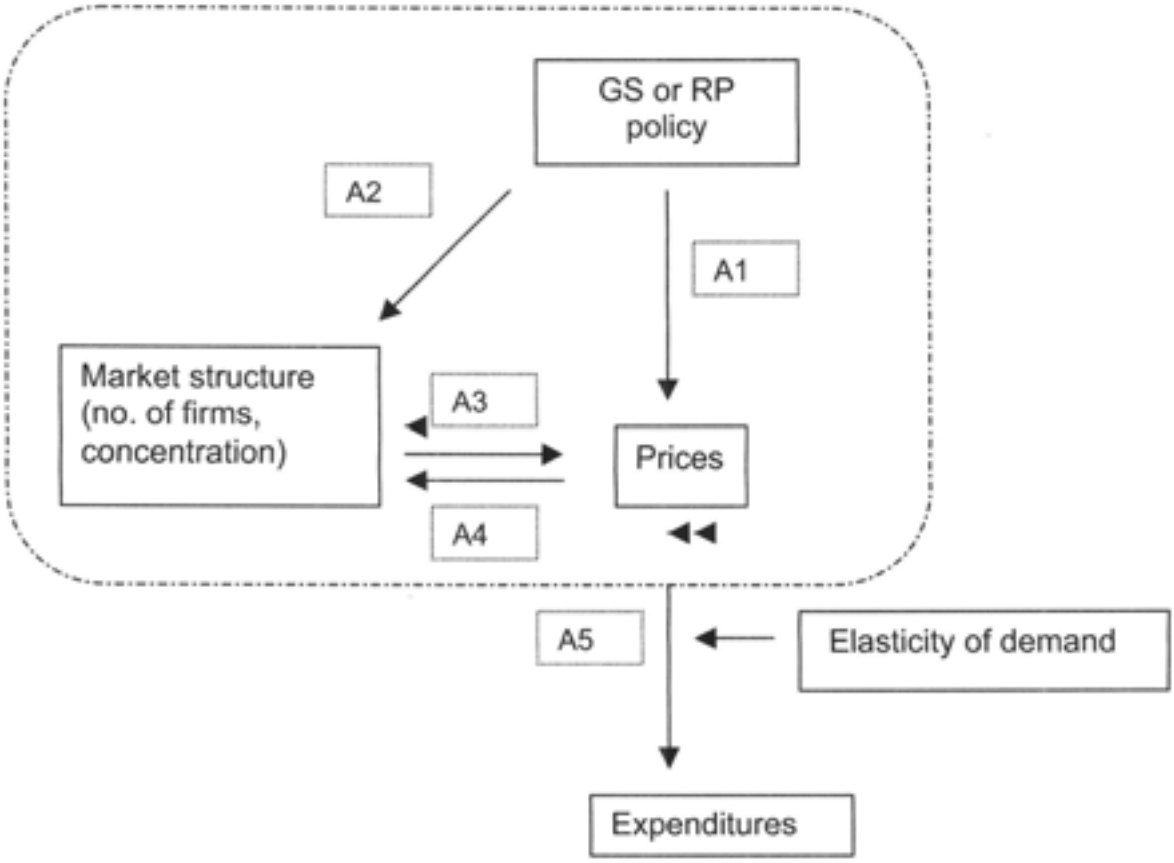
We next present the empirical models that we employ to examine both direct and indirect effects of the policy of generic substitution.

4.2.1 Effect of the GS policy on market structure

Our theoretical framework is illustrated in Figure 1, which is reproduced with some modifications in Figure 2. In this section, we focus on the variables inside the rounded rectangle in Figure 2 and raise two questions concerning the price effects of the generic substitution policy. We first aim to quantify the direct effect that the policy has had on the prices of pharmaceuticals (Arrow 1) on Finnish pharmaceutical markets. Secondly, we examine the effect of the policy on prices through market structure. The second task

(Arrow 2) and then the impact of the market structure on the prices of pharmaceuticals. In the latter part, we also discuss the potential problem of an endogenous market structure.

Figure 2. *Generic substitution policy and prices of pharmaceuticals*



Our first interest is in the effect of the generic substitution policy on the market structure (Arrow 2 in Figure 2). For this purpose, we consider the following empirical model:

$$1)\ g(FIRMS_{gt}) = f(\theta_0 + \theta_g + \theta_1 GS_{gt} + \theta_2 GS_{gt}*(TIME-25) + \theta_3 SUBS_g + \theta_4 TIME + \theta_5 SALES_{gt-1})$$

where the variable $FIRMS_{gt}$ is the number of firms selling pharmaceuticals with pharmacological substance g in time period t. The variable $SALES_{gt-1}$ is the total sales in group g (pharmacological substance g), measured in wholesale prices and lagged by one period. The literature examining market entry (see e.g. Berry and Reiss (2008) and Scott-Morton (2000)) suggests that post-entry profits determine the market structure, because they influence the likelihood of entry (Arrow A4 in our model). The $SALES_{gt-1}$-

variable approximates average profits. The parameter θ_0 is the constant term and the variable θ_g captures persistent differences across pharmaceuticals in different pharmacological groups. The TIME variable captures the time trend in the data.

The variable GS_{gt} is defined as the product GSP_t*$SUBS_g$, where the dummy variable GSP_t obtains a value of zero before the implementation of the generic substitution policy (25^{th} quarterly time-point in our data) and a value of 1 otherwise. We treat GS_{gt} as the reform variable of interest. The variable $SUBS_g$ obtains a value of 1 if pharmacological group g contains pharmaceuticals to which the generic substitution policy is being applied (henceforth substitutable pharmaceuticals), and a value of 0 if the group does not contain such pharmaceuticals. The latter types of groups form the control group in our study. The variable $SUBS_g$ was included in the model in order to control for time-independent differences between the pharmaceuticals in the intervention and control groups.

We estimate the log-linear and the Poisson specification of the above model 1). In the log-linear specification we specify $g(FIRMS_{gt})$ as $\ln(FIRMS_{gt})$ and $f(w_{gt}) = w_{gt} + \varepsilon_{gt}$, ε_{gt} is normal error term. In addition, we apply the Poisson model in order to capture the discrete (count data) nature of the dependent variable. The variable $FIRMS_{gt}$ is a count measure for the number of firms in marketg.

4.2.2 Price effects

We then concentrate on examining the price effects of the generic substitution policy. We are interested in finding both the direct effect of the generic substitution policy on the prices of pharmaceuticals (Arrow 1 in Figure 2) and also the effect that arises through a change in the market structure (Arrow A3 in Figure 2). In order to accomplish this, we construct a log-linear empirical model in which prices of pharmaceutical products are explained by variables measuring market structure and the time the generic substitution policy was implemented. In particular, our interest is in the following log-linear model:

$$2)\ \ln(PRICE_{igt}) = \alpha_0 + \alpha_i + \alpha_1 GS_{gt} + \alpha_2\, GS_{gt}*(TIME-25) + \alpha_3 SUBS_g + \gamma_1 TIME + \beta_1 FIRMS_{gt-1} + \varepsilon_{itg}$$

where $PRICE_{igt}$ is the price of pharmaceutical product i in pharmacological group g in time period t. A log-linear model is estimated, because log-transformed prices better satisfy the standard model assumption that the stochastic terms of the model ε_{itg} follow a normal distribution. The parameter α_0 is the constant term and the variable TIME is a linear time trend. The variable α_i captures persistent and time-independent differences across the prices of pharmaceutical products. In this respect, we estimate both the fixed- and random-effects specifications of the model. Because the prices and market structure

in period t may be jointly determined, we explain prices in time period t by the number of firms in the previous time period t-1.

The variable GS_{gt} is defined as the product GSP_t*$SUBS_g$. The variable $SUBS_i$ obtains a value of 1 if pharmaceutical i belongs to the class of pharmaceuticals to which the generic substitution policy is being applied, and a value of 0 if pharmaceutical does not belong to this class. The generic substitution policy does not affect pharmaceuticals that are not classified as substitutable pharmaceuticals. Such pharmaceuticals form the control group in our study. We also include the variable $SUBS_g$ in the model in order to control for potential price differences between the pharmaceuticals in the intervention and control groups.

Economic theory suggests that the degree of product market competition and costs of production influence the prices of goods. The variable $FIRMS_{gt}$ is assumed to measure the degree of product market competition. We have no data on the costs of producing pharmaceuticals and, therefore, we assume that the variable α_i captures the cost-related, time-invariant differences across pharmaceutical products.

In order to examine the price effects of the generic substitution policy, we estimate three specifications of model 2). In the first specification we examine the effect of the generic substitution policy on the prices of pharmaceuticals. This is done by assuming that the market structure has no influence on the prices of pharmaceuticals, and $\beta_1 = 0$. If this assumption holds true in general, the generic substitution policy has only direct effects on the prices of pharmaceuticals (as indicated by Arrow 1 in Figure 2). In the second specification we assume that any effects that the policy has on the prices of pharmaceuticals arise through a change in the market structure, and $\alpha_1 = \alpha_2 = \alpha_3 = 0$. If this assumption holds true in general, the price effects of the policy arise only through changes in the market structure. Finally, we also estimate the model as it appears in equation 2). The general form allows both direct and indirect effects (both Arrow 1 and Arrow 3 in Figure 2) to exist simultaneously.

4.3 Results

4.3.1 The generic substitution policy and market structure

Our first goal is to quantify the effect of the policy on the degree of competition in the market, which is measured by the number of competing firms selling drugs containing the same pharmacological substance.

Construction and characteristics of the data

The generic substitution (= GS_{gt}) variable was constructed as a 'treatment' variable. The variable obtains a value of zero before the beginning of the second quarter in 2003, and

after that the variable obtains a value of 1 for those substances that were substitutable and a value of 0 for those that were not substitutable. To be able to better observe the effect of the reform on competition, we removed from the data those substances that became substitutable later than at the beginning of the second quarter in 2003.

Table 2. Variables in the models

Variable	N	Mean	Std.dev.	Min	Max
FIRMS (= No. of firms)	3543	1.777	1.705	1	14
ln(FIRMS)	3543	0.345	0.582	0	2.639
TIME	3543	23.327	12.333	2	44
GS	3543	0.143	0.350	0	1
Substitutable (= SUBS)	3543	0.289	0.454	0	1
GS*TIME	3543	1.462	4.141	0	19
$SALES_{t-1}$	3543	7.179	22.563	1.47E-05	269.1

The number of firms can be seen as count data (having only non-negative integer values: 1, 2, 3, etc.), and thus should be modelled using Poisson or negative binomial models. Moreover, the variable describing the number of firms has a skewed distribution (mean is 2.1, the minimum is 1 and the maximum is 14). The chosen modelling strategy was as follows: The number of firms (in logarithmic form to correct the skewedness of the distribution) was modelled by random-effect regression with the marketing authorization number as the group variable, after testing the specification against a fixed-effect model using the Hausman test. Secondly, the number of firms was modelled using Poisson models.

By modelling the competition in these ways, we assume that the firms compete in markets defined by pharmacological substances (active substances). In other words, we assume that products with the same pharmacological substances are substitutes, and their demand may depend on each others' prices (cross-price elasticities are not zero).

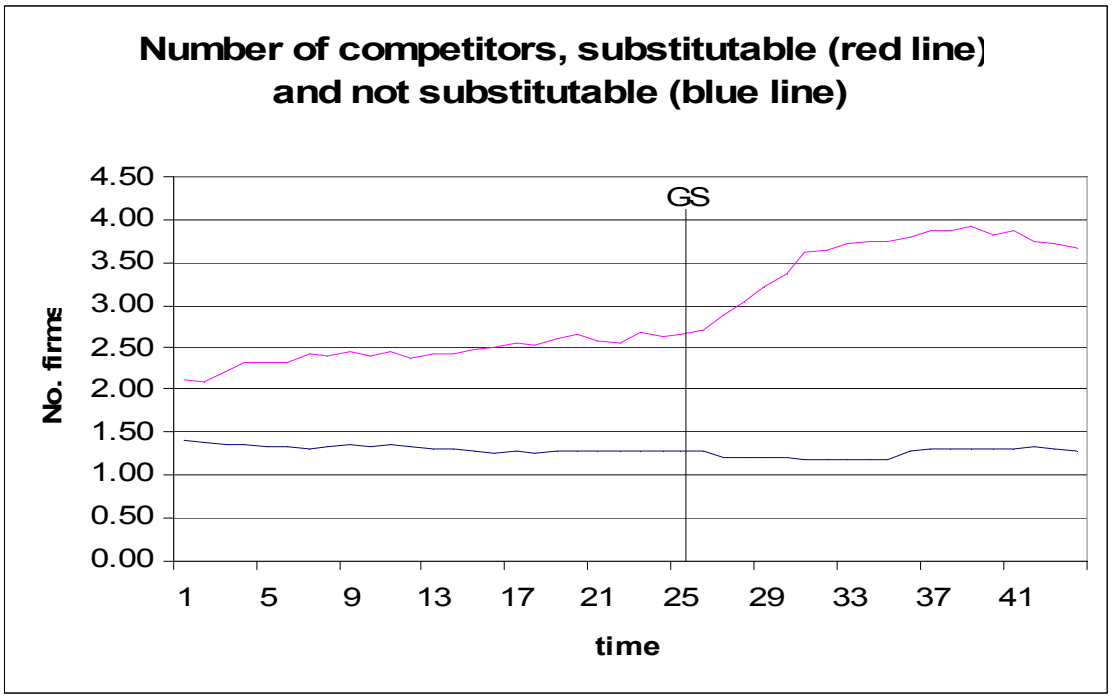
The GSP reform can potentially change the market structure by opening new business opportunities in the market. The business opportunities are determined by the size of the market and the generic substitution reform. As discussed in Section 3, the reform might cause a change in the number of competitors, and it might also affect time trend in the number of competitors in each substance market.

Results

A larger number of firms were found to be marketing those drugs that later, with the introduction of generic substitution, became substitutable (see Figure 1). The average number of firms was above 2 in the substitutable group, whereas in the non-substitutable group it was less than 1.5. After the GSP reform the number of competitors

increased, but towards the end of 2007 the number of competitors appears to have declined. There appears to have been a small declining trend in the non-substitutable group.

Figure 3. *Number of firms in the intervention and control groups (GS = the implementation of the generic substitution reform)*



According to Figure 3, the variation in the number of competing firms in the substitution (= intervention) group appears to be larger than in the non-substitution (= control) group, and the variation in the number of competing firms appears to be increasing over time in the substitution group.

Table 3. The number of firms in the substitution and non-substitution groups

Time		Non-substitution group	Substitution group
Year 2003, 2nd quartal	Mean	1.27	2.52
	Std.dev	0.69	1.85
	Coefficient of variation	54.3	73.5
Year 2007, 4th quartal	Mean	1.24	4.03
	Std.dev	0.60	3.31
	Coefficient of variation	48.3	82.1

When estimating the effect of the GSP reform on the market structure, both sets of models (linear and count data models) produce similar results. The generic substitution increases the number of competitors, but, as we can see from Figure 3, this effect might not be caused only by the reform itself. The number of firms in the substitution group is increasing already before the GSP reform. However, the reform seems to cause an increasing trend over time. In comparison to the control group (outside generic substitution), the substitutable drugs have more competitors and the number of competitors is increasing in time. Of the variables included in model 1), the size of the market (lagged sales) has a positive sign, that is, the number of firms increases with the size of the market, as expected.

Table 4. The effect of the GSP reform on the market structure

Dependent variable: number of firms within pharmacological substance markets								
	Random-effects regression (robust standard errors) on ln(FIRMS)		Fixed-effects regression (robust standard errors) on ln(FIRMS)		Random effects Poisson regression on FIRMS		Fixed effects Poisson re-gression on FIRMS	
N	3543		3543		3543		3543	
No. of pharma-cological sub-stances	114		114		114		114	
R^2:								
within	0.532		0.532					
between	0.292		0.288					
overall	0.459		0.458					
	Coef.	P>|z|	Coef.	P>|t|	Coef.	P>|z|	Coef.	P>|z|
TIME	-0.002	***	-0.002	***	-0.002		-0.002	
GS	0.301	***	0.303	***	0.316	***	0.313	***
GS*(TIME-25)	0.032	***	0.033	***	0.040	***	0.040	***
$SALES_{t-1}$	0.011	***	0.010	***	0.008	***	0.008	***
Constant	0.166	***	0.235	***	0.277	***		
σ_u	0.330		0.372					
σ_e	0.229		0.229					

When we take into account that the number of competitors is already higher in the substitutable group before the generic substitution reform, we model it with a dummy variable 'substitutable' (1 if substitutable and 0 if non-substitutable for all time periods). This variable can only be included in the random effect models, and is not statistically significant in either of the models (see Table 5). This might be caused by the large variation in the number of competitors in the substitutable group.

Table 5. The effect of the GS policy on the market structure

Dependent variable: number of firms in the pharmacological substance markets								
	Random-effects regression (robust standard errors) on ln(FIRMS)		Fixed-effects regression (robust standard errors) on ln(FIRMS)		Random effects Poisson regression on FIRMS		Fixed effects Poisson regression on FIRMS	
N	3543		3543		3543		3543	
No. of pharmacological substances	114		114		114		114	
R^2:								
within	0.532		0.532					
between	0.294		0.288					
overall	0.460		0.458					
	Coef.	P>|z|	Coef.	P>|t|	Coef.	P>|z|	Coef.	P>|z|
TIME	-0.002	***	-0.002	***	-0.002		-0.002	
SUBS	0.008		na.		0.169		na.	
GS	0.300	***	0.303	***	0.296	***	0.313	***
GS*(TIME-25)	0.032	***	0.033	***	0.039	***	0.040	***
SALES,t-1	0.011	***	0.010	***	0.008	***	0.008	***
Constant	0.164	***	0.235	***	0.225	***		
σ_u	0.358		0.372					
σ_e	0.272		0.229					

According to the estimation results in Table 5, there is no statistically significant difference in the number of firms between the intervention and control groups. However, the GS policy reform seems to have a clear effect on the number of competitors in this model. We also find a significant time trend.

In practice, the scale of the effects can easily be evaluated from the linear models: the coefficients are elasticities. They express the relative change in the explanatory variable (number of firms in the markets) after the generic substitution is implemented. The coefficient of the GS variable is around 0.3, and thus the implementation of generic substitution increased the number of firms in the substitution group by 30 per cent. The

time trend implies an annual 3 per cent increase in the number of competitors as a consequence of the GSP reform. The average number of competitors in the substitution group in period 26 was 2.52, and thus a 30 per cent increase in this would correspond to 0.7 to 0.8 firms. The effect of the time trend over four years (12 quarters) would be an increase of 50 to 60%, that is an addition of 1.3 - 1.5 firms from the starting value of 2.52.

In the Poisson models, the estimated equation expresses the values of ln(expected value of the variable) as a linear function of the explanatory variables. Thus, the estimated effect of the GS reform is around 34-37 per cent (exp(.296),exp(.313)). The effect of the time trend over four years would be an increase of around 60 per cent in the number of competitors. Both model types produce similar estimates for the size of the effect of the GSP reform on the market structure.

4.3.2 Price effects

We first study the direct effect of the GS policy on prices. The data comprise 27 104 different packets (products having a market authorisation number). Only packets that were either substitutable or non-substitutable at the time of the implementation of the GSP were included in the data. This selection was carried out so we that could better analyse the impact of the reform. Pharmaceuticals that later became substitutable are left out of this data set. We thus have 121 different pharmacological substances, 44 quarters and a total of 1408 products in the data. The price variable was calculated from the total sales in wholesale prices by dividing this by the quantity of packages sold. The price thus represents wholesale prices per packet.

Table 6. Descriptive statistics on the prices of drugs (€/packet)

		non-substitutable	substitutable
Before GSP			
	N	8938	4532
	Mean	24.9	38.8
	Std.dev.	38.3	36.3
	Coefficient of variation	153.5	93.7
After GSP			
	N	5651	8650
	Mean	34.9	22.6
	Std.dev.	50.6	25.2
	Coefficient of variation	145.0	111.3

It appears that the prices of pharmaceuticals that later became substitutable were higher before the GS policy reform (Table 6 and Figure 4). After the reforms, the prices declined, but their variation increased (see coefficient of variation). The prices of non-substitutable pharmaceuticals appeared to increase after the GS reform.

Figure 4. *Mean prices in the intervention and control groups*

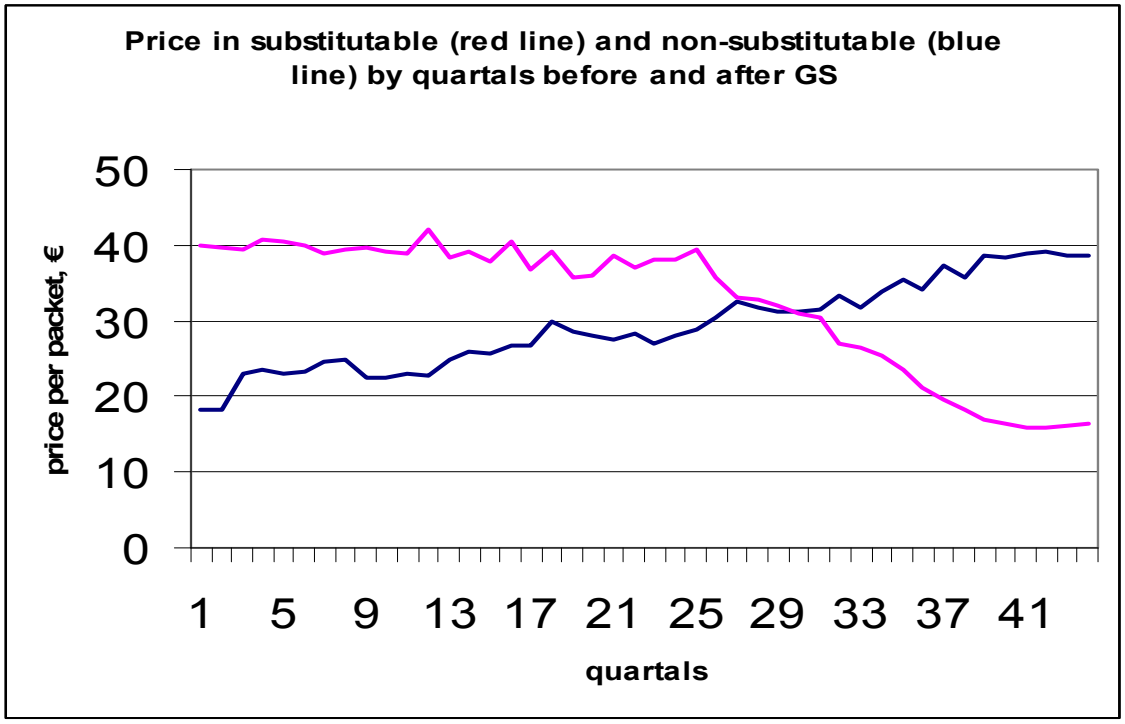


Table 7. Descriptive statistics, N = 27104

Variables	Mean	Std. dev	Min	Max
PRICE	28.34	38.19	0.53	606.0
ln(PRICE)	2.74	1.11	-0.64	6.41
GS	0.31	0.46	0	1
GS*TIME	3.43	5.85	0	19
TIME	24.85	12.77	1	44
SUBS	0.48	0.50	0	1
FIRMS	3.61	3.13	1	14

The price variable is skewed to the right, and the logarithmic transformation was used in all models. The benefit of this is that the coefficients in the models express the size of the relative (percentage) change in the prices.

The direct effect of the GS policy reform on prices

We first examine the direct effect of the GS policy on the prices of pharmaceuticals and estimate model 2) under the constraint $\beta_1 = 0$. Table 8 displays the estimation results. The first two models are regular panel data models. In the third model (Prais-Winsten model) the auto-correlation and potential panel-level heteroscedasticity of the observations are taken into account.

Table 8. The direct effect of the GS reform on prices (log)

Dependent variable: ln(PRICE)						
	Fixed-effects regression (robust standard errors)		Random effects regression (robust standard errors)		Prais-Winsten regression with AR(1) error terms (heterosce-dastic panels and corrected standard errors terms)	
N	27700		27700		27700	
No. of groups	1408		1408		1408	
R^2:						
within	0.421		0.421			
between	0.029		0.047			
overall	0.022		0.064		0.646	
corr(u_i,Xb)	-0.103					
	Coef.	P>|t|	Coef.	P>|z|	Coef.	P>|z|
GS	0.127	***	0.126	***	-0.040	***
GS*TIME	-0.054	***	-0.054	***	-0.062	***
TIME	-0.001	***	-0.001	***	0.005	***
SUBS	n.a.		0.359	***	0.478	***
Constant	2.924	***	2.748	***	2.713	***
σ_u	1.092		1.028			
σ_e	0.205		0.205			
ρ					0.976	

In all of the models, the reform causes a downward trend in the prices. The size of the effect is 5 - 6 per cent per year. In the first two models, which do not control for auto-correlation, the GS reform seems to have an increasing effect on prices, about 13 per cent. In the autoregressive model, on the other hand, the policy causes a small downward shift. The third model is the most appropriate one for final conclusions due to auto-correlated disturbance terms (see the estimate for ρ in Table 8). Those pharmaceuticals that later became substitutable were more expensive than those that were left outside the substitution.

The effect of competition on prices

We then examine the effect of competition on prices by estimating model 2) under the constraints $\alpha_1 = \alpha_2 = \alpha_3 = 0$. The distribution of the number of firms is again skewed towards the right. In fact, in 63 per cent of all observations, the number of competing firms is three or less (Table 9).

Table 9. Descriptive statistics on the FIRMS variable

FIRMS	Freq.	%
1	8788	32.3
2	5327	19.6
3	3047	11.2
4	2300	8.5
5	1721	6.3
6	1474	5.4
7	1435	5.3
8	526	1.9
9	621	2.3
10	253	0.9
11	265	1.0
12	927	3.4
13	408	1.5
14	83	0.3
Total	27175	100.0

Table 10. The effect of exogenous competition on prices (log)

Dependent variable: ln(PRICE)						
	Fixed effects regression (robust standard errors)		Random effects regression (robust standard errors)		Prais-Winsten regression with AR(1) error terms (heteroscedastic panels and corrected standard errors)	
No obs.	26608		26608		26608	
No. groups	1375		1375		1375	
R^2:						
Within	0.313		0.313			
Between	0.050		0.050			
Overall	0.028		0.028			
corr(u_i,Xb)	-0.130					
			Coef.	P>|z|	Coef.	P>|z|
	Coef.	P>|t|				
$FIRMS_{t-1}$	-0.094	***	-0.093	***	-0.036	***
TIME	-0.006	***	-0.005	***	-0.009	***
Constant	3.215	***	3.241	***	3.142	***
σ_u	1.079		1.028			
σ_e	0.226		0.226			
ρ					0.977	

In the three models estimated above we have assumed that competition is exogenous, i.e. given to the model. Technically, this is done by using lagged values of the FIRMS variable. According to the results in Table 10, competition lowers the prices. One additional firm reduces the prices by from 3 to 9 per cent. There is also a small declining trend over time. In the model in which autocorrelation is accounted for, the effect of increased competition is smaller than in the other two models.

GS reform and competition effects together

When estimating the full model 2), we meet the multicollinearity problem. The GSP reform variables (dummy and time trend) correlate strongly with the competition variable. The number of firms increases after the GSP reform, and the correlation with time and the GSP reform dummy is quite high. Consequently, the independent effects of these variables, i.e. the magnitudes of their independent effect on prices, are difficult to identify.

Table 11. The correlation matrix of the potential explanatory variables

	GS	GS*(Time-25)	Time	No. firms	SUBS
GS	1				
GS*TIME	0.87	1			
TIME	0.59	0.62	1		
FIRMS	0.71	0.71	0.44	1	
SUBS	0.71	0.61	0.28	0.58	1

If we estimate the full model (despite the difficulties), we find that the effect of the GSP reform seems to be similar to that in the previous models, and the effect of competition seems to be somewhat smaller than in the previous models.

Table 12. The effect of competition (number of firms) on prices (log)

	Fixed effects regression (robust standard errors)		Random effects regression (robust standard errors)		Prais-Winsten regression with AR(1) error terms (heteroscedastic panels and corrected standard errors)	
N	27104		27104		27104	
No. of groups	1382		1382		1382	
R^2:						
within	0.447		0.447			
between	0.045		0.080			
overall	0.029		0.086		0.661	
corr(u_i,Xb)	-0.121					
	Coef.	P>|z|	Coef.	P>|z|	Coef.	P>|z|
GS	0.170	***	0.170	***	-0.040	***
GS*TIME	-0.051	***	-0.051	***	-0.063	***
TIME	-0.001	***	-0.001	***	0.007	***
$FIRMS_{t-1}$	-0.035	***	-0.036	***	-0.014	***
SUSB	n.a.	***	0.452	***	0.526	***
Constant	3.012	***	2.809	***	2.700	***
σ_u	1.084		0.995			
σ_e	0.202		0.202			
ρ					0.971	

To overcome the multicollinearity problem, we estimated these models separately for the substitution and non-substitution group, and included the competition variable and time as a set of dummy variables in the model. The idea is that the competition variable catches the effect of competition and time dummies all other effects than competition, including the time trend and the effect of the GSP reform. This model does not suffer from multicollinearity.

Table 13. The effect of competition (number of firms) and time on prices (log)

	Non-substitution group		Substitution group	
N	14220		12884	
No. of groups	618		764	
R^2:				
within	0.037		0.532	
between	0.130		0.177	
overall	0.011		0.205	
corr(u_i,Xb)	-0.128		0.088	
	Coef.	P>|t|	Coef.	P>|t|
FIRMS	0.000		-0.040	***
Quartals				
from the 1st quartal to the 20th quartal no statistically significant coefficients				
21	0.000		0.056	*
22	0.000		0.053	*
23	0.005		0.099	***
24	0.006		0.076	**
25	0.007		0.101	***
Implementation of GS, 26	-0.003		0.035	
27	0.010		0.017	
28	0.018		-0.002	
29	0.023	*	0.026	
30	0.021	*	-0.003	
31	0.012		-0.040	*
32	-0.014		-0.142	***
33	-0.011		-0.183	***
34	-0.014		-0.216	***
35	-0.013		-0.249	***
36	-0.016		-0.319	***
37	-0.063	***	-0.435	***
38	-0.071	***	-0.517	***
39	-0.093	***	-0.605	***
40	-0.071	***	-0.668	***
41	-0.068	***	-0.662	***
42	-0.067	***	-0.681	***
43	-0.062	***	-0.694	***
44	-0.069	***	-0.705	***
Constant	2.656	***	3.302	***
σ_u	1.247		0.892	
σ_e	0.129		0.254	

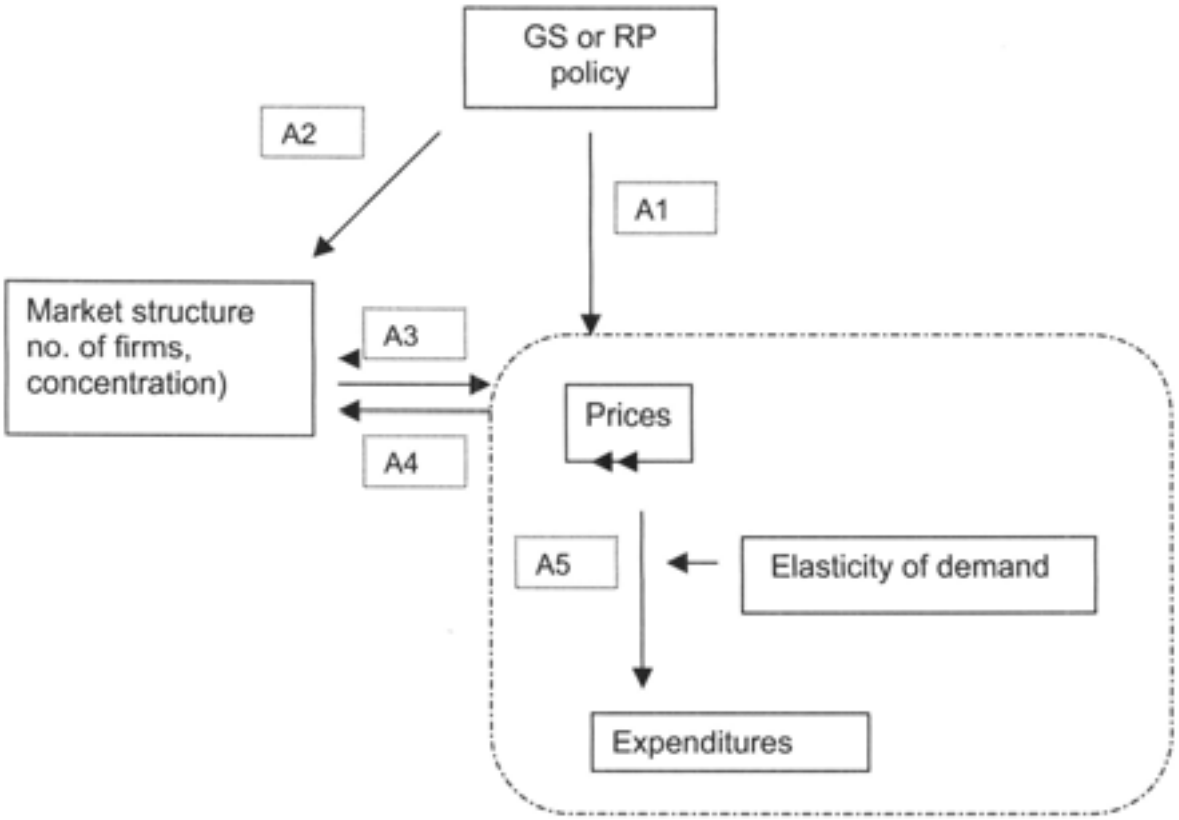
The results in Table 13 show that competition does not have an effect on prices in the substitution group. There is a small statistically significant declining trend in the prices after quarter 37 (from the beginning of 2006). In the substitution group, however, competition seems to have a small price effect. If one extra firm enters the market, the prices decline by about 4 per cent. From 1997 onwards to the 20th quarter there are no statistically significant time effects. However, in a few periods before the GSP reform the prices are increasing. It might be the case that the firms are preparing for the reform by increasing their prices. After the implementation of the GSP reform there is a clear time trend, with prices starting to decline quite rapidly.

When we compare the relative size of the direct price effect and the effect via competition, the direct GS reform effect is larger in size. This can be interpreted to mean that in the existing markets both the pharmaceutical firms and the consumers changed their behaviour, and the change in prices due to this behavioural change were larger than the price effects arising via increased competition.

5 Effect of a change in prices on pharmaceutical expenditures

According to the literature review (see Appendix), the implementation of the reference pricing system has reduced prices by from 10% to 29% in countries that have adopted the system. In the previous section we estimated that the generic substitution policy reduced wholesale prices of pharmaceuticals by 5-6% per year in Finland. In this part of the study we examine the impact of a price change on pharmaceutical expenditures (Arrow 5 in Figure 5). This effect depends on the demand elasticity of pharmaceuticals. In this section we first estimate demand elasticities and then assess the change in pharmaceutical expenditures that is caused by a certain reduction in the prices of pharmaceuticals.

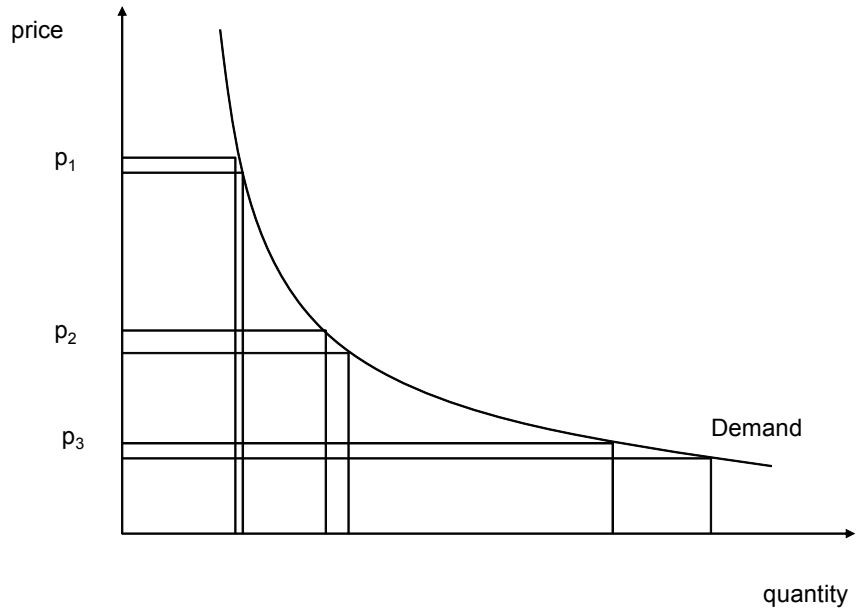
Figure 5. *Prices and expenditures*



5.1 Impact of prices on pharmaceutical expenditures

The standard demand analysis suggests that a reduction in the price of a pharmaceutical will increase (decrease) pharmaceutical expenditures, if the demand for the pharmaceutical is price elastic (inelastic). A reduction in the price has no impact on pharmaceutical expenditures if the demand for the pharmaceutical is unit elastic. This relationship between price and pharmaceutical expenditures is illustrated below in Figure 6.

Figure 6. *Price change and pharmaceutical spending*



The demand for pharmaceutical is inelastic at price p_1. In this case, a reduction in price of the pharmaceutical will reduce pharmaceutical expenditures. On the other hand, at price p_3 the demand for the pharmaceutical is elastic and a reduction in the price of the pharmaceutical will increase pharmaceutical expenditures. In case of the unit elastic demand, at the price level p_2, a price change has no impact on pharmaceutical expenditures.

The effect of price on expenditures can also be expressed formally. In order to formalize the concept in Figure 1, we consider the demand for pharmaceutical i. We first assume that the demand for pharmaceutical i depends only on its own price p_i. Let us denote the demand for pharmaceutical i as $q_i(p_i)$ and assume that the demand decreases strictly when the price of pharmaceutical i increases. Pharmaceutical expenditures on pharmaceutical i are given by $E_i(p_i) = p_i q_i(p_i)$. The effect of a change in the price p_i on pharmaceutical expenditures can be computed as

3) $$dE_i(p_i)/dp_i = q_i(p_i)(1 + \varepsilon_{ii}),$$

where $\varepsilon_{ii} \equiv (dq_i/dp_i)(p_i/q_i)$ is the elasticity of the demand for pharmaceutical i with respect to its own price p_i. According to equation (1), a reduction in the price of pharmaceutical i will reduce (increase) pharmaceutical expenditures if the demand for pharmaceutical i is inelastic (elastic). In case of unit elastic demand, price p_i has no effect on pharmaceutical expenditures.

Instead of absolute changes, it may be more convenient to examine the elasticity of pharmaceutical expenditures i with respect to a change in price i. This elasticity can be computed as follows:

4) $$[dE_i(p_i)/dp_i][p_i/E(p_i)] = q_i(p_i)(1 + \varepsilon_{ii})[p_i/E_i(p_i)] = 1 + \varepsilon_{ii.}$$

The intuition of the above paragraph applies similarly to the above equation.

In the above discussion, we have examined one pharmaceutical product by assuming that a change in the price of pharmaceutical i affects the demand for pharmaceutical i only. This may not be a realistic approach in practice, because pharmaceutical products often have substitutes (and perhaps also complements) on the market. The market for lovastatins provides one example. The branded pharmaceutical in the market is Mevacor. In addition, the market for lovastatins consists of several generic substitutes competing with Mevacor. Therefore, it is reasonable to argue that a change in the price of Mevacor will also affect the demand for generic substitutes on the market.

Let us consider a pharmaceutical market with n pharmaceuticals. The demand for pharmaceutical i = 1,2,...,n is denoted by $q_i(p)$, where the variable $p = (p_1,p_2,...,p_n)$ contains the prices of all pharmaceutical products on the market. Expenditures on n pharmaceuticals on the market are defined as $E(p) = \Sigma_i p_i q_i(p)$. The effect of a change in price p_i on pharmaceutical expenditures is given as:

5) $$dE(p) = [p_i q_i(p)(1 + \varepsilon_{ii}) + \Sigma_{j\neq i}\, p_j q_j\, \varepsilon_{ji}]\, dp_i/p_i$$

where $\varepsilon_{ji} \equiv (\partial q_j/\partial p_i)(p_i/q_j)$ is the cross-price elasticity of demand for pharmaceutical j with respect to price p_i. If one allows all prices to change simultaneously, the resulting change in pharmaceutical expenditures is

6) $$dE(p) = \sum_i [p_i q_i(p)(1 + \varepsilon_{ii}) + \Sigma_{j\neq i}\, p_j q_j\, \varepsilon_{ji}]\, dp_i/p_{i.}$$

We use equation (6) to compute the effect of a price change on pharmaceutical expenditures.

5.2 Empirical model

As the above section demonstrates, information on the demand elasticity of pharmaceuticals is needed in order to evaluate the impact of a price change on pharmaceutical expenditures. At minimum, one would like to have reliable estimates of the own-price elasticities. Moreover, depending on the scope one uses to define a pharmaceutical market, it may also be necessary to gather information on cross-price elasticities.

In order to estimate demand elasticities, we apply the empirical model developed by Ellison et al. (1997). Their model can be used to estimate both own-price elasticities of demand and cross-price elasticities of demand. The demand for a pharmaceutical product is determined in a two-stage process, in which a physician first decides which pharmaceutical is to be prescribed and, conditional on the choice of a pharmaceutical, the physician or a patient (or even a pharmacist) decides whether the patient ends up using the branded or a generic version of the pharmaceutical. Following Ellison et al. (1997), we call the first level demand model the top-level equation and the second level demand model the bottom-level equation.

At the bottom level, the market shares of branded and generic versions of pharmaceuticals (with a given active agent) are explained by the total quantity and relative prices of branded and generic versions of the pharmaceutical. Let us consider a situation in which there are n pharmaceuticals on the market. The bottom-level equation is defined as:

$$7) \qquad s_{ib} = \alpha_{ib} + \beta_{ib} \ln(r_i/p_i) + \gamma_{ibb} \ln(p_{ib}) + \gamma_{igb} \ln(p_{ig})$$

where p_{ib} and p_{ig} are the prices of the branded and generic versions of pharmaceutical i = 1,2,...,n, s_{ib} is the market share of the branded version of pharmaceutical i, that is $s_{ib} = p_{ib}q_{ib}/r_i$, and $r_i = p_{ib}q_{ib} + p_{ig}\, q_{ig}$ is the total revenue of pharmaceutical i. The price of pharmaceutical i is computed as the (Stone-weighted) price $p_i = p_{ib}^{sib} p_{ig}^{sig}$, where s_{ib} and s_{ig} are market shares of the branded and generic versions of pharmaceutical i. Unknown parameters α_{ib}, β_{ib}, γ_{ibb} and γ_{igb} are estimated from the data. Following Ellison et al. (1997), we assume throughout that $\gamma_{igb} = -\gamma_{ibb}$.

One can also estimate a model for generic pharmaceutical i. In this case the left hand side variable in the bottom-level equation 7) is the market share of the generic pharmaceutical i. In order to separate these branded and generic equations from each other, we denote the parameters of the bottom equation of the generic pharmaceutical α_{ig}, β_{ig}, γ_{ibg} and γ_{igg}. Because it always holds true that $s_{ib} + s_{ig} = 1$, it must also be the case that $\alpha_{ib} + \alpha_{ig} = 1$, $\beta_{ib} = -\beta_{ig}$, $\gamma_{ibb} = -\gamma_{ibg}$, and $\gamma_{igb} = -\gamma_{igg}$.

The top-level equation explains the quantity of pharmaceutical i by the total revenue and relative prices of all n pharmaceuticals (with different active agents, but substitutes) on the market. The top-level equation is defined as:

8) $$\ln(q_i) = \eta_i + \theta_i \ln(R) + \delta_i \ln(p_i/P_j),$$

where the variable q_i denotes the quantity of pharmaceutical i, R is the total sales of all pharmaceuticals on the market and i = 1,2,...,n. The variable $P_j = \prod_{j \neq i} p_j^{sj}$ is the Stone-weighted (Cobb-Douglas) price of pharmaceutical j. Prices p_j for all j =1,2,...,n were defined above. The unknown parameters η_i, θ_i and δ_{ij} are estimated from the data.

Both the bottom-level and the top-level equation are estimated using the seemingly unrelated regression (SUR) method. We add stochastic terms u_i and v_i to equations 1) and 2), respectively, and estimate both equations simultaneously for all pharmaceutical products i = 1,2,...,n. First, we assume that error terms u_i (and v_i) are correlated across n equations. If the data do not support this assumption, each equation is estimated separately using the OLS method.

The model allows the derivation of conditional and unconditional demand elasticities. Conditional elasticities can be derived from the bottom-level equation by assuming that the total revenue of pharmaceutical i is fixed. In the derivation of unconditional elasticities, on the other hand, the revenue of pharmaceutical i is allowed to change when the prices of pharmaceuticals change.

Conditional and unconditional elasticities can be derived from the bottom-level and top-level equations. The conditional (revenue r_i is kept fixed) own-price elasticity of the demand for branded pharmaceutical i is given as:

9) $$(\partial q_{ib}/\partial p_{ib})(p_{ib}/q_{ib}) = (1/s_{ib})(-\beta_i s_{ib} + \gamma_{ib}) - 1$$

Other conditional elasticities (such as the conditional cross-price elasticity of the demand for branded pharmaceutical i with respect to the price of generic pharmaceutical i) can be similarly derived. Table 1 displays conditional elasticity equations.

Table 14. Conditional elasticity formulas

	p_{ib}	p_{ig}
D_{ib}	$(1/s_{ib})(-\beta_{ib}\, s_{ib} + \gamma_{ibb})$ -1	$(1/s_{ib})(-\beta_{ib}\, s_{ig} + \gamma_{igb})$
D_{ig}	$(1/s_{ig})(-\beta_{ig}\, s_{ib} + \gamma_{ibg})$	$(1/s_{ig})(-\beta_{ig}\, s_{ig} + \gamma_{igg})$ -1

In Table 14 it holds true that $\beta_{ib} = -\beta_{ig}$, $\gamma_{ibb} = -\gamma_{ibg}$, $\gamma_{igb} = -\gamma_{igg}$.

Unconditional elasticities can be derived by allowing the revenue of pharmaceutical i to change when prices change. The unconditional own-price elasticity of the demand for branded pharmaceutical i is given as:

10) $$(\partial q_{ib}/\partial p_{ib})(p_{ib}/q_{ib}) = (1/s_{ib})(\beta_i\, \delta_{ii}\, s_{ib} + \gamma_{ib}) + s_{ib}(1+ \delta_{ii}) - 1$$

Other formulas for unconditional elasticities can be similarly derived. Table 15, below, displays all necessary equations to be used to compute all own-price and cross-price elasticities.

Table 15. Unconditional elasticity formulas

	p_{ib}	p_{ig}	p_{jb}	p_{jg}
D_{ib}	$(1/s_{ib})[\beta_{ib}\, \delta_i\, s_{ib} + \gamma_{ibb}] + s_{ib}(1+ \delta_i) - 1$	$(1/s_{ib})[\beta_{ib}\, \delta_i\, s_{ig} + \gamma_{igb}] + s_{ig}(1+ \delta_i)$	$(1/s_{ib})[\beta_{ib}(-\delta_i)s_j s_{jb}] + (-\delta_i)s_j s_{jb}$	$(1/s_{ib})[\beta_{ib}(-\delta_i)s_j s_{jg}] + (-\delta_i)s_j s_{jg}$
D_{ig}	$(1/s_{ig})[\beta_{ig}\, \delta_i\, s_{ib} + \gamma_{ibg}] + s_{ib}(1+ \delta_i)$	$(1/s_{ig})[\beta_{ig}\, \delta_i\, s_{ig} + \gamma_{igg}\,] + s_{ig}(1+ \delta_i) - 1$	$(1/s_{ig})[\beta_{ig}(-\delta_i)s_j s_{jb}] + (-\delta_i)s_j s_{jb}$	$(1/s_{ig})[\beta_{ig}(-\delta_i)s_j s_{jg}] + (-\delta_i)s_j s_{jg}$

In Table 15 it again holds true that $\beta_{ib} = -\beta_{ig}$, $\gamma_{ibb} = -\gamma_{ibg}$, $\gamma_{igb} = -\gamma_{igg}$.

6.3 Data

The data that were used to estimate the bottom-level and the top-level equations were provided by National Agency for Medicines in Finland. As explained earlier in Section 4.1, the original data covered 8 ATC groups with 53,674 observations. To estimate elasticities we use data on statins, and from the ATC group C10 we include simvastatins, lovastatins and fluvastatins.

Atorvastatins, pravastatins, rosuvastatins and serivastatins were excluded from the data set, either due to the lack of generic competition or the lack of observations. For

example, in the case of atorvastatins the generic competition took place in the 30th period. The inclusion of atorvastatins in the data set would have restricted the total number of observations to the last 14 periods for all groups. For pravastatins, the generic competitor entered in the 14th period, but market shares only started changing in period 31. Rosuvastatins entered in the 27th period and no generic substitute existed within the study period. Serivastatins lacked generic competition throughout the study period. Liquid drugs were excluded, because these are generally used in hospitals. Ellison et al. (1997) divided consumers into public buyers and hospitals, but it was not possible to divide our data into similar groups of consumers. Quarterly data cover the time period from 1997 to the end of 2007.

The original data contained information about the quantities and sales revenue (in wholesale prices) of pharmaceutical products on the Finnish pharmaceutical market. Prices and quantities were entered for each drug and size of dose in the original data. Following Ellison et al. (1997), we created representative branded and generic pharmaceuticals in each group of statins. This was done by aggregating product-level observations across strength, packet size and dose. Using the market shares of individual pharmaceuticals as weights, we computed weighted prices for representative branded and generic pharmaceuticals.

As a result, for 44 time periods we have for each active ingredient the market share, weighted price, sum of sales, weighted price of DDDs and logarithmic DDDs for branded and generic drugs. The variables are presented and defined in Table 16 below.

Table 16. Variable definitions

Bottom level variables	
ln(r/p)	DDD quantity weighted by market share (revenue/ (log[weighted price ddd]) or Cobb-Douglas price
$\ln(p_{ib})$	logarithmic (DDD) price for brand drug i
$\ln(p_{ig})$	logarithmic (DDD) price for generic drug i
Top level variables	
$\ln(q_i)$	Logarithmic sum of sold branded and generic DDDs of drug i
ln(R)	Logarithmic total sales in wholesale prices of branded and generic drug
relprice	Relative price of branded and generic drug for each ingredient
Elasticity tables	
$D(Drug)_i$	Demand for Drug (sim, lov, flu), *i*=b(rand),g(eneric) type, with (column)
$P(Drug)_i$	Price of Drug (sim, lov, flu), *i*=b(rand),g(eneric) type, with (row)

5.4 Results

In the bottom level analysis we estimated the sub-group elasticities using the SUR (seemingly unrelated residuals) method. We concentrated on three groups of statins: simvastatins, lovastatins and fluvastatins. With these groups the SUR estimation could be performed with 41 observations for both generic and branded pharmaceuticals. For comparison, however, we also estimated the bottom-level equation using the data set including data on pravastatins. Below, Table 17 displays the market shares of the branded and generic pharmaceuticals in each group of statins.

Table 17. Market shares of branded and generic drugs

Marketshare	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
branded	43,84 %	19,98 %	36,35 %	27,98 %
generic	56,16 %	80,02 %	63,65 %	72,02 %

The SUR estimates of the bottom-level equation are displayed in Table 18 below. The number of observations decline from 44 to 41, because the branded lovastatin exited the market after the 41st period.

Table 18. Bottom-level equation for the market shares of the branded pharmaceuticals, SUR-GLS

Dependent variable: Market share for branded pharmaceutical, s_b						
	Simvastatins		Lovastatins		Fluvastatins	
	coefficient	standard error	coefficient	standard error	coefficient	standard error
ln(r/p)	-0.20513***	0.02713	0.26471*	0.14992	-0.02575	0.0187952
ln(p_b)	-0.19661***	0.03546	-0.27516***	0.06147	-0.64522***	0.0533402
ln(p_g)	0.19661***	0.03546	0.27516***	0.06147	0.64522***	0.0533402
constant	2.56152***	0.23313	-1.37513	1.10397	0.84556***	0.1375588
N	41		41		41	
Breush-Pagan	15.960***					

*** = statistically significant at 0.01% significance level
** = statistically significant at 0.05% significance level
* = statistically significant at 0.10% significance level

Most of the parameter estimates are statistically significant at reasonable significance levels. The estimate of the parameter β_i for fluvastatins is not significant at the 5 per

cent significance level. Below we also display the SUR estimates using the extended data set, which includes pravastatins. By doing so, most of the parameter estimates are statistically significant at the one per cent significance level, but the number of observations is diminished to 11 quartiles.

Table 19. Bottom level SUR-estimates for Simvastatins, Lovastatins, Fluvastatins and Pravastatins

Dependent variable: s_b								
	Sim		Pra		Lov		Flu	
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.
ln(r/p)	-0,23115	0,009399	-0,28048*	0,120448	-0,85443	0,100213	-0,290272	0,028082
$\ln(p_b)$	0,126102	0,006036	-0,7382	0,065857	-0,56567	0,047643	0,206751	0,053832
$\ln(p_g)$	-0,1261	0,006036	0,738195	0,065857	0,565667	0,047643	-0,206751	0,053832
constant	0,988023	0,03429	1,566075	0,2514	1,445806	0,118754	0,857737	0,052854
N	11		11		11		11	
Breush-Pagan	20,353**							

* = statistically significant at 0.05% significance level
(others statistically significant at 0.01% significance level)

We then estimated the top-level equation 6). Our top-level equation differs from the original model developed by Ellison et al. (1997). We also estimated the original model, but high correlations between the price variables caused most of the parameter estimates to be statistically insignificant. We therefore ended up using the model 6), where instead of log-prices we use relative prices in the log form. The top level estimates are presented for simvastatins, lovastatins and fluvastatins. The number of pharmaceuticals used in the estimation also determines the number of unconditional elasticities that needs to be calculated. Results of estimation are listed in Table 20 below.

Table 20. Top-level level SUR-estimates for Simvastatins, Lovastatins and Fluvastatins

Dependent variable: ln(q)						
	Simvastatin		Lovastatin		Fluvastatin	
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.
ln(R)	1, 317383***	0,042761	0,193839***	0,040733	0,965664***	0,082021
relprice	-1,264538***	0,020586	-0,67712***	0,103468	1,38917***	0,07997
constant	3, 68488***	0,380569	12,58726***	0,358203	5, 859844***	0,716624
N	41		41		41	
Breush-Pagan	17,652***					

*** = statistically significant at 0.01 significance level

Conditional elasticities

Table 21 displays the estimates of conditional elasticities. Diagonal elements in Table 21 display the own-price elasticities of the branded and generic pharmaceuticals. To pick one example, the estimated own-price elasticity of the branded version of simvastatins is -1.116. Off-diagonal elements, on the other hand, are cross-price elasticities. For example, the estimated cross-price elasticity of the demand for branded simvastatin with respect to the price of generic simvastitin is 0.451.

Table 21. Conditional elasticities, standard errors† in parenthesis

	$PSim_b$	$PSim_g$	$PLov_b$	$PLov_g$	$PFlu_b$	$PFlu_g$
$DSim_b$	-1.116*** (0.08078944)	0.451*** (0.04586175)				
$DSim_g$	0.183 (0.12771032)	-1.712*** (0.07249733)				
$DLov_b$			-1.909*** (0.05116654)	0.289 (0.3397511)		
$DLov_g$			0.678*** (0.03817454)	-1.216*** (0.25348104)		
$DFlu_b$					-2.069*** (0.10208379)	1.112*** (0.08395544)
$DFlu_g$					1.535*** (0.14660634)	-2.597*** (0.12057154)

† = standard errors are computed using the delta method
*** = statistically significant at 0.01 significance level
** = statistically significant at 0.05 significance level
* = statistically significant at 0.1 significance level

From Table 21 we notice that all calculated elasticities are reasonable, assuming that pharmaceuticals containing the same active substance are substitutes. Estimated elasticities are also statistically significant at the 1 per cent significance level. Branded simvastatins have the smallest own-price elasticity, while lovastatins and fluvastatins have higher elasticities. Fluvastatins have the highest cross-price elasticity.

Unconditional elasticities

When considering the unconditional elasticities, we allow the price change of one pharmaceutical to also affect the demand for pharmaceuticals containing other active pharmacological substances. The change in the price of the branded version of fluvastatins may affect the demand for the branded or generic simvastatins. This was not possible in the cases of conditional elasticities, where a price change is assumed to only influence the demand for pharmaceuticals containing the same pharmacological substance.

Table 22 displays own- and cross-price elasticities of demand for the branded and generic pharmaceuticals in each group. For the three groups of statins, there are 36 elasticity estimates in total.

Table 22. Own- and cross-price unconditional elasticises of demand

	$PSim_b$	$PSim_g$	$PLov_b$	$PLov_g$	$PFlu_b$	$PFlu_g$
$DSim_b$	-1,224	0,383	0,062	0,082	0,100	0,070
$DSim_g$	-0,065	-1,869	0,141	0,190	0,231	0,161
$DLov_b$	0,421	0,266	-1,685	0,589	0,131	0,091
$DLov_g$	0,140	0,088	0,752	-1,116	0,043	0,030
$DFlu_b$	-0,510	-0,322	-0,097	-0,130	-0,722	2,050
DFlug	-0,566	-0,358	-0,108	-0,145	3,032	-1,555

The results in Table 22 suggest that own-price elasticities in the diagonal are reasonable, but some of the cross-price elasticities have unexpected signs. For example, the demand for generic simvastatin increases when the price of branded simvastatin increases. The own-price elasticity of the branded fluvastatin is negative, as expected. The cross-price elasticities for simvastatins with respect to the prices of lovastatins and fluvastatins are positive. This also applies to lovastins. Cross-price elasticities of fluvastatins, however, behave oddly. This could be because certain groups of statins were left out of the top-level analysis.

6 Assessing the effect of the RP policy on pharmaceutical expenditures

According to the literature review (see Appendix), in countries that have adopted the RP policy the prices of pharmaceuticals have decreased by from 10% to 29%. We use this finding, estimated unconditional elasticities in Table 22 and formula 6) to predict the expenditure effects of the reference pricing policy in the Finnish pharmaceutical market. The estimated reduction in pharmaceutical expenditures is based on the price-elasticity estimates of simvastatins, lovastatins and fluvastatins.

Equation 6) can be used to estimate the change in pharmaceutical expenditures when elasticities and the relative change in prices are known. According to our data, the total sales of simvastatin, lovastatin and fluvastatins were €6.25 million. If the RP were to reduce the prices of pharmaceuticals by 100 per cent, the corresponding reduction in pharmaceutical expenditures (according to equation 6) is €3.4 million. Therefore, a 10% reduction in pharmaceutical prices would reduce the total pharmaceutical expenditures on simvastatins, lovastatins and fluvastatins by €337 000. This is approximately 5.38% of the total expenditures (€6.25 million).

In Table 23 we assume that the reference pricing policy reduces drug prices by 10, 20 or 30 per cent and compute the corresponding reduction (in relative terms) in pharmaceutical expenditures. The obtained estimates are based on elasticities in Table 22 and equation 6).

Table 23. Estimated savings on pharmaceutical expenditures with reference price system

The effect of the RP on prices of pharmaceuticals	The relative reduction in pharma-ceutical expenditures
10 %	5,38%
20%	10,77%
30%	15,61%

If we assume that all pharmaceuticals have similar elasticities and demand structures to simvastatins, lovastatins and fluvastatins, the above results in Table 23 can be generalized to all pharmaceuticals in Finland. We admit that such an assumption is too strong to be made. We therefore emphasize that there is a need for further research that could produce a more general picture of the demand structure in the pharmaceutical market in Finland.

7 Final evaluation

The impact of reference pricing in other countries: literature survey

i) Effects on prices

The empirical evidence is consistent with the prediction of price drops following the introduction of RP. In fact, initial price reductions have been reported in all countries where RP has been introduced, and price differences between brand name drugs and generics have generally been reduced. This effect is a short-term undisputed impact of the RP system. The long-term effects of RP on prices are more ambiguous, partly because the empirical literature on the topic does not really exist, the only exception being Danzon and Ketcham (2003). If the RP is not changed by government intervention, no firm will have the incentive to lower the RP. In the long term, the effects of the RP are therefore likely to be nill. For this reason, many governments have often intervened by arbitrarily reducing the RP.

ii) Effects on quantities and total expenditure

According to the results reported in a systematic review for the Cochrane Collaboration by Aaserud, Dahlgren, Kosters, Oxman, Ramsay and Sturm (2008), the average effect on drug use six months after the transition period following the introduction of RP is a relative increase in the level of use of referenced drugs, estimated to be between 87% and 251%, and a relative decrease in the level of use of cost-share drugs estimated at between -35% and -41%. The authors also report that the average effect on drug expenditures six months after the transition period following the introduction of RP is a relative decrease estimated between -18% and -47%, and that the associated savings in drug expenditures are estimated to lie between a relative decrease of -3% and a relative increase of 48%.

The estimated effects strongly depend on the type of RP under analysis. In generic referencing, where RP only applies to off-patent chemicals, the literature shows a slow but constant reallocation of the demand towards products still under patent protection. It is not clear, however, how much of this replacement is actually due to RP.

In therapeutic referencing, on the other hand, it is logical to expect consistent savings in public/private expenditure, but no real effect on the overall number of prescriptions can be expected *ex ante*. The wide range of results also reflects the lack of clear-cut evidence.

Although the lack of more formal approaches does not represent a problem when the outcome is price, quantities and expenditure are more difficult to evaluate. First of all, data do not generally show evident breaks in the overall market trends. Secondly, while variations are rare for prices, the variability in quantities is high and in most cases researchers can only rely on few covariates to explain the high levels of variance. Conclusions are thus less robust and self-evident than in the analysis of prices.

iii) Other effects

Besides prices and quantities, the two other main issues considered in the literature are the impact of RP on either the market shares of generics or on patient health. From the literature, generics seem to gain market shares following the introduction of RP. It seems safe to claim that the demand for off-patent products is very elastic (in most situations, brand-name prices high above the reimbursement level have been associated with evident drops in market shares). There is no evidence that RP affects patient health.

If the clusters in RP are narrowly defined (e.g. generic referencing), the application of the RP policy should not affect the natural flow of pharmaceutical innovation. On the other hand, therapeutic referencing might create a strong disincentive for the launch of new products.

The impact of generic substitution on competition, prices and total expenditures: data analysis

Generic substitution has increased competition in pharmaceutical markets. The markets here were defined as markets of pharmaceutical active agents, i.e., drugs with same active agents were assumed to compete with each other. Before the implementation of generic substitution, there were already more firms in the markets for those pharmaceuticals that later became substitutable in 2003 than in the markets for those that were left outside the substitution system. The number of firms in substitutable markets has increased by between 1 to 2 firms per active pharmaceutical agent, whereas the average number of firms was 2.5 at the beginning of 2003. There has been no change in the number of firms in markets outside the substitution system.

The prices of pharmaceuticals that became substitutable in 2003 were higher before the implementation of the substitution reform than the prices of non-substitutable pharmaceuticals. Generic substitution dramatically lowered the prices of substitutable pharmaceuticals, by about 60 per cent at the end 2007. Analysis of the causes of this change faces some difficulties, because the variables measuring the change in competition and the direct (behavioural) effect of the generic substitution reform are correlated. When the direct effect of the reform and the competition effect of the reform on prices are estimated separately, it seems that most of the price reductions can be explained as a direct effect of the generic substitution reform. This direct effect consists of changes in the pricing behaviour of firms and the behaviour of doctors and consumers in prescribing and buying pharmaceuticals. A smaller part of the change is caused by increased competition.

The price elasticities were estimated using pharmaceutical data on statins. Here it was assumed that statins all act as potential substitutes for each other. The price elasticities were estimated using orthodox demand analysis modelling. The estimated price elasticities generally behave in the expected way. The absolute values of the price elasticities are low, and thus we can expect that the total expenditures on pharmaceuticals decrease when the prices of pharmaceuticals decrease.

A summary of the results:

According to the literature survey, the reference pricing systems have caused a reduction of 10 to 29 per cent in pharmaceutical prices in other countries.

According to the results of this empirical study, we estimate that the new reference pricing system in Finland will reduce the prices of pharmaceuticals by between 10 and 30 per cent, and the total expenditure on pharmaceuticals by between 5 and 16 per cent.

Evaluation of the effects of reference pricing is difficult for two reasons: Before the implementation of the reference pricing system, generic substitution was introduced in Finland, and has already caused similar effects to those that would have oserved with the reference pricing system. Secondly, a large proportion of the changes caused by generic substitution seem to have resulted from changes in the behaviour of firms, doctors and consumers as a direct consequence of the reform, and not via increased competition. It is difficult to estimate *ex ante* these changes, because at the moment we know too little about the pricing strategies of the pharmaceutical companies, as well as doctors' prescribing practices, to be able to competently estimate the magnitude of the changes caused by pharmaceutical regulation schemes.

References

Berry, S. and P. Reiss (2008), Empirical Models of Entry and Market Structure in Armstrong M. and R.P. Porter (eds.) Handbook of Industrial Organization, Vol. 3, Elsevier, Amsterdam.

Ellison, S.F, I. Cockburn, Z. Griliches, J. Hausman (1997), Characteristics of demand for pharmaceutical products: an examination of four cephalosporins, RAND Journal of Economics, 28(3), 426-446.

Danzon, P.M. (2001). Reference Pricing: Theory and Evidence. The Wharton School University of Pennsylvania, Mimeo.

Danzon, P.M. and Ketcham, J.D. (2003), Reference Pricing of Pharmaceuticals for Medicare:
Evidence from Germany, the Netherlands and New Zealand, NBER Working Paper Series, WP 10007, http://www.nber.org/papers/w10007

Frank, R. and Salkever (1992), Pricing, patent loss and the market for pharmaceuticals, Southern Economic Journal, 59, 165-179

Kanavos, P. and U. Reinhardt (2003), Reference Pricing for Drugs: Is It Compatible With U.S. Health Care, Health Affairs, May/June 2003.

Lopez-Casasnovas. G. and J. Puig-Junoy (2000), Review of the literature on reference pricing, Health Policy, 54, 87-123.

Paldan, M.,K. Hartikainen-Herranen, E. Kostiainen and T. Voipio (2004), First year of generic substitution, Finnish Statistics on Medicines 2003, National Agency for Medicines and Social Insurance Institution, Helsinki.

Rajaniemi, S. (2004), Pharmaceuticals Pricing Board and reasonable wholesale prices, Finnish Statistics on Medicines 2003, National Agency for Medicines and Social Insurance Institution, Helsinki.

Salop, S. and J. Stiglitz (1977), Bargains and Ripoffs: A Model of Monopolistically Competitive Price Dispersion, Review of Economic Studies, 44, 493-510.

Scott-Morton, F. (2000), Barriers to entry, brand advertising, and generic entry in the U.S. pharmaceutical industry, International Journal of Industrial Organization, 18, 1085-1104

Stakes (2007), Health Care Expenditure and Financing in 2006

Tirole, J. (1988), The Theory of Industrial Organization, MIT Press, Cambridge, Massachusetts

Viscusi, W.K., J.E. Harrington, Jr. and J.M. Vernon (2005), Economics of Regulation and Antitrust, 4th ed., MIT Press, Cambridge, Massachusetts.

Economic Effects of Reference Pricing in Pharmaceutical Markets: A Literature Review

October 2008

***EconMetrixLab* Report 0108**

Prepared for

Department of Health Management and Policy, University of Kuopio
Finnish Government Institute for Economic Research

Financed by

Finnish Ministry of Social Affairs and Health

Written for *EconMetrixLab* by

Matteo M Galizzi
Simone Ghislandi
Marisa Miraldo

Table of Contents

1. Models and predictions by economic analysis

Even though the existing literature on Reference Pricing (RP) has been mainly empirical, some authors have contributed to the analysis through the development of theoretical frameworks.

The existing literature seems to point towards the conclusion that the effectiveness of RP in enhancing competition and controlling expenditure ultimately depends on a series of context specific factors such as demand elasticity, market structure, degree of differentiation of the pharmaceutical sector, timing of implementation and reference price rule. Despite being theoretical contributions many of these models draw on a series of assumptions, often country specific, and therefore results should not be generalized.

The majority of the literature has focused on analysing the effects of reference pricing on firms pricing strategies and market shares by considering off patent drugs where branded and generic drugs compete.

In the work by Mestre-Ferrandiz (2003), the author compares the impact of a reference price and a co-payment system in the pharmaceutical market with generic competition. Using a horizontal differentiated model where two firms compete *á la Bertrand*, the author concludes that, just for a specific reference price level, the reference price policy can control pharmaceutical expenditure by reducing drug prices. In more detail, the author analyzes the effects of introduction of RP in Spain and studies a market composed by two horizontally differentiated duopolists, where the patent of the active ingredients for the branded good has already expired and a generic alternative exists in the market. The author assumes that in the market there exists a continuum of consumers of the same type facing either a co-payment regime or a RP scheme. Under a co-payment regime, consumers pay a co-payment irrespective of what drug they buy, generic or branded while under the RP scheme consumers face a different situation. In fact, if they decide to buy the generic good, they still have to pay the co-payment, while if they decide to buy the branded drug, they have to pay a proportion of the RP plus the difference between the price of the branded good and that proportion. The author finds that RP can achieve the two envisaged objectives of reducing prices and public pharmaceutical expenditure only if RP is set in a certain interval, where both gross and net prices are lower for both products. The author also finds that, even though demand is higher for the branded product and lower for its generic alternative in this interval, total demand is higher under RP. The author finds, however, that profits for the generic producer can be unambiguously reduced if the RP is set anywhere in this interval and that the greater the value of the proportion of the RP to be paid by consumers, the more costly it would be to finance branded goods and the cheaper to finance generics.

Merino Castellò (2003) analyzes a vertical differentiation model with two firms operating in the market: one firm produces the brand-name drug whose patent has already expired, while the other produces the corresponding generic version of the branded drug. The author assumes a two-stages game where, in the first stage, firms choose the perceived quality of the good they want to produce and, in the second stage, a competitive process occurs where firms set prices. The author also assumes that, at each stage of the game, firms make their decisions about quality and prices either simultaneously or sequentially, so that four scenarios can be analysed. The quality game is solved by taking into account two different assumptions about the timing of the game: branded copies or "me-too" drugs enter the market simultaneously with the original product while generic drugs enter the market after the patent on the corresponding brand-name drug has already expired. The author solves the price-setting sub-game by assuming either Bertrand or Stackelberg competition. The author finds that, under the RP system, branded drug producers decrease prices substantially in order to adapt to the new competitive situation while generic prices remain more or less constant. The author also finds that in Bertrand models, market shares do not change after the introduction of RP, while in Stackelberg models, the market share of the branded drugs even increases and that of generic drugs decreases. Furthermore, results show that in both cases, the branded drug producers compensate for the decline of profits by selling greater quantities instead of charging higher prices.

On a broader set-up, a couple of other papers analyse the impact of RP on market structure.

Cabrales (2003) aims at explaining through a formal model the tendency of regulation to generate higher market shares for the higher-priced versions of a product. The author proposes a multi-stages duopoly model of vertical product differentiation in which, first, the government announces a price ceiling, such as a RP scheme. The firms, then, set a level of "perceived" quality for the product and, finally, compete in prices, taking into account the price ceiling set by the government. The author finds that the lower the RP-like price ceiling, the higher the market share of the higher-priced variety. The author also notices that such a result is independent of the parameter values of the model capturing the size and variety of tastes in the market and the size and convexity of the costs of producing perceived quality. The author suggests as intuition behind the result stated above the fact that market shares depend on the ratio of the price ceiling to the high quality, but the quality responds to the price ceiling less than proportionally, due to the convexity of the costs of quality.

Miraldo (2007) within a horizontal differentiation model, where duopolists compete non-cooperatively on a quality-then-price game, analyses the relative effects of reference pricing and co-payment reimbursement on firms pricing and quality strategies as well as on market coverage under different market structures: competitive market, local monopolies and exogenous full market coverage. In the general set up with

consumers in the market that might opt out from not buying any of the drugs the author shows that by comparing co-payment with reference pricing neither reimbursement policy can be assumed to be always unambiguously superior in terms of pharmaceutical expenditure control, quality and market coverage under any market structure. Even if drugs prices are lower under one particular policy, this might arise at a high welfare cost if quality or market coverage vary negatively by the introduction of such a policy. Within the set-up where the market is exogenously fully covered, the author has shown that the reference pricing is nested in the co-payment system, and therefore RP is equivalent, in terms of prices and qualities, to a system where there is no reimbursement. The only role of reference pricing is acting as "reimbursement ceiling" for the third party payer. Therefore, the author concludes that, contrary to the co-payment rate, reference price can not be used as a regulatory instrument for the determination of prices, qualities or for market coverage.

Miraldo (2008) goes one step further with respect to these contributions by assuming that reference pricing is endogenously obtained as a function of firms pricing strategies and by assuming that firms are non-naive in the sense that they anticipate the impact of their strategies on reference price calculation. By considering weak substitutability between drugs within a horizontal and vertical differentiation framework the author studies the impact of different reference pricing formulations on firms pricing strategies, market coverage, public and private expenditure. In particular, the author considers two reference pricing rules: (i) reference price as the minimum of the observed prices in the market, (ii) reference price as a linear combination of firms' prices. Results show that under the "minimum policy" firms are not able to coordinate on higher prices while the "linear policy", implicitly, provides a coordination device. Also, relatively to the "linear policy", when the reference price is the minimum of observed prices, after policy implementation, total and private expenditures are higher and consumer surplus and firms' profits are lower. With quality differentiation both the minimum and linear policies unambiguously lead to higher prices.

In the same line, another bulk of research considers the impact of reference price by explicitly modelling the criteria used to define the product clusters to which different reference price rules apply.

Brekke, Konigbauer and Straume (2007) analyze the effects of RP systems for pharmaceuticals, focusing on a specific therapeutic market with potentially three firms. Two of the firms offer horizontally differentiated brand-name drugs. One of these drugs is off-patent and faces competition from a generic version offered by a third firm. The other drug is on-patent and will be introduced in the market if the profits are sufficient to cover the entry costs. Within this framework, the authors compare three scenarios: one with no RP (NRP), one with a generic RP (GRP) and one with a therapeutic RP (TRP). The authors find that TRP triggers competition most, resulting in lower equilibrium prices for every drug in the therapeutic market. The authors also find that GRP distorts drug choices most, resulting in a higher level of patient health risks,

measured in terms of aggregate mismatch costs, than the other two reimbursement systems. Thus the authors argue that TRP is preferable from the perspective of both the third party payer and the patients and notice that such beneficial role of TRP crucially relies on the assumption that the new on-patent drug enters the market. If the market entry costs are sufficiently high, TRP may in fact result in a worse outcome than both GRP and NRP. The authors also argue that TRP may induce pharmaceutical firms to invest more in drastic innovations, not subject to RP, rather than non-drastic innovations, which are likely to be included in a RP group.

Brekke, Grasdal and Holmas (2008) present a formal model on the impact of regulatory regimes on pharmaceutical price setting. The authors consider a therapeutic market with an original brand-name drug facing competition from a generic version, and with consumers partially insured and facing a co-payment when buying a drug. The authors assume that the demand for a drug is decreasing in the co-payment for that drug, but increasing in the co-payment for the alternative drug. The authors also assume that the demand structure is such that the brand-name firm is able to charge a higher price than the generic firm without losing all demand, implicitly meaning that the two products cannot be perceived as perfect substitutes despite being therapeutically equivalent. The authors study two regulatory scenarios. Under a price-cap regulation, the regulator imposes a maximum price that the firms can charge for their products. The authors find that, under such a scenario, there is a positive relationship between the price-cap and the generic price, so that a stricter price-cap directly reduces the brand-name price and indirectly induces the generic firm to lower its price in order to maintain market shares. Under the RP scenario, on the other hand, the pharmaceutical firms are free to set their prices at any level, while the regulator imposes a RP which is the maximum reimbursement for a group of drugs with similar therapeutic properties. The authors notice that, since the RP is set somewhere between the brand-name and the generic price, an effect of the introduction of RP is that a patient demanding a high-priced brand-name drug have to cover the price difference. The authors find higher demand responsiveness to price changes for the brand-name drug and notice. The authors also find that, since RP imposes a higher brand-name co-payment, brand-name demand is also lower for given prices, so that RP introduces an incentive for the branded drugs' firm to lower its price in order to maintain market shares. The authors argue that the incentives for the generic firm under RP are, however, weaker and more ambiguous. The authors notice that, since RP implies a higher brand-name co-payment, shifting consumers toward the generic firm, for the generic firm facing higher demand it may be optimal to increase its price. The authors observe, however, that, since the brand-name firm responds to RP by lowering its price, the net effect on equilibrium market prices is ambiguous. Moreover, the authors find that the ranking of price levels under price-cap regulation and RP is ambiguous.

Only a limited number of research actually recognizes the primary role of physicians as prescribers by analysing the way RP shapes physicians incentives is in line with RP aims.

Zweifel and Crivelli (1996) using a duopoly set-up, have studied the effects of reference pricing on physicians' prescriptions and on pharmaceutical companies pricing strategies. In their model physicians chose between a branded breakthrough and a generic drug. Results show that RP has different effects depending on the type of physicians. Indeed, the authors show that keeping the price above the RP level may induce substitution at least among those physicians who do not give emphasis on whether a drug is breakthrough or not. Those physicians that are considerably concerned with the drug adverse reactions will keep on prescribing the original brand. On the other hand, those physicians that weigh more the effect of decreased consumption due to co-payment, will prescribe more of the generic drug. The authors conclude that, if the share of physicians of the first type is predominant, the optimal strategy will be to price above the RP, even though at a lower level than in absence of RP. Otherwise drug companies will chose prices equal to the RP level. Another important result of the present paper is that the authors analyze the pricing strategies prior to RP, when firms anticipate this policy. The higher the expected RP level the higher the currently optimal price.

Danzon and Liu (1996) by using a *kinked demand model*, analyse the impact of reference price on pricing strategy. In their model, the physician is the decision maker and acts as an imperfect agent to the patients. The authors show that, by considering only effects on incentives of physicians and patients, RP implies a demand curve for the manufacturer that is kinked at the reference price level. Given that for prices above this level demand is very elastic while for prices below this level demand is inelastic the authors show that the optimal strategy for pharmaceutical firms is to set prices at the kink implying, therefore, a decrease in the branded drug prices but an increase in the generic prices.

Finally on the impact on R&D evidence is limited to Bommier, Jullien and Bardey (2006) that study the effects of reference pricing on the innovation effort of pharmaceutical firms. The authors model a dynamic game with three agents: pharmaceutical firms, consumers and a regulatory entity. In a first stage pharmaceutical firms invest in R&D and introduce new molecules or treatments. In a second stage, the regulatory agency and the producers negotiate on prices using a Nash bargaining solution concept. Finally, patients and doctors jointly determine the consumption of drugs. The RP formulation considered by these authors is very specific and consists of assuming that all the drugs in the therapeutic class are sold at the same price and that there are no drugs sold at prices above the official price. Results on the net effect of the uniform pricing rule within a therapeutic class are ambiguous. Indeed, the authors find that if on the one hand a decrease in price due to the production of *me-too* drugs reduces the incentives to create pioneer drugs, on the other, the introduction of *me-too* drugs is delayed, which gives positive incentives to launch pioneers.

2. Empirical evidence on economic effects of RP policies

2.1. Methodology

The reviewed papers are categorized according to three main characteristics. In this short section we explicit these three criteria.

The first choice to be made for an empirical assessment of the impact of the RP policies is the outcome variable to be used for the evaluation. Traditionally, the RP literature concentrates on either prices or quantities, with a frequent extension to the effects in terms of total (public) expenditure. In the following, the existing studies are categorized according to the outcome used for the evaluation. To the mentioned prices and quantities, a further category is added: other effects, i.e. all the outcomes different from prices and quantities (expenditure). Specifically, most of the studies included in this group address two main issues: the effect of the RP on the market structure (e.g. number of generics) and the effects of the RP on patients' health.

The second critical point in every empirical assessment is the country analyzed. Once the analysis moves away from the abstractions of the theoretical models, the knowledge of the specific regulatory framework under analysis is fundamental for the interpretation of the results. Moreover, it should be pointed out that correct statistical analyses rely on the previous identification of all the policy interventions that might have affected treated and counterfactual groups (see below). A well-constructed empirical study must then also include country-specific policy-related covariates in order to capture the effects of policy interventions not directly linked with the RP regulation. In the following, the abovementioned categorization according to the outcomes is enriched by a further distinction by country. In addition, a short country specific description of the RP policy will be included. As a note of caution, however, it must be clear that the description of the regulatory framework is synthetic and referred only to the information needed to interpret the empirical results.

The third important issue in evaluating the empirical literature on RP policies is the methodology used for the analysis. Many studies used only observational graphs on aggregated data, with no formal test. Others exploited the time-series dimension of their dataset, comparing the outcomes before and after the introduction of the RP. The most complete studies also identified a proper counterfactual, generally represented by a category of drugs to which the RP did not apply. Below the general classification of the empirical approaches used in the reviewed studies is described. Each study is then categorized accordingly.

In the following, papers are hierarchically categorized according to the three criteria described above. The general idea is that each of the outcome-section (i.e. prices, quantities, other effects), is self containing, i.e. the reader does not need to refer back to previous parts. For this reason, at the beginning of each country between two and seven

lines of regulatory description are added. This part is repeated each time the country is considered in one of the three different outcome-sections. Each study is also categorized according to its empirical approach, and the category, repeated each time a study is quoted, is specified in parenthesis, next to the year of publication.

2.1.1. Classification of the empirical approaches

The reviewed studies are classified according to their methodological profile in four categories:

DD: The study has a clearly defined time of intervention. The study entails a formal statistical analysis in which the treated group is observed before and after the intervention and compared with a control group, also observed for the same period of time.

BA: The study has a clearly defined time of intervention. The study entails a formal statistical analysis in which the treated group is observed before and after the intervention *but it is not* compared with a control group.

The typical analysis method for DD and BA studies is a more or less complicated linear regression analysis with time and group related dummies. DD represents the benchmark for any policy analysis. BA is a second-best choice, often dictated by data availability. In any case, these two approaches represent by far the most reliable source of empirical results on the impact of the RP.

DES: The study entails basic statistical regression analyses, some descriptive statistics or some data-based case study. In these studies the empirical strategy is not related with the micro-econometric literature on policy impact evaluation, i.e. the analysis is not determined in terms of treatment/control or before/after. Examples of DES studies are hedonic price approaches, price levels as a function of number of firms, but also graphical inspection of novel series of data.

REV: The study reports some empirical evidence from other sources or describes a case-study without novel data. This group includes, among other studies, reviews of existing literature and commentaries on the state of the art of RP policies.

If the effects are strong and clear from, for example, graphical inspection, the DES and the REV methodologies might represent a reliable source of information. It is very critical, however, that the description of the regulatory intervention is complete and that the confounding factors are somehow controlled for.

2.2. Overview of economic effects of RP policies

2.2.1. Effect on prices

General overview. The empirical evidence is consistent with the prediction of price drops following RP introduction. In fact, initial price reductions are reported in all countries where RP has been introduced and price differences between brand names drugs and generics is generally reduced. This effect is a short-run undisputed impact of the RP system.
The long run effects of the RP on prices are more ambiguous, also because the empirical literature on the topic does not really exist (only exception, Danzon and Ketcham, 2003). If the RP is not changed by government intervention, no firm will have the incentive to lower the RP. In the long run, thus, the effects of the RP are likely to be null. For this reason many governments have often intervened by arbitrarily reducing the RP.
In terms of statistical methodology and quality of data, the number of DD and BA studies is high compared to the studies focusing on other outcome measures. The most rigorous studies concentrate on Germany (Pavnick, 2002), Canada (Schneeweiss and colleagues, 2002-2003; Grootendorst and colleagues, 2005-2006) and Spain (Puig-Junoy 2007). The descriptive evidence, however, is not ambiguous and provides a sufficient amount of results that are mostly consistent with each other.

Germany

In Germany the RP was introduced in 1989. Germany applied RP sequentially to different categories of products. Class 1 includes products with the same active ingredient (generic equivalents), Class 2 applies to therapeutically and pharmacologically similar active ingredients, and Class 3 applies to compounds with comparable therapeutic effect, especially combinations. Class 3 RP is rarely applied. The level of the RP is found as a weighted average (cobb-douglas) of existing prices. Pharmacists can not substitute (until 2001).

Zammit-Lucia and Dasgupta (1995; REV) observe that the series of aggregated pharmaceutical data for the period 1988-1992 show that prices of drugs subject to RP decreased, with the exception of those with initial prices below the RP, which increased, and that prices of drugs not subject to RP increased at higher rates.

Maassen (1996; REV) finds that, after the introduction of RP, most producers of brand-name drugs, with very few exceptions, decreased their prices at the level of the RP, while prices of generics on average did not change, even if in some case increased at the level of RP.

Lopez-Casanovas and Puig-Junoy (2001; REV) observe that prices of products subjected to RP decreased by 1.5% in 1991-92 whereas the prices of those not under the RP scheme increased by 4.1%.

Danzon (2001; REV) concludes that evidence from Germany clearly shows that RP has reduced the average price per molecule for drugs under RP, primarily because originator brand prices are reduced to the RP in order to minimize the loss of market share.

Danzon and Liu (1996; DES) observe that pharmaceutical firms respond to the introduction of RP with different pricing strategies according to the demand elasticity for their products. The authors also argue that pharmaceutical firms' best response is to set price at the RP, which generally means a price cut for originator products, where generics that were prices below the RP may raise their prices to the RP. The author's test the above kinked demand model using data on 1989-94 prices and observe that virtually all brand manufacturers dropped their prices to the RP to reduce loss of market share. In the first year, prices were cut approximately by 13% and an additional 2-10% thereafter. Conversely, some lower-priced products either maintained or even raised their prices.

VFA (2000; DES) reports that, between 1992 and 1999, prices of drugs under RP fell by 14%, while prices of products outside RP system and the cost of living increased by 6% and 13%, respectively.

Danzon (2001; DES) observes that in the period January-August 1998 the decrease of -2.1% in the average prices for drugs subject to RP and the opposite increase of 2.5% in the average price of products not covered by RP translated in an aggregate decline in the total average price of drugs of about -0.2%.

Giuliani, Selke and Garattini (1998; DES) study data from official statistics on consumption and average prices per Defined Daily Dose (DDD) (which is the therapeutical daily dose of active ingredient usually taken by a patient for a given pathology) in period 1989-96 for drugs within 8 therapeutic groups: beta-blockers, calcium antagonists, non-opiate analgesics, oral hypoglicemics, NSAIDs, expectorants, coronary dilators and systemic antibiotics. The authors observe that in most cases, each group's average price per DDD declined, predictably, after the introduction of RP and that most brand prices dropped to the RP. In particular, initial levels of average prices per DDD decreased within all the therapeutic groups expect systemic antibiotics and oral hypoglicemics, for which the authors observe a shift towards drug products with more costly active ingredients, not covered by RP.

Pavnick (2002; DD), performs a series of semilogarithmic regressions with the purpose of identifying the effect of the RP policy on prices. She includes two groups of drugs: anti-diabetics and antiulcerants. Data are quarterly observations of prices per Defined Daily Dosage (DDD) for the period January 1986-December 1996. Depending on the therapeutic group and on the estimation specifications, she finds that prices reductions due to the RP policies range between 10% and 26%. Moreover, generic competition seems to play an important role, with prices drops being positively correlated to the number of generics in the market.

Danzon and Ketcham (2003; DES) estimate a hedonic price equation for Germany, the Netherlands and New Zealand. The data used are cross-sectional, so that the only possible estimation strategy is to rely on between groups variation. Authors want to estimate the impact of different covariates on the price per DDD. Among other findings, they show that the number of generics affects negatively the average price, but this reduction is very limited for Germany: prices drop of 1% for each generic entry. Moreover, they find no evidence that the RP is lower for more competitive markets. Authors point out that RP policies, despite being set with the purpose to increase competition, are not actually sensitive to the competitive pressure from generics (because generics have no real incentives to lower their prices below the RP).

The Netherlands

A RP was introduced in 1991. The Dutch RP system included almost all on-patent and off-patent drugs. Classification decisions were made by the Ministry of Health, with input from a panel of medical advisors. The RP level is set as a median of existing prices. In 1996 maximum wholesale price policy was introduced.

Zammit-Lucia and Dasgupta (1995; DES) find no significant impact of the introduction of RP on pharmaceutical prices.

Bloor, Maynard and Freemantle (1996; DES) and Lopez-Casanovas and Puig-Junoy (2001; REV) observe that the initial effect of the first phase of RP introduction was lower prices, by 5% between 1991 and 1993, for drugs under RP, while for those drugs that were not included prices increased by more than 20% per annum since 1988.

However, de Vos (1996; REV) and Dickson and Redwood (1998; REV) point out that prices of drugs covered by RP decreased much less than predicted. It was exactly because of the still high prices in the Netherlands, compared with other Western European countries, that the government decided to implement the Maximum Price Regulation Law on Drugs in 1996.

Danzon (2001; REV) observes that the 1996 Maximum Price Law resulted in price reductions averaging 15%, although with considerable variations across compounds. Moreover, while in January 1996, the average price differences between brand and generic, and between brand and parallel import drugs were 19% and 14.7%, respectively, in 1997 these differences fell to 9.6% and 7.1% due to the Maximum Price Law. The author argues that these small price differences further confirm the lack of aggressive generic price competition in list prices. Moreover, she observes that, whereas the RP system alone led to convergence of list prices at the RP - including price increases for products previously below the RP, according to the kinked demand model by Danzon and Liu (1996) -, the Maximum Price Law forced a greater spread in the prices of different compounds within a cluster. Prices for different products in each compound were bunched at that compound's maximum price and all capped by the RP. Since in 1998, RP were reduced, based on these lower, price-capped prices, in 1999 most firms dropped their prices. The author also observes that the Maximum Price Law and the increased interdependence of markets may change firm's response to the RP scheme with respect to the kinked demand model. In fact, if the Dutch RP is below the pharmaceutical firm's Europe-wide target price, the firm may set its price above RP and may attempt to rebate the difference directly to the patient. The author concludes that RP has reduced prices on branded products, particularly new products, while the Maximum Price Law has presumably further reduced prices of innovative drugs relative to generics.

Danzon and Ketcham (2003; DES) estimate a hedonic price equation for Germany, the Netherlands and New Zealand. The data used are cross-sectional, so that the only possible estimation strategy is to rely on between groups variation. Authors want to estimate the impact of different covariates on the price per DDD. For the Netherlands, they show that the number one generic firm entering the market induces a small (1.6%) reduction in prices. As with Germany, they interpret this finding as evidence of the low long-run effect of the RP policies in absence of further price-cut interventions from the government.

New Zealand

Reference pricing was introduced in July 1993. All reimbursed products are assigned to therapeutic subgroups with similar health effects. Patent status is not considered. New Zealand sets the RP at the lowest price in each subgroup, regardless of patent status. Generic substitution rules permit the pharmacist to substitute generics unless the physician explicitly prescribes the brand.

Klethco, Moore and Jones (1995; REV) and Pharmac (1996; REV), the pharmaceutical public agency which operates the national scheme, consider RP to have been a highly effective and powerful tool, because pharmaceutical firms have tended to lower their

prices to the subsidy level, rather than risking their market shares, and, where prices were not lowered, patients tended to switch to fully subsidized alternatives rather than pay a premium.

Woodfield, Fountain and Borren (1997; REV) observe that, in February 1996, Pharmac introduced the RP scheme in the angiotensin-converting enzyme (ACE) inhibitors. The lowest-priced ACE inhibitor based on Pharmac's weighted average daily cost (WADC) methodology was the market leader, enalapril, which thus determined the subsidy offered to all ACE inhibitors. The prices of ACE inhibitors generally fell to match enalapril's WADC. This seemed consistent with Pharmac's argument that RP stimulates competition among drugs with the same or similar therapeutic effect. But it is also consistent with the author's argument that the competition stimulated by RP may be limited in that there may be no incentive for a company to cut the price of a fully subsidized medicine, particularly when all medicines are fully subsidized. The authors also observe that, in the case of ACE inhibitors, while nearly comprehensive price matching followed the introduction of RP in enalapril, widespread price reductions did not follow the massive reduction by 60% in the price of quinapril. It seems clear that most suppliers were willing to accept a reduction in market share rather than further reducing prices, contrary to the predictions of RP. In the case of leading brands, these market share reductions were very significant, and might have generated lower profits in the New Zealand market compared to price reductions or matching.

Lopez-Casanovas and Puig-Junoy (2001; REV) observe that there is evidence of a downward trend in the real price of subsidized pharmaceuticals prior to the introduction of RP, raising questions such as whether RP was responsible for reducing the price of subsidized drugs more than would have occurred in its absence (there are no DD studies on this country). The authors also observe small average differentials in prices between generics and pioneer brands and argue that RP is not effectively keeping generic price levels low. The authors also report that firms might have set prices above the subsidy level: the price of Roche's anti-inflammatory Naprosyn, for instance, rose 20% between 1995 and 1996.

Woodfield (2001; REV) points out that in until July 1997, the statins were not subject to RP and were fully subsidized. They were also subject to stringent quantity rationing under Pharmac's special authority scheme. Simvastatin had dominated this market, while fluvastatin had almost no penetration. Simvastatin, however, was much costlier to subsidize. In August 1997 a new therapeutic group emerged in the Pharmac RP scheme, comprising fluvastatin, pravastatin and simvastatin. The outcome of RP produced very significant changes. While fluvastatin continued to be fully subsidized at the previous rate, the subsidies for the other two drugs fell dramatically, for instance by 75% for simvastatin 20mg. As a result, the supplier's price for simvastatin was 75% (20mg) or even 129% (10mg) above its respective subsidy level. However, since, according to the authors, some evidence existed that the three statins did not have the same ability to reduce cholesterol to levels recommended for patients with high cholesterol,

prescriptions did not switched away from simvastatin, so that its market share did not radically fall.

Danzon and Ketcham (2003; DES) estimate a hedonic price equation for Germany, the Netherlands and New Zealand. The data used are cross-sectional, so that the only possible estimation strategy is to rely on between groups variation. Authors want to estimate the impact of different covariates on the price per DDD. For New Zealand, results show that one generic firm entering the market induces a significant (15%) reduction in prices. They justify this finding, which is not in line with the results for Germany and the Netherlands, as a consequence of the "requirement that new generic entrants offer a reduction in price and RP as a condition of reimbursement."

Sweden

The RP was introduced in 1993 and dropped in 2002. It was a generic referencing, i.e. it applied only to products with expired patents and generic equivalents (same form, same active substance and same quality).

Jonsson (1994; REV) and Drummond, Jonsson and Rutten (1997; REV) observe that the introduction of the RP scheme resulted in pharmaceutical manufacturers cutting the price of those drugs that were prices above the RP in anticipation of the fact that consumers would not have paid higher prices. Therefore, the prices of brand name products fell close to that of the generics.

Lopez-Casanovas and Puig-Junoy (2001; REV) show that for original prices within the RP scheme, the price, with very few exceptions, dropped to the reimbursement price and that generic prices were reduced to the price of the lowest generic. However, the authors also observe that there was no incentive to set a price lower than that reimbursed and that, therefore, since their prices increased, some products were actually delisted.

Bergman and Rudholm (2003; BA) analyse data from the Swedish Medical Product Agency (SMPA) from 1972 to 1996 for 18 pharmaceutical substances. The authors use an unbalanced data panel consisting of 1184 observations, on prices and quantities sold, each quarter, for the package size with the largest recorded sales volume for each substance. The authors estimate several panel regressions of the price of the brand-name product on product-specific dummies and a set of explanatory variables. The authors find that the Swedish RP system was only effective for products which already faced generic competition at the introduction of the system. The authors estimate that, in those cases, prices fell about 16-21% when the system was introduced. The authors argue that, while the introduction of RP lowered the prices of those incumbent products with faced actual generic competition, the RP system had no effect for products facing only potential generic competition.

Denmark

The RP was introduced in 1993. Products are grouped on the basis of type of pack. All products, which have at least one copy version, including generics and parallel imports, are included. The RP is the average of the two cheapest drugs in the market. Pharmacists have the right of substitution.

Zammit-Lucia and Dasgupta (1995; REV) observe that it is very difficult to discern any single pattern in pricing, even though individual firms seemed clearly they were optimizing their own position, given the specific market conditions surrounding their own products.

Clausen (1995; REV), on the other hand, observes that there is no doubt that the introduction of RP has generally resulted in lower drug prices.

Australia

RP was introduced in 1998. It is a therapeutic RP which applies to six therapeutic categories: H2 receptor antagonists (ulcer), statins, calcium channel blockers, ACE inhibitors, beta blockers (CVD). Pharmacist has the right to generic substitution. RP is the lowest price in the market.

Ioannides-Demos, Ibrahim and McNeil (2002; REV) observe that, after the introduction of RP scheme, for some drug groups, such as the statin group of cholesterol-lowering drugs, all manufacturers reduced prices to a level satisfactory to the government. The patient contribution remained the same as that prior to the introduction of the scheme for medicines at the RP. Patients who chose to stay with a higher priced drug paid an additional average premium of about A$2 (Australian dollars). Only four drugs had a premium greater than A$3: ramipril 2.5 mg and 5 mg, amlodipine 10 mg and cimetidine effervescent tablets. At the time of introduction of the scheme, the costs for 50% of the drugs remained the same. The authors observe that the data from the Pharmaceutical Benefits Analysis Section suggest that price reduction occurred with many therapeutic groups. The average dispensed price of ACE inhibitors on the Pharmaceutical Benefits Scheme was A$31.19 in the 1998 calendar year, compared with A$33.18 in 1997. Similarly, the average dispensed price of calcium channel blocks was A$25.50 in 1998 and A$26.39 in 1997. The category that did not attract a Therapeutic Group Premium, namely the statins, was the drug group with the highest increased cost to the government in 1999-2000.

Canada (British Columbia)

RP was introduced in 1995. Under Type 1 RP, only chemically equivalent drugs are considered interchangeable, either branded or generic versions of the same drug.

Under Type 2 RP, all drugs from the same therapeutic class are considered interchangeable. This therapeutic RP applied to some specific clusters: H2 Antagonists, NSAIDs, ACE inhibitors, calcium channel blockers. Usually the reference for reimbursement is the least expensive product. Generic substitution is allowed.

Schneeweiss, Soumerai, Maclure, Dormuth, Walker and Glynn (2002; BA) analyze monthly data of claims from British Columbia for 24 months before and 12 months after implementation of RP and identify 119074 patients, 65 years of age or older, for whom at least one ACE inhibitor was dispensed between January1995 and June 1998. For each of the 8 ACE inhibitors, the authors determine the median monthly dose (MMD, in mg) dispensed during the 8-month period from November 1995 to June 1996, for patients who filled at least one prescription during a period of 120 days before, and a period of 120 days after the 8-month period. The authors plotted trends over time with 95% confidence intervals and use generalized linear models for repeated measures to estimate sudden changes in trends or levels of ACE inhibitor use after the introduction of RP. The authors' regression models include a constant term, a term for linear time trend before RP and assume autocorrelated covariance structures. The authors find that the RP policy did not appear to produce a systematic change in drug prices per MMD across substances: the mean change was -C$0.15 per MMD, with a standard deviation of C$0.19.

Marshall, Grootendorst, O'Brien, Dolovich, Holbrook and Levy (2002; DD) consider aggregate monthly claims data, from January 1993 to May 1999, for hystamine-2 receptor antagonists (H2RAs), proton pump inhibitors (PPIs), sucralfate, prokinetic agents and misoprostol, from Pharmacare, the publicly funded drug subsidy program for seniors and various other residents of British Columbia. The data included the numbers of prescriptions and unit doses dispensed, the costs reimbursed by Pharmacare and the payments made by the beneficiaries. The authors analyzed claims data only for patients 65 years of age or older. For both H2RAs and PPIs, expenditure trends observed in the first 3 periods were estimated with regression models and then projected forward to predict the expenditures that would likely have accrued in the absence of policies. For all periods analyzed, the mean reimbursement by Pharmacare per defined daily dose (DDD) of restricted H2RAs fell from C$0.98 to C$0.76 between the baseline period and the 12-month period after the RP policy went into effect, but remained above the RP because some restricted H2RAs were still reimbursed at full cost for beneficiaries who had been granted exemption from the policy. In the same time interval, reimbursement by Pharmacare per DDD of all H2RAs fell by more than half, from C$0.85 to C$0.40, which reflected both the shift to greater use of generic cimetidine and the declining reimbursement per DDD of restricted H2RAs. In contrast, reimbursement by Pharmacare per DDD of PPIs and other gastrointestinal drugs, such as cisapride, did not change appreciably.

Schneeweiss, Soumerai, Maclure, Dormuth, Walker and Glynn (2003; BA) select a cohort of 35886 patients, 65 years of age or older, who received a dihydropyridine calcium channel blockers (DCCBs) between December 1995 and March 1996. The authors define median monthly doses (MMDs) for each of 4 DCCBs as the median of all doses dispensed per month in mg averaged over a 8-month period starting on November 1995. The authors plot time trends as MMD dispensed per 10000 patients with 95% confidence intervals, and use generalized linear models for repeated measures to estimate sudden changes in trends or levels of DCCB use after the introduction of RP. To compare utilization trends, the authors use a longitudinal repeated-measures design with individual-level data over 42 monthly observations. The authors find that the RP policy did not appear to produce a systematic change in drug prices per MMD across substances: the mean change was -C$0.80 per MMD, with a standard deviation of C$0.60.

Grootendorts, Marshall, Holbrook, Dolovich, O'Brien and Levy (2005; BA) consider monthly data over the period February 1993 to June 2001 from retrospective population-based claims, to examine patterns of drugs' prices under the application of RP by Pharmacare, the publicly funded drug subsidy program for seniors and various other residents of British Columbia. The authors consider the application of RP to the nonsteroidal antiinflammatory drugs (NSAIDs). The authors observe that Type 2 RP appeared to have a substantial effect on reimbursement prices: Pharmacare expenditure per day of dispensed NSAIDs dropped by almost half, from C$0.80 to C$0.44. By contrast, Type 1 RP had a much smaller effect on prices. The authors also find that prior to the introduction of RP, the unrestricted NSAIDs cost Pharmacare C$0.23 per day, whereas the other NSAIDs cost up to six times as much. Whereas, after the introduction of Type 1 RP such a difference reduced only marginally, after the introduction of Type 2 RP and the delisting of various NSAIDs in November 1996, the restricted NSAIDs cost about four times more than the unrestricted ones. The authors also find that there is no evidence that RP increased retail prices of either the unrestricted or restricted drugs.

Grootendorst and Stewart (2006; DD) critically assess the identifying assumption inherent in the "before and after" (BA) design, namely that pre-RP trends accurately predict counterfactual outcomes. The authors estimate the impact of RP on *expenditure* on ACE inhibitors and calcium channel blockers (CCBs) by Pharmacare, the publicly funded plan for seniors and various other residents of British Columbia. The authors also use similar data from a public plan in Ontario (Ontario Drug Benefit plan) that had not introduced RP, to estimate the effects on drug expenditures of patent expiration, secular changes in prescribing patterns and various other factors common to all Canadian public drug plans that could potentially confound the BA estimates of the effect of RP on drug plan expenditures. Using monthly data from January 1994 to December 2000, they find that average monthly reduction on the reimbursement price in the post-RP period was C$0.07 for ACE inhibitors and C$0.08 for CCB, about half the BA estimates by previous studies (see for instance the study above by Schneeweiss, Soumerai, Maclure, Dormuth, Walker and Glynn, 2003). The authors suggest that pre-

RP expenditure trends for CCB are likely biased counterfactual estimates and that part of the reduction in the daily cost of dispensed therapy is likely due to factors other than RP.

Spain

A RP system was effectively introduced in Spain in December 2000. This system is applied to off-patent drugs with the same active ingredient. Initially, the RP was 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 sales.

Puig-Junoy (2007; DD) aims at evaluating the intended and unintended impact on pharmaceutical use and volume of sales of the Spanish generic RP system for statins. The author develops a DD analysis of 46 monthly drug use and volume of sales ratios, from January 2001 to October 2004, valued at regulated ex-factory prices. Data are from IMS, a marketing research company, and from the centralized National Health System pharmaceutical consumption database of the Spanish Ministry of Health. The author observes that brand-name lovastatin and simvastatin and their generic substitutes, with a price higher than the RP, immediately reduced their price to the RP, after its introduction. The introduction of RP system tends to decrease the price of the original drug relative to the price of generics. Moreover, the author observes that 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. Furthermore, the author finds that the price of all products already on the market before the introduction of RP with a price equal to, or lower than, the RP 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. Finally, the author notices that RP was not effective in reducing the consumer price of products with a price initially below the RP and that 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 RP level. The author concludes that price decline for brand-name and generic products was not clearly explained by variation in their exposure to competition, and only depended on arbitrary regulatory decisions as to the period for which the product was covered by the RP system and the moment at which the RP was revised.

Ubeda, Cardo, Selles, Broseta, Trillo and Fernandez-LLimos (2007; BA) describe the evolution of antidepressant use in primary care in the Valencian region from 2000 to 2004 and analyze the effects of the introduction of RP and generic drugs on drug utilization and cost saving. The authors analyze the prescription pattern of antidepressants using sales collected for the period 2000-04, converted into DDD per 1000 inhabitants according to the methodology by the WHO Centre for Drugs Statistics. The authors observe that the implementation of RP forced the prices of the original brand to lower. For instance, the price of the original fluoxetine (Prozac capsules) that,

prior to RP, was about €1.07, in 2004 decreased to a similar cost/DDD of generic capsules, about €0.4: the reduction of cost was not evident until the beginning of 2001 (€0.89), and was specially marked in 2004, when it reached €0.58. The authors notice that, generally, most consumed branded antidepressants (paroxetine, fluoxetine, citalopram) suffered similar price reductions due to the generic competition, together with an implementation of RP, although this was not the case for other pharmaceutical forms: for instance, the fluoxetine orally disintegrating tablets maintained a cost/DDD rate of €0.83.

Italy

In Italy the RP was introduced in December 2001. It applies to off-patent drugs only (same dosage, same pack). The RP is the minimum price in the market. Pharmacists are allowed to substitute.

Ghislandi, Krulichova and Garattini (2005; DES) show data on prices and volumes from January 2001 to April 2003 for the commonest packs of the top three active substances in terms of revenue, with at least one generic version: tipoclidine, nimesulide and ranitidine. The authors observe that in all three products prices clearly tended to fall, and that, in particular, there were steep drops for nimesulide and ticlopidine at the end of 2001, when the reimbursement limit was redefined, while ranitidine prices started falling at the beginning of 2002, after the launch of the first generic.

Belgium

The RP was first introduced in 2001. It is a generic referencing, i.e. the RP applies to drugs with the same active compound. The RP is initially set 16% lower than the branded product's price. Over time, the Belgian government has progressively reduced the level of the RP. Generic substitution is allowed.

Simoens, De Bruyn, Bogaert and Laekeman (2005; DES) analyze data on general trends and on evolution of particular drug classes. The former data are from IMS Health Belgium and relate to drug consumption of a representative panel of 2550 community pharmacies, about 50% of all Belgian pharmacies. The latter data are from Ifstat database, which brings together data on reimbursable drugs transmitted by community pharmacies to the third-party payer for the purpose of reimbursement. The authors observe that manufacturers of original drugs have reacted to the introduction of RP scheme in several ways. The authors notice that, as the RP scheme financially penalised patients from purchasing the more expensive original drugs, some pharmaceutical

companies reduced prices of original drugs in return for the abolition of prescribing conditions. In particular, the authors observe that, in these cases, the agreement to reduce the price of the original drug was accompanied by a switch of the drug from "Chapter IV" regulation, meaning that prescription required a priori approval by a physician from a health insurance find, to "Chapter I" regulation, implying unconditional prescription. The authors notice, for example, that this was applied to Zocor, the leading brand-name simvastatin.

Hungary

The first version of the RP was introduced in 1999. It was a generic referencing (i.e. RP applies to drugs with the same chemical). In 2003, a therapeutic referencing (i.e. RP applies to a cluster of chemicals) was introduced for some groups (including statins). The RP is the cheapest drug with a cumulative market share of 50%.

Kalò, Muzbek, Bodrogi and Bidlò (2007; DES) analyze the Hungarian experience in introducing a therapeutic RP for statins in September 2003. The authors use as baseline period August 2003, the last month before the introduction of RP, and compare the average ex-factory and public prices, reimbursement level, patients' co-payment and DDDs of prescribed units of statins with the ones in March 2004, using an IMS Health database built on sales reports of pharmaceutical wholesalers. In order to separate the impact of therapeutic RP from the generic RP and the decreased patient co-payment, the authors employ a time series analysis with the assumption that simvastatin price erosion was the sole consequence of generic RP, and estimated the impact of generic price erosion by deducting the potential expenditure on simvastatins, that is numbers of simvastatin prescriptions multiplied by their original prices, from the actual expenditure over the investigated period. The authors calculate the impact of therapeutic RP based upon dividing total ex-factory market growth by the impact of unit growth and generic price erosion, while calculate the budget impact of increased reimbursement, generic price erosion and therapeutic RP by comparing the relatively homogenous period of September 2003-March 2004, with February 2003-August 2003. The authors find that the main expected benefit of RP was the incentive for manufacturers to reduce the prices of original products. The authors find, however, that the price of patented original products (atorvastatin and fluvastatin) remained constant, and did not change even beyond the investigated period either, except temporarily during the government-decreed 15% price cut period between April and June 2004. The authors also notice that as a result of price per DDD reimbursement, higher doses of the same substance became cheaper for the patients after the introduction of RP. Despite significant generic price erosion of simvastatin, the average unit price of statins was reduced by only 3.1% over 7 months after the introduction of RP.

Norway

A version of the RP was introduced in 2003 for a sub-sample of off-patent drugs already facing generic competition in six chemical substances targeted for depression, anti-ulcer, allergy, high blood pressure and nigh cholesterol. It was a generic a therapeutic referencing (i.e. RP applies to a cluster of chemicals). The RP is an index price calculated as the sales-weighted sum of producer prices included in each sub-group. The government decided to terminate the system at the end of 2004.

Brekke, Grasdal and Holmas (2008; DD) use a dataset from Farmastat providing information, over the four-year period from 2001 through 2004, on sales value (in pharmacy purchase price); volume (in DDD) for each package of drugs sold on the Norwegian pharmaceutical market; name, manufacturer, package size, dosage and launch date of each drug; and on whether the product was a brand-name or a generic drug. The authors look at the data on average prices for brand-names and generics for 3 groups of pharmaceuticals: the drugs subject to RP; the drugs which are therapeutic substitutes under the alternative price-cap regulation; and the drugs which are independent in consumption and exposed to price-cap regulation. The authors observe that average prices of the drugs subject to RP displayed a pronounced decrease after the implementation of RP: average price of drugs subject to RP in the pre-regulation period was about NOK 4.7, while average pricing during RP was about NOK 3.3, implying a price reduction of more than 29%. The authors also conduct an econometric investigation to compare inter-temporal variation in prices before and after the implementation of the RP reform, using panel data and a treatment group, for drugs subjected to RP, and a control group for drugs not subject to the RP reform. The authors estimate that the effect of the RP reform was an average price reduction of about 24%, and that RP triggers a stronger price reduction in brand-names, 30%, than in generics, 19%. The authors also find that the prices on products that are therapeutic substitutes to those included in the RP system also responded to the reform: in particular, while the effect on branded therapeutic substitutes in not statistically significant, the therapeutic substitute generics reduced prices of 6.4%. The authors conclude that RP stimulates generic competition and is more effective in lowering drug prices than a price-cap regulation.

2.2.2. Effects on quantities and total expenditure

General overview. According to the results reported by the systematic review for the Cochrane Collaboration by Aaserud, Dahlgren, Kosters, Oxman, Ramsay and Sturm (2008), the average effect on drug use six months after the transition period following the introduction of RP is a relative increase in the level of use of referenced drugs

estimated between 87% and 251%, a relative decrease in the level of use of cost-share drugs estimated between -35% and -41%. Aaserud, Dahlgren, Kosters, Oxman, Ramsay and Sturm (2008) also report that the average effect on drug expenditures six months after the transition period following the introduction of RP is a relative decrease estimated between -18% and -47%, and that the associated savings in drug expenditures are estimated between a relative decrease of -3% and a relative increase of 48%.
The estimation of the impact changes strongly according to the type of RP under analysis. In generic referencing, where the RP applies only to off-patent chemicals, the literature shows a slow but constant reallocation of the demand towards products still under patent protection. It is not clear, however, how much of this replacement is actually due to the RP. Formal DD analyses are missing on this issue. In a therapeutic referencing, on the other hand, it is logical to expect consistent savings in public/private expenditure, but no real effect on the overall number of prescription can be expected *ex ante*. Some evidence seems to confirm this point (Schneeweiss et al, 2003), although some other studies found a low but not null elasticity in the overall demand for a whole therapeutic category (Puig-Junoy, 2007).

The wide range of results reflects also the lack of clear-cut evidence. Appropriate BA or DD studies on the topic are rare. The most convincing evidence in terms of methodological appropriateness comes from Canada (Schneeweiss and colleagues, 2002-2003; Grootendorst and colleagues, 2005-2006) and Spain (Puig-Junoy, 2007). Although the lack of more formal approaches does not represent a problem when the outcome is price, quantities and expenditure are more difficult to evaluate. First of all, data do not generally show evident breaks in the overall market trends. Secondly, while for prices variations are rare, for quantities variability is high and in most cases researchers can rely only on few covariates for explaining high levels of variance. Conclusions are thus less robust and self-evident than in the analyses of prices.

Germany

The RP was introduced in 1989. Germany applied RP sequentially to different categories of products. Class 1 includes products with the same active ingredient (generic equivalents), Class 2 applies to therapeutically and pharmacologically similar active ingredients, and Class 3 applies to compounds with comparable therapeutic effect, especially combinations. Class 3 RP is rarely applied. The level of the RP is found as a weighted average (cobb-douglas) of existing prices. Pharmacists can not substitute (until 2001).

Zammit-Lucia and Dasgupta (1995; REV) observe that series of aggregate data for the period 1988-1992 show that, with the only exception of 1989, the rate of growth of the total pharmaceutical expenditure remained unaltered after the introduction of RP.

Ulrich and Wille (1996; REV) show that drug spending between 1992 and 1993 declined as a percentage of total healthcare spending, from 16.1% to 13.1%.

Belien (1996; REV) and Schoffski (1996; REV) observe that, while reimbursed pharmaceutical expenditure was steadily increasing from DM13.8 billion in 1981 to DM20.6 billion in 1988, following the introduction of RP in 1989, reimbursed pharmaceutical expenditure was DM20.7 billion and notice that this decline in the rate of increase was not maintained in the following years, a period of increasing inflation.

von der Schulenberg (1997; REV) points out that, although RP resulted in substantial savings in 1993, there are claims that compensatory increased occurred in costs of drugs not subject to RP, patient referrals and hospital admissions.

Bloor, Maynard and Freemantle (1996; REV) and Drummond, Jonsson and Rutten (1997; REV) observe that in 1996 prescription drugs regulated by RP represented 61.4% of total drug sales in Germany. Nerine and Sen (1997; REV) observe that the savings in the categories of products subject to RP estimated on July 1993 were a figure about DM1.5 million per year, amounting on average to 15% of the total expenditure.

Schneeweiss, Schoffski and Selke (1998; DES) observe an absence of significant effects on the volumes and estimate the total savings for the pharmaceutical expenditure in about DM425 million per year due to the initial implementation of phase 1 RP.

Dickson and Redwood (1998; DES) show, with time series data from the public health body GKV that, with the only exception of 1989, the rate of growth of the total pharmaceutical expenditure in the years 1990-1992 was higher than the average one during the 7 years before the introduction of RP.
VFA (2000; REV) reports total savings from RP at DM3.1 billion in 1999, approximately 19.7% of retail pharmacy sales at ex-factory prices.

Lopez-Casanovas and Puig-Junoy (2001; REV) observe that in 1995 products subject to RP represented 66% of the total sickness funds expenditure on medicines, that public expenditure on drugs subject to RP showed a steady increase after an initial reduction and that total savings in period 1992-1994 was a figure of about DM5 billion, consisting in a saving of DM3 billion from altered prescribing behaviour by doctors, DM1 billion from substitution of products with identical active compounds and DM1 billion from the increased charges on patients.

Giuliani, Selke and Garattini (1998; DES) study data from official statistics on consumption and average prices per Defined Daily Dose (DDD) (which is the therapeutical daily dose of active ingredient usually taken by a patient for a given pathology) in period 1989-96 for drugs within 8 therapeutic groups: beta-blockers, calcium antagonists, non-opiate analgesics, oral hypoglicemics, NSAIDs, expectorants, coronary dilators and systemic antibiotics. The authors observe an increase in the

consumption volumes (per DDD) within all the therapeutic groups. The authors observe that the pharmaceutical expenditure slightly decreased, or remain steady, in three therapeutic groups only (non-opiate analgesics, NSAIDs and coronary dilators), for which the decrease in average prices prevailed on the increased in volumes, despite an increase in DDDs prescribed for the first two of these groups. The authors notice, however, that within all the other five therapeutic groups' expenditure increased. In particular, turnover of oral hypoglycaemic slightly dropped immediately after the RP introduction, mainly due to glibenclamide. The turnover of this group, however, increased significantly in the later years, with a sizeable growth of DDDs prescribed. Beta-blockers, calcium antagonists and expectorants did not decline at all in the short term. Finally, both turnover and DDDs grew at a considerable rate for antibiotics. The authors conclude that expenditure of drugs subject to RP showed a steady increase after an initial reduction, mainly due to volume growth.

Danzon (2001; REV) observes that, although the RP system reduced prices for reference priced products, total expenditure continued to rise initially, because for the phase 1 RP, generics already accounted for over 50% of scripts in 1989, so that the potential phase 1 savings from reducing brand-name drugs' prices and volumes were already small. The author notices that, in general, RP cannot be expected to control expenditures because it has no direct effect on volume and structural shift, the main driver of pharmaceutical expenditures in Germany. Moreover, the author argues that, until the 1993 drug budgets, RP might have increased volume because drugs under RP were exempt from the co-payment of DM3, and RP might also have encouraged switching to non-referenced products, which entailed no risk of explanation requirements for doctors or excess charges for patients. The author observes that, consistent with this, data on the components of expenditure growth show an increase in the inter-drug effect, that is switching to more expensive products, in 1991-1992, compared to 1987-1990.

Petkanchin (2006; REV) points out that RP policy may have saved to compulsory health insurance funds in Germany more than €15 billion from its establishment in 1989 up to 2002.

The Netherlands

A RP was introduced in 1991. The Dutch RP system included almost all on-patent and off-patent drugs. Classification decisions were made by the Ministry of Health, with input from a panel of medical advisors. The RP level is set as a median of existing prices. In 1996 maximum wholesale price policy was introduced.

Zammit-Lucia and Dasgupta (1995; DES) find no significant impact of the introduction of RP on pharmaceutical volumes.

Bloor, Maynard and Freemantle (1996; DES) notice that, although the overall drug expenditure increased by 11% from 1991 to 1992, the costs of drugs covered by RP increased less than predicted, while the costs of non-classified drugs increased by more than 20% per annum since 1988.

Lopez-Casanovas and Puig-Junoy (2001; REV) observe that whereas, prior to the Medicines Reimbursement System, expenditure increased by 11.2% from 1989 to 1990 and by 8.3% from 1990 and 1991, pharmaceutical expenditure increased by 11.7% and 11.2% in 1992 and 1993, respectively.

Danzon (2001; DES) observes that that RP had at most modest effects on expenditure trends. In fact, the author reports that expenditure on pharmaceutical grew by 11.2% from 1989 to 1990, by 8.3% in 1991, with RP in effect for 6 months, but accelerated to 11.1% in 1992, with most of the growth in the unclustered drugs. Moreover, the author observes that, in period 1989-93, RP had no lasting effect on volume and argues that this appears to be a perverse effect on price change, which was negative in 1989 and 1990, before RP, and slightly positive for 1991-93, after the introduction of RP. The author also reports that, from 1994 to 1997, average expenditure growth was 5.6% per year and notices that strong structural growth, due to volume increases and a shift to newer products, were offset by a 5% price cut in 1994, reduction in pack size in 1994 and the 15% price cut following the Maximum Price Law in 1996. Thus the author argues that, to the extent that the Netherlands has had negative price growth, this reflects pure price controls superimposed on RP and that the effect of RP appears to had been largely a one-off price reduction for branded products at the outset, followed by a second round of price cuts after the RP levels were reduced in 1999.

New Zealand

Reference pricing was introduced in July 1993. All reimbursed products are assigned to therapeutic subgroups with similar health effects. Patent status is not considered. New Zealand sets the RP at the lowest price in each subgroup, regardless of patent status. Generic substitution rules permit the pharmacist to substitute generics unless the physician explicitly prescribes the brand.

Pharmac (1996; DES) estimates that, in the 1995-96 financial year, savings attributed to RP were about NZ$48 million and notices that, although the growth rate on drug spending had slowed, the trend had continued upward at a rate exceeding inflation: for instance, for the period March 1995 to March 1996, the growth rate was 8.15% and pharmaceutical expenditure was approximately NZ$716 million.

Braae, McNee and Moore (1999; DES) and Martin and Begg (2000; DES) estimate that the average growth rate from 1993 to 1998 was 5%, with a decrease of approximately 5% between 1998 and 1999.

Lopez-Casanovas and Puig-Junoy (2001; REV) report that from June 1993 to June 1994, the subsidy per head, corrected for population aged more than 60 years, increased by 11% but declined by -0.6% from June 1994 to June 1995.

Danzon (2001; DES) observes that the average annual percentage increase in government pharmaceutical expenditures for the period 1987-96 was 4.7% in nominal terms and 0.7% in real terms, after adjusting for CPI inflation. Moreover, the author calculate that, adjusting for population, the real rate of growth of spending per capita is -0.2% on average in that period. The author notices, however, that breaking down the overall average into three-year subperiods, indicates a slower real rate of growth for the period 1987-93, before the launch of RP, compared to 1993-96, the first three years of RP under Pharmac. This evidence, according to the author, casts doubt on the charge that real expenditure per capita was growing excessively prior to 1993 and that Pharmac significantly reduced the rate of growth, at least during the first three years of RP. The author also observes that, in period from 1993 to 2000, the price index has declined, but total spending has increased, reflecting growth in volume and mix.

Sweden

The RP was introduced in 1993 and dropped in 2002. It was a generic referencing, i.e. it applied only to products with expired patents and generic equivalents (same form, same active substance and same quality).

Zammit-Lucia and Dasgupta (1995; DES), looking at series of aggregate data, notice that RP had only a temporary effect on the pharmaceutical expenditure. In fact, the authors report that in 1993, the year of introduction of RP, the rate of growth of the total expenditure, 12.7%, was lower than in the previous year, 15.3%. However, the authors notice that such an effect disappeared in the immediately following year, when the rate of growth followed the previous trend and reached the highest level of the five previous years, 15.8%. Moreover, the authors observe that, from 1993, the prescribing mix component of the total expenditure increased its relative importance. The authors also observe that the lower expenditures in the products subject to RP were more than compensated by the higher expenditures in the drugs not subject to RP.

Liungkvist, Andersson and Gunnarsson (1997, DES) estimate that savings in the national drug bill were about SEK400 million in 1993 and a further SEK50 million in 1994, while no further significant savings were expected with the current RP system, and observe that, despite RP, the yearly percentage change of pharmaceutical costs in 1993-95 ranged from 12.7% to 15.8%, which were similar to the range 10.6-15.3% from 1988 to 1992.

Lopez-Casanovas and Puig-Junoy (2001; REV) report that the total change in public expenditure in 1993 was a reduction of SEK485 million and that the factors contributing to such change were the price reductions (-SEK305 million); the costs over RP charged to the consumers (-SEK30 million); the switch to less expensive drugs (-SEK80 million); and the drugs falling outside the reimbursement system (-SEK70 million). The authors also observe that the change in public expenditure also implied a corresponding change in the distribution of the financing burden, implying reduced revenues for the pharmaceutical industry (-SEK300 million) and for the pharmacies (-SEK85 million) and an increased expenditure for patients (SEK100 million). Moreover, the authors report that the total reimbursement saving for the period 1993 to 1996 can be estimated at about SEK1 billion.

Denmark

The RP was introduced in 1993. Products are grouped on the basis of type of pack. All products, which have at least one copy version, including generics and parallel imports, are included. The RP is the average of the two cheapest drugs in the market. Pharmacists have the right of substitution.

Zammit-Lucia and Dasgupta (1995; DES), using series of aggregate data, observe that, in 1993, the year of introduction of RP, the rate of growth of total pharmaceutical expenditure, 4.5%, was lower than the rates of growth in the two years before, 15% and 9.8% for 1991 and 1992, respectively, although the rate was higher, 5.4%, in the following year, 1994.

Clausen (1995; REV) observes that, despite having decreased the price levels of the relevant drugs, public expenditure still increased, partly due to the prescribing of new and more expensive drugs. Lopez-Casanovas and Puig-Junoy (2001; REV) observe that in the first year after RP, growth in pharmaceutical expenditure was lower than at any point in the previous six years.

Australia

RP was introduced in 1998. It is a therapeutic RP which applies to six therapeutic categories: H2 receptor antagonists (ulcer), statins, calcium channel blockers, ACE inhibitors, beta blockers (CVD). Pharmacist has the right to generic substitution. RP is the lowest price in the market.

Ioannides-Demos, Ibrahim and McNeil (2002; REV) observe that in the financial year 1996-97, healthcare expenditure in Australia was A$2863 million, whereas in 1997-98,

the year the Therapeutic Group Premiums Scheme was implemented, the total Pharmaceutical Benefits Scheme (PBS) costs increased to A$3097 million despite the prediction of costs savings of A$560 million over four years. The authors also observe that in 1999-2000, government expenditure for PBS prescriptions increased by 14% and that considerable cost savings occurred with therapeutic groups subject to RP: the only three therapeutic categories to grow more slowly in 1998 compared to 1997 were the three categories affected by Therapeutic Group Premiums: antiulcer agents, ACE inhibitors and calcium antagonists. On the other hand, the authors observe that the category that did not attract a Therapeutic Group Premium, the statins, showed an increased expenditure since the introduction of the scheme and was the drug group with the highest increased cost to the government in 1999-2000. The authors also notice that the latter increase in expenditure also reflected an increase in volume of prescriptions due to the expansion of indications to patients with existing coronary heart disease and to patients with a blood cholesterol level higher than 4 mmol/L.

Canada (British Columbia)

RP was introduced in 1995. Under Type 1 RP, only chemically equivalent drugs are considered interchangeable, either branded or generic versions of the same drug. Under Type 2 RP, all drugs from the same therapeutic class are considered interchangeable. This therapeutic RP applied to some specific clusters: H2 Antagonists, NSAIDs, ACE inhibitors, calcium channel blockers. Usually the reference for reimbursement is the least expensive product. Generic substitution is allowed.

Boulet and Tessier (1997; REV) observe that total healthcare expenditure was approximately C$72 billion per annum in 1994 and that, although prescription drugs accounted for just over 5% of this expenditure, drugs represented the fastest growing proportion of total health spending.

Vandergrift and Kanavos (1997; DES) observe that, since the introduction of the RP policy, prescribing of the reference anti-ulcer drug cimetidine increased 5 times, while prescribing for other drugs in the class decreased by over 50%; that prescribing for the sustained-release nitrates fell by more than 50% while that for the reference nitrate tripled, and that prescribing of less expensive NSAIDs saved over C$5 million.

Maclure and Potashnik (1997; DES) estimate total drug savings in the first year in about C$30 million, approximately 7.5% of the drug budget, plus projected annual savings of C$14 million. Mullens (1998; DES) estimates cost savings in about C$74 million for the 2 years since the programme was launched, while McGregor (1998; DES) estimates the figure in about C$44 million per year.

Narine, Senathirajah and Smith (1999; REV) report that initial data from Pharmacare demonstrated an increase in prescriptions for drugs under RP and a decrease in drugs not subject to RP, with an associated decrease in annual costs for drugs within RP categories from C$42 million in the year before the introduction of RP to C$23.7 million in 1996.

Lopez-Casanovas and Puig-Junoy (2000; REV) report that total drug expenditures were figures about C$406 million, C$396 million and C$430 million in financial years 1995-96, 1996-97 and 1997-98, respectively, and that the government claimed to have saved C$30 million and C$44 million in the first and the second year, respectively, after the introduction of the RP system.

Schneeweiss, Soumerai, Maclure, Dormuth, Walker and Glynn (2002; BA) analyze monthly data of claims from British Columbia for 24 months before and 12 months after implementation of RP and identify 119074 patients, 65 years of age or older, for whom at least one ACE inhibitor was dispensed between January 2005 and June 2008. For each of the 8 ACE inhibitors, the authors determine the median monthly dose (MMD, in mg) dispensed during the 8-month period from November 1995 to June 1996, for patients who filled at least one prescription during a period of 120 days before, and a period of 120 days after the 8-month period. The authors observe that in January 1995, 1230 MMDs of cost-shared ACE inhibitors were dispensed per 10000 patients and that such figure increased by 16 MMDs (1.3%) per month before RP became effective in January 1997. The authors find that, after a sharp drop of 462 MMDs (29% of the predicted value) following the implementation of RP, the utilization rate stabilized at about 1150 MMDs, 38% below the rate projected for June 1997 on the basis of pre-RP data. In June 1997, mean monthly expenditure per patient was $9.40, 19% less than the expenditure projected from the pre-RP trend, and the rate of increase ($0.46 per patient per month) was also slightly lower than the projected trend. On the basis of the difference between observed expenditure and expenditures projected from pre-implementation trends, the authors estimate that cost savings to Pharmacare for all ACE inhibitors prescriptions was $6.7 million in the first year.

Schneeweiss, Soumerai, Maclure, Dormuth, Walker and Glynn (2003; BA) select a cohort of 35886 patients, 65 years of age or older, who received a dihydropyridine calcium channel blockers (DCCBs) between December 1995 and March 1996. The authors define median monthly doses (MMDs) for each of 4 DCCBs as the median of all doses dispensed per month in mg averaged over a 8-month period starting on November 1995. The authors find that, after a sharp drop of 150 MMDs (21% of the predicted value) following the implementation of RP, the utilization rate stabilized at about 560 MMDs, 38% below the rate projected for June 1997 on the basis of pre-RP data. On the other hand, the authors find that while the use of no-cost DCCBs increased from 117 MMDs per 10000 patients during the pre-policy period by 1 MMD (0.9%) per month, during the 5 months after the introduction of RP, utilization increased by 19 MMDs per month to 233 MMDs in April 1997, representing a 60% increase compared

with the predicted value in November 1996, just before the introduction of RP. Therefore, the authors find that the aggregate outcome of these two effects was that utilization of all DCCBs dropped from 823 MMDs per 10000 patients in November 1996 to an average of 730 MMDs during the first 3 months after the policy, corresponding to a 11.3% decrease. After this transition period, the post-policy level rose to 780 MMDs in June 1997, still 9.3% below the expected value (860 MMDs) for June 1997 based on the projected pre-policy trend. The authors also report that there was a temporal decrease in average monthly expenditure per patient.

Marshall, Grootendorst, O'Brien, Dolovich, Holbrook and Levy (2002; BA)consider aggregate monthly claims data, from January 1993 to May 1999, for hystamine-2 receptor antagonists (H2RAs), proton pump inhibitors (PPIs), sucralfate, prokinetic agents and misoprostol, from Pharmacare, the publicly funded drug subsidy program for seniors and various other residents of British Columbia. The data included the numbers of prescriptions and unit doses dispensed, the costs reimbursed by Pharmacare and the payments made by the beneficiaries. The authors analyzed claims data only for patients 65 years of age or older. For both H2RAs and PPIs, expenditure trends observed in the first 3 periods were estimated with regression models and then projected forward to predict the expenditures that would likely have accrued in the absence of policies. The authors consider the 12-month period from September 1994 to August 1995 as baseline. During such baseline period, the mean monthly number of DDD of H2RAs prescribed was 137855 per 100000 senior beneficiaries, of which 24536 (18%) were for the reference standard, cimetidne. From the baseline period to the 12-month period immediately after implementation of RP (January to December 1996) there was only a modest 21% increase in the mean monthly number of DDD of H2RAs dispensed, but there were pronounced changes in the mix of individual H2RAs. For instance, mean monthly cimetidine prescriptions raised by 379%, whereas prescribing of restricted H2RAs fell by 55%. The mean monthly number of DDD of PPIs prescribed fell by 26% in the 12-month period after RP implementation, but climbed to 9% over baseline in the follow-up period. A 300% increase in monthly Pharmacare expenditures for cimetidine was offset by lower expenditures for restricted H2RAs. Thus, overall monthly expenditures for H2RAs fell to 58% of baseline in the 12-month period after the implementation of RP, and remained low in the follow-up period. In contrast, monthly expenditures for PPIs fell to 74% of baseline in the 12 months after implementation of the special authority policy, but rose to 107% of baseline in the subsequent follow-up period. The projections of trends in expenditure from before to after the change in policy for H2RAs and PPIs revealed that for H2RAs the total estimated savings for the period January 1996 to May 1999, were between C$1.8 million per year, while for PPIs, they were C$5.5 million per year.

Grootendorts, Marshall, Holbrook, Dolovich, O'Brien and Levy (2005; BA) consider monthly data over the period February 1993 to June 2001 from retrospective population-based claims, to examine patterns of drugs' prices under the application of RP by Pharmacare, the publicly funded drug subsidy program for seniors and various

other residents of British Columbia. The authors consider the application of RP to the nonsteroidal antiinflammatory drugs (NSAIDs). The authors find that Type 2 RP appeared to have little effect on the total volume of NSAIDs dispensed and that most of the savings from the introduction of RP were attributable to substitutions of low cost unrestricted for higher cost restricted NSAIDs. The authors also notice that rates of prescribing unrestricted NSAIDs doubled after the introduction of Type 2 RP. The authors estimate total savings of C$7.5 million for Type 1 RP and C$22.7 million for Type 2 RP. The annualized savings amounted to C$1 million and C$4 million, respectively, corresponding to about 11% and 44% of the C$9.1 million Pharmacare spent on NSAIDs in the 12 months prior to Type 2 RP. The authors notice, however, that some of the savings attributed to Type 2 RP, an annual estimate of about C$400000, were actually because of the delisting of the second line restricted NDAIDs.

Grootendorst and Stewart (2006; DD) critically assess the identifying assumption inherent in the "before and after" (BA) design, namely that pre-RP trends accurately predict counterfactual outcomes. The authors estimate the impact of RP on expenditure on ACE inhibitors and calcium channel blockers (CCBs) by Pharmacare, the publicly funded plan for seniors and various other residents of British Columbia. The authors also use similar data from a public plan in Ontario (Ontario Drug Benefit plan) that had not introduced RP, to estimate the effects on drug expenditures of patent expiration, secular changes in prescribing patterns and various other factors common to all Canadian public drug plans that could potentially confound the BA estimates of the effect of RP on drug plan expenditures. Using monthly data from January 1994 to December 2000, the authors estimate the reduction in prices attributable to RP by a DD estimator. The authors observe that the introduction of RP did not appear to substantially affect dispensing volumes for ACE inhibitors or CCB. The authors notice, however, that RP appears to have large effects on the mix of high- and low-cost drugs dispensed within each category. The substitution of lower cost for higher-cost drugs, coupled with the reduced reimbursement of higher-cost drugs for non-expemted beneficiaries, had the effect of lowering average expenditure per day of ACE inhibitor and CCB therapy. They estimate that the application of RP to ACE inhibitors reduced Pharmacare expenditure over the 4-years period between January 1997 to December 2000 by about C$10 million, while the corresponding savings estimate for CCBs was in order of C$8 million. The authors also notice that savings declined over time.

Spain

A RP system was effectively introduced in Spain in December 2000. This system is applied to off-patent drugs with the same active ingredient. Initially, the RP was 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 sales.

Puig-Junoy (2007; DD) aims at evaluating the intended and unintended impact on pharmaceutical use and volume of sales of the Spanish generic RP system for statins. The author develops a DD analysis of 46 monthly drug use and volume of sales ratios, from January 2001 to October 2004, valued at regulated ex-factory prices. Data are from IMS, a marketing research company, and from the centralized National Health System pharmaceutical consumption database of the Spanish Ministry of Health. The author calculates that, while 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 Andalusian Public Health Service (APHS), 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 (SHS) and €772.8 in the APHS), but the average difference between the two regions had narrowed slightly (18.1%). For statins as a whole, volume of sales increased during this period by 35.4% in the rest of Spain and 39.8% in Andalusia. Moreover, the author observes that the largest increase in volume of sales and number of prescriptions for 1000 inhabitants was observed for the two on-patent statins, namely fluvastatin and atorvastatin. Importantly, the paper shows that the overall 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 (6.5% in SHS and 24.3% in APHS), although the other statins maintained their time trend growth as observed before RP. The author also notices that, in contrast, price reduction of simvastatin was accompanied by a slight increase in its growth rate (86.4% in the rest of Spain, 21.5% in APHS), and also a slight decrease in the number of prescriptions of atorvarstatin, the top-selling on patent statin. The author concludes that the market demand for a given drug, that is the combined demand for the original drug and its generic substitute, is not perfectly inelastic in relation to its own price change induced by RP. Finally, the author calculates that, in the rest of the Spanish Health System, the mean monthly saving for the 12 and 10 months, respectively, after intervention attributed to the initial application of RP to lovastatin and simvastatin were 16.7% and 51.8%, respectively, of total sales of those drugs, representing 1.1% and 13.9%, respectively, of total volume of sales of statins.

Ubeda, Cardo, Selles, Broseta, Trillo and Fernandez-LLimos (2007; DES) describe the evolution of antidepressant use in primary care in the Valencian region from 2000 to 2004 and analyze the effects of the introduction of RP and generic drugs on drug utilization and cost saving. The authors analyze the prescription pattern of antidepressants using sales collected for the period 2000-04, converted into DDD per 1000 inhabitants according to the methodology by the WHO Centre for Drugs Statistics. The authors report that antidepressants represented around 4.5-5% of the total drug expenditure of the Valencian region (€1316 million in 2004), which, in turn, represented about 29% of the Valencian public health budget. The authors observe that the total cost of prescribed antidepressants in the Valencian region steadily increased from 2000 to 2003, from €40 million to €59 million, at constant prices, and remained at this point in 2004, representing an increase of 47%. Therefore, the authors argue that even though

the lowered cost of many medicines implied by the introduction of RP had not reduced pharmaceutical expenditure, at least it helped to moderate its increase. The authors observe a trend towards an increase in the utilization of other antidepressants, such as venlafaxine and escitalopram, which were not affected by the RP policy, an undesirable effect as it does not usually correlate with a significant improvement in effectiveness and involves increased costs. The authors estimate that, during the analyzed 5-years period, the reduction of fluoxetine's cost/DDD represented an approximate saving of €8.6 million for the Valencian Health System. However, they also point out that the impact that RP had on fluoxetine utilization might have contributed to the progressive reduction in its total market share (while generic use reached a relevant level, about 33% in 5 years). The authors also argue that, through the strategy to lower their prices, brand-name drugs manufacturers attempted to avoid the substitution for the alternative generic and were able to maintain loyalty to the trade mark: in the case of brand-name fluoxetine, for instance, this explains why prices were reduced for the original products and not for the orally disintegrating fluoxetine tablets, which were not interchangeable by generic forms. The authors conclude that the above displacement of drugs included in this system to other new higher-priced medicines might have contributed to the yearly increase in average cost per prescription, that was 2.5% in 2000, 3.3% in 2002 and 4.98% in 2003.

Italy

In Italy the RP was introduced in December 2001. It applies to off-patent drugs only (same dosage, same pack). The RP is the minimum price in the market. Pharmacists are allowed to substitute.

Ghislandi, Krulichova and Garattini (2005) show data on prices and volumes from January 2001 to April 2003 for the commonest packs of the top three active substances in terms of revenue, with at least one generic version: tipoclidine, nimesulide and ranitidine. The authors observe that the impact of RP on the total sales volumes of the three substances is more uneven than for the prices, depending on the different competitive scenarios and, in particular, the existence of under-patent "me-too"drugs. The authors notice, for instance, that the sharp drop in total volumes of ranitidine may be explained by the availability of many in-patent drugs with the same therapeutic indication (such as omeprazole and its derivatives), strongly promoted by companies to avoid price competition.

Belgium

The RP was first introduced in 2001. It is a generic referencing, i.e. the RP applies to drugs with the same active compound. The RP is initially set 16% lower than the branded product's price. Over time, the Belgian government has progressively reduced the level of the RP. Generic substitution is allowed.

Simoens, De Bruyn, Bogaert and Laekeman (2005; DES) analyze data on general trends and on evolution of particular drug classes. The former data are from IMS Health Belgium and relate to drug consumption of a representative panel of 2550 community pharmacies, about 50% of all Belgian pharmacies. The latter data are from Ifstat database, which brings together data on reimbursable drugs transmitted by community pharmacies to the third-party payer for the purpose of reimbursement. The authors report an interesting case study concerning lisinopril, an ACE inhibitor, after the introduction of its generic versions in the Belgian market in October 2002. The authors report that, on the one hand, the price of Zestril, one of two original lisinopril drugs was dropped to around the price level of generic versions of lisinopril in return for unconditional prescriptions, thereby sustaining its consumption in terms of DDDs. On the other hand, the authors report that Novatec, the other original drug, upheld its price and its prescription continued to be subject to "Chapter IV" regulation, thus translating into a 43% reduction in consumption of Novatec. The authors observe that, focusing on those active principles for which generic drugs are available, expenditure on original drugs fell significantly. The authors argue that the difference in the expenditurerepresent net savings to the third-party payer as a result of generic competition. The authors calculate that, expressing savings as a proportion of expenditure on all drugs, rather than expenditure on active principles for which generic drugs are available, the introduction of RP scheme was associated with savings amounting to 1.8% of pharmaceutical expenditure by the third-party payer in 2001 and to 2.1% in 2002. The authors argue that these findings indicate that the fall in expenditure on original drugs exceeded increased expenditure on generic drugs as a result of the lower price of generic drugs, thereby generating savings to the third-party payer.

Hungary

The first version of the RP was introduced in 1999. It was a generic referencing (i.e. RP applies to drugs with the same chemical). In 2003, a therapeutic referencing (i.e. RP applies to a cluster of chemicals) was introduced for some groups (including statins). The RP is the cheapest drug with a cumulative market share of 50%.

Kalò, Muzbek, Bodrogi and Bidlò (2007; DES) analyze the Hungarian experience in introducing a therapeutic RP for statins in September 2003. The authors use as baseline period August 2003, the last month before the introduction of RP, and compare the average ex-factory and public prices, reimbursement level, patients' co-payment and DDDs of prescribed units of statins with the ones in March 2004, using an IMS Health database built on sales reports of pharmaceutical wholesalers. The authors calculate that the price erosion of simvastatins resulted in €11.2 million savings over the 7-months investigation period. The authors, however, observe that, as a result of the fact that higher doses of the same substance became cheaper for the patients after the introduction of RP, many patients were switched from low to high dose statins, so that the DDD per prescriptions was increased by 45%, from 1.14 to 1.65. The majority of this DDD growth was driven by patented products such as atorvastatin and fluvastatin: the most striking change was the growth of atorvastatin DDD from 1.16 to 3.36. The authors also notice that therapeutic RP and the consequent DDD growth increased the statin sales by 55.9%. In fact, the average monthly –ex-factory sales of statins was €2809 million between February and August 2003, and €3553 million between September 2003 and March 2004, representing a 26.5% market growth. The authors conclude that overall the therapeutic RP in several therapeutic categories, affecting 38.3% of the total public pharmaceutical budget, had limited impact on the nominal growth of pharmaceutical expenditure. Actual public pharmaceutical expenditure grew by 16.7% (or 10% in real terms) after excluding the impact of VAT increase in 2003-05, compared to 16.5% in between 1994 and 2002 (1.6% in real terms), despite the introduction and subsequent extension of therapeutic RP, and mandated 15% price cut over a 3-month period.

Norway

A version of the RP was introduced in 2003 for a sub-sample of off-patent drugs already facing generic competition in six chemical substances targeted for depression, anti-ulcer, allergy, high blood pressure and nigh cholesterol. It was a generic a therapeutic referencing (i.e. RP applies to a cluster of chemicals). The RP is an index price calculated as the sales-weighted sum of producer prices included in each sub-group. The government decided to terminate the system at the end of 2004.

Brekke, Grasdal and Holmas (2008; BA) use a dataset from Farmastat providing information, over the four-year period from 2001 through 2004, on sales value (in pharmacy purchase price); volume (in DDD) for each package of drugs sold on the Norwegian pharmaceutical market; name, manufacturer, package size, dosage and launch date of each drug; and on whether the product was a brand-name or a generic drug. The authors notice that, since total demand is highly price inelastic, the fact that RP is more effective in lowering drug prices than a price-cap regulation implies that RP is superior in reducing pharmaceutical expenditures. The authors notice that in 2002, the

total sales value of the drugs included in the RP system amounted in NOK 474.4 million, with a brand-name market share of about 72%. The authors calculate cost savings for the introduction of RP system of about NOK 75 million, based upon their estimated price reductions of about 18% for brand-name drugs and 8% for generics.

2.2.3. Other Effects

General overview. Besides prices and quantities, the main two other issues considered in the literature are the impact of the RP on either generics' market shares or patients' health. From the literature, generics seem to gain market shares with the RP, although it must be pointed out that no study conducted a proper DD or BA analysis to test the hypothesis of a real impact of the RP. In general, however, it seems safe to claim that the demand for off-patent products is very elastic (in most situations brand-name prices highly above the reimbursement level have been associated to evident drops in market shares). On the other hand, the case of British Columbia provides the only significant studies of the effect of the RP on patients, showing that there is no evidence that the RP affects patients' health.

Among the reviewed papers, one (Danzon and Ketcham, 2003) analyzes the impact on the RP on the launch of new pharmaceuticals. If the clusters in the RP are narrowly defined (e.g. generic referencing), the application of the RP should not affect the natural flow of innovation in a country. On the other hand, therapeutic referencing might create a strong disincentive to the launch of new products. These relations are confirmed by this first empirical inspection. However, they have never been replicated again by other studies. Moreover, conclusions are based on very simple correlation pattern, with no control for innovation patterns and quality of the compounds, so that further evidence is needed on this issue.

In general, like for the two previous parts, the best studies in terms of appropriateness of the dataset and of the statistical analyses have been conducted in Canada (Schneeweiss, Soumerai, Maclure, Dormuth, Walker and Glynn, 2002; Schneeweiss, Soumerai, Maclure, Dormuth, Walker and Glynn, 2003), mainly because these studies are the only ones based on individual level data.

Germany

In Germany the RP was introduced in 1989. Germany applied RP sequentially to different categories of products. Class 1 includes products with the same active ingredient (generic equivalents), Class 2 applies to therapeutically and

pharmacologically similar active ingredients, and Class 3 applies to compounds with comparable therapeutic effect, especially combinations. Class 3 RP is rarely applied. The level of the RP is found as a weighted average (cobb-douglas) of existing prices. Pharmacists can not substitute (until 2001).

Ulriche and Wille (1996; REV) report that, between 1989 and 1992, generic share of scripts for multisource compounds increased by 10.9%, from 53.2% to 58.3% of the market, whereas generics' share of sales increased by 14.9%, from 42.2% to 48.5% of the market, consistent with a generic gain in volume share despite higher relative prices.

Belien (1996; REV) observes that, by 1993, sales of the seven largest research-intensive drug manufacturers declined by 16.5%, while the sales of the four largest generic drugs firms increased by 36%.

Maassen (1996; REV) points out that in the few cases in which pharmaceutical companies did not decreased drugs' prices at the RP level, their products were affected by massive reduction in the market shares, and that even small differences in the prices charged to patients (e.g. DM3) implied large falls in the market shares.

Schneeweiss, Schoffski and Selke (1998; DES) finds a considerable reduction of the sales for all the brand-name whose prices were not decreased at the RP level.

Lopez-Casanovas and Puig-Junoy (2001; REV) report that the volume's share of generics increased from 34% in 1991 to 38.6% in 1995, whereas the share of patent protected prescribed drugs increased from 11.7% in 1991 to 20% in 1995.

Giuliani, Selke and Garattini (1998; DES) study data from official statistics on consumption and average prices per Defined Daily Dose (DDD) (which is the therapeutical daily dose of active ingredient usually taken by a patient for a given pathology) in period 1989-96 for drugs within 8 therapeutic groups: beta-blockers, calcium antagonists, non-opiate analgesics, oral hypoglicemics, NSAIDs, expectorants, coronary dilators and systemic antibiotics. The authors observe that sales of original branded products declined strongly, with decreases in both volume and prices. According to the authors, this probably reflected patients' negative attitude towards co-payment, which led companies to cut the prices of branded drugs down to the reimbursement level. The authors, however, observe that savings of drugs subject to RP were balanced by the growth of turnover of those not subject and argue that this probably resulted from an industrial strategy aimed at facing the RP constraints by launching new active ingredients, possibly adding little innovation but sustaining high prices. In particular, the authors observe that, for the calcium antagonists, the pharmaceutical companies in the period 1989-1994 launched six new calcium antagonists, all characterized by therapeutic effects similar to the drugs already present in the market, but not subject to RP.

Danzon and Ketcham (2003, DES) examine the hypothesis, common in the theoretical models but never tested in the empirical evidence, that widely defined RP clusters are associated to fewer launches of innovative pharmaceutical products. The sample used is a cross-section of many therapeutic groups for three countries: Germany, the Netherlands and New Zealand. Authors look at the date of the first launch of the molecules in the market and relate this with the application of the RP in the country. Moreover, as a benchmark, they consider the launch lag relative to the launch in the US. For Germany, "the percent of molecules available does not show a strong trend after the introduction of reference pricing in 1989 compared to the pre-RP period, with roughly 90 percent of compounds launched. After 1994, this declines to 68 percent of the post-1994 cohort launched, which may reflect diffusion lags with censored data." This result is interpreted as being the consequence of the relatively narrow definition of the RP effectively used in the German system (most of the compounds are included in Class 1 type of RP).

The Netherlands

A RP was introduced in 1991. The Dutch RP system included almost all on-patent and off-patent drugs. Classification decisions were made by the Ministry of Health, with input from a panel of medical advisors. The RP level is set as a median of existing prices. In 1996 maximum wholesale price policy was introduced.

Zammit-Lucia and Dasgupta (1995; DES) find no significant impact of the introduction of RP on physicians' prescribing mix.

Lopez-Casanovas and Puig-Junoy (2001; REV) observe that in 1993-1995 market shares of cheaper generics and parallel import drugs increased by 40%.

Danzon (2001; REV) observes that the authorization of pharmacists to substitute generics and parallel imports resulted in competitive discounting to pharmacists, but the RP system was not well designed to take advantage of this for payers and consumers.

Danzon and Ketcham (2003, DES) examine the hypothesis, common in the theoretical models but never tested in the empirical evidence, that widely defined RP clusters are associated to fewer launches of innovative pharmaceutical products. The sample used is a cross-section of many therapeutic groups for three countries: Germany, the Netherlands and New Zealand. Authors look at the date of the first launch of the molecules in the market and relate this with the application of the RP in the country. Moreover, as a benchmark, they consider the launch lag relative to the launch in the US.

For the Netherlands, it is found that the molecules launched after the introduction of reference pricing in 1991 (59-60 percent) compared to 78 percent in 1987-1990, immediately prior to RP, are fewer, suggesting that "the Netherlands' requirement that most new products join established RP clusters as a condition of reimbursement deterred the launch of some new compounds."

New Zealand

Reference pricing was introduced in July 1993. All reimbursed products are assigned to therapeutic subgroups with similar health effects. Patent status is not considered. New Zealand sets the RP at the lowest price in each subgroup, regardless of patent status. Generic substitution rules permit the pharmacist to substitute generics unless the physician explicitly prescribes the brand.

Lopez-Casanovas and Puig-Junoy (2001; REV) observe a low market penetration of generics, consistent with their low, not favourable, price differential.

Danzon (2001; DES) reports that in 1997, Pharmac considered 84 applications for subsidy, of which 55 were listed and 29 were declined, implying an acceptance rate of 65%. The author also notices that of the 97 applications declined between 1994 and 1997, 42 (43%) were for new chemical entities (NCEs) and the remainder were for new presentations or new products of existing compounds. The author argues that these data suggest that Pharmac significantly restricted entry, both for new compounds and for new forms of old compounds. The author also argues that the evidence from countries with competitive retail pharmacy sectors and hence competitive generic markets (such as United States, United Kingdom, Canada) indicates that restrictions on new forms of old compounds restrict competition, leading to foregone savings on off-patent compounds, which is contrary to the stated objective of RP.

Danzon and Ketcham (2003, DES) examine the hypothesis, common in the theoretical models but never tested in the empirical evidence, that widely defined RP clusters are associated to fewer launches of innovative pharmaceutical products. The sample used is a cross-section of many therapeutic groups for three countries: Germany, the Netherlands and New Zealand. Authors look at the date of the first launch of the molecules in the market and relate this with the application of the RP in the country. Moreover, as a benchmark, they consider the launch lag relative to the launch in the US. For New Zealand, it is found that only 12% of the molecule launched in the US between 1995 and 1998 was launched in the country. Before 1991, before the RP was introduced, the same value was 60%. Authors also show that there is a positive correlation between the relative RP levels and number of compounds launched, interpreting the results as evidence that launched are either delayed or cancelled because of excessively low reimbursement prices. Note, however, that the quality of the new compounds is not controlled for in any way and that authors do not distinguish between firms' decision not to launch and authorities' decision not to reimburse.

Sweden

The RP was introduced in 1993 and dropped in 2002. It was a generic referencing, i.e. it applied only to products with expired patents and generic equivalents (same form, same active substance and same quality).

Jonsson (1994) observes that the total market share of the brand-name products decreased from 65% in 1992 to 51% of 1993, while the generics' market share increased from 35% in 1992 to 49% in 1993.

Lopez-Casanovas and Puig-Junoy (2001) observe that, while, in 1993, sales growth in the segment of products not subject to RP was 18.3% and in the overall Swedish market was 12.6%, drug sales under the RP system increased in volume by 4.6% and decreased in cost by 16.9%.

Denmark

No evidence found in the literature.

Australia

RP was introduced in 1998. It is a therapeutic RP which applies to six therapeutic categories: H2 receptor antagonists (ulcer), statins, calcium channel blockers, ACE inhibitors, beta blockers (CVD). Pharmacist has the right to generic substitution. RP is the lowest price in the market.

Lopez-Casanovas and Puig-Junoy (2001; REV) report an increase in the market share of generic drugs from 12% up to 19% of the market.

Canada (British Columbia)

RP was introduced in 1995. Under Type 1 RP, only chemically equivalent drugs are considered interchangeable, either branded or generic versions of the same drug. Under Type 2 RP, all drugs from the same therapeutic class are considered interchangeable. This therapeutic RP applied to some specific clusters: H2 Antagonists, NSAIDs, ACE inhibitors, calcium channel blockers. Usually the reference for reimbursement is the least expensive product. Generic substitution is allowed.

Lopez-Casanovas and Puig-Junoy (2001; REV) point out that, since British Columbia already had the highest generic substitution rate in Canada before the implementation of RP, with generics representing a share of 45% of all prescribed drugs in December 1995, the effect on generics was minimal.

Schneeweiss, Soumerai, Maclure, Dormuth, Walker and Glynn (2002; BA) analyze monthly data of claims from British Columbia for 24 months before and 12 months after implementation of RP and identify 119074 patients, 65 years of age or older, for whom at least one ACE inhibitor was dispensed between January 2005 and June 2008. The authors find that patients with low-income status were the most likely to either switch to no-cost ACE inhibitors or to stop any antihypertensive therapy. However, this group also had a greater rate of discontinuation of antihypertensive therapy 7 and 12 months before implementation of RP. In general, after RP patients were more likely to either change to other groups of anti-hypertensives or stop their therapy. However, 46% of patients maintained cost-shared ACE inhibitors despite higher out-of-pocket payments, also because a part of these were probably covered by additional insurance.

Schneeweiss, Soumerai, Maclure, Dormuth, Walker and Glynn (2003; BA) select a cohort of 35886 patients, 65 years of age or older, who received a dihydropyridine calcium channel blockers (DCCBs) between December 1995 and March 1996. The authors find almost no switching from cost-shared DCCBs to no-cost drugs before the policy intervention, but a rapid increase in switching immediately after the policy implementation: 6% of cost-shared DCCB users switched to no-cost DCCBs each month. Among the 23116 prevalent users of high-priced cost-shared DCCBs, 76.9% continued to take their cost-shared DCCBs, 9.3% changed to no-cost DCCBs, 5.8% switched to another antihypertensive medication class, 5.1% switched to nitrates and 3% stopped all antihypertensive drug treatment. The authors did not observe any increase in physician visits in the entire cohort of patients subject to policy. However, switchers had 18% increase in physician visits compared to non-switchers during the first 2 months after policy. The authors, did neither detect any increase in hospitalizations overall or through the emergency department, nor in admissions to long-term care facilities.

Spain

A RP system was effectively introduced in Spain in December 2000. This system is applied to off-patent drugs with the same active ingredient. Initially, the RP was 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 sales.

Puig-Junoy (2007; DD) develops a DD analysis of 46 monthly drug use and volume of sales ratios, from January 2001 to October 2004, valued at regulated ex-factory prices.

Data are from IMS, a marketing research company, and from the centralized National Health System pharmaceutical consumption database of the Spanish Ministry of Health. The author shows that market shares for generics in the off-patent chemicals (lovastatin and simvastatin) increased constantly over time after patent expiry (from 4% to 18% for lovastatin and from 0% to 23% for simvastatin). However, he does not test formally the hypothesis that the RP had an impact in the generics' market share trend.

Italy

In Italy the RP was introduced in December 2001. It applies to off-patent drugs only (same dosage, same pack). The RP is the minimum price in the market. Pharmacists are allowed to substitute.

Ghislandi, Krulichova and Garattini (2005) show data on prices and volumes from January 2001 to April 2003 for the commonest packs of the top three active substances in terms of revenue, with at least one generic version: tipoclidine, nimesulide and ranitidine. The authors observe that generics gained market shares in all three cases, with a greater increase where the price gap between generics and originators was larger. The authors also notice that, despite these successful examples, the overall market for reimbursed generics was still under-developed in Italy, being their share of public pharmaceutical expenditure only 1.2% in 2002. They observe that, while part of the reasons for this delay is due to longer patent protection (and thus less off-patent chemical in the whole market), the fact that most brand-name products reduced their price to the RP negatively affected the development of the market for generics.

Belgium

The RP was first introduced in 2001. It is a generic referencing, i.e. the RP applies to drugs with the same active compound. The RP is initially set 16% lower than the branded product's price. Over time, the Belgian government has progressively reduced the level of the RP. Generic substitution is allowed.

Simoens, De Bruyn, Bogaert and Laekeman (2005; DES) analyze data on general trends and on evolution of particular drug classes. The former data are from IMS Health Belgium and relate to drug consumption of a representative panel of 2550 community pharmacies, about 50% of all Belgian pharmacies. The latter data are from Ifstat database, which brings together data on reimbursable drugs transmitted by community pharmacies to the third-party payer for the purpose of reimbursement. The authors observe that the introduction of the RP scheme in 2001 was associated with an increased market share of generic drugs, both in terms of volume and value. In terms of number of

pack sold, the average market share for generic drugs amounted to 2.05% of the total pharmaceutical market from January 1998 to June 2001, as compared with 6.11% from July 2001 to December 2003. The authors observe that, even though the volume of generic drugs sold rose substantially, the mandatory reduction in their prices means that the value of generic drugs sold increased at a slower rate, growing from 1.16% in January 1998 to June 2001, to 4.05% in July 2001 to December 2003. The authors also observe that, as new generic drugs were introduced in Belgium, their market share tended to increase during the first couple of months and then levelled off. The authors, for instance, report that the market share of generic drugs available during 2001 increased during that year, partially as a consequence of the introduction of RP scheme in June 2001, but remained relatively constant around 5-6% in 2002, 2003 and the first half of 2004. The authors argue that rising market share of generic drugs in subsequent years can be attributed to the introduction of new generic drugs. The authors also observe that, in response to increased generic competition resulting from the introduction of the RP scheme, some manufacturers of original drugs launched new variants of their original drug, thereby effectively extending the period of patent protection. The authors, for instance, report the case of Cipramil, a selective serotonin reuptahe inhibitor that is based on the active principle citalopram: as generic drugs of citalopram became available on the Belgian market in March 2003, the pharmaceutical company introduced a new variant, Sipralexa.

Hungary

The first version of the RP was introduced in 1999. It was a generic referencing (i.e. RP applies to drugs with the same chemical). In 2003, a therapeutic referencing (i.e. RP applies to a cluster of chemicals) was introduced for some groups (including statins). The RP is the cheapest drug with a cumulative market share of 50%.

Kalò, Muzbek, Bodrogi and Bidlò (2007; DES) analyze the Hungarian experience in introducing a therapeutic RP for statins in September 2003. The authors use as baseline period August 2003, the last month before the introduction of RP, and compare the average ex-factory and public prices, reimbursement level, patients' co-payment and DDDs of prescribed units of statins with the ones in March 2004, using an IMS Health database built on sales reports of pharmaceutical wholesalers. The authors notice that as a consequence of the fact that the majority of DDD growth was driven by patented products such as atorvastatin and fluvastatin, the value market share of patented products was not significantly reduced. In fact, the market share of patented atorvastatin and fluvastatin was reduced only by 2.4%, while the 20.4% market share growth of generic simvastatin between August 2003 and March 2004 stemmed mainly from the reduced original simvastatin sales.

Norway

A version of the RP was introduced in 2003 for a sub-sample of off-patent drugs already facing generic competition in six chemical substances targeted for depression, anti-ulcer, allergy, high blood pressure and nigh cholesterol. It was a generic a therapeutic referencing (i.e. RP applies to a cluster of chemicals). The RP is an index price calculated as the sales-weighted sum of producer prices included in each sub-group. The government decided to terminate the system at the end of 2004.

Brekke, Grasdal and Holmas (2008; BA) use a dataset from Farmastat providing information, over the four-year period from 2001 through 2004, on sales value (in pharmacy purchase price); volume (in DDD) for each package of drugs sold on the Norwegian pharmaceutical market; name, manufacturer, package size, dosage and launch date of each drug; and on whether the product was a brand-name or a generic drug. The authors observe a gradual increase in the sales of generic substitutes also before the RP introduction and notice that, during the months when RP was in place, the difference in market shares between branded and generic products was reduced considerably. The authors also argue that the negative cross-price effect on therapeutic substitutes outside the RP system may represent a potentially detrimental effect of RP, as it may affect the patent rents and thus potentially stifle innovation.

3. References

Aaserud M., Dahlgren A.T., Kosters J.P., Oxman A.D., Ramsay C., Sturm H. (2008): Pharmaceutical policies: effects of reference pricing, other pricing and purchasing policies (Review). Cochrane Library, 4, The Cochrane Collaboration, Wiley Publishers.

Belien P. (1996): Healthcare reform in Europe. Pharmacoeconomics, 10 (2), 94-99.

Bergman M.A., Rudholm N. (2003): The relative importance of actual and potential competition: empirical evidence from the pharmaceuticals market. Journal of Industrial Economics, 51 (4), 455-467.

Bardey D, Bommier A, Julien B. (2006): Retail price regulation and innovation: reference pricing in the pharmaceutical industry. IDEI Working Paper, No. 432, December

Boulet A.P, Tessier G. (1997): Reference-based pricing in British Columbia: implications for cardiologists – An analysis. Canadian Journal of Cardiology, 13, 46-51.

Braae R., McNee W., Moore D. (1999): Managing pharmaceutical expenditure while increasing access: the Pharmaceutical Management Agency (Pharmac) experience. Pharmacoeconomics, 16 (6), 649-660.

Brekke K.R, Konigbauer I., Straume O.R. (2007): Reference pricing of pharmaceuticals, Journal of Health Economics, 26, 613-642.

Brekke K. R., Grasdal A.L., Holmas T.H. (2008): Regulation and pricing of pharmaceuticals: Reference pricing or price cap regulation? European Economic Review, forthcoming, doi:10.1016/j.euroecorev.2008.03.004

Clausen J. (1995): Financing of prescription drugs in Denmark: alternative designs of the reimbursement system. Paper presented at the III European Conference on Health Economics, Stockholm, Sweden.

Cabrales A. (2003): Pharmaceutical generics, vertical product differentiation and public policy, Working Paper, *Department d'Economia i Empresa, Universitat Pompeu Fabra*.

Danzon, P.M., Liu H., (1996): Reference Pricing and Physician Drug Budgets: The German Experience in Controlling Pharmaceutical Expenditures. Wharton School, Working Papers Series.

Danzon P. (2001): Reference pricing: theory and evidence, in Reference Pricing and Pharmaceutical Policy, edited by G. Lopez-Casasnovas and B. Jonnson, Springer-Verlag Iberica, 2001, Barcelona.

Danzon P., Ketcham J. (2003): Reference Pricing of Pharmaceuticals for Medicare: Evidence from Germany, The Netherlands and New Zealand. NBER WP 10007.

De Vos C.M. (1996): The 1996 pricing and reimbursement policy in the Netherlands. Pharmacoeconomics, 10 (2), 75-80.

Dickson M., Redwood H. (1998): Pharmaceutical reference prices. How do they work in practice? Pharmacoeconomics, 14(5), 471-479.

Drummond M., Jonsson B., Rutten F. (1997): The role of economic evaluation in the pricing and reimbursement of medicines. Health Policy, 40, 199-215.

Ghislandi S., Krulichova I., Garattini L. (2005): Pharmaceutical policy in Italy: towards a structural change? Health Policy, 72, 53-63.

Giuliani G., Selke G., Garattini L. (1998): The German experience in reference pricing. Health Policy, 44, 73-85.

Grootendorts P.V., Marshall J.K., Holbrook A.M., Dolovich L.R., O'Brien B.J, Levy A.R. (2005): The impact of reference pricing of nonsteroidal anti-inflammatory agents on the use and costs of analgesic drugs. Health Services Research, 40 (5), 1297-1317.

Grootendorst and Stewart (2006): A re-examination of the impact of reference pricing on anti-hypertensice drug plan expenditures in British Columbia. Health Economics, 15, 735-742.

Ioannides-Demos L.L., Ibrahim J.E., McNeil J.J. (2002): Reference-based pricing schemes: effect on pharmaceutical expenditure, resource utilization and health outcomes. Pharmacoeconomics, 20 (9), 577-591.

Jonsson B. (1994): Pricing and reimbursement of pharmaceuticals in Sweden. Pharmacoeconomics, 6, 51-60.

Kalò Z., Muzbek N., Bodrogi J., Bidlò J. (2007): Does therapeutic reference pricing always result in cost-containment? The Hungarian evidence. Health Policy, 80, 402-412.

Kletchko S.L., Moore D.W., Jones K.L (1995): Targeting medicines: rationalizing resources in New Zealand – A preliminary paper. Pharmaceutical Management Agency Ltd., Wellington.

Liungkvist M.O., Andersson D., Gunnarsson B. (1997): Cost and utilization of pharmaceuticals in Sweden. Health Policy, 41, 55-69.

Lopez-Casasnovas G., Puig-Junoy J. (2001): Review of the literature on reference pricing, in Reference Pricing and Pharmaceutical Policy, edited by G. Lopez-Casasnovas and B. Jonnson, Springer-Verlag Iberica, 2001, Barcelona.

Maclure M., Potashnik T.M. (1997): What is direct evidence-based policy making: experience from the drug benefits program for seniors in British Columbia. Canadian Journal of Aging, 16 (1), 132-146.

Maassen B.M. (1996): Reimbursement of medicinal products: the German reference price system – law, administrative practice and economics. Centre for the New Europe, Zellik, Belgium.

Martin J., Begg E. (2000): Reference pricing: is it in public interest? New Zealand Medical Journal, 113, 422-425.

Marshall J.K, Grootendorst P.V., O'Brien B.J., Dolovich L. R., Holbrook A. M., Levy A.R. (2002): Impact of reference-based pricing for hystamine-2 receptor antagonists and restricted access for proton pump inhibitors in British Columbia. Canadian Medical Association Journal, 166 (13), 1655-62.

McGregor M. (1998): Coverage of drug costs: reference-based pricing. Canadian Journal of Cardiology, 14, 666-668.

Merino-Castelló, A. (2003): Impact of the Reference Pricing System on the Pharmaceutical Market: A Theoretical Approach. *Universitat Pompeu Fabra*, Working Paper Series, Working Paper 524a

Mestre Ferrandiz J. (2003): Reference prices: the Spanish way. *Investigaciones Economicas*, 27 (1), 125-149.

Miraldo M. (2007): Reference pricing versus co-payment in the pharmaceutical industry: price, quality and market coverage Centre for Health Economics, University of York, Research Paper 25; 2007

Miraldo, M (2008), Reference pricing and firms' pricing strategies. Journal of Health Economics, forthcoming doi:10.1016/j.jhealeco.2008.09.006

Mullens A. (1998): Reference-based pricing: will other provinces follow the BC lead? CMAJ, 158, 239-241.

Narine L., Sen M. (1997): Pharmaceutical cost containment policies: intended and unintended impacts. Report prepared for the Pharmaceutical Manufacturers Association of Canada. Department of Health Administration, University of Toronto.

Narine L., Senathirajah M., Smith T. (1999): Evaluating reference-based pricing: initial findings and prospects. CMAJ, 161, 286-288.

Petkanchin V. (2006): Economic effects of Germany's reference pricing policy for drugs. Centre for the New Europe Research Paper, Brussels.

Pharmac (1996): Pharmaceutical Management Agency Annual 1996 Review, Pharmac Ltd., Wellington.

Schneeweiss S., Schoffski O., Selke G. (1998): What is Germany's experience on reference based drug pricing and the etiology of adverse health outcomes or substitution? Health Policy, 44, 253-260.

Schneeweiss S., Soumerai S.B., Glynn R.j., Maclure M., Dormuth C., Walker A.M. (2002): Impact of reference-based pricing for angiotensin-converting enzyme inhibitors on drug utilization. Canadian Medical Association Journal, 166 (6), 737-745.

Schneeweiss S., Soumerai S.B., Maclure M., Dormuth C., Walker A.M., Glynn R.J. (2003): Clinical and economic consequences of reference pricing for dihydropyridine calcium channel blockers. Clinical Pharmacology and Therapeutics, 74 (4), 388-400.

Schoffski O. (1996): Consequences of implementing a drug budget for office-based physicians in Germany. Pharmacoeconomics, 10 (2), 37-47.

Simoens S., De Bruyn K., Bogaert M., Laekeman G. (2005): Pharmaceutical policy regarding generic drugs in Belgium. Pharmacoeconomics, 23 (8), 755-766.

Ubeda A., Cardo E., Selles N., Broseta R., Trillo J.L., Fernandez-LLimos F. (2007): Antidepressant utilization in primary care in a Spanish region: Impact of generic and reference-based pricing policy (2000-2004). Psychiatry Epidemiology, 42, 181-188.

Ulrich V., Wille E. (1996): Healthcare reform and expenditure on drugs: the German experience. Pharmacoeconomics, 10 (2), 81-88.

Vandergrift M., Kanavos P. (1997): Health policy vs industrial policy in the pharmaceutical sector: the case of Canada. Health Policy, 41, 241-260.

VFA (2000): *Verband Forschender Arznemittelherstteller Statistics*, Berlin.

Von de Schulenberg J.M.G. (1997): Management of cost and utilization of pharmaceuticals in Germany. Health Policy, 41, 45-53.

Woodfield A., Fountain J., Borren P. (1997): Money and medicines: an economic evaluation of reference pricing and related public-sector cost-containment systems for pharmaceuticals with special reference to New Zealand. Merck Sharp & Dohme (NZ) Ltd., Christchurch.

Woodfield A. (2001): Augmenting reference pricing of pharmaceuticals in New Zealand with strategic cross-products agreements, Pharmacoeconomics, 19 (4), 367-377.

Zammit-Lucia J., Dasgupta R. (1995): Reference Pricing. The European experience. Health Policy Review Paper, 10, St. Mary's Hospital Medical School, London.

Zweifel P., Crivelli L. (1996): Price regulation of drugs: lessons from Germany. Journal of Regulatory Economics, 10, 257-273.