PHARMACEUTICAL POLICY ANALYSIS – A EUROPEAN PERSPECTIVE ON PRICING AND REIMBURSEMENT IN CHALLENGING TIMES

Christine Leopold

The research presented in this PhD thesis was conducted under the umbrella of the Utrecht World Health Organization (WHO) Collaborating Centre for Pharmaceutical Policy and Regulation, which is based at the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, the Netherlands. The Collaborating Centre aims to develop new methods for independent pharmaceutical policy research, evidence-based policy analysis and conceptual innovation in the area of policy making and evaluation in general.

The research in this thesis was performed in collaboration with the Gesundheit Österreich GmbH / Austrian Health Institute / WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policy, Vienna, Austria.

Leopold, C.

Pharmaceutical Policy Analysis – A European perspective on pricing and reimbursement in challenging times

Thesis Utrecht University – with ref. – with summary in Dutch and German

ISBN: 978-94-6182-363-2

Printed by: Off Page, www.offpage.nl

PHARMACEUTICAL POLICY ANALYSIS – A EUROPEAN PERSPECTIVE ON PRICING AND REIMBURSEMENT IN CHALLENGING TIMES

Prijzen en vergoeding van geneesmiddelen in een economische recessie
- farmaceutisch beleid in perspectief
(met een samenvatting in het Nederlands)

Analyse arzneimittelpolitischer Maßnahmen
– ein Blick auf Europa in wirtschaftlich schwierigen Zeiten
(mit einer Zusammenfassung in deutscher Sprache)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 8 januari 2014 des ochtends te 10.30 uur

door

Christine Leopold

geboren op 29 september 1979 te Wenen, Oostenrijk

Promotores:	Prof. dr. H.G.M. Leufkens
	Prof. dr. R.O. Laing
Co-promotores:	Dr. A.K. Mantel-Teeuwisse
	Dr. S. Vogler

TABLE OF CONTENTS

CHAPTER 1

General introduction

BACKGROUND

National pharmaceutical policies are embedded in a framework with many different stakeholders, different levels of legal requirements and different national policy objectives such as ensuring public affordability of health care while rewarding innovation [1,2]. In European Union (EU) Member States, policy makers are taking their decisions within a framework of legal regulations at national and European level. They have to relate to the political and social context of their country, while at the same time consider European and international developments. Within a national pharmaceutical system policy makers have many different policy choices, for example policies targeting at regulating prices, reimbursement limits and rational use of medicines. However, policy making is also shaped by the diverse interests and power of other stakeholders in the system such as prescribers, regulators, pharmacists, payers, industry and patients [2].

The pharmaceutical policy environment is dynamic as new medicines are being developed and different medical needs arise. Tensions are especially noticeable with respect to pricing and reimbursement of medicines; what health care plans may view as necessary to maintain equitable access to medicines, industry may view as inimical to research and development (R&D) and innovation [3]. Therefore, the question for policy makers is, given that resources will always be too limited to address all problems at the same time, which aspects of a pharmaceutical policy should they prioritize to obtain the best public health for the lowest cost [4]. To ensure a sustainable environment governments are required to regularly monitor policies, implement new ones and readjust existing polices. For this reason pharmaceutical policy analysis aims at assessing the effects and the performance of these implemented policies and policy changes at different levels: at the starting point of research and innovation; at the regulatory and policy making level; at the level of outcomes or finally at the level of measuring the impact on public health, as illustrated in Figure 1. Policy analysis examines the intended and unintended impacts of policies or policy changes on various outcomes such as medicine prices, pharmaceutical expenditure, medicine utilization and eventually on overall public health such as mortality rates of a population.

Although an increasing number of descriptions of national pharmaceutical systems were published in recent years to address the need for country specific information, analyses and evaluations of the impact of national pharmaceutical pricing and reimbursement policies are still rare [4-8]. Besides peer-reviewed articles, reports by international organizations such as the Organization for Economic Co-operation and Development (OECD) [9-16], the World Health Organization (WHO) [17], the European Commission [18-19] and networks of European of public authorities [20,21] became key references for research on pricing and reimbursement policies. However, as the pharmaceutical policy landscape is rapidly evolving, research and impact analyses are constantly needed.

This thesis is a body of work belonging to a series of pharmaceutical policy analysis projects undertaken under the umbrella of the Utrecht WHO Collaborating Centre for Pharmaceutical Policy and Regulation, all focusing on different aspects of the policy cycle depicted in Figure 1 [22-25]. The focus of this thesis is to understand pharmaceutical policies through the lens of analyzing European pricing and reimbursement policies and their impacts.

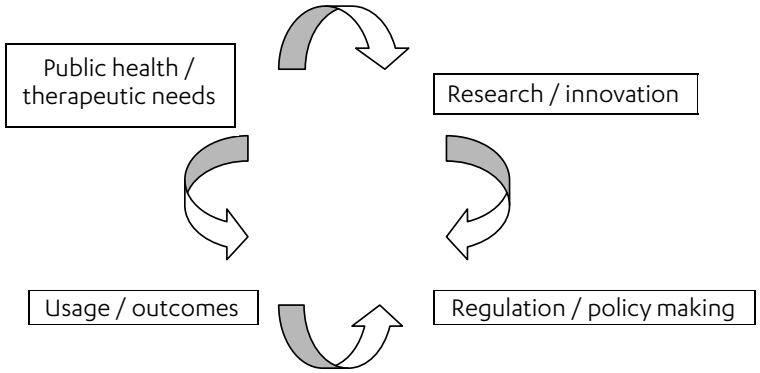


Figure 1. Pharmaceutical Policy Analysis. Source: WHO Collaborating Centre for Pharmaceutical Policy and Regulation, Utrecht Institute for Pharmaceutical Sciences, Utrecht University

THE PHARMACEUTICAL POLICY LANDSCAPE GLOBALLY AND IN EUROPE

In the last decades pharmaceutical expenditure accounted for a considerable proportion of total health care spending in Europe and worldwide. These percentages of total health care expenditure varied to a great extent among countries ranging from 6.8% in Norway to 28.5% in Greece and 33.4% in Hungary in 2011; examples from other high income countries outside of Europe showed ranges from 9.4% in New Zealand to 16.6% in Canada in 2011 [26]. These variations in pharmaceutical expenditure can be explained by decisions made by national policy makers. They are acting within a triangle of granting access to medicines within the limits of available public resources and ensuring sustainability in funding and at the same time rewarding innovation. Each of the three pillars within this triangle creates challenges for policy makers who need to take national situations such as wealth of a country, the political climate as well as cultural and historical developments into account:

Access to medicines: Even though marketing authorization is harmonized in Europe through the implementation of the European Medicine Agency (EMA) and EU legislation on marketing authorization on the basis of a medicine's quality, safety and efficacy [27], discrepancies in access to medicines still appear. Reasons include delays during the pricing and reimbursement process, which can be caused by authorities or by insufficient documentation of companies or strategic behavior of companies after the decision on pricing and reimbursement is taken, as prices in one country influence the prices in other countries due to policies such as external price referencing [28].

Cost-containment and ensuring of sustainable public funds: In Europe reimbursable medicines (which account for the majority of medicines on the market) are paid for – either fully or partially – by third party payers such as national health services or social health insurance institutions. Hence, European countries are continuously adjusting their pharmaceutical policy framework with respect to pricing and reimbursement of medicines to guarantee public funding of needed medicines. In the last five years several European countries have been suffering from an economic recession, forcing many of these countries to cut public spending in many sectors including healthcare [29-31].

Reward for innovation: The pharmaceutical industry is an important player in European countries, not only as a supplier or distributor of (new) medicines but also as knowledge economy employer. Pricing and reimbursement policies can be critical factors in the reward for innovation. This objective of reward for innovation can be potentially conflicting with the governments' obligation to guarantee public affordability of medicines. This becomes evident when it comes to the question of granting a "premium" price of a medicine that provides major added value [32,33].

Besides these challenges, two additional factors play an important role in the complex pharmaceutical policy environment. First, the demand for medicines is rising in Europe in the last years due to the demographic shift associated with the ageing of the population. Older people often suffer from multiple diseases demanding numerous medicines. In addition, more highly specialized treatment options, such as medicines which require prior genetic testing as is the case for personalized medicines, are now becoming more widely available [34]. Second, the common rules of a free market do not apply to the pharmaceutical market – as for health care in general – because information asymmetries and market failures exist: information asymmetries between prescribers, dispensers and consumers regarding the quality, safety, efficacy and value for money of individual medicines, which could allow prescribers and dispensers to prescribe or dispense certain branded medicines instead of lower priced generics to increase their own profits; imperfect competition as patented medicines have a monopolistic position and product proliferation does not automatically induce competition; inelasticity of demand as medicines are not commodity products because the patient will pay whatever s/he has to when s/he gets sick; market failures because of a moral hazard as consumers are inclined to over-consume because they do not directly bear the cost of consumption; and finally the underinvestment for particular diseases [35-37].

To account for the described challenges within the triangle and the market failures the WHO has been encouraging countries to develop a national medicine policy including regulations and policies. A national medicine policy is defined by the WHO as *'a commitment to a goal and a guide for action. It expresses and prioritizes the medium- to long-term goals set by the government for the pharmaceutical sector, and identifies the main strategies for attaining them. It provides a framework within which the activities of the pharmaceutical sector can be coordinated. It covers both the public and the private sectors, and involves all the main actors in the pharmaceutical field'* [38]. A national medicine policy shall aim to ensure access (equitable availability and affordability of essential medicines), quality (the quality, safety and efficacy of all medicines), and rational use (the promotion of therapeutically sound and cost-effective use of medicines by health professionals and consumers) [38].

PHARMACEUTICAL POLICY ANALYSIS THROUGH THE LENS OF PRICING AND REIMBURSEMENT

During the last decades European countries implemented a variety of pricing and reimbursement policies, primarily to improve a more rational use and affordability of medicines. In order to target both the price of a medicine (supply side) and prescribed volume of a medicine

(demand side), policy makers can choose from a variety of supply side measures including regulating prices or reimbursement limits of medicines and demand side measures aiming at limiting prescribing behaviors of doctors by implementing prescribing budgets [17,20,39,40]. Important to highlight in this context is that, in contrast to harmonized processes of marketing authorization at the EU-level, designing a pharmaceutical pricing and reimbursement policy is still a national competence of each EU Member State, provided that each country complies with the rules such as the EU Transparency Directive (Council Directive 89/105/EEC) which provide a common procedural framework for pricing and reimbursement decisions with regard to time-lines and how decision should be communicated [41,42].

In many countries worldwide there is a distinction between the public sector where medicines, for example those on the essential medicines list, are purchased and distributed by the state – often free of charge, and the private sector where medicines are handled by private actors and are required to be purchased fully out-of pocket. Many of these countries, e.g. low and middle income countries like India, Pakistan, Egypt, South Africa and China, have a rather small public sector, meaning that patients have to buy the majority of medicines out-of-pocket in the private sector, where free or market-based pricing of medicines is common [9,17,37]. In many high income European countries such as the EU Member States this distinction between public and private sector is not always clear. Although medicines are often supplied through private channels they are to a great extent publicly funded through extensive insurance coverage (either social health insurance or national health services, so-called third party payers). Therefore, they often have medicine price regulations or price negations for medicines that are dispensed at the cost of the third party payer (= reimbursable medicines). Free or market-based pricing is only applied to non-reimbursable medicines, which are often over-the-counter medicines [17,20].

When regulating medicine prices which all EU Member States do at least for reimbursable medicines many countries apply external price referencing (EPR) [20]. EPR is defined by the WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies as *'the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiation the price of the product in a given country'* [43]. However, an up-to-date description of the differences in EPR methodologies in Europe and the impact of this pricing policy on medicine prices as well as its possible implication on price convergence has not been studied before.

Besides regulating the ex-factory price, policy makers may also regulate distribution margins for wholesalers and pharmacies. While the majority of EU Member States apply statutory wholesale mark-ups, all EU Member States regulate pharmacy margins, usually in the form of regressive schemes or linear mark-ups. Finally, European policy makers may apply value-added taxes (VAT) to medicines at very different rates and sometimes even differentiating between reimbursable and non-reimbursable medicines [44,45]. During the recent economic recession many countries implemented price cuts – either targeting at the ex-factory price level or at the distribution margins – as one way to control public spending. Analyzing the impact of these price cuts is important to understand whether it affected accessibility of affordability of medicines.

Studies which analyze the impact of pharmaceutical policies usually focus on reimbursable medicines as the vast majority of medicines in Europe are included in national positive lists, which is a list of medicines that may be prescribed at the expense of the third party payer. Again many different policies with respect to reimbursement are applied in the different EU Member States. One of the very commonly used cost-containment reimbursement policies is a therapeutic reference price system [46-48], which is defined as *'a third party payer determines a maximum price (=reference price) to be reimbursed for certain pharmaceuticals in an ATC 4 or ATC 5 group'* [43]. Studying the impact of the implementation of such a system on the use of medicines is an example of a policy outcome analysis (see Figure 1).

Besides the focus on regulating prices as well as limiting reimbursement, countries also choose to implement measures related to the rational use of medicines. Most of these demand side regulations target at prescribers and pharmacies and other dispensaries, e.g. generic prescribing, generic substitution, prescriptions guidelines and prescribing budgets for doctors [49-51]. Especially generic policies were among the many policy options which were implemented or adjusted by policy makers during the economic recession to control public spending on medicines.

All of the above mentioned policies are primarily relevant for reimbursable medicines dispensed in the out-patient sector. Reimbursement of medicines dispensed in hospital settings differs from the out-patient setting – funding is mainly through hospital budgets or regional healthcare budgets – and different pricing and payment policies are applied [52]. Certain medicines, such as personalized medicines – defined as the treatment plan based on molecular screening and prior genetic testing that define which regime will be most effective in specific patients [53,54] – are often used at the interface of those two sectors. Hence, they fall under the scope of different funding bodies. Nowadays, policy makers are recognizing the need to adjust pricing and reimbursement policies to face these new circumstances. Hence, there is a research gap in the assessment of the pricing and reimbursement mechanisms applied for personalized medicines at the interface of the hospital and out-patient sector.

IMPACT OF ECONOMIC RECESSION ON PUBLIC AFFORDABILITY OF MEDICINE CONSUMPTION

Since the crash of the housing market in USA at the end of 2007, the world has been struggling with an economic recession [55,56]. Europe has faced difficulties in recovering from the crisis in 2007 and was confronted with an unemployment rate of up to 12.1% for EU-28[1] in July 2013 compared to 8.5% in 2001; with the lowest rate of 4.8% in Austria compared to Greece (27.6%) and Spain (26.3%) having the highest rate in July 2013 [57]. In terms of gross domestic product (GDP) the EU-27 countries had a GDP growth rate of +3.2% in 2007, whereas in 2009 it went down to a negative growth of -4.3%, recovering in July 2009 to +0.1% [58]. These developments have forced EU Member States to implement measures for budget savings and policies to contain costs which might negatively impact accessibility and affordability.

[1] EU-28 = EU-27 countries plus Croatia (since 1 July 2013).

In times of economic recession policy makers are confronted with four main challenges: 1) predictability of public funding for health care services as sudden interruptions to public revenue streams can make it difficult to maintain the previous level of health care, 2) cuts to public spending on health made in response to an economic shock typically come at a time when a health system may require more, not fewer resources (to address the adverse health effects of unemployment), 3) arbitrary cuts to essential services may further destabilize the health system if they erode financial protection, equitable access to care and the quality of care provided, increasing costs in the longer term. In addition to introducing new inefficiencies, cuts across the board are unlikely to address existing inefficiencies, potentially exacerbating the fiscal constraint; and 4) patients – especially vulnerable groups such as older people or low-income people – may refrain from demanding healthcare services as they cannot afford to pay for the services or the out-of-pocket costs [59].

Only a few studies have been published which looked at the impact of the recent financial crisis on global health and in particular on pharmaceutical consumption [60-64], showing that pharmaceutical consumption went down especially in the Baltic countries and that European countries had to implement a variety of pricing and reimbursement policies in response to reduced public budgets. Investigating the impact of these policy changes and the declines in pharmaceutical consumption or medicine prices is crucial for policy makers to understand whether public affordability and accessibility to medicines is still guaranteed.

GOALS AND OBJECTIVES OF THIS THESIS

The goal of this thesis is to understand pharmaceutical pricing and reimbursement policies and their impact on medicines prices and consumption in Europe. The underlying basis for this thesis is pricing and reimbursement policy data in European countries, which are analyzed in descriptive as well as through statistical methods by evaluating the impact of these policies on medicine prices and consumption, especially during the economic recession.

THESIS OUTLINE AND OVERVIEW

Chapter 2 addresses the question as to how national pharmaceutical policies aim at controlling public pharmaceutical spending by regulating medicine prices. In particular, **chapter 2.1** gives a descriptive overview of one of the most commonly used pricing policies in Europe: external price referencing. **Chapter 2.2** explores how national medicine prices may be affected by policies such as external price referencing. The aspect of how national policies affect the overall medicine price level in European countries and whether these policies lead to price convergence across Europe is addressed in **chapter 2.3**.

Chapter 3 focuses on how countries re-evaluate and adjust national policies in times of economic recession. **Chapter 3.1** analyses which pharmaceutical pricing and reimbursement policies were implemented by countries during the time of the economic recession and evaluates the correlation with medicines sales in eight European countries. **Chapter 3.2** presents a detailed evaluation of the impact of different policy measures on the consumption of antipsychotic medicines in Portugal and Finland during the time of the economic recession.

In Europe, there is an increasing use of personalized medicines which require prior genetic testing which entail new challenges to policy makers with respect to pricing and reimbursement. In specific, **chapter 4.1** looks into how European pricing and reimbursement authorities deal with the increasing challenge of how to evaluate and assess these 'treatment packages' which included both new and often expensive medicines as well as medical devices such as diagnostics.

The concluding chapter (**chapter 5**) of this thesis contains a general discussion of the benefits and limitations of research on pharmaceutical pricing and reimbursement policy interventions. In specific, methodological challenges of comparing medicines prices are described and the policy implications of all study findings are presented. Finally, areas for future research are identified which could improve access and affordability of medicines.

REFERENCES

1. Almarsdottir AB, Traulsen JM. Studying and evaluating pharmaceutical policy – becoming a part of the policy and consultative process. Pharm World Sci. 2006 Feb;28(1):6-12. Epub 2006 Jun 30.
2. Bigdeli M, Jacobs B, Tomson G, Laing R, Ghaffar, Dujardin B, Van Damme W. Access to medicines from a health system perspective. Health Policy Plan. 2013 Oct;28(7):692-704. doi: 10.1093/heapol/czs108. Epub 2012 Nov 22.
3. Jacobzone S. Pharmaceutical policies in OECD countries: reconciling social and industrial goals. Labor market and social policy – occasional paper No. 40. OECD. 2000. Available from: http://www.oecd-ilibrary.org/social-issues-migration-health/pharmaceutical-policies-in-oecd-countries_323807375536. Accessed 20 June 2013.
4. Seiter A. A Practical Approach to Pharmaceutical Policy. Directions in Development. The World Bank, Washington 2010. Available from: http://www-wds.worldbank.org/external/default/WDSContentServer/WDSP/IB/2010/06/22/000334955_20100622050742/Rendered/PDF/552030PUB0Phar10Box349442B01PUBLIC1.pdf. Accessed 14 August 2013.
5. Wladysiuk M, Araszkiewicz A, Godman B, Szabert K, Barbui C, Haycox A. Influence of patient co-payment on atypical antipsychotic choice in Poland: implications once generic atypical are available. Appl Health Econ Health Policy. 2011 Mar 1;9(2):101-10. doi: 10.2165/11318840-000000000-00000.
6. Gregson N, Sparrowhawk K, Mauskopf J, Paul J. Pricing medicines: theories and practice, challenges and opportunities. Nat Rev Drug Discov. 2005 Feb;4(2):121-30.
7. Vogler S, Habl C, Bogut M, Voncina L. Comparing pharmaceutical pricing and reimbursement policies in Croatia to the European Union Member States. Croat Med J. 2011 Apr 15;52(2):183-97.
8. Andersson K, Petzol MG, Sonesson C, Lönnroth K, Carlsten A. Do policy changes in the pharmaceutical reimbursement schedule affect drug expenditures? Interrupted time series analysis of cost, volume and cost per volume trend in Sweden 1986-2002 Health Policy. 2006;79:231-243.
9. Docteur E, Paris V. Pharmaceutical pricing policies in a global market. Paris: OECD Health Policy Studies; 2007. Available from: http://www.oecd.org/fr/els/systemes-sante/pharmaceuticalpricingpoliciesinaglobalmarket.htm. Accessed on 14 August 2013.
10. Paris V, Belloni A. Value in Pharmaceutical Pricing. OECD Health Working Paper. 2013. No. 63. Available from: http://www.oecd-ilibrary.org/social-issues-migration-health/value-in-pharmaceutical-pricing_5k43jc9v6knx-en. Accessed on 14 August 2013.
11. Kaló Z, Docteur E, Moïse P. Pharmaceutical Pricing and Reimbursement Policies in Slovakia. OECD Health Working Paper. 2007. No. 31.
12. Moïse P, Docteur E. Pharmaceutical Pricing and Reimbursement Policies in Mexico. OECD Health Working Paper.2007. No. 25.
13. Moïse P, Docteur E. Pharmaceutical Pricing and Reimbursement Policies in Sweden. OECD Health Working Paper. 2007. No. 28.
14. Paris V, Docteur E. Pharmaceutical Pricing and Reimbursement Policies in Canada. OECD Health Working Paper. 2006. No. 24.
15. Paris V, Docteur E. Pharmaceutical Pricing and Reimbursement Policies in Switzerland", OECD Health Working Paper. 2007. No. 27.
16. Paris V, Docteur E. Pharmaceutical Pricing and Reimbursement Policies in Germany. OECD Health Working Paper. 2008. No. 31.
17. Kaplan W, Writz VJ, Mantel-Teuwisse A, Stolk P, Duthey B, Laing R. Priority Medicines Report for Europe and the World Update 2013. World Health Organization. 2013. Available from: http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf. Accessed 20 August 2013.
18. European Commission DG Competition. Pharmaceutical sector inquiry final report. Brussels, 2009. Available from: http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf. Accessed 20 May 2013.
19. High Level Pharmaceutical Forum. High Level Pharmaceutical Forum 2005-2008. Conclusions and Recommendations. European Commission DG Health & Consumers 2008. Available from: http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/pharmaceutical-forum/index_en.htm. Accessed 20 April 2013.
20. Vogler S, Habl C, Leopold C, Rosian-Schikuta I, de Joncheere K, Lyager Thomsen T. Pharmaceutical Pricing and Reimbursement Information (PPRI): final report. Luxembourg. DG Health and Consumer Protection of the European Commission. 2007; Available from: http://whocc.goeg.at/Publications/BooksReports. Accessed 20 June 2013.

21. Pharmaceutical Pricing and Reimbursement Information (PPRI): country reports. 2007-2013; Available from: http://whocc.goeg.at/Publications/CountryReports. Accessed 20 June 2013.
22. Waning B. Innovative approaches for pharmaceutical policy research in developing countries: the view through a market lens [PhD thesis]. Utrecht: Utrecht University; 2011.
23. Cameron A. Understanding access to medicines in low-and middle income countries through the use of price and availability indicators [PhD thesis]. Utrecht: Utrecht University; 2013.
24. Hoebert JM. Cross-country variation in medicines use. A pharmaceutical system perspective [PhD thesis]. Utrecht: Utrecht University; 2013.
25. Tafuri G. Exploring the regulatory decision-making process for medicines [PhD thesis]. Utrecht: Utrecht University; 2013.
26. OECD. Pharmaceutical expenditure. As percentage of total expenditure on health. Health: Key Tables from OECD. 2013; doi: 10.1787/pharmexp-table-2013-1-en. Accessed 17 August 2013.
27. European Commission regulation N°726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.30.4.2004;OJ L:136.
28. Eichler HG, Pignatti F, Flamion B, Leufkens HG, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. Nat Rev Drug Discov. 2008;7(10):818-826. doi: 10.1038/nrd2664.
29. Bouvy J, Vogler S. Pricing and Reimbursement Policies: Impacts on Innovation. Background paper to chapter 8.3 of the WHO Priority Medicines for Europe and the World 2013. World Health Organization 2013. Available from: http://www.who.int/medicines/areas/priority_medicines/BP8_3_pricing.pdf. Accessed on 12 July 2013.
30. Ecorys a. Competitiveness of the EU market and industry for pharmaceuticals. Volume I: Welfare implications of regulation. European Commission, Directorate General Enterprise & Industry, 2009.
31. Ecorys b. Competitiveness of the EU market and industry for pharmaceuticals. Volume II: Markets, Innovation & Regulation. European Commission, Directorate General Enterprise & Industry, 2009.
32. Morgan S, McMahon M, Greyson D. Balancing health and industrial objectives in the pharmaceutical sector: lessons learned from Australia. Health Policy 2008;87:133-145.
33. Vandergrift M, Kanavos P. Health policy versus industrial policy in the pharmaceutical sector: the case of Canada. Health Policy 1997;41:241-260.
34. Daniels N, Sabin J. Limits to health care: fair procedures, democratic deliberation, and the legitimacy problem for insurers. Philosopy & Public Affairs 1997:303-350.
35. World Health Organization. Public-Private Roles in the Pharmaceutical Sector – Implications for Equitable Access and Rational Drug Use. Health Economics and Drug Series, No. 005. Geneva, Switzerland: World Health Organization 2009. Available from: http://archives.who.int/tbs/global/whozip27e.pdf. Accessed 20 June 2013.
36. Marquis MS, Phelps CE. Price Elasticity and Adverse Selection in the Demand for Supplementary Health Insurance. Economic Inquiry 1987;25:299-313.
37. Cameron A, Mantel-Teuwisse A, Leufkens HG, Laing R. Switching from originator brand medicines to generic equivalents in selected developing countries: how much could be saved? Value health. 2012;15:664-673.
38. World Health Organization. How to develop and implement a national drug policy. Second edition. Updates and replaces Guidelines for Developing National Drug Policies, 1988. Available from: http://apps.who.int/medicinedocs/pdf/s2283e/s2283e.pdf. Accessed 20 May 2013.
39. Zuidberg C. The pharmaceutical system of the Netherlands. A comparative analysis between the Dutch out-patient pharmaceutical system, in particular the pricing and reimbursement characteristics, and those of the other European Union Member States, with a special focus on tendering-like systems. Vienna: Gesundheit Österreich GmbH, 2010. Available from: http://whocc.goeg.at/Literaturliste/Dokumente/BooksReports/The%20pharmaceutical%20system%20of%20the%20Netherlands_FINAL.pdf. Accessed 14 April 2012.
40. Vogler S, Espin J, Habl C. Pharmaceutical Pricing and Reimbursement Information (PPRI) - New PPRI analysis including Spain. Pharmaceuticals Policy and Law 2009;11:213-34.
41. Council Directive of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems (89/105/EEC). http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31989L0105:en:HTML. Accessed 12 August 2013.
42. European Commission. Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF

THE COUNCIL relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of public health insurance systems. 2012. Available from: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/transpadir_finalprop01032012_en.pdf. Accessed 12 July 2013.

43. WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies. Pharmaceutical Pricing and Reimbursement glossary. Updated version as of July 2013. Available from: http://whocc.goeg.at/Glossary/. Accessed 20 August 2013.
44. Kanavos P, Schurer W, Vogler S. Pharmaceutical Distribution Chain in the European Union: Structure and Impact on Pharmaceutical Prices. London/Vienna: 2011. Available from: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/structimpact_pharmaprices_032011_en.pdf. Accessed 15 May 2013.
45. Mossialos E, Mrazek M, Walley T. Regulating pharmaceuticals in Europe: striving for efficiency, equity, and quality. Maidenhead (UK): Open University Press. 2004; Available from: http://www.euro.who.int/__data/assets/pdf_file/0008/98432/E83015.pdf . Accessed June 2012.
46. Pohjolainen L. Reference price and price competition – evidence from the Finnish pharmaceutical market. Master's thesis. Aalto University, School of Economics, Department of Economics. February 2012. Available from: https://aaltodoc.aalto.fi/handle/123456789/3456. Accessed 20 August 2012.
47. Vogler S. Preisbildung und Erstattung von Arzneimitteln in der EU - Gemeinsamkeiten, Unterschiede und Trends. Pharmazeutische Medizin 2012;14(1):48-56.
48. Jansson S. Implementing accountability for reasonableness – the case of pharmaceutical reimbursement in Sweden. Health Econ Policy Law. 2007 Apr;2(Pt 2):153-71. doi: 10.1017/S1744133107004082.
49. Regan TL. Generic entry, price competition, and market segmentation in the prescription drug market. International Journal of Industrial Organization 2008;26:930-948.
50. Paraponaris A, Verger P, Desquins B, et al. Delivering generic without regulatory incentives? Empirival evidence from French general practitioners about willingness to prescribe international non-proprietary names 2004;70:23-32.
51. Gonzalez J, Sismeiro C, Shantanu D, Stern P. Can branded drugs benefit from generic entry? The role of detailing and price in switching to non-bioequivalent molecules. Intern. J. of Research in Marketing 2008;25:247-260.
52. Vogler S, Zimmermann N, Mazag J. Procuring medicines in hospitals: results of the European PHIS survey. European Journal of Hospital Pracitice 2011;(2):21.
53. Coggi PT. A European view on the future of personalized medicine in the EU. European Journal of Public Health 2011; 21(1):6-7. Epub 2011/01/21.
54. Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med. 2010 Jul 22;363(4):301-4. doi: 10.1056/NEJMp1006304. Epub 2010 Jun 15.
55. Shelburne R, Trentini C. Public Health in Europe: the 2007-2009 financial crisis and UNECE activities. Discussion paper of the United Nations Economic Commission For Europe. November 2009. Available from: http://www.unece.org/fileadmin/DAM/oes/disc_papers/ECE_DP_2009-2.pdf. Accessed 20 June 2012.
56. United Nations Economic and Social Council. The economic situation in the Economic Commission for Europe region: Europe, North America and the Commonwealth of Independent States in 2008-2009. Substantive session of 2009. Available from: http://www.un.org/regionalcommissions/crisis/ececis.pdf. Accessed 20 June 2013.
57. EUROSTAT. Unemployment rate, annual average, by sex and age groups (%). EUROSTAT. 2013. Accessed on 11 August 2013.
58. EUROSTAT. Gross domestic product growth rates (%). EUROSTAT. 2012. Accessed on 11 September 2012.
59. Mladovsky P, Srivastava D, Cylus J, Karanikolos M, Evetovits T, Thomson S, McKee M. Health policy response to the financial crisis in Europe. WHO regional office for Europe. Policy Summary 5. 2012. Available from: http://www.euro.who.int/__data/assets/pdf_file/0009/170865/e96643.pdf. Accessed 20 June 2012.
60. Buysse IM. Impact of the economic recession on the pharmaceutical sector. Utrecht University, WHO CC for Pharmacoepidemiology & Pharmaceutical Policy Analysis.2010. Available from: http://www.pharmaceuticalpolicy.nl/Publications/Reports/Buysse_report%20impact%20recession_2010.pdf. Accessed 8 August 2012.
61. Garuoliene K. Pharmaceutical policy and the effects of the economic crisis: Lithuania. Eurohealth 2011;17(1):1-4. Available from: http://www.euro.who.int/__data/assets/pdf_file/0017/147104/Eurohealth_Vol-17_No-1_web.pdf. Accessed 20 May 2012.

62. Rüütel D, Pudersell K. Pharmaceutical policy and the effects of the economic crisis. Estonia. Eurohealth 2011;17(1):5-8. http://www.euro.who.int/__data/assets/pdf_file/0017/147104/Eurohealth_Vol-17_No-1_web.pdf. Accessed 20 May 2012.

63. Behmane D, Innus J. Pharmaceutical policy and the effects of the economic crisis. Latvia. Eurohealth 2011;17(1):8-10. http://www.euro.who.int/__data/assets/pdf_file/0017/147104/Eurohealth_Vol-17_No-1_web.pdf. Accessed 20 Max 2012.

64. Vogler S, Zimmermann N, Leopold C, de Joncheere K. Pharmaceutical policies in European countries in response to the global financial crisis. South Med Rev. 2011;4(2):32.

CHAPTER 2

External price referencing
and its impact on medicine prices

CHAPTER 2.1

Differences in external price referencing in Europe - A descriptive overview

Health Policy. 2012;104(1):50-60

Christine Leopold, Sabine Vogler,
Aukje Mantel-Teeuwisse, Kees de Joncheere,
Bert Leufkens, Richard Laing

ABSTRACT

Objective: This study aimed to provide an up-to-date description as well as comparative analysis of the national characteristics of pharmaceutical external price referencing (EPR) in Europe.

Methods: Review of the country-specific PPRI (Pharmaceutical Pricing and Reimbursement Information) Pharma Profiles written by representatives of the PPRI Network. The Profiles were analysed according to predefined criteria.

Results: Of 28 analysed European countries 24 applied EPR in 2010. The majority of countries have statutory rules to implement EPR. Most countries had less than 10 countries in their reference baskets. Higher-income countries tend to include higher-income countries in their basket, whereas lower-income countries refer to lower-income countries. Taking the average price of all countries in the basket as the basis to calculate the national price was the most common strategy (n=8). The methodology of EPR has changed in most European countries over the past 10 years (n=19).

Conclusions: EPR is a widely used pricing policy in Europe and is still actively used as well as adjusted by national authorities. However, we still see room for improvement by implementing more detailed legislations in terms of the revision of prices and by identifying alternative countries in case a product is not on the market. We also see the need for formal information sharing (e.g. congresses dedicated to pricing strategies and systems) with other public pricing authorities to learn about the different EPR methodologies as well as the national experiences. These congresses might also give room to better understand national pricing methods including discussions on possible limitations of these pricing methods.

INTRODUCTION

All European countries have different national pharmaceutical systems due to historic, political, legal and economic developments but also due to the ways in which the health care system is funded [1]. These countries all face the same challenge of guaranteeing their populations affordable access to medicines within their limited public resources.

National governments take different interests into consideration when shaping a national pharmaceutical policy. Notably, payers are under pressure from citizens and other stakeholders to promote public health and to ensure prompt access to affordable medical treatment. At the same time there is also pressure for some countries to serve the objectives of a national industry policy, by offering relatively high ex-factory prices or other concessions intended to incentivise or reward the domestic pharmaceutical industry [2-4].

Another relevant aspect to consider is that market dynamics in the pharmaceutical markets differ from other markets for consumer products. Market demand for medicines is characterised by low price sensitivity (as reimbursable medicines are paid to a large extent by Third-Party Payers) and a relatively high level of asymmetric information between patient and prescriber (as prescribers decide which medicine the patient should take). In addition supply is characterised by a market with imperfect competition (pharmaceutical companies and distributors have a significant amount of market power). This situation requires that the state intervenes either to promote competition or to implement regulations to prevent exploitation of sick patients who may be willing to pay excessive amounts for an unreasonable hope of cure [5-8].

In the early nineties, most governments in Europe decided to implement a mix of different pharmaceutical policies which aimed at containing public spending while stimulating research and development (R&D) and industrial development. These policies focused on either controlling medicine prices and/or on containing the prescribed volume of medicines or both. Until today, there is still no agreement as to which policies or interventions are perceived as successful. However, time has shown that it is crucial to regularly adjust these policies and to have a fair mix of pricing and volume-control polices [9]. Otherwise it would lead to a so called "pendulum effect", meaning that the desired cost-saving effects would diminish as market players adjust [10].

Pharmaceutical price regulations can occur at various points along the distribution chain, from manufacturer to wholesaler to pharmacists and patient. Regulations of the ex-factory price may be direct or indirect. Measures for direct price setting include negotiations, statutory pricing – either through external price referencing or internal price comparisons - and price cuts/freezes. External price referencing refers to prices of other countries whereas internal price referencing (or also referred to as national reference pricing) is a method to compare prices of medicines in a country with the price of identical pharmaceutical or similar product level or even with therapeutic equivalent treatment (not necessarily a medicine) in a country). Other measures have taken a more indirect approach to regulating medicine prices by regulating profits or calculating "cost-effective" prices using pharmaco-economic analysis [11].

Most research studies in the field of pharmaceutical policy analysis describe different pricing as well as volume regulations and analyse their impact on pharmaceutical expenditure (e.g. Mrazek

(2002) aimed in her study to review pharmaceutical pricing policies in Europe to understand the impact of regulations on pharmaceutical expenditures and evidence of actual outcomes) [12].

Only a few studies have described the detailed characteristics of one particularly widely used pricing policy, namely external price referencing (EPR also referred to as international price benchmark/comparison). EPR is defined by the European Pharmaceutical Pricing and Reimbursement Information (PPRI) glossary as "the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country" [8]. EPR is however a policy that is applied by countries worldwide and often European countries are taken as reference countries. Examples of countries which use European country prices as reference prices are Jordan[1], Brazil[2] and South Africa[3] [9]. As a consequence price changes in one country influence prices in other countries worldwide. Stargardt showed in his study that a marginal price change in Germany led to price changes in countries that have Germany in the country basket [13].

In order to analyse and understand pricing policy trends in Europe, attention needs to be given to the different characteristics of each single pricing policy. This needs to be done as many countries use a combination of methods. The objective of this study was to examine the differences and commonalities of EPR in all 27 European Union (EU) Member States plus Norway by describing and analysing the different methodologies taking into account the geographic distribution of EPR, the reference countries, the price calculation methodology and any changes in the EPR methodology over time. In this study only the out-patient sector is analysed and no comparison of impact on prices has been attempted. This study will provide policy makers and scientists in the field of pharmaceutical policy an up-to-date picture on the pricing policy tool EPR in Europe and will discuss whether this tool is still appropriate for all countries and in which ways.

MATERIALS AND METHODS

The main source of data was information published by the PPRI network. The PPRI network started as an EU-funded project from 2005 until 2007 and continues as a sustainable network for public authorities in pricing and reimbursement in Europe. Within the scope of the PPRI network country-specific reports, PPRI Pharma Profiles, on national pricing and reimbursement systems of the European Member States as well as associated countries were published. This approach of collecting information is unique as the PPRI Pharma Profiles were written by representatives of public authorities, such as Ministries of Health or third party payers, who are responsible for pricing and reimbursement[4].

---

[1] Jordan refers to among other countries United Kingdom, France, Spain, Italy, Belgium, Greece and the Netherlands

[2] Brazil refers to among other countries Portugal, Spain, France, Italy, and Greece

[3] South Africa refers to among other countries Spain; and Lebanon refer to among other countries France, United Kingdom, Belgium, Italy, Spain and Portugal

[4] Pharmaceutical Pricing and Reimbursement Information, available online http://ppri.goeg.at, latest access 25 February 2011

As the PPRI Pharma Profiles referred to the years 2007 and 2008, further research was required to obtain the most recent information available. This was done through written communication with members of the PPRI network. The information on EPR presented is what was available as of November 2010.

In order to best describe the EPR systems in Europe, the basic principles of the EPR system, which are the most commonly occurring elements, were taken for the analysis. The following principles were chosen:

- Existence of external price referencing
- National legal framework
- Composition of country basket
- Calculation method of the reference price (package size, frequency of updating of prices, what price level is taken: manufacturer, wholesale, pharmacy)
- Changes in the EPR methodologies over time
- Coverage of patent protected medicines or also including generics

To measure whether countries referenced other countries of similar economic level, countries were ranked by gross domestic product (GDP) per capita as provided by EUROSTAT[5]) for 2009. Then the average rank of all reference countries in the basket was calculated. Correlation between GDP/per capita rank and the average rank of the reference countries in the basket was assessed using Kendall's rank correlation tau (a measure for ranked data).

RESULTS

Existence of EPR in the EU and Norway

EPR was implemented in 24 countries (23 out of the 27 EU Member States plus Norway). Denmark, Germany, Sweden and United Kingdom did not use EPR in 2010. When setting national medicine prices, EPR was either applied as the main criterion or as supportive information (see Figure 1). In Belgium, EPR was just one of many pricing criteria, other criteria include economic assessments. In Finland, the price in other countries of the European Economic Area is only one criterion among many others, such as expected sales volume, R&D costs, and impact on available funds that are considered when approving the "reasonable" wholesale price. Cyprus stated that EPR is the sole criterion for pricing of all imported pharmaceutical products including over-the-counter (OTC) products (see Table 1).

Other countries use EPR within the reimbursement system by setting the price, which might be determined at manufacturer, wholesale or pharmacy level (see also Table 1). Hungary for instance stated: The manufacturer price of a newly included preparation containing active ingredient(s) that is not yet reimbursed cannot be higher than the lowest of the existing manufacturer prices in the countries listed in the application (France, Ireland, Germany, Spain, Portugal, Italy, Greece, Poland, Czech Republic, Slovenia, Slovakia, Belgium, Austria and one additional country).

[5] EUROSTAT public health database, available online http://epp.eurostat.ec.europa.eu/portal/page/portal/health/introduction; latest access 25 February 2011

Table 1. Overview on EPR methodology

	Existence of EPR		Composition of basket			
C.	adoption depth of EPR	Scope	# of countries in basket	GDP (2009)	income rank (GDP 2009)	Ø rank of countries in basket
AT	main criterion	reimb. Medicines	24	29300	24	15
BE	supportive information	all medicines	24	27400	20	15
BG	main criterion	POM	9		1	10
CY	main criterion	imported medicines	4	23200	14	19
CZ	main criterion	all medicines	8	19200	11	11
DE	EPR not applied			27400	21	
DK	EPR not applied			28400	23	
EE	main criterion	reimb. Medicines	4	15000	6	8
EL	main criterion	all medicines	22	22100	13	14
ES	main criterion	innovative medicine	not defined	24300	15	
FI	main criterion	reimb. Medicines	16	26600	19	19
FR	main criterion	innovative medicine	4	25400	17	18
HU	main criterion	reimb. Medicines	14	15300	7	15
IE	main criterion	POM	9	29800	25	20
IT	supportive information	reimb. Medicines	not defined	24400	16	
LT	main criterion	reimb. Medicines	6	12900	4	7
LU	main criterion	all medicines	1	64000	28	
LV	main criterion	reimb. Medicines	2	12200	3	5
MT	main criterion	reimb. Medicines		19000	10	9
NL	main criterion	POM	4	30800	26	19
NO	main criterion	POM	9	42000	27	22
PL	main criterion	reimb. Medicines	17	14300	5	17
PT	main criterion	POM	4	18900	9	15
RO	main criterion	reimb. Medicines	12	10900	2	12
SE	EPR not applied			28000	22	
SI	main criterion	reimb. Medicines	3	20700	12	21
SK	main criterion	reimb. Medicines	26	17200	8	14
UK	EPR not applied			26500	18	

CZ: this methodology is only applicable for pricing; for reimbursement prices of all other EU Member States are checked and the lowest price per basket is taken

DE: since 2011 EPR is used as supportive information for innovative medicines for the price review after one year.

MT: since 2011 EPR is applied.

AT = Austria, BE = Belgium, BG = Bulgaria, c. = country, CY = Cyprus, CZ = Czech Republic, DE = Germany, DK = Denmark, EE = Estonia, EL = Greece, EPR = external price referencing, ES = Spain, FI = Finland, FR = France,

Calculation of reference price		Changes in EPR methods	
price basis	calculation	country basket	calculation method
ex factory	Ø of all countries	2005	no change
ex factory	Ø of all countries	n.a.	n.a.
ex factory	3 lowest prices	no change	2000, 2010
pharmacy purchase	Ø of the 4 lowest plus 3% to cover transport costs	n.a.	n.a.
ex factory	Ø of all countries	2009	2009
		abolishment of EPR in 2005	
ex factory	not defined	2005	no change
ex factory	3 lowest price	2010	2005, 2010
ex factory	not defined	no change	2005, 2010
pharmacy purchase	Checking of the price level and the range of the prices in EEA countries according to this ranking: NL, BE, BG, ES IE, IS, UK, IT AT, EL, CY, LV, LI, LU, MT, NO, PT, PL, FR, RO, SE, DE, DK, SI, SK, CZ, HU, EE	n.a.	n.a.
ex factory	Prices "similar" to those in the reference countries (DE, ES, IT, UK)	2003	no change
pharmacy purchase	lowest price per basket	n.a.	2005
pharmacy purchase	Ø of all countries	2006	2006
ex factory	Ø of all countries	various times	various times
ex factory	Declared manufacturer price is compared with 95% of the average manufacturer prices in reference countries	n.a.	2005
pharmacy retail	lowest price per basket	n.a.	n.a.
ex factory	Third lowest price and not higher than the price in LT + EE	n.a.	2005, 2008, 2011 plans
pharmacy retail	Ø of all countries	no change	no change
pharmacy retail	Ø of the 3 countries	n.a.	n.a.
ex factory	lowest price per basket	n.a.	n.a.
Pharmacy retail, ex factory	Ø of all countries	2007	2007
ex factory	lowest price per basket	n.a.	2010
		abolishment of EPR in 2002	
ex factory	95% of the average of the 3 countries	2005	plans 2011
ex factory	Ø of the 6 lowest countries in the basket	2009	2009, plans for 2011

GDP = gross domestic product, HU = Hungary, IE = Ireland, IT = Italy, LT = Lithuania, LU = Luxembourg, LV = Latvia, MT = Malta, NL = Netherlands, NO = Norway, PL = Poland, POM = prescription-only medicine, PT = Portugal, SE = Sweden, SI = Slovenia, SK = Slovakia, reimb. = reimbursable, UK = United Kingdom
Source for abbreviations: http://publications.europa.eu/code/en/en-370100.htm
Source about external referencing: http://ppri.goeg.at
Source of GDP: EUROSTAT, http://epp.eurostat.ec.europa.eu/portal/page/portal/health/introduction

Figure 1. Map of external price referencing in Europe, 2010. Source: http://ppri.goeg.at

Belgium, the Czech Republic, Greece and Luxembourg applied EPR to all medicines on the market. Other countries used EPR only for specific categories of medicines, such as reimbursable, prescription-only medicines or innovative medicines as was the case in France.

Legal framework

In most EU Member States, EPR was based on statutory regulations or legislated pricing rules. These statutory rules may define the different characteristics of EPR in detail or may leave room for interpretations. Ireland, a country with the tradition to regulate its policies through agreements, has no laws or decrees for EPR. However the agreements between the Irish Pharmaceutical Healthcare Association and the Association of Pharmaceutical Manufacturers of Ireland contain the formal rules to be applied.

On the other hand, Portugal is an example of a country, which defined detailed rules as to how to apply EPR in the Decree-Law Nr. 65/2007, 14th March.

According to some PPRI Network members it might also be true for some countries that the national law may define a detailed EPR methodology, which might not always be fully applied due to lacking information (e.g. no availability of prices in some countries). National legislation might be modified by further legally relevant documents.

Composition of country baskets

European countries generally tend to choose European countries with similar economic comparability and/or geographic proximity.

As shown in Table 2 there was great variation in the number of countries included in the reference country basket. The most common methodology in Europe was to have less than ten countries in the basket; six countries defined between 10-20 countries in their basket and four countries (Austria, Belgium, Malta and Slovakia) had more than 20 countries in the basket. Italy had not specified the countries that it was using as EPR is only a supportive tool when setting prices. Slovakia had the maximum number of countries in the reference basket (n=26) and Luxembourg had the minimum number of reference countries (n=1). Germany (n=13), Spain (n=13), France (n=11) and United Kingdom (n=11) were the countries most frequently referenced.

As shown in Figure 2, there is a relationship between GDP per capita rank and the average rank of the reference countries in the basket (Kendall's rank correlation tau: 0.556263, p-value = 0.0005331). But within this analysis it is clear that outlier countries exist such as Poland which has a low-income rank and refers to higher-income countries. Lower-income countries refer

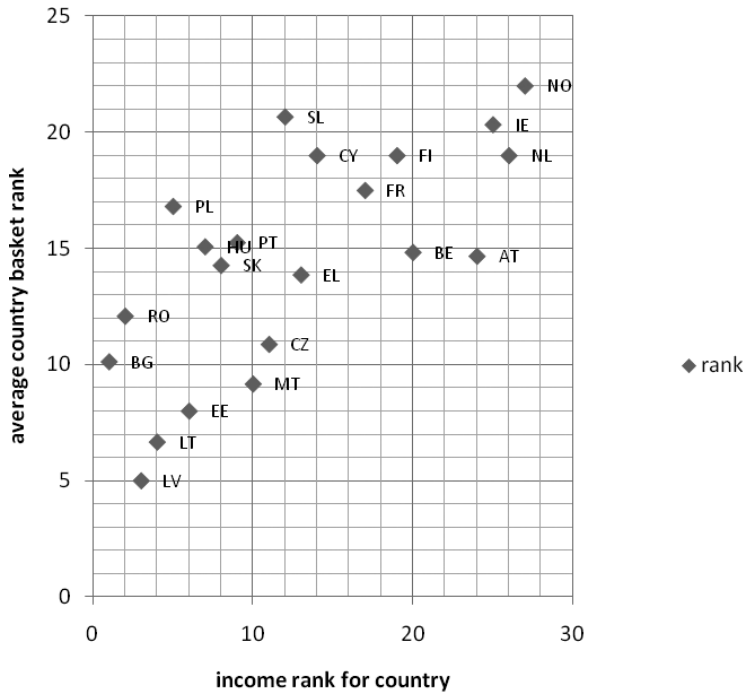


Figure 2. Kendall`s rank correlation tau: correlation between GDP per capita rank and the average rank of the reference countries in the basket. Kendall's rank correlation Tau: 0.556263 (p-value= 0.0005331). AT = Austria, BE = Belgium, BG = Bulgaria, CY = Cyprus, CZ = Czech Republic, DE = Germany, DK = Denmark, EE = Estonia, EL = Greece, ES = Spain, FI = Finland, FR = France, HU = Hungary, IE = Ireland, IT = Italy, LT = Lithuania, LU = Luxembourg, LV = Latvia, MT = Malta, NL = Netherlands, NO = Norway, PL = Poland, PT = Portugal, SE = Sweden, SI = Slovenia, SK = Slovakia, UK = United Kingdom. (Source for abbreviations: http://publications.europa.eu/code/en/en-370100.htm)

to other lower-wealth countries, more wealthy countries frequently define high-income states as reference countries. As mentioned earlier, most countries have statutory regulations on the composition of the reference countries; however only a few countries specify alternative countries in case of non-availability of a medicine. For example, Cyprus and Portugal had precise rules how to carry out price comparisons, in particular how to proceed if identical or similar pharmaceuticals were not on the market in the reference countries and how to adjust for different countries. Countries which do not legally define alternative countries in case of non-availability of the medicine might see the limitations of external price referencing as it could happen that none of the reference countries have a price for that medicine.

Calculation of the reference price

Some countries defined very detailed methodologies about calculating the reference price e.g. by specifying which exchange rate to use or whether to refer to Purchasing Power Parities. Norway for instance stated: "Price comparison is based on the price in the local currency, converted to Norwegian Krones. The mean exchange rate of the last six whole months, as presented by the Central Bank of Norway, is used as the basis for the comparison of prices". However, other countries decided to be vague when defining the methodology for calculating the price. France, for instance, stated that the price should be consistent with prices of comparators, which leaves room for case-by-case negotiations between authorities and manufacturers.

As summarised in Table 1 the most commonly used pricing method within EPR was to take the average of the country basket. Bulgaria, Greece and Norway defined the average of the three lowest countries as their reference price, whereas Hungary, Luxembourg, Poland and Romania took the lowest price per basket. It was reported by PPRI network members that in most cases, Greece had the lowest price per basket. Germany and Spain were the countries most referenced to, followed by France and the United Kingdom (see also Table 2).

Prices of medicines change over time, which needed to be taken into account when applying EPR. The majority of countries had some kind of agreements with manufacturers for them to report price changes to public authorities, which resulted in adjusting the prices used within the EPR system. In addition, public pricing authorities (in most countries either the Pharmaceutical Department within the Ministry of Health or third party payers) checked the prices which were reported in the application by manufacturers, putting a substantial burden on pricing authorities. Austrian Social Insurance legislation, for example, provides for a public health institution which runs a medicines price service of all EU Member States (Pharmaceutical Price Service) to check the prices on a random basis [14]. However the frequency of reviewing prices differs among countries, e.g. Portugal reviews its prices on a quarterly basis and Norway published a schedule[6] on which it is made transparent in advance when prices of the different products according to their anatomical therapeutic chemical (ATC) class are reviewed; other countries like Hungary do not regularly review their prices.

[6] Norwegian Medicine Agency, available online http://legemiddelverket.no/upload/50116/Revurderingsrekkefølge%202011%20-%20nettutgave%20korrigert.xls, latest access 20 June 2011

Table 2. Overview of country baskets in Europe, 2010

Countries in the basket																													
C.	**AT**	**BE**	**BG**	**CY**	**CZ**	**DE**	**DK**	**EE**	**EL**	**ES**	**FI**	**FR**	**HU**	**IE**	**IT**	**LT**	**LU**	**LV**	**MT**	**NL**	**NO**	**PL**	**PT**	**RO**	**SE**	**SL**	**SK**	**UK**	**Additional c.**	**Nr. Of c.**
AT		■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■		■	■	■	■		24
BE	■			■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■		■	■	■	■		24
BG	■				■					■			■									■	■	■			■		Russia	9
CY[1]	■								■			■													■					4
CZ[2]								■	■	■		■	■		■	■							■							8
DE																														
DK																														
EE													■			■		■											c. of origin	4
EL	■	■	■	■	■	■				■	■	■	■	■	■	■	■	■		■		■	■	■		■	■	■		22
ES																													Countries of Euro zone	
FI	■	■				■	■		■	■		■		■	■		■			■	■		■		■				IS	16
FR						■				■					■													■		4
HU	■	■			■	■			■	■		■		■	■							■	■			■	■		1 add. c	14
IE	■	■				■	■			■	■	■								■								■		9
IT																													Not spec.	
LT					■			■					■					■				■					■			6
LU								■																					c. of origin	1
LV								■								■														2
MT				■	■			■	■				■			■		■				■	■			■	■	■		12
NL		■				■						■																■		4
NO	■	■				■	■				■			■							■					■			■		9
PL		■			■	■	■		■	■		■	■	■	■	■	■				■			■		■			■	CH	17
PT									■	■		■			■															4
RO	■	■	■		■	■			■	■			■		■	■							■					■		12
SE																														
SL	■					■						■																		3
SK	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	■		26
UK																														
Reference frequency	11	10	3	5	10	13	7	7	11	13	6	12	10	8	11	10	6	7	3	8	1	9	10	3	8	6	8	12		

[1] Alternative countries: BE, DE, DK, ES, IT, PT

[2] CZ: this methodology is only applicable for pricing; for reimbursement prices of all other EU Member States are checked and the lowest price per basket is taken.

AT = Austria, BE = Belgium, BG = Bulgaria, c. = country, CH = Switzerland, CY = Cyprus, CZ = Czech Republic, DE = Germany, DK = Denmark, EE = Estonia, EL = Greece, ES = Spain, FI = Finland, FR = France, HU = Hungary, IE = Ireland, IS = Iceland, IT = Italy, LT = Lithuania, LU = Luxembourg, LV = Latvia, MT = Malta, NL = Netherlands, NO = Norway, PL = Poland, PT = Portugal, SE = Sweden, SI = Slovenia, SK = Slovakia, UK = United Kingdom

(Source for abbreviations: http://publications.europa.eu/code/en/en-370100.htm)

External versus internal price referencing

The methodology of EPR requires that countries compare prices of the same brand product in different countries. On contrary, within the methodology of internal price referencing prices of the same medicine within a country are compared – either at ATC 5 or ATC 4 level. External price referencing in combination with internal price referencing is used by 18 countries, only internal price referencing is used in four countries and only EPR in six countries. However, internal price referencing is exclusively used for setting the reimbursement price often within a reference price system; whereas EPR is also used for setting prices of all products in the market (Belgium, Czech Republic, Greece and Luxembourg) or for innovative medicines (France and Spain). For both methodologies it is of importance to define the unit of comparison. While some countries define if the product is compared on a unit level (meaning e.g. per tablet, per dose) others don't. Norway for example has defined exact rules within the EPR methodology what they consider as a small package (<30 units) or a large (>30 units) as well as clear exemptions to the rules e.g. for injections [15].

Changes in EPR methodologies over time

As shown in Table 1, over the last ten years, countries decided to change either the composition of the country basket, which was done by at least twelve countries, or the price calculation method (eleven countries).

In case countries have changed the country basket, it was observed that the number of countries included in the basket was increased. This was the case in Austria (in 2005 increased the basket from 14 to 24 countries), in the Czech Republic (since 2009 price referencing in the reimbursement system to all EU countries and before only to 8 countries), Greece (since 2010 change from three countries to 22 countries in the basket), Ireland (now nine countries are in the basket and before 2006 there were only five countries) and Slovakia changed in 2009 from eight reference countries to all other EU countries). For the remaining countries no exact information on the change in methodology was available.

Interesting to note was that two countries, Denmark and Sweden, stopped using EPR during this time. Up to 2002 Denmark, however, only used EPR to set the reimbursement price in the out-patient sector. Nevertheless, Denmark decided in 2009 – by agreement with the industry – to introduce EPR only for new medicines in the hospital sector. According to personal conversations with Swedish PPRI representatives the change in their country was due to achieving more cost-savings by implementing other pricing strategies such as cost-effectiveness policies.

Conversely, Malta has implemented EPR for new medicines in 2010. It was decided to include 12 countries in the reference basket and to take the average price. In addition, Greece changed its EPR methodology from three countries in the reference basket to 22 European countries. In 2010, Germany, a country that traditionally has free pricing at ex-factory price level, decided in 2010 to use EPR as one of many criteria in case price negotiations would fail [16].

Planned changes for 2011 were stated by Italy, the Netherlands and Latvia. Italy was exploring the possibility to apply EPR for generics and Latvia was negotiating to expand the countries included in the country basket. The Netherlands are in the process of evaluating their EPR system, especially the country basket, as it has not been reviewed since the implementation in 1995/1996 [17].

DISCUSSION

This study showed that EPR is a widely used pharmaceutical pricing tool in Europe (in 24 of 28 European countries). Including fewer than 10 countries in the reference basket and taking the average of the reference prices were the most common EPR methodologies. The results also showed that EPR is a dynamic policy tool which is adjusted by policy makers over time.

According to the results of this study, we see that national authorities in Europe consider EPR as a relevant pricing policy. They regularly adjust their EPR methodologies as was observed over the last years and stated for next year; e.g. since 2010 Malta uses EPR to set prices for new medicines. Over past years countries have gained experiences in shaping their EPR methodology to better reach their policy goal of lower medicine prices by including more countries in the reference basket or applying a different price calculation method. We therefore do not agree with the forecast by Seiter (2010) from the World Bank who has suggested that EPR will soon reach the end of its useful life cycle [18]. He acknowledged that EPR has been a useful tool in establishing an objective benchmark for pricing policies and responding to the opportunistic, profit-centred pricing policies of international and national drug companies. However, when almost all countries reference each other the differences between countries diminish. EPR will then eventually lead to one price level and other policies e.g. pharmaceutical expenditure evaluation might be more cost-effective. Policy makers seem to see opportunities to contain costs by regulating prices of medicines through benchmarking them with the prices of other countries. Different research studies have provided evidence that using EPR as pricing policy leads to lower prices, e.g. Windmeijer who measured the effects of the implementation of EPR in the Netherlands and came to the conclusion that EPR resulted in lower prices [19]. Merkur and Mossialos simulated the effect of EPR on medicine prices in Cyprus and showed that this would lower prices and contain costs after identifying Cyprus as a high price country for pharmaceuticals [20]. Filko stated that due to the policy change of EPR in Slovakia in 2009, which included the introduction of EPR based on the arithmetic mean of the six lowest countries within EU 26 countries as well as the implementation of the €, the proportion of pharmaceutical expenditure as% of total health care spending declined by approximately 25% [22]. In addition, Stargardt showed in his study that the composition of the country basket and possible price reductions have an influence on the price level in other countries [13].

It has been argued that EPR is in some countries only a "price collection" exercise which has no real impact on national pricing [9]. This might only be true for those countries which use EPR as supportive information (e.g. Belgium, Italy). In fact most European countries have well defined pricing rules and regulations. This study showed that many countries shaped their policies as Docteur (2007) highlighted in her study of having fixed and well-defined rules, such as capping the allowable price at the average of prices in the comparator countries or choosing the median having the advantage of not being sensitive to outlier prices in comparator countries [2].

Over the last couple of years a trend towards the inclusion of more countries in the reference basket was noticed. Countries, which have recently adjusted their EPR policy, e.g. Greece, have moved from only a few countries to over twenty countries in the reference basket. This trend

seems surprising as it is known that EPR is a time consuming and complex methodology. In times of the financial crisis, countries may not be willing to spend public money on regularly checking the prices of all reimbursable products in other countries on a regular basis. But with a limited basket of countries there is a risk that there will be no comparable products available.

Another result of the study showed that there was a tendency to include high-income countries such as Germany in the basket. Thirteen countries had Germany and/or Spain and eleven countries included France and/or United Kingdom in the basket. This leads to the question as to why some countries with a lower gross domestic product (GDP) such as some Central and Eastern European countries have high-income countries such as Germany in their comparator basket. Arguments to include Germany in the country baskets is that it is very often a first launch country as it does not have price control at ex-factory price level. As stated by Docteur (2007), this may be, to some extent, opportunistic in that these large high income countries are likely to have prices available for reference soon after first launch [2,23-26]. However, the comparable price in Germany is often much higher than in other European countries. Hence, public authorities need to find the right balance between easily accessible information on comparable medicines in countries of similar national incomes or the use of other methods of price determinants such as pharmaco-economic evaluation as used in Sweden.

Another point of discussion is whether EPR is a useful pricing policy for all types of medicines (over-the-counter medicines, patent protected products, generics, reimbursable and non-reimbursable medicines). Within the framework of some overall EU legislation (in particular the Transparency Directive), pricing and reimbursement remains a national decision for prescription-only medicine (POM) or reimbursable medicines [21]. In contrast in 2003 the European Commission adopted free pricing for "medicines neither purchased nor reimbursed by the state" [27,28]. In practice, many EU Member States have opted for determining the scope of their pricing regulation to the reimbursement segment, and this is also the case for external price referencing (see Table 1). Still some countries (e.g. France, Spain) even focus on applying external price referencing for innovative medicines. Even though this study did not explicitly address this research question as data were not readily available, it seems that EPR is mainly used for patent protected products that are widely marketed and most of the time reimbursable; as other market dynamics and policy tools are applied for generics and OTC (e.g. market competition) and newly launched products (pharmaco-economic evaluation). However for small countries applying EPR for off-patent medicines is an effective tool as often generic competition fails due to few competitors being in the market. The present overview showed that EPR was mainly applied for reimbursable medicines. However, according to experiences reported by the members of the PPRI network this is only the starting point for further confidential price negotiations between public authorities and industry.

Why is it crucial to understand the differences and commonalities of EPR systems? EPR may seem to be a fairly easy pricing procedure. Nevertheless, those who have practical experience with applying EPR reported that EPR is time consuming and challenging exercise when it comes to understanding prices in other countries. As Espin (2010) listed in his paper, price comparisons – hence EPR - are complex due to the following facts: considerable resources (human and

material) are needed to analyse the price data and in-depth knowledge on pharmaceutical systems are required to identify the same product (different commercial names, dosage forms and packaging in other countries) but also to be able to understand the different prices quoted (different margins, taxes and confidential agreements in other countries) to be compared [9]. Depending on the EPR methodology – e.g. taking the lowest price per basket – prices of countries may vary to a great extent. Choosing the right EPR methodology in terms of price calculation method and countries in the basket is crucial. This study could not identify a best practice EPR model as the national policy framework always needs to be taken into account. However, certain elements are of importance when applying EPR such as regular price revisions and informal exchange of information on prices. Networking initiatives, such as the PPRI network and the network of competent authorities on pricing and reimbursement under the lead of the EU Presidencies with the Directorate General (DG) Enterprise, provide the possibility to exchange on the experiences with different pricing policies as well as to informally exchange information on prices of reimbursable medicines to better understand the "real" price of the product in the other country especially important for discounts/rebates or other price-volume agreements. In addition, elements such as package size, price type, dosage as well as time of price calculation and time of price gathering or strategies in case a product is not on the market in a reference country should be defined in legislation. These factors may affect how EPR is implemented as for instance large packages have a lower average price per unit than smaller packages. Furthermore, authorities need to decide which calculation method to use in case e.g. only larger package sizes are available on the market. Other factors such as size of the population, gross domestic product, national industrial policy, prescribed volume and other pricing policies may influence the level of the final price [11]. In case the product is not on the market in the reference countries an alternative could be to use internal price referencing by comparing the prices of the same medicine with alternatives on ATC 5 or ATC 4 level.

The method of EPR may have effects on the access to reimbursable medicines as industry might not provide all needed information for authorities to set prices, as it was shown by Filko (2009) [22]. He described the experiences Slovakia made when changing the EPR methodology. Slovakia changed its EPR methodology by including all 27-EU Member States in the reference basket. Difficulties were faced when companies tried to ignore the newly implemented EPR methodology or actively lobbied for exemptions of their products. This could lead to delays in accessibility. However, Filko came to another conclusion that companies were initially willing to lower the prices to the requested level, however only on condition that the price would not appear on any kind of official price list to prevent "reverse referencing" to the prices in other bigger markets in the EU. These attempts of industry were not agreed to by public officials in Slovakia.

Pharmaceutical companies – not only in Europe but also in the US – apply strategic pricing methods when launching products [25]. Products are first launched in high price countries, such as Germany, with relatively high prices [27]. However, Germany is an example of a country that applies tendering-like systems for reimbursable medicines. This means, that industry and insurance institutions reach lower prices through discounts/rebates. However, these prices are confidential and are not published. This leads to the effect that the initial high list price

is taken as a benchmark when other countries have Germany in their baskets. Therefore, public authorities need to be aware of those dynamics and take them into consideration when choosing or adjusting the pricing policies for their countries. Any pricing policy is only effective if its regulation is enforced by public authorities as well as regularly reviewed. This means that prices delivered by pharmaceutical industry need to be checked and analysed to see if they are correct. In addition, set prices should be reviewed on a regular basis to adjust to price developments in other countries. However, even though supply side controls have an effect on expenditure these might be completely counteracted by overspending and the use of expensive originators when generics are available [29]. Thus, the widespread use of this policy tool may serve to save public funds by efficient price setting but will not prevent pharmaceutical companies to "gaming" the system to increase prices in Europe or globally through their launch sequences in order to increase prices.

CONCLUSIONS

This study comes to the conclusion that EPR is a dynamic and widely used pricing policy in Europe, with many different national characteristics; some countries even recently implemented EPR. A tendency of changing the EPR methodology over time was noticed; in particular in terms of the composition of the reference basket as the number of reference countries in the basket has increased over time in many countries. We conclude that over the past years European countries have increasingly established expertise on the EPR methodology. However, we still see room for improvement by implementing more detailed legislations in terms of the revision of prices and by identifying alternative countries in case a product is not on the market. These recommendations could lead to less bureaucracy and the time consuming process of checking prices might be reduced. We also see the need for formal information sharing (e.g. congresses dedicated to pricing strategies and systems) with other public pricing authorities to learn about the different EPR methodologies as well as the national experiences. These congresses might also give room to better understand national pricing methods including discussions on possible limitations of these pricing methods.

ACKNOWLEDGMENT

Deep acknowledgements are given to the members of the PPRI network. The work that was achieved by the PPRI network members by writing the PPRI Pharma Profiles are of great value. In addition, they supported the work of this study by giving information on recent changes or by raising critical questions.

REFERENCES

1. PPRI network. PPRI / PHIS Pharma Profiles. Available from: http://whocc.goeg.at/Publications/CountryReports. PPRI (Pharmaceutical Pricing and Reimbursement Information), 2007-2013.
2. Docteur E, Paris V. Pharmaceutical pricing policies in a global market. Paris: OECD Health Policy Studies; 2007. Available from: http://www.oecd.org/fr/els/systemes-sante/pharmaceuticalpricingpoliciesinaglobalmarket.htm. Accessed on 14 August 2013.
3. Seiter A. Access to Medicines and the Innovation Dilemma — Can Pharmaceutical Multinationals be Good Corporate Citizens? Business Ethics of Innovation Ethics of Science and Technology Assessment 2007;31:89-100.
4. Vandergrift M, Kanavos P. Health policy versus industrial policy in the pharmaceutical sector: the case of Canada. Health Policy 1997;41(3):241-260.
5. Scherer F.M. The Pharmaceutical Industry – Price and Progress. Health Aff (Millwood). 2009 Jan-Feb;28(1):w161-4. doi: 10.1377/hlthaff.28.1.w161. Epub 2008 Dec 16. Available from: http://www.colorado.edu/geography/class_homepages/geog_3682_f08/Articles/Scherer%20-%20pharmaceuticals.pdf. Accessed on 12 February 2011.
6. Amemiyat. Advanced Econometrics. Cambridge. Mass. Harvard University Press 1985.
7. Marquis MS, Phelps CE. Price Elasticity and Adverse Selection in the Demand for Supplementary Health Insurance. Econ Inq. 1987 Apr;25(2):299-313.
8. Morrisey M. Price Sensitivity in Health Care: Implications for Health Care Policy. Washington D.C. The National Federation of Independent Business Foundation 1992.
9. Espin J, Rovira J, de Labry AO. Working Paper 1: External Price Referencing. WHO/HAI project on medicines prices and availability Review Series on Pharmaceutical Pricing Policies and Interventions. May 2011.
10. Rosian I, Vogler S, Stürzlinger H. Internationale Arzneimittelpreisvergleiche: Meta-Analyse. Pharmig 2004; Available from: http://whocc.goeg.at/Publications/BooksReports. Accessed 20 July 2012.
11. Danzon PM, Chao LW. Cross-national price differences for pharmaceuticals: how large, and why? J Health Econ. 2000 Mar;19(2):159-95.
12. Mrazek M. Comparative Approaches to Pharmaceutical Price Regulation in the European Union. Croat Med J. 2002 Aug;43(4):453-61.
13. Stargardt T, Schreyögg J. The impact of cross-reference pricing on pharmaceutical prices – manufacturers' pricing strategies and price regulation. Department of Health Care Management, University of Technology. Berlin. 2006.
14. Pharma Price Information (PPI) service. Gesundheit Österreich GmbH (Austrian Health Institute); 2012.
15. Norwegian Medicines Agency (NOMA). Available online: http://www.legemiddelverket.no. Accessed 20 April 2010.
16. Pharma Pricing and Reimbursement. Germany: 2009 impact of voluntary discount agreements & 2010 trends. IMS Health July 2010,15(7):200-203.
17. Pharma Pricing and Reimbursement. Netherlands: latest market developments. IMS Health November 2010;15(11):326-328.
18. Seiter A. A Practical Approach to Pharmaceutical Policy. Directions in Development. The World Bank, Washington 2010. Available from: http://www-wds.worldbank.org/external/default/WDSContentServer/WDSP/IB/2010/06/22/000334955_20100622050742/Rendered/PDF/552030PUB0Phar10Box349442B01PUBLIC1.pdf. Accessed 14 August 2013.
19. Windmeijer F, de Laat E, Douven R, Mot E. Pharmaceutical promotion and GP prescription behavior. Health Econ. 2006 Jan;15(1):5-18.
20. Merkur S, Mossialos E. A pricing policy towards the sourcing of cheaper drugs in Cyprus. Health Policy. 2007 May;81(2-3):368-75. Epub 2006 Sep 1.
21. Vogler S, Habl C, Bogut M, Voncina L. Comparing pharmaceutical pricing and reimbursement policies in Croatia to the European Union Member States. Croat Med J. 2011 Apr 15;52(2):183-97.
22. Filko M, Szilagyiova P. The Slovak experience in the international price benchmarking for prescription drugs. Value in Health.2009;12(7):229 – 230.
23. Danzon PM, Wang R, Wang Y. The Impact of Price Regulation on the Launch Delay of New Drugs. Health Econ. 2005 Mar;14(3):269-92. Available from: http://www.nber.org/papers/w9874. Accessed 20 February 2010.
24. Ellison S, Wolfram C. Coordinating on Lower Prices: Pharmaceutical Pricing under Political Pressure. Mimeo. Haas School of Business. U.C. Berkeley. 2004.Available from: http://www.jstor.org/discover/10.2307/25046244?uid=3737528&uid=2129&uid=2&uid=70&uid=4&sid=21102677681963. Accessed 20 February 2010.

25. Kyle M. Pharmaceutical Price Controls and Entry Strategies. Mimeo. Fuqua School of Business, Duke University. 2004.

26. Kyle M. The Role of Firm Characteristics in Pharmaceutical Product Launches. Mimeo. Fuqua School of Business. Duke University. 2004.

27. European Commission. The High Level Group on Innovation and Provision of Medicines. Recommendations for action. May 2022. Available onlinehttp://ec.europa.eu/enterprise/sectors/healthcare/files/phabiocom/docs/g10-medicines_en.pdf. Accessed 10 January 2010.

28. European Commission. A stronger European-based Pharmaceutical Industry for the Benefit of the Patient – A Call for Action. 2003. Available online http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2003:0383:FIN:en:PDF. Page 15. Accessed 10 January 2010.

29. European Commission Competition Directorate-General. Pharmaceutical sector inquiry final report. Brussels, 2009. Available from: http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf. Accessed 20 May 2010.

CHAPTER 2.2

Impact of external price referencing on medicine prices – a price comparison among 14 European countries

South Med Rev 2012;5(2):34-41

Christine Leopold, Aukje Mantel-Teeuwisse,
Leonhard Seyfang, Sabine Vogler,
Kees de Joncheere, Richard Laing, Bert Leufkens

ABSTRACT

Objective: This study aims to examine the impact of external price referencing (EPR) on on-patent medicine prices, adjusting for other factors that may affect price levels such as sales volume, exchange rates, gross domestic product (GDP) per capita, total pharmaceutical expenditure (TPE), and size of the pharmaceutical industry.

Methods: Price data of 14 on-patent products, in 14 European countries in 2007 and 2008 were obtained from the Pharmaceutical Price Information Service of the Austrian Health Institute. Based on the unit ex-factory prices in €, scaled ranks per country and per product were calculated. For the regression analysis the scaled ranks per country and product were weighted; each country had the same sum of weights but within a country the weights were proportional to its sales volume in the year (data obtained from IMS Health). Taking the scaled ranks, several statistical analyses were performed by using the program "R", including a multiple regression analysis (including variables such as GDP per capita and national industry size).

Results: This study showed that on average EPR as a pricing policy leads to lower prices. However, the large variation in price levels among countries using EPR confirmed that the price level is not only driven by EPR. The unadjusted linear regression model confirms that applying EPR in a country is associated with a lower scaled weighted rank (p=0.002). This interaction persisted after inclusion of total pharmaceutical expenditure per capita and GDP per capita in the final model.

Conclusions: The study showed that for patented products, prices are in general lower in case the country applied EPR. Nevertheless substantial price differences among countries that apply EPR could be identified. Possible explanations could be found through a correlation between pharmaceutical industry and the scaled price ranks. In conclusion, we found that implementing external reference pricing could lead to lower prices.

INTRODUCTION

The pharmaceutical market is characterized by low price elasticity and strong market power not only in Europe, but in all markets in which health insurance is widespread and patents are enforced. In countries, where medicines are subsidised, patients do not generally see the true price of a medicine, thus appearing to have low price elasticity and patent holders often have the market power [1,2]. Even without price controls, this is not an unregulated market; European governments generally provide health coverage to their citizens and grant patents, so there is already extensive intervention in the market [3,4]. Guaranteeing sustainable health coverage, in specific funding of public pharmaceutical expenditure, requires certain supply and demand side policy measures. Due to historic developments, cultural differences and different ways of health care funding, European countries have implemented various policies to contain pharmaceutical expenditure [5].

One of the supply side measures is regulating medicine prices. The most commonly used pricing policy in Europe (applied by 24 out of 28 European countries) is external price referencing (EPR), which is defined as "the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country" [3,4,6]. One may argue that due to the fact that EPR is frequently used this makes it a powerful tool to influence not only national medicine prices but also prices worldwide due to the interlinking of prices [7,8]. Hence, it is necessary to understand whether European public authorities in charge of pricing of medicines are actually reaching the desired aim of EPR, thus stabilising and eventually lowering medicine prices. Of particular interest is to understand whether differences among lower or higher income countries and different EPR methodologies can be observed.

Only a very small number of studies addressed general aspects of EPR as a policy. Heuer [9] looked at the relationship of external price referencing and delays in the launch of medicines. In addition, Mariñoso [10] developed a scenario in which the potential drivers for a country to either engage in external price referencing or to directly negotiate prices were analysed. Only a few studies have explicitly analysed the impact of external price referencing on medicine prices. Stargardt [11] developed an analytic model to simulate the effect of a price reduction in Germany. They found that if there was a one € price reduction in Germany this would lead to a reduction of € 0.15 to € 0.36 in 15 European countries that use EPR and have Germany in their basket. Another perspective was developed by Richter [12], who argued in his study that pharmaceutical companies tend to keep prices higher in Germany for the reason that the prices in those countries would later become references for other countries.

Economic evidence on the impact of external reference pricing is scarce, but literature has generally shown that the introduction of EPR reduced prices. Windmeijer [13] measured the effects of the implementation of EPR in the Netherlands and found that EPR resulted in lower prices. Merkur [14] simulated the effect of EPR on medicine prices in Cyprus, after having found that Cyprus had relatively high prices compared to other European Union (EU) countries, they showed that EPR would lead to lower prices. Filko [15] stated in 2009 that due to the policy change to use EPR in Slovakia, which included the introduction of EPR based on the arithmetic mean of the six lowest countries within all other European Union countries as well as the

implementation of the €, the proportion of pharmaceutical expenditure as percentage of total health care spending declined by approximately 25%. On the contrary Kaiser [16] came to the conclusion that in Denmark medicine prices decreased more than 26% after a policy change from EPR to internal price referencing. Further the patient co-payment went down by 3 percent and government expenditure by 5.6% and producer's revenues by 5%.

Building upon the findings of these previous studies, this research aims to examine the impact of EPR on medicine prices using a sample of 14 originator products in 14 European countries. The medicines prices were obtained from a period of 2007-2008. It is known that price levels may vary across countries as a result of differences in factors such as national pricing and reimbursement policies, sales volume, exchange rates, gross domestic product (GDP) per capita, total pharmaceutical expenditure (TPE) and size of the pharmaceutical industry [17]. While conducting the present study, these additional factors were also taken into account. This study provides policy makers and scientists in the field of pharmaceutical policy with detailed information as to whether the desired effect of EPR – to have lower medicine prices – was achieved for originator products in 2007 and 2008.

METHODS

Selection of countries and products

A basket of fourteen European countries with different economic situations and from different parts of the (EU) was selected. Three EU Member States which currently do not apply external price referencing were also included. The countries included were Austria, Belgium, Denmark, Germany, Greece, Finland, France, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, Slovak Republic.

A basket of fourteen products was chosen. The main criterion for choosing the products was the patent status of each medicine: it had to be on-patent in 2007 and 2008 in the countries under investigation; therefore the date of market authorisation was checked either at the website of the European Medicines Agency (centralised procedure) or at the Austrian Medicines Agency. In addition, the medicines were predominantly prescribed in the out-patient sector and were included in the reimbursement system. Finally, price data had to be available. As shown in Table 1 products represent a broad spectrum of therapeutic areas such as obesity, diabetes, HIV/aids and others. The products are a combination of products that recently came on the market (and therefore have relatively low sales volumes) and others that have been on the market for nearly ten years (and therefore have relatively high sales volumes).

Data Sources

Policy data on EPR were obtained from the European Pharmaceutical Pricing and Reimbursement Information PPRI network [19] as well as from Leopold [7] which is a descriptive study on EPR in European countries.

Price data were provided by the Austrian Health Institute, which has been running a Pharmaceutical Price Information Service (PPI) for many years [20]. Based on Austrian law, the PPI service was set up in the late 1990's as a supportive tool for the Austrian Price Commission

Table 1. List of selected products included in this study

ATC code	Therapeutic Area	INN	Product	Strength	Pharmaceutical form	Company	EMA Authorisation [18]
A02BC04	Proton pump inhibitors	Rabeprazole	Pariet	10 mg	Tabs	Janssen-Cilag	November 1998
A08AA10	Obesity	Sibutramine	Reductil	10 mg	Caps	Abbott	April 2001
A08AB01	Obesity	Orlistat	Xenical	120 mg	Tabs	Roche	July 1998
A10BG02	Diabetes	Rosiglitazone maleate	Avandia	4 mg	Tabs	GSK	July 2000
A10BG03	Diabetes	Pioglitazone hydrochloride	Actos	30 mg	Tabs	Eli Lilly	October 2000
B01AB05	Acute coronary syndrome	Enoxaparin	Lovenox	100 mg	Prefilled syringe	Sanofi-Aventis	November 2000
B01AX05	Other antithrombotic agents	Fondaparinux	Arixtra	2.5 mg/0.5 ml	Prefilled syringe	GSK	March 2002
J05AE07	Protease inhibitors	Fosamprenavir calcium	Telzir	700 mg	f/c tabs	GSK	July 2004
J05AE10	Protease inhibitors	Darunavir	Prezista	300 mg	Tabs	Janssen-Cilag	February 2007
J05AF06	HIV	Abacavir sulfate	Ziagen	300 mg	Tabs	GSK	July 1999
J05AF07	HIV	Tenofovir disoproxil fumarate	Viread	245 mg	Tabs	Gilead	February 2002
J05AG03	Non-nucleoside reverse transcriptase inhibitors	Efavirenz	Stocrin	600 mg	f/c tab	MSD	May 1999
J05AX09	Other antiviral	Maraviroc	Celsentri	150 mg	Tabs	Pfizer	September 2007
L01BC06	Oncology	Capecitabine	Xeloda	500 mg	Tabs	Roche	February 2001

ATC = Anatomical Therapeutic Chemical, INN = International Non-Proprietary Name, f/c=film coated

and since 2004 to also check prices reported by manufacturers in the process of EPR in Austria. Prices are obtained from official price databases of Ministries of Health or Social Health Insurance Institutions. The validation of the PPI prices is high, as for the interpretation of the prices knowledge on the underlying pharmaceutical system is required which the Austrian Health Institute offers as well. The price data referred to October / November 2007 and 2008 and represent ex-factory prices per unit. The price data were collected for the same product, the same strength, the same pharmaceutical form and, if available, the same pack size. In case the country did not use the €, the conversion rate was taken from the Austrian National Bank of the previous month in that year. Discounts or rebates were not considered. As prices refer to the ex-factory price level, no value added tax (VAT) was included. For the price comparisons the prices were analysed in prices per units. If products were known to be used exclusively in hospitals in some countries, their prices were disregarded.

To perform the statistical analysis volume data of the 14 products in both years as well as data on economic variables such as national gross domestic product or total health expenditure were collected. Volume data were provided by IMS Health Institute [21]. IMS Health collects pharmaceutical consumption data from wholesalers, hospitals and/or dispensing outlets such as pharmacies or drugstores. The volume data referred to annual sales data of 2007 and 2008 of the same products, same strengths and companies as the price data. IMS displays its volume data in standard units (SU). This is a measure used by IMS and is derived from the commonest dosage forms. It is measured differently depending on the formulation of the medicine. Usually one SU equals one capsule, one tablet, one prefilled syringe, one dose of inhaled medicine or 5 ml of an oral suspension etc. If IMS does not collect data from all suppliers in a country they project the sample of a particular distribution channel to the national level. These projections are validated annually.

Data on economic variables such as gross domestic product per capita, total pharmaceutical expenditure (TPE) per capita in € Purchasing Power Parities as well as data on inhabitants per 100,000 were extracted from the Organization of Economic Co-operation and Development (OECD) Health database and referred to 2006 [22]. The calculation of per capita Purchasing Power Parities (PPPa) followed the methodology suggested by OECD.

In addition to economic factors, it was tested whether there is a possible relationship between the importance of national pharmaceutical industry and medicine prices, as national governments seek to find the right balance between social/health policies and economic policies. The variable employment in pharmaceutical industry population was collected as a proxy for the importance of the pharmaceutical industry in a country. Data were taken from the European Federation of Pharmaceutical Industry Association (EFPIA) and referred to 2006 [23]. This was converted into a rate per 100,000 population.

Statistical analysis

The unit ex-factory prices in € of all products, all countries and of both years were adjusted to a fixed exchange rate for 2007/2008, as some exchange rates (e.g. Norwegian Krone) fluctuated more than the price differences. The prices were converted to scaled ranks so that different price levels were ineffectual as well as it guaranteed a robust data set.

For the regression analysis the scaled ranks per country and product were weighted. Each country had the same sum of weights. Within a country the weights were proportional to its sales volume in the year. Based on the scaled ranks several analyses were performed by using the Program "R" version 2.11.1 [24]:

- An analysis was undertaken to assess how homogeneous the price level in a country was by looking at each product. It also showed whether countries with EPR had lower prices than countries that do not apply EPR.
- The relationship between the scaled ranks and several explanatory variables was modelled by a linear regression model. The following variables were considered as predictors in the model: EPR, TPE per capita and GDP per capita.
- The correlation between EPR and pharmaceutical employment per 100,000 inhabitants was plotted separately as there is interaction between the two variables (cf. figure 4). It is unknown in which direction the interaction of the two variable goes.

RESULTS

Out of the fourteen analysed countries, three did not apply EPR (Germany, Denmark, Sweden) at the time of investment. As shown in Table 2, large variations in GDP per capita (ranging from Portugal € 14,684 to Norway € 41,346) and TPE per capita (ranging from Denmark € PPPa 246 to Greece € PPPa 503) existed among the included countries. Employment in pharmaceutical industry also showed large variations within Europe (10-fold difference; Slovak Republic 37 employees/100,000 inhabitants and Denmark 313 employees/100,000 inhabitants).

Figure 1 shows the distribution of the scaled ranks in a country as well as across countries. The median of the scaled ranks (incl. both years) of the countries varies from as low as 0.23 in Italy to 0.83 in Denmark. It is visible that two of the countries that do not apply EPR (Germany and Denmark) have the highest scaled ranks. But it is also visible that the scaled ranks vary to a great extent among the countries that apply EPR.

Figures 2 and 3 give a more detailed picture on the variances of the scaled ranks among products within a country and over time. These segment plots confirm that those countries without EPR (Denmark, Germany, Sweden) had in general higher price levels. This result is especially true for Germany in both years (2007: 8 out of 14 products for which price data were available were among the most expensive products of the products under observation, 2008: 11 out of 14 products were among the most expensive ones of the products included in the study) but also Denmark and Sweden had in each year around two or three products with high price levels but also had some products where the price level was relatively low.

As mentioned before, those countries who apply EPR still show different price levels. Figures 2 and 3 show that countries with a high GDP per capita (Norway, the Netherlands, Finland, Austria and Belgium) have higher price scores than countries with a lower GDP per capita such as Spain, Greece and Portugal. The Netherlands, a country that applies EPR, is an example of a country where the price level of the different products was all around the average. None of the products showed a very high price nor a very low price. The unadjusted linear regression model confirms that applying EPR in a

Table 2. Overview of EPR, economic variables and the median of scaled ranks

C.	EPR (Y/N)	GDP per capita in € 2006	TPE per capita in € PPPa 2006 [2]	Pharmaceutical empl. industry per 100,000	Median of the scaled ranks
AT	Y	31,067	413	127	0.64
BE	Y	30,187	469	281	0.42
DE	N	28,184	416	129	0.71
DK	N	21,145	246	313	0.84
EL	Y	19,123	503	121	0.26
ES	Y	22,291	453	92	0.33
FI	Y	31,709	327	114	0.64
FR	Y	28,601	475	169	0.50
IT[1]	Y	25,419	443	119	0.23
NL	Y	33,031	351	98	0.52
NO	Y	41,346	327	99	0.50
PT	Y	14,684	391	97	0.33
SE	N	29,025	365	173	0.46
SK	Y	23,797	330	37	0.54

AT = Austria, BE = Belgium, C. = country, DE = Germany, DK = Denmark, empl. = employment, EPR = External price referencing, EL = Greece, ES = Spain, FI = Finland, FR = France, GDP = Gross Domestic Product, IT = Italy, n.a. = not available, NL = Netherlands, NO = Norway, PE = Pharmaceutical Expenditure, PPPa = Purchasing Power Parities adjusted, PT = Portugal, SE = Sweden, SK = Slovak Republic, TPE = Total Pharmaceutical Expenditure
Italy: EPR is only an additional pricing policy complementing negotiations between the manufacturer and the Medicines Agency
TPE for the Netherlands and Norway as of 2007

country is associated with a lower scaled rank (p=0.002). This association persisted after inclusion of total pharmaceutical expenditure per capita and GDP per capita in the final model (see Table 3).

Looking at the relationship of pharmaceutical employment per 100,000 inhabitants and the scaled ranks per country and product in Figure 4, it is visible that there is a significant correlation (p-value: 0.0063). This means the higher the scaled ranks the higher the employment in pharmaceutical industry. However it is unknown in which direction the causality of the two variables goes: do companies (thus pharmaceutical employment) decide to produce in countries with high prices or do countries with high prices attract investments by companies?

DISCUSSION

This study showed that in general the use of EPR as a pricing policy is associated with lower prices. However, the large price variation among countries confirms that prices are not only driven by EPR policies but also by other unobserved factors (such as other pricing policies).

One of the results of the study was that price differences among countries could be observed. This was especially the case in countries which apply EPR. One reason could be the fact that EPR is very differently applied in the countries in terms of the country basket, frequency of price updates

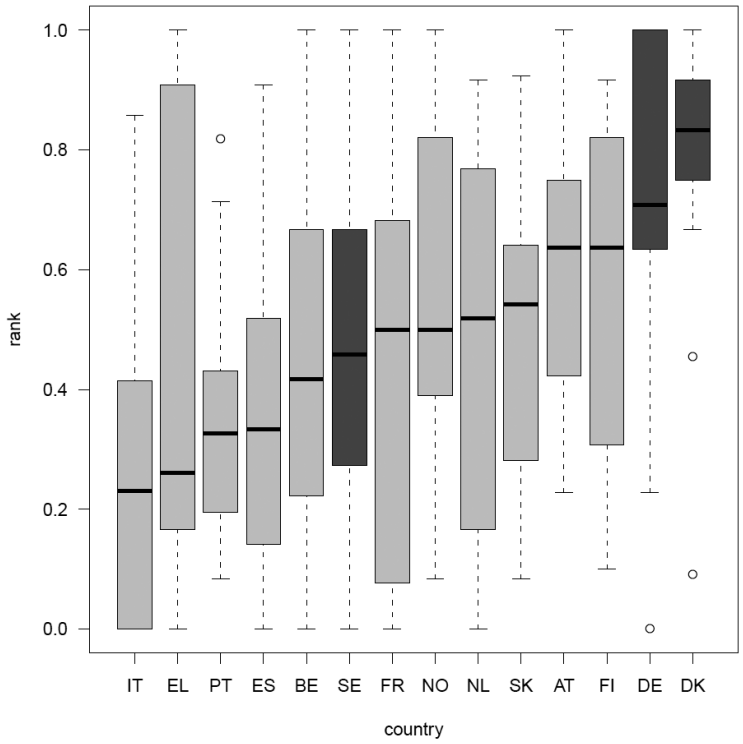


Figure 1. Impact of EPR on scaled ranks (incl. both years). AT = Austria, BE = Belgium, C. = country, DE = Germany, DK = Denmark, EL = Greece, ES = Spain, FI = Finland, FR = France, IT = Italy, NL = Netherlands, NO = Norway, PT = Portugal, SE = Sweden, SK = Slovak Republic. *Reading support*: light grey boxes are countries that apply EPR, dark grey boxes are countries that do not apply EPR. The thick line in each box equals the median of the scaled ranks per country.

and the price calculation method [3-5]. Another confounding factor is that EPR is only one of many pharmaceutical price regulation policies applied in each country. For instance Italy uses EPR only as an additional pricing policy complementing price negotiations between the manufacturer and the Medicine Agency. While Italy states this supplementary role of EPR very openly, the relevance of EPR versus (confidential) negotiation is not so clear for other countries. Another fact is the time lag between the variables; referencing pricing in countries does not happen instantaneously, so the current price factor may be explained by the previous time periods' independent variables.

An additional explanation for the price variances can be found in the selection of the products included in this study: Most products were reimbursable medicines in the out-patient sector. We observed that in a few countries e.g. Portugal, the prices of several products were not available. The reasons were that either the products were not on the market or some of the products (e.g. Telzir (fosamprenavir calcium), Viread (tenofovir disoproxil fumarat) or Ziagen (abacavir sulfat)) were only used in a hospital setting for which the price was not available.

The fact that some products are hospital medicines can be seen as a limitation of this study. It was decided to exclude the prices of products exclusively applied in hospitals as firstly EPR is commonly

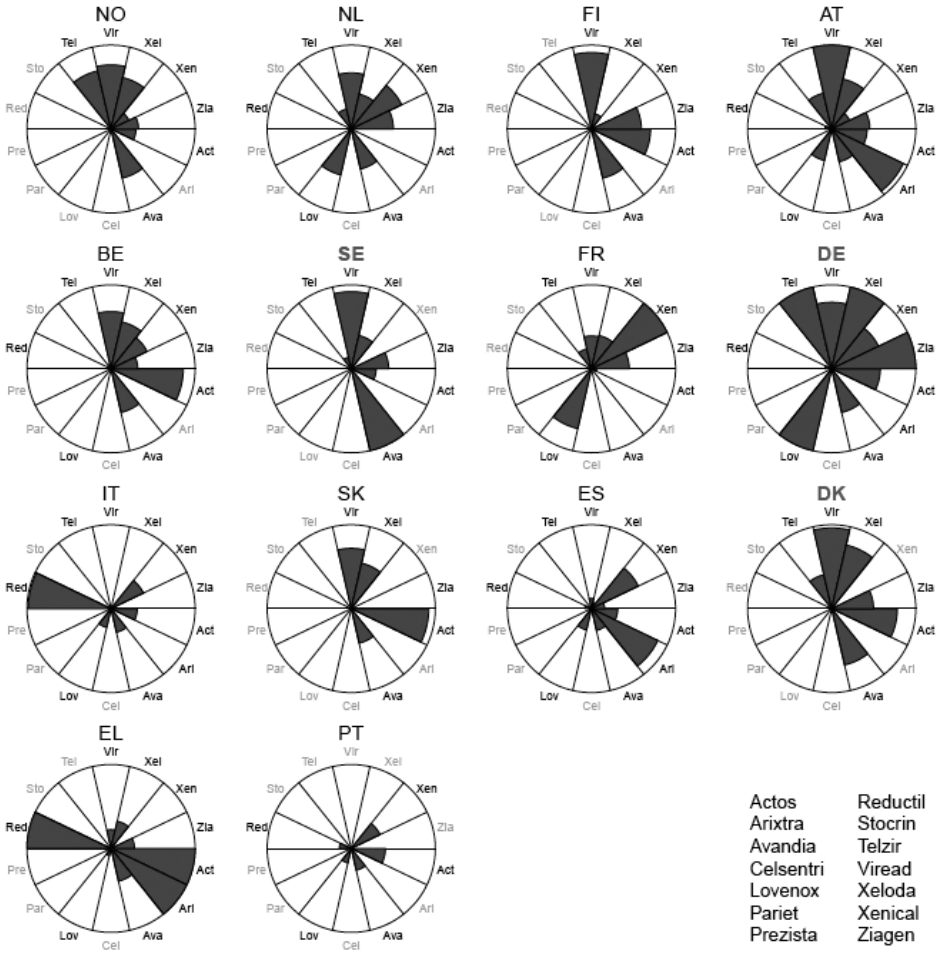


Figure 2. Price variances among the selected products within individual countries; countries are displayed in order of GDP per capita in 2007. Reading support: Each pie chart displays one country in the year 2007 (Figure 2) and the year 2008 (figure 3); each piece of the pie representing the scaled score for the selected 14 products. If the piece of the pie for one product is fully grey (= rank 1) then this product has a high price in this country in this year. In case the legend of the product is light grey this indicates that the product was either not on the market or that the information on the price was not available or the product was excluded from the survey as it was only used in hospitals. Taking Austria in 2008 (cf. Figure 3) as an example, it is visible that there was no price information for Xeloda. Viread is the product with the highest price and the standardised price rank of Reductil is very close to 0.

not applied for hospital products and secondly actual hospital prices are often the outcome of negotiations which are not made public [25]. However, as this pertained to only a limited number of products and countries, we do not feel that this will have affected our overall results.

Another point for discussion is whether countries take into account possible discounts and rebates when they are applying EPR. Very often publicly available prices for reimbursable medicines do not reflect discounts from price negotiations between third party payers and

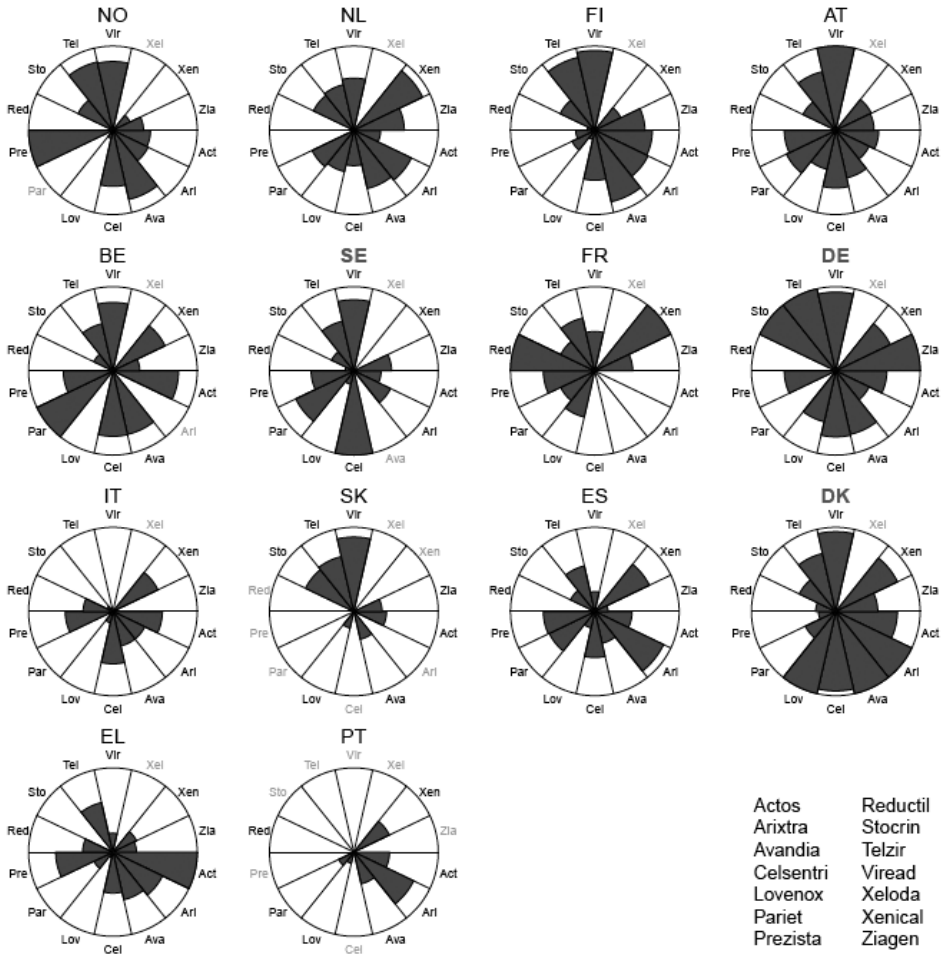


Figure 3. Price variances among the selected products within individual countries; countries are displayed in order of GDP per capita in 2008.

companies as they are confidential. This limits the positive effects of EPR by not taking into account the lower discounted prices when referencing to other countries.

Even though the selected products are not primarily subject to parallel trade, it needs to be mentioned that parallel trade plays an important role also with respect to EPR. Parallel trade effectively arbitrage price differences across countries and therefore has a similar effect to EPR in terms of compressing price differences and inducing strategic launch behaviour by firms. The presence of parallel trade reduces the incentive of countries with high prices to adopt EPR [26,27].

With regard to the methodology chosen in this study it was decided to take the unit ex-factory price as the majority of the countries that apply EPR also use the ex-factory price level for the price comparison (exceptions are Denmark, Finland, the Netherlands and Sweden which set their

Table 3. Linear multivariable regression

	Estimate	Std. Error	t-value	P-value
(Intercept)	0.5362546	0.0905139	5.925	0.00000
EPR	-0.1427916	0.0458698	-3.113	0.00206
Total pharmaceutical expenditure per capita	0.0000019	0.0000012	1.614	0.10781
GDP per capita	0.0000004	0.0000029	0.142	0.88718

Dependent variable: scaled ranks per country and product; N = 262

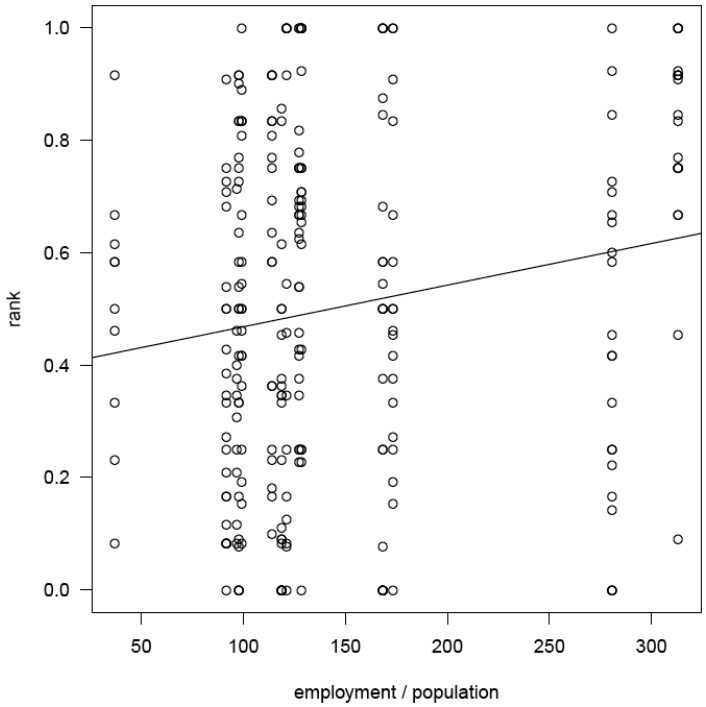


Figure 4. Scatter plat of pharmaceutical employment per 100,000 inhabitants vs. the scaled ranks.

prices at pharmacy purchasing level). Furthermore this methodological approach is supported by literature on price comparisons [2, 28]. The decision to use the unit ex-factory price is supported by the argument that price comparison on pharmacy purchasing or pharmacy retail price level is difficult due to different remuneration schemes (and distribution margins) and VAT on medicines.

With respect to price comparisons, either with prices in other countries or with similar existing treatments, numerous studies have discussed different methodological approaches. Danzon [29] argued that "valid measures of average price levels can only be obtained from comparisons based on a comprehensive or representative sample of products, appropriately weighted, following standard index number methods". Following these considerations the

methodology chosen in this study takes into account an indicative sample of 262 observations (including the 14 products and volume data from two years).

Medicine prices are the results of many different policy effects. Hence the price of a medicine may change as soon as it is included in the reimbursement schemes or as soon as a generic equivalent enters the market. Therefore, it is difficult to separate the effects of one pricing policy on medicine prices. This was the reason why only medicines that were on-patent in the observed countries in 2007 and 2008 were included in the study. In addition, it should be acknowledged that other factors (e.g. other national pricing policies) were not considered which may account for variation in price levels as well. For example by barring endogenous responses by firms (changing their launch strategies) EPR would be expected to compress the distribution of prices across countries, which makes finding any difference in the cross-section more of a challenge.

Our results support the assumption that EPR places greater pressure on countries that are selected by others as a reference country to keep prices high, especially if they want early market entry of new products or in order to support a national pharmaceutical industry. A consequence of EPR is illustrated by a tendency for pharmaceutical industries to set high entry prices for new products in countries without basic regulations. These pricing levels then become indicative for the other countries that use EPR for regulating prices on their markets [30].

This argument is supported by a report by the European Commission (Sector Inquiry), which stated that companies preferred to initiate their product launch in countries with no direct price control (Germany, Sweden and United Kingdom) or in countries that are used as references by others and have received approval from the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (Italy and Sweden) [31]. The results of our study showed the same trend. For example, Germany - a country with the tradition of free pricing at ex-factory price level - was not only the country with the highest prices in both years but also with the highest availability of products. Hence, it can be concluded that ERP may have negative impacts on individual country prices and unexpected consequences in countries applying such policies.

CONCLUSIONS

This study demonstrated that for patented products prices were generally lower in the countries which applied external reference pricing. Possible explanations could be found through an association of the scaled ranks with the pharmaceutical industry size and scaled weighted price ranks. However, it needs to be acknowledged that huge price difference could be found between countries which apply external price referencing. This could be explained by different methodologies with respect to the selection of countries in a reference basket or the method for calculating the price.

ACKNOWLEDGMENTS

Deep acknowledgements are given to Peter Stephens from IMS Health for providing sales volume data for 2007 and 2008 for the 14 products. We would like to express sincere gratitude to the Austrian Health Institute for providing price data and to the PPRI network members for providing data on implementation of EPR in their respective countries.

REFERENCES

1. Marquis MS, Phelps CE. Price Elasticity and Adverse Selection in the Demand for Supplementary Econ Inq. 1987 Apr;25(2):299-313.
2. Brekke K, Holmås TH, Straume OR. Are pharmaceuticals inexpensive in Norway? A comparison of prices of prescription pharmaceuticals between Norway and nine west European countries. Institute for Research in Economics and Business Administration. 2008 May.
3. Docteur E, Paris V. Pharmaceutical Pricing Policies in a global market. Paris. OECD Health Policy Studies. 2007; Available from: http://www.oecd.org/document/44/0,3343,en_2649_37407_41382764_1_1_1_1,00.html. Accessed 20 June 2011.
4. Kanavos P, Vandoros S, Irwin R, Nicod E, Casson M. Differences in costs of and access to pharmaceutical products in the EU 2011; IP/A/ENVI/ST/2010-12. European Parliament, Brussels. Available from: http://www.europarl.europa.eu/document/activities/cont/201201/20120130ATT36575/20120130ATT36575EN.pdf. Accessed 20 June 2011.
5. Vogler S, Habl C, Leopold C, Rosian-Schikuta I, de Joncheere K, Lyager Thomsen T. Pharmaceutical Pricing and Reimbursement Information (PPRI): final report. Luxembourg. DG Health and Consumer Protection of the European Commission. 2007; Available from: http://whocc.goeg.at/Publications/BooksReports. Accessed on 20 May 2011.
6. Vogler S. Preisbildung und Erstattung von Arzneimitteln in der EU - Gemeinsamkeiten, Unterschiede und Trends. Pharmazeutische Medizin. 2012;14(1):48-56.
7. Leopold C, Vogler S, Mantel-Teeuwisse AK, de Joncheere K, Leufkens HG, Laing R. External Price Referencing in Europe – a descriptive overview of one policy with many national characteristics. Health Policy. 2012 Jan;104(1):50-60. doi: 10.1016/j.healthpol.2011.09.008. Epub 2011 Oct 19.
8. Espin J, Rovira J, De Labry AO. External Reference Pricing, WHO/HAI Project on Medicine Prices and Availability. WHO review series on Pharmaceutical Pricing Policies and Interventions, Working Paper. 2011.
9. Heuer A, Mejer M, Neuhaus J. The National Regulation of Pharmaceutical Markets and the Timing of New Drug Launches in Europe. Institute for the World Economy Working Paper No. 437. 2007. Available from: http://www.ifw-kiel.de/ausbildung/asp/asp-wp/2007/aspwp437.pdf.
10. Mariñoso BG, Jelovac I, Olivella P. External referencing and pharmaceutical price negotiation. GATE Groupe d'Analyse et de Théorie Économique. Working paper 08-15. 2008. Available from: http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1168822.
11. Stargardt T, Schreyögg J. The impact of cross-reference pricing on pharmaceutical prices – manufacturers' pricing strategies and price regulation. Appl Health Econ Health Policy 2006;5(4):235-47.
12. Richter A. Assessing the impact of global price interdependencies. Pharmacoeconomics 2008;26(8):649-59.
13. Windmeijer F, de Laat E, Douven R, Mot E. Pharmaceutical promotion and GP prescription behavior. Health Econ. 2006 Jan;15(1):5-18.
14. Merkur S, Mossialos E. A pricing policy towards the sourcing of cheaper drugs in Cyprus. Health Policy. 2007 May;81(2-3):368-75. Epub 2006 Sep 1.
15. Filko M, Szilagyiova P. The Slovak experience in the international price benchmarking for prescription drugs. Value in Health 2009;12(7):229 – 230.
16. Kaiser U, Mendez SJ, Ronde T. Regulation of pharmaceutical prices: evidence from a reference price reform in Denmark. Centre for European Economic Research. Discussion Paper No. 10-062. Available from: ftp://ftp.zew.de/pub/zew-docs/dp/dp10062.pdf.
17. Kyle MK. The Role of Firm Characteristics in Pharmaceutical Product Launches. The RAND Journal of Economics 2006;37(3):602-618.
18. European Medicine Agency. [updated 2012; cited 2012/1/05]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124.
19. PPRI network. PPRI / PHIS Pharma Profiles. Available from: http://whocc.goeg.at/Publications/CountryReports. PPRI (Pharmaceutical Pricing and Reimbursement Information), 2007-2013.
20. Pharmaceutical Price Information (PPI), Austrian Health Institute. [updated 2012/08/01; cited 2012/01/05]. Available from: http://www.goeg.at/en/Reports-Service.html.
21. IMS Health MIDAS. 2007-2008.
22. OECD Health database. Available from: http://www.oecd.org/document/19/0,3746,en_21571361_33915056_39091923_1_1_1_1,00.htm
23. European Federation of Pharmaceutical Industry Association (EFPIA). [updated 2012/08/01; cited

2012/01/05]. Available from: http://www.efpia.eu/content/default.asp?PageID=559&DocID=9158.

24. R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2010. Vienna, Austria. ISBN 3-900051-07-0 Available from: http://www.R-project.org.

25. Vogler S, Habl C, Leopold C, Morak S, Mazag J, Zimmermann N. PHIS Hospital Pharma Report 2010. Pharmaceutical Health Information System. Available from: http://phis.goeg.at/downloads/hospitalPharma/PHIS_Hospital%20Pharma_Report.pdf. Accessed on 12 July 2011.

26. Costa-i-Font J, Kanavos P. Medicines in parallel trade in the European Union: a gravity specification. LSE Health working papers 2007 June. London School of Economics and Political Science, London, UK.

27. Glynn D. The effects of parallel trade on affordable access to medicines. Eurohealth 2009;15(2):1-4.

28. Rosian I, Vogler S, Stürzlinger H. Internationale Arzneimittelpreisvergleiche: Meta-Analyse. Pharmig 2004; Available from: http://whocc.goeg.at/Publications/BooksReports. Accessed 20 July 2012.

29. Danzon PM, Chao LW, Cross-national price differences for pharmaceuticals: how large, and why? J Health Econ. 2000 Mar;19(2):159-95.

30. Danzon PM, Wang RY, Wang L. The Impact of Price Regulation on the Launch Delay of New Drugs - Evidence from Twenty-Five Major Markets in the 1990s. Health Econ. 2005 Mar;14(3):269-92.

31. European Commission Competition Directorate-General. Pharmaceutical sector inquiry final report. Brussels, 2009. Available from: http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf. Accessed 20 May 2011.

CHAPTER 2.3

Is Europe still heading to a common price level for on-patent medicines? An exploratory study among 15 Western European countries

Health Policy. 2013;112(3): 209-216

Christine Leopold, Aukje Mantel-Teeuwisse, Sabine Vogler, Kees de Joncheere, Richard Laing, Bert Leufkens

ABSTRACT

Background: Previous studies have suggested that medicines prices in Europe converge over time as a result of policy measures such as external price referencing.

Objective: To explore whether ex-factory prices of on-patented medicines in Western European countries have converged over a recent period of time.

Methods: Prices of ten on-patent medicines in five years (2007, 2008, 2010, 2011, 2012) of 15 European countries were analyzed. The unit of analysis was the ex-factory price in € per defined daily dose (exchange rate indexed to 2007). A score (deviation from the average price) per product and per country as well as the ranges were calculated for all medicines.

Results: The prices between countries and selected products varied to a great extent from as low as an average price of € 1.3/DDD for sitagliptin in 2010-2012 to an average of € 221.5/DDD for alemtuzumab in 2011. Between 2008 and 2012, a price divergence was seen which was fully driven by two countries, Germany (up to 27% more expensive than the average) and Greece (up 14 to 32% cheaper than the average). All other countries had stable prices and centered around the country average. Prices of less expensive medicines remained relatively stable or decreased over time, while prices of expensive medicines relatively increased.

Conclusions: Our study period included the time of the recession and several pricing policy measures may have affected the prices of medicines. Instead of the expected price convergence we observed a price divergence driven by price changes in only two of the 15 countries. All other European countries remained stable around the country average. Further research is needed to expand the study to a bigger sample size, and include prescribing data and Eastern European countries.

INTRODUCTION

In the last decades pharmaceutical expenditure accounted for a considerable percentage of total health care spending in Europe. These percentages varied to a great extent among countries ranging from 6.8% in Norway to 33,4% in Hungary followed by Greece (28.5%) and Slovak Republic (27.4%) in 2011 [1]. To control public spending on medicines countries have been implementing different cost-containment mechanisms – focusing on medicine prices and/or on their prescribed volume. As pharmaceutical policies are national competences European countries adopt different approaches to regulating medicines prices. The majority of countries opt for implementing pricing policies restricted to reimbursable medicines. Only a few countries (e.g. Denmark) have free pricing at the manufacturer price level. Differences also exist in terms of which pricing policy (external or internal price referencing) is applied and which methodology (e.g. for external price referencing which and how many countries are included in the basket or taking the minimum versus an average price in a basket) is chosen [2-5]. External price referencing (EPR) is the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country [6]. It is the most frequently used pricing policy in Europe (in 2012, 24 European countries excluding Denmark, Sweden and United Kingdom [7-10]). All of these factors may lead to a magnitude of differences in prices of medicines [11-17].

Looking at the broader picture of consumer goods such as food, clothing and footwear, significant differences in consumer prices exist across Europe according to Eurostat 2011. A recent study highlighted these differences across Europe: prices in Denmark were 43% higher than the average of the 27 EU Member States (EU-27), while in Macedonia prices were 56% lower than this average. Between 1995 and 2010 a price convergence could be identified for the group of EU-27 countries [18]. However, it is known that the rules of the market do not apply for medicines since the market for medicines, as does the market for health care in general, is characterized by asymmetries and market failures [19]. Hence, the pharmaceutical market is a highly regulated market. Still, parallel trade plays an important role allowing for trade of lower priced medicines from other countries [20,21].

With respect to medicine prices research showed that depending on the extent of market regulation, medicine prices in Europe vary to a great extent: prices for branded medicines in countries with free or semi-regulated prices – such as the United Kingdom and Germany, previously – are higher than in countries where statutory price regulations are applied (such as Italy, France or Spain) [22,23]. This leads to price differences of up to a 25% between the lowest and the highest price in 11 surveyed EU Member States. Differences are due to a range of factors: the amount of pharmaceuticals dispensed, the mix comprising different kind of medicines ranging from expensive original medicines to lower priced generics, the share of the price that is reimbursed by third party payers as well as pricing strategies of pharmaceutical companies. Despite significant price differences, there appears to be price convergence for on-patent medicines across EU countries, as the combined effect of regulation at the level of single Member States, parallel trade and EPR [24].

The European Competiveness Report 2006 illustrated that EU price convergence for medicines was more rapid in the second half of the 1990s as a results of the process of EU monetary

convergence. Starting from 2000 two clusters of countries were identified: the core EU countries (France, Italy, Benelux countries, Sweden, Finland, Denmark, United Kingdom and Ireland) with a 15% average price gap; and the cluster of newer EU Member States as well as Spain, Portugal and Greece, who had average prices almost 40% lower than the EU-15 level [25-27].

Since the economic recession in 2008 many European countries have been forced to implement cost-containment policies to maintain their high-level healthcare services. Countries which were hit significantly by the crisis (the Baltic countries, Greece, Spain and Portugal) implemented a bundle of pricing and reimbursement policy measures (such as price cuts, changes in reimbursement rates and value added tax on medicines), while all other European countries also appeared to have been constantly working on optimizing their pharmaceutical systems [28]. As a consequence these policy changes may have had an influence on medicine prices and on European price convergence.

This study follows up on the results of previous research on price convergence of medicine prices in Europe. The objective of this study is to examine the hypothesis that price convergence of on patented medicines in Western European countries remains in times of economic recession. Particularly, this exploratory study aims at analyzing whether medicine prices of a small sample of 10 on-patent medicines in Western European countries have converged during the time of the recession (2007 – 2012).

METHODS

Study design and data sources

A longitudinal study design over six years for a selected sample of ten on-patent medicines in 15 Western European countries was chosen for this study. The country basket included the following countries: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Norway, Portugal, Spain, Sweden and Switzerland.

A basket of ten products (cf. Table 1) was selected according to the following criteria:

1) *Patent status*: On-patent during the observation period. As information on patent expiry in the individual countries is scarce, the date of authorization according to the European Medicine Agency was used [29]. It was assumed that the patent would not expire within the next ten years. In addition, the price data was delivered for the active substance, which gave another indication which products were on the market. This information on whether generics were already on the market was included in Table 1. However, in the price analysis only the prices of the on-patent products were considered.

1. *ATC groups*: Five different therapeutic classes each represented by two medicines
2. *Reimbursement*: Inclusion in the reimbursement market and therefore under price control
3. *Marketing authorization holder*: Variety of marketing authorization holders
4. *Price segment*: Different price segments (i.e. less expensive: ≤ € 99/DDD and expensive: ≥ € 100/DDD, DDD = defined daily dose according to [30])

Price data were provided by the research institute Gesundheit Österreich GmbH / Austrian Health Institute, which has been running the Pharmaceutical Price Information (PPI) service for many years

Table 1. Overview of the selected medicines

ATC code	Therapeutic class	Active ingredient	Brand name	Marketing authorization holder	EMA date of authorization	Generics available	Price segment*
A10BH01	Type 2 diabetes mellitus	sitagliptin	Januvia	MSD	21/03/2007	No	Less expensive
A10BX04	Type 2 diabetes mellitus	exenatide	Byetta	Eli Lilly	20/11/2006	No	Expensive
J05AE06	Direct acting antiviral /HIV	lopinavir / ritonavir	Kaletra	Abbott	20/03/2001	No	Less expensive
J05AF09	Direct acting antiviral /HIV	emtricitabine	Emtriva	Gilead	24/10/2003	No	Less expensive
L01XC06	Antineoplastic agents	cetuximab	Erbitux	MSD	29/06/2004	No	Expensive
L01XC04	Antineoplastic agents	alemtuzumab	MabCampath	Bayer Schering	06/07/2001 (withdrawal August 2012)	No	Expensive
L03AB10	Interferon / Hepatitis C	peginterferon alfa-2b	PegIntron	Bayer Schering	25/05/2000	No	Less expensive
L03AB11	Interferon / Hepatitis C	peginterferon alfa-2a	Pegasys	Roche	20/06/2002	No	Less expensive
L04AD02	Immunosuppressants	tacrolimus	Advagraf	Astellas Pharma	23/04/2007	Yes	Less expensive
L04AA10	Immunosuppressants	sirolimus	Rapamune	Wyeth/Pfizer	13/03/2001	No	Less expensive

ATC = Anatomical Therapeutic Chemical Classification; DDD = defined daily dose; EMA = European Medicines Agency; WHO CC = World Health Organization Collaborating Centre for Drug Statistics Methodology
*less expensive: ≤ € 99/DDD and expensive: ≥ € 100/DDD

[31]. Reasons for choosing price data from the Austrian Health Institute were: 1) accessibility of the data by the authors, 2) reliability as the data have been collected as part of legal obligations [32] for the Austrian Pricing Committee [33] and 3) the PPI service became a point of reference for the European Commission and for many EU Member States. The price data provided for this survey did not include information on official (statutory) discounts nor on commercial (voluntary) rebates.

Definition of product

Table 2 gives an overview of the available strengths, pharmaceutical forms and pack sizes of the selected products in the European countries. For the purpose of this study, we have selected the presentation (i.e. the strength, the pharmaceutical form and the pack size) which was most commonly available in the 15 countries under investigation, which is also listed in Table 2. In many cases these selected strengths were the same as the recommended DDD by the WHO Collaborating Centre for Drug Statistics Methodology [30]. We cannot draw any conclusions on whether these selected products also represent the products with the highest consumption, as we did not have any consumption data available.

Definition of price type

The unit of analysis was the ex-factory price per unit in €. To account for currency fluctuations exchange rates for Denmark, Norway, Sweden and Switzerland were indexed the exchange rate as of 1 January 2007. To enhance comparability the unit prices were calculated into defined daily doses (DDD) as defined by the WHO Collaborating Centre for Drug Statistics Methodology [30]. For two active substances (cetuximab and alemtuzumab) no recommended DDD was available. Therefore the authors followed the recommendations of the European Public Assessment Report (EPAR) as published on the website of the European Medicine Agency [29]. Information on the recommended DDDs is provided in Table 2.

Data analysis

To analyze the price variance between countries for each product the range (the country with the highest and the lowest price level) as well as the average of the unit ex-factory price in € per DDD indexed to 2007 (= referred to as price) was calculated in each year. To test for price convergence, a score per country was calculated, which is expressed as the percentage deviation of the average price of all countries in each year:

Score per country year x = (average price country A year x – average price of all countries year x) / average price of all countries year x

To illustrate the price development per product over time, a score per product was calculated, which is expressed as the percentage deviation of the average price of all products in each year:

Score per product year x = (average price of product 1 year x – average price of all products year x) / average price of all products year x

This score per product was indexed to the year 2007 to show the price development over time.

Table 2. Details on the selected medicines included in the study

Active substance (brand name)	Available strengths	Available pharmaceutical forms	Available pack sizes	Most commonly used presentation as basis for this study*	WHO recommended DDD
Alemtuzumab (Mabcampath)[1]	10 or 30 mg	1 ml vial containing concentrate for solution for infusion	3 units	30 mg, 1 ml vial containing concentrate for solution for infusion, 3 units	No recommendation, parenteral
Cetuximab (Erbitux)	2 or 5 mg	20 or 50 or 100 ml vial containing solution for infusion	1 unit	5 mg/ml 20 ml vial for 1 infusion, 1 unit	No recommendation, parenteral
Emtricitabine (Emtriva)	200 or 10 mg	Capsules or 170 ml bottle containing oral solution	1 or 30 units	200 mg, capsules, 30 units	0.2 g, oral
Exenatide (Byetta)	0.25 mg	2.4 ml prefilled pen with solution for injection or 1.2 ml prefilled pen with solution for injection	1 or 3 units	0.25 mg, 2.4 ml prefilled (=10 mcg) pen with solution for injection, 1 unit	15 mcg, oral
Lopinavir / ritonavir (Kaletra)	100+25 or 133,33+33,3 or 200+50 or 80+20 mg	60 mg oral solution or capsules	5, 60, 120, 180, 360 units	80+20 mg, 60 mg oral solution, 5 units	0.8 g, oral
Peginterferon alfa-2a (Pegasys)[2]	134, 270, 350 mcg	0.5 ml prefilled syringe containing solution for injection	1, 4, 12 units	135 mcg, 0.5 ml prefilled syringe containing solution for injection, 4 units	26 mcg, parenteral
Peginterferon alfa-2b (PegIntron)	50, 80, 100, 120, 150, 160, 200, 240, 300 mcg	Vial containing powder for injection	1, 4 units	80 mcg, vial containing powder for injection, 1 unit	7.5 mcg, parenteral
Sirolimus (Rapamune)	0.5, 1, 2 mg	Film coated tablets, 60 ml bottle containing oral solution	1, 30, 100 units	2 mg, f/c tabs, 30 units	3 mg; oral
Sitagliptin (Januvia)	25 or 50 or 100 mg	Film coated tablets	14, 28, 50, 56, 98 units	100 mg, 28 units	0.1 g, oral
Tacrolimus (Advagraf)	0.5, 1, 3, 5 mg	prolonged release capsules	30, 50, 100 units	5 mg prolonged release capsules, 50 units	5 mg, oral

DDD = defined daily dose; WHO CC = World Health Organization Collaborating Centre for Drug Statistics Methodology

* The Nordic countries and Switzerland have traditionally bigger pack sizes e.g. 98 units

[1] In August 2012 the EMA marketing authorization of alemtuzumab was withdrawn

[2] In 2012 discontinuation of the 135 mcg strength

RESULTS

Price variance

Table 3 shows the average and the range (minimum and maximum) of ex-factory medicine prices for all products. The prices between countries and selected products varied to a great extent from as low as an average price of € 1.3/DDD for sitagliptin in 2010-2012 to an average of € 221.5/DDD for alemtuzumab in 2011. Germany (n=10 out of 50 maximum prices), Denmark (n=10) and Finland (n=8) were the countries with the highest prices; Greece was the country with the lowest prices (n=20), followed by Italy (n=5), Spain and France (n=4). The price range (expressed as percentage of the average price) was relatively small and constant over the years for some products such as exenatide, cetuximab and sitagliptin, but larger and increasing, especially in more recent years, for products such as tacrolimus, and lopinavir/ritonavir. The active substance sirolimus had the largest relative price difference between countries, especially in the years 2010-2012 (2012: Greece € 4.7/DDD (-61% compared to the average) and Germany € 22.2/DDD (+88%)).

Price convergence – score per country

Figure 1 displays the score per country for the selected products. In 2007 a price divergence is noticeable: the product basket in Finland is 15% more expensive than the country average; whereas Greece is nearly 20% cheaper than the country average. In 2008 the price divergence decreases, more countries are in a price range of 10% below or above the average. From 2008 until 2012 the price divergence is only driven by two countries: Greece and Germany. Greece continues to be the cheapest country with up to 32% lower prices in 2012. On the other side Germany remains the most expensive country with up to 27% higher prices in 2012. The other countries in the basket are fairly stable and continue to center around 10% lower or above the country average.

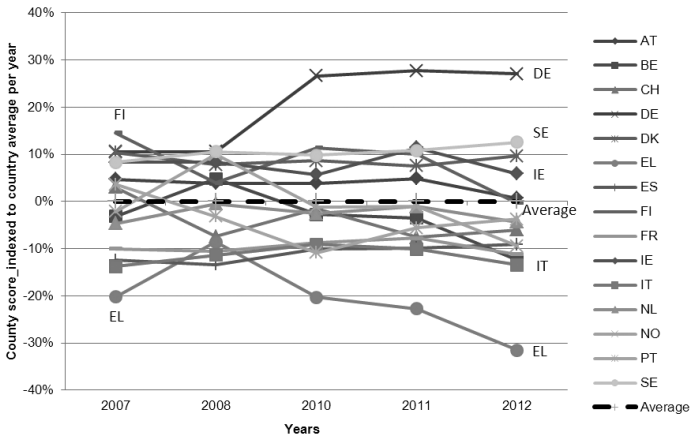


Figure 1. Country score 2007 - 2012.2007: exclusion of FI, IE, PT not sufficient number of data points (<4 data points). 2012: exclusion of alemtuzumab EMA withdrawal in August 2012. Average = average of all countries included in the study, AT = Austria, BE = Belgium, CH = Switzerland, DE = Germany, DK = Denmark, EL = Greece, ES = Spain, FI = Finland, FR = France, IE = Ireland, IT = Italy, NL = Netherlands, NO = Norway, PT = Portugal, SE = Sweden

Price development – score per product

Figure 2 illustrates the price development per product over time as compared to the average price of all products within a specific year. The indexed score for most less expensive products remained stable and close to 1 across the study period, meaning that the average price per year of the group of less expensive products did not change over time as compared to the average price of all products. Only the indexed score of lopinavir / ritonavir decreased in 2012; i.e. the difference with the average price became smaller because the average price of lopinavir / ritonavir, a relatively less expensive product, increased in 2012 (see also Table 3). On the contrary two of the three products in the group of expensive medicines (alemtuzumab and cetuximab scored above 1, meaning that the average price of the group of expensive products increased over time as compared to the average product price.

DISCUSSION

This study confirms the findings of previous studies [34-39] that prices of the same medicine differ among European countries. Our study cannot confirm previous clear trends of price convergence. Our results rather showed that there was a growing price divergence between the lowest price country (Greece) and the highest price country (Germany) with the other countries remaining stable within a price range of 10% lower or higher as the country average. Further, the average prices of products which are less expensive seemed to remain stable over time, whereas the average prices of expensive products increased over time.

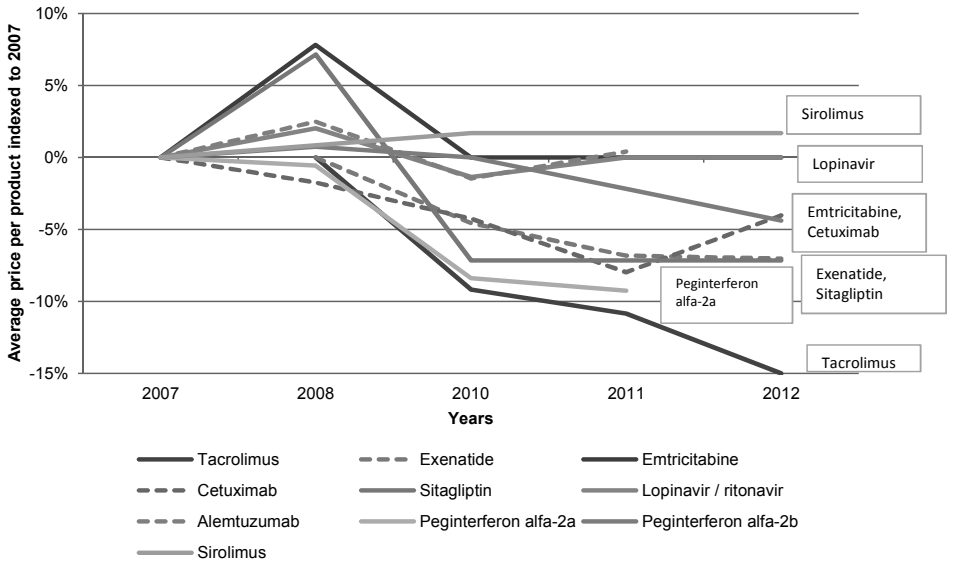


Figure 2. Average price per product 2007 – 2012 indexed to 2007. 2007: no data for tacrolimus and exenatide, therefore products scores were indexed to 2008 2012: no data for of alemtuzumab (EMA market withdrawal in August 2012) and peginterferon alfa-2a (discontinuation of the 135 mcg strength). Products from the price segment "expensive" are labeled with dotted lines.

Table 3. Overview of averages and ranges of ex-factory medicines prices in €/DDD (exchange rate indexed to 2007) for all products in the basket (2007-2012)

Active substance (product)	Indicator	2007	2008	2010	2011	2012
Alemtuzumab (Mabcampath)	Minimum (as% of average)	191.4 (87%)	184.7 (82%)	169.4 (78%)	159.8 (72%)	-
	Average	220.6	226.1	217.4	221.5	-
	Maximum (as% of average)	261.5 (119%)	261.5 (116%)	266.9 (123%)	273.8 (124%)	-
Cetuximab (Erbitux)	Minimum (as% of average)	123.0 (97%)	108.9 (87%)	109.4 (90%)	65.1 (56%)	107.7 (88%)
	Average	126.9	124.7	121.5	116.8	121.8
	Maximum (as% of average)	134.9 (106%)	142.8 (115%)	135.5 (111%)	135.3 (116%)	135.3 (111%)
Emtricitabine (Emtriva)	Minimum (as% of average)	4.9 (77%)	4.9 (71%)	4.9 (76%)	9.2 (77%)	4.5 (70%)
	Average	6.4	6.9	6.4	6.4	6.4
	Maximum (as% of average)	7.5 (117%)	8.7 (127%)	7.7 (119%)	4.9 (144%)	8.5 (134%)
Exenatide (Byetta)	Minimum (as% of average)	-	124.4 (90%)	114.3 (87%)	114.3 (89%)	112.5 (88%)
	Average	-	138.1	131.8	128.7	128.4
	Maximum (as% of average)	-	166.1 (120%)	146.1 (111%)	150.4 (111%)	140.0 (109%)
Lopinavir / ritonavir (Kaletra)	Minimum (as% of average)	11.5 (78%)	11.4 (76%)	11.1 (76%)	11.1 (75%)	10.1 (68%)
	Average	14.8	15.1	14.6	14.8	14.8
	Maximum (as% of average)	20.5 (139%)	20.5 (136%)	21.2 (145%)	21.2 (143%)	21.2 (107%)
Sitagliptin (Januvia)	Minimum (as% of average)	1.3 (91%)	1.3 (86%)	1.2 (86%)	1.2 (87%)	1.1 (82%)
	Average	1.4	1.5	1.3	1.3	1.3
	Maximum (as% of average)	1.5 (107%)	1.7 (116%)	1.4 (107%)	1.5 (112%)	1.5 (116%)
Sirolimus (Rapamune)	Minimum (as% of average)	5.8 (49%)	5.8 (49%)	5.3 (45%)	5.0 (42%)	4.7 (39%)
	Average	11.8	11.9	12.0	12.0	12.0
	Maximum (as% of average)	17.1 (144%)	17.1 (144%)	22.2 (185%)	22.2 (185%)	22.2 (184%)
Peginterferon alfa-2a (Pegasys)	Minimum (as% of average)	28.5 (82%)	27.6 (80%)	22.3 (70%)	24.7 (78%)	-
	Average	34.6	34.4	31.7	31.4	-
	Maximum (as% of average)	47.4 (137%)	42.7 (124%)	37.5 (118%)	37.5 (119%)	-
Peginterferon alfa-2b (PegIntron)	Minimum (as% of average)	11.3 (83%)	11.0 (79%)	11.0 (80%)	11.0 (82%)	10.5 (80%)
	Average	13.7	13.8	13.7	13.4	13.1
	Maximum (as% of average)	17.4 (127%)	17.4 (126%)	17.2 (126%)	17.2 (129%)	16.7 (127%)
Tacrolimus (Advagraf)	Minimum (as% of average)	-	9.9 (83%)	7.6 (69%)	7.6 (71%)	5.2- (51%)
	Average	-	12.0	10.9	10.7	10.2
	Maximum (as% of average)	-	13.7 (115%)	16.2 (148%)	16.2 (151%)	16.2 (159%)

€ = Euro, DDD = defined daily dose

There is a magnitude of factors leading to price differences, some of which include variations in a country's income level, different value assessment of pharmaceuticals, different pharmaceutical policy regulations, other policies outside the pharmaceutical or healthcare sector such as a country's political decision on balancing social and industrial interests as well as market forces which include exchange rate fluctuations or competition post patent expiry [34-39]. Especially three factors are relevant for our study:

1) *Differences in pharmaceutical policies*: since 2008 European countries have been struggling with an economic recession leading to cuts in healthcare budgets. Hence, public authorities are under pressure to contain public spending on medicines. Especially the introduction of short-term policy measures such as price cuts for reimbursable medicines, but also shifts of costs from public payers to patients through increased out-of-pocket payments are common measures European authorities implemented in the last five years [28]. In 2010/2011 Greece but also Portugal had to decrease their prices by an average of 20-25%. Due to policies such as external price referencing in Europe these price cuts are influencing the price level of other countries [21]. Our results clearly showed that these price cuts led to a price divergence when looking at the sample of 15 countries, but this divergence was largely driven by Greece having substantial lower prices starting in 2010. In contrast, some countries have managed to introduce well in advance prepared policy measures, e.g. Finland introduced generic substitution in 2003 followed by a reference price system in 2009, which resulted in price decreases over a longer period of time [40].

2) *Price regulations for medicines*: European countries tend to regulate prices of reimbursable medicines. Only a few countries (Denmark, Germany, Sweden and United Kingdom) traditionally do not regulate medicines prices at manufacturer level (Sweden only controls prices at wholesale level and via value-based pricing). Another fact is, that these countries have a long tradition of pharmaceutical industry representations in their countries. For this reason, they are very often first launch countries for new medicines as manufacturers may set prices freely which has again an influence on prices within other European countries due to external price referencing. This effect might be unfortunate for countries with less ability to pay, such as Portugal or Greece or even more for Eastern European countries as the high reference prices of the early launch countries are higher than their national possibilities to pay [35-37]. But Germany with the implementation of the AMNOG health care reform which links pharmaceutical pricing to added therapeutic benefit scores in 2011 and Sweden with its plans to implement external price referencing in 2013/2014 suggest that even more affluent European countries are urged to control public spending on medicines.

3) *Currency fluctuations*: As the currencies of non-Euro countries fluctuate over time, we decided to index the exchange rates of Denmark, Norway, Sweden and Switzerland to the year 2007. The real annual exchange rate of all countries of Norway and Sweden increased from 2007 – 2008, but decreased from 2008 – 2012 to around 10% below the 2007 rate. In Switzerland the exchange rate continuously decreased to around 20% below the rate in 2007. The exchange rate in Denmark remained more or less stable. These facts need to be taken into account when interpreting the results.

We acknowledge that we faced several limitations during our study. The first limitation is the disregard of discounts/rebates: the unit ex-factory price as listed in national price lists disregards official (statutory) as well as commercial (voluntary) discounts/rebates. This is an issue of transparency as price convergence might have taken place but was „hidden" as discounts and rebate dynamics are not transparent. Reasons for the decision of taking the unit ex-factory price were: 1) countries apply external price referencing on the ex-factory price level, 2) no margins or (value-added) taxes (which vary to a great extent among European countries) [4] are applied on the manufacturer price level and 3) other policy mechanisms are applied when taking for instance the reimbursement price such as reference pricing and price negotiations including discounts and rebates [4,6,21,37]. A second limitation is the unavailability of volume data: due to limited financial resources volume data could not be acquired. A few authors suggest weighing medicine prices according to volume for better comparability [13]. However, as we looked at price convergence trends, we believe that additional information on volume would not have affected our results. Finally, we had a small sample size. Due to this small sample size it is a study with an explorative character, and we can only draw tentative conclusions. However, the findings of the study add value to existing literature as it takes into account the current economic recession which leads countries to implement cost-containment policy measures.

CONCLUSIONS

This exploratory study confirms differences in medicine prices across countries and over time. Instead of the expected price convergence we observed a price divergence driven by price changes in only two of the 15 countries. All other European countries remained stable around the country average. We suggest further research in this area taking into account a larger product sample size, and include prescribing data as well as Eastern European countries.

ACKNOWLEDGEMENTS

Special thanks are given to the Austrian Health Institute for providing price data for the ten products.

REFERENCES

1. OECD. Pharmaceutical expenditure. As percentage of total expenditure on health. Health: Key Tables from OECD. 2013; doi: 10.1787/pharmexp-table-2013-1-en. Accessed 17 August 2013.
2. Vogler S, Habl C, Bogut M, Voncina, L: Comparing pharmaceutical pricing and reimbursement policies in Croatia to the European Union Member States. In: Croat Med J. 2011 Apr 15;52(2):183-97.
3. Dukes MNG, Haaijer-Ruskamp FM, et al. Drugs and Money. Prices, affordability and cost containment. WHO Regional Office for Europe 2003; Available from: http://apps.who.int/medicinedocs/pdf/s4912e/s4912e.pdf. Accessed 10 May 2011.
4. Vogler S, Habl C, Leopold C, Rosian-Schikuta I, de Joncheere K, Lyager Thomsen T. Pharmaceutical Pricing and Reimbursement Information (PPRI): final report. Luxembourg. DG Health and Consumer Protection of the European Commission. 2007; Available from: http://whocc.goeg.at/Publications/BooksReports. Accessed 20 May 2011.
5. Mossialos E, Mrazek M, Walley T. Regulating pharmaceuticals in Europe: striving for efficiency, equity, and quality. Maidenhead (UK): Open University Press. 2004; Available from: http://www.euro.who.int/__data/assets/pdf_file/0008/98432/E83015.pdf. Accessed June 2012.
6. WHO Collaborating Centre for Pharmaceutical Pricing 301 and Reimbursement Policies. Glossary of pharmaceutical terms. Latest update of print version: 2011; regularly updated online. Available from: http://whocc.goeg.at/Glossary/Search. Accessed June 2012.
7. Leopold C, Vogler S, Mantel-Teuwisse AK, de Joncheere J, Leufkens HG, Laing R. External Price Referencing in Europe – a descriptive overview of one policy with many national characteristics. Health Policy. 2012;104(1):50-60. doi: 10.1016/j.healthpol.2011.09.008. Epub 2011 Oct 19.
8. Kanavos P, Nicod E, Espin J, van den Aardweg S. Short- and long-term effects of value based pricing versus external price referencing. EMINet. 2010. Available from: http://whocc.goeg.at/Literaturliste/Dokumente/FurtherReading/Short-%20and%20longterm%20effect%20of%20value-based%20pricing.pdf. Accessed 20 May 2011.
9. Espin J, Rovira J, de Labry AO. Working Paper 1: External Price Referencing. WHO/HAI project on medicines prices and availability Review Series on Pharmaceutical Pricing Policies and Interventions. May 2011.
10. Vogler S, Zimmerman N, Piessnegger J, Bucsics A. Discounts and rebates granted to public payers for medicines in European countries. South Med Rev. 2012 Jul;5(1):38-46. Epub 2012 Jul 23.
11. Rosian I, Vogler S, Stürzlinger H. Internationale Arzneimittelpreisvergleiche: Meta-Analyse. Pharmig 2004; Available from: http://whocc.goeg.at/Publications/BooksReports. Accessed 20 July 2012.
12. Wagner JL, McCarthy E. International differences in drug prices. Annu Rev Public Health. 2004;25:475–95. doi: 10.1146/annurev.publhealth.25.101802.123042.
13. Danzon PM, Chao LW. Cross National Price Differences for Pharmaceuticals: How large and why? J Health Econ. 2000 Mar;19(2):159-95.
14. Brekke KR, Holmås TH, Straume OR. Are Pharmaceuticals Still Inexpensive in Norway? A Comparison of Prescription Drug Prices in Ten European Countries. SNF report no. 08/10. Bergen: 2010.
15. Simoens S. International comparison of generic medicine prices. Curr Med Res Opin. 2007;23(11):2647-54.
16. Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. TLancet. 2009 instead of The Lancet.
17. Von der Schulenberg F, Vanderos S, Kanavos P: The effects of drug market regulation on pharmaceutical prices in Europe: overview and evidence from the market of ACE inhibitors. Health Econ Rev. 2011;1(1):18. Available from: http://www.healtheconomicsreview.com/content/1/1/18. Accessed 20 April 2011.
18. Kurkowiak B. Significant differences in consumer prices across Europe: comparative price levels in 37 European countries for 2010. EUROSTAT. Statistics in focus. 28/2011. Available from: http://epp.eurostat.ec.europa.eu/cache/ITY_OFFPUB/KS-SF-11-028/EN/KS-SF-11-028-EN.PDF. Accessed July 2012.
19. Marquis MS, Phelps CE. Price Elasticity and Adverse Selection in the Demand for Supplementary Health Insurance. EEcon Inq. 1987;25:299-313.
20. Vicién F. Why Parallel Imports of Pharmaceutical Products Should be Forbidden. European Competition Law Review 1996;219-224.
21. Danzon PM, Towse A. Differential pricing for pharmaceuticals: reconciling access, R&D and

patents. International Int J Health Care Finance Econ. 2003 Sep;3(3):183-205.

22. Pammolli F, Magazzini L, Orsenigo L. The Intensity of Competition after Patent Expiry in Pharmaceuticals: A Cross-Country Analysis. Revue of Economie Industrielle 2002;(99):107-132.
23. Magazzini L, Pammolli F, Riccaboni M. Dynamic Competition in Pharmaceuticals: On Patent Expiry, Generic Penetration and Industry Structure. Eur J Health Econ. 2004 Jun;5(2):175-82.
24. Kanavos P, Vandoros S, Irwin R, Nicod E, Casson M. Differences in costs of and access to pharmaceutical products in the EU 2011; IP/A/ENVI/ST/2010-12. European Parliament, Brussels. Available from: http://www.europarl.europa.eu/document/activities/cont/201201/20120130ATT36575/20120130ATT36575EN.pdf. Accessed 20 June 2011.
25. European Commission. European Competitiveness Report 2006: Economic reforms and competitiveness. Key messages from the European Competitiveness Report. 2006. Available from: http://ec.europa.eu/enterprise/sectors/ict/files/euro_comp_report_2006_en.pdf. Accessed 20 May 2011.
26. Kyle MK, Allsbrook JS, Schulman KA. Does Reimportation Reduce Price Differences for Prescription Drugs? Lessons from the European Union. Health Serv Res. 2008 Aug;43(4):1308-24. doi: 10.1111/j.1475-6773.2008.00838.x. Epub 2008 Mar 12.
27. Cambridge Pharma Consulting. Pricing and Market Access Review 2005. IMS Intelligence 2006.
28. Vogler S, Zimmermann N, Leopold C, de Joncheere K. Pharmaceutical policies in European countries in responds to the global financial crisis. South Med Rev 2011;4(2):22-32.
29. European Medicine Agency. European public assessment 384 reports. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124. Accessed May 2012.
30. WHO Collaborating Centre for Drug Statistics Methodology. Available from: http://www.whocc.no/atc_ddd_index. Accessed May 2012.
31. Pharma Price Information (PPI) service. Gesundheit Österreich GmbH (Austrian Health Institute); 2012.
32. General Social Insurance Act § 351c, Federal Law No. 189/1955, latest change by Federal Law I No. 398/2011 [in German]. 2012.
33. Bundesministerium für Gesundheit. Regelung für die Vorgehensweise der Preiskommission bei der Ermittlung des EU-Durchschnittspreises gemäß § 351c Abs. 6 ASVG. 1 January 2008.
34. European Commission. Pharmaceutical Sector Inquiry. 2009. Available from: http://ec.europa.eu/. Accessed 20 June 2012.
35. Desogus C. Competition and regulation in the EU regulation of pharmaceuticals. European Studies in Law and Economics. 2012;4.
36. Friederiszick H, Tosini N, de Vericourt F, Wakeman S. An economic assessment of the relationship between price regulation and incentives to innovate in the pharmaceutical industry. ESMT White Paper 2009. Available from: http://www.esmt.org/economic-assessment-relationship-between-price-regulation-and-incentives-innovate-pharmaceutical. Accessed 20 May 2011.
37. Mrazek M, Mossialos E. Regulating pharmaceutical prices in the European Union. In Regulating pharmaceuticals in Europe: striving for efficiency, equity and quality. 2004. Geneva: World Health Organization.
38. Pellényi G. The Relationship between relative productivity and price levels in Europe. ICEG European Center. Working Paper No. 33. 2007. Available from: http://icegec.hu/index.php?option=com_publications&Itemid=57&serieslId=4&old=yes&page=5. Accessed 20 June 2012).
39. Kanavos P, Kowal S. Does pharmaceutical parallel trade serve the objectives of cost control? Eurohealth 2008;14(8):22–26.
40. Pohjolainen L. Reference price and price competition – evidence from the Finnish pharmaceutical market. Masters thesis. Aalto University, School of Economics, Department of Economics February 2012. Available: https://aaltodoc.aalto.fi/handle/123456789/3456. Accessed 20 August 2012.

CHAPTER 3

Re-evaluation and adjustment of pharmaceutical policies in times of economic recession

CHAPTER 3.1

Impact of the recession on the pharmaceutical policy environment and medicines sales in eight European countries

Submitted

Christine Leopold, Aukje Mantel-Teeuwisse, Sabine Vogler, Silvia Valkova, Kees de Joncheere, Bert Leufkens, Anita Wagner, Dennis Ross-Degnan, Richard Laing

ABSTRACT

Objective: To analyze how European pharmaceutical pricing and reimbursement policies have changed and to describe changes in pharmaceutical sales within major therapeutic classes during the economic recession. We hypothesized that differences would exist between economically stable and less stable countries in terms of implemented policy measures and expected declines in pharmaceutical expenditure.

Methods: Based on a literature review, we describe pharmaceutical policy changes (2008-2011). Using IMS Health data (2006-2011), we analyzed quarterly sales of products in the 10 highest-selling therapeutic classes in eight European countries, in IMS standard units (volume) and constant dollars (value). We present sales growth rates, comparing economically stable versus less stable countries classified based on 2012 fiscal consolidation plans of OECD member countries.

Results: Economically stable countries (Austria, Estonia, Finland) implemented between two and seven policy changes each; whereas economically less stable countries (Greece, Ireland, Slovak Republic, Spain, Portugal) implemented between 10 and 22 policy changes. Most policy changes occurred in 2010 (n=33/88) and 2011 (n=40/88) and included changes in out-of-pocket payments (n=16/88), changes in price mark-up schemes (n=13/88) and price cuts (n=11/88). All countries showed moderate increases in sales volumes (except Portugal and Greece, both showing slight declines after 2009), while sales value decreased in both country groups, with greater declines in economically less stable countries.

Conclusions: Countries' responses to the recession differed. We observed a higher density of policy changes implemented by less economically stable countries. Unexpectedly almost all countries showed moderate increases in pharmaceutical sales volume despite declines in sales value, especially in the less economically stable countries.

INTRODUCTION

European public authorities have struggled to maintain high levels of access to care, while restraining increases in expenditure due to higher demand for care and increasingly older populations [1-4]. The recent global recession has exerted additional pressure on public budgets [5-6].

In Europe, Iceland was one of the first countries affected by the financial crises with the collapse of all three major banks in September 2008, followed by the Baltic countries (Latvia, Lithuania and Estonia) [7-9]. The recession in Europe continued and impacted especially Southern European countries (Greece, Spain, Portugal and Italy) and Ireland in 2010 and 2011. Soon the recession was not only a financial debt problem of individual European countries, but a crisis of the whole Eurozone and a high priority of the European Central Bank and the European Parliament. All countries were urged to implement public cost-saving measures, which affected public financing of healthcare [10].

Historical experience has shown that a recession, defined as two successive quarters of negative growth in GDP, can have severe negative impacts on population health due to a strong association between economic downturns and declines in health care utilization and deterioration in health outcomes [11]. For example, suicides and homicides increased among working-age men and women when unemployment rose rapidly during times of recession in Europe [12]; the number of uninsured non-elderly Americans increased by 5.6 million between 2007 and 2009 [13] and over a quarter of Americans reported reducing routine medical care during this recession [14]. Over the same period, deductibles and co-payments for office visits and prescription medicines increased, leading to greater cost burden for consumers [15-17]. Similar effects were seen in Greece. Kentikelenis and colleagues looked at the health effects caused by the economic crisis in Greece and among many results they found that patients lost access to care and preventive services and that patients were facing higher risks of HIV and sexually transmitted diseases [18]. The World Health Organization (WHO) examined the impact of the recession on medicines sales, expenditures and prices between 2007 and 2009 in 84 countries. The authors concluded that the economic recession had mixed effects, with the largest declines in medicines sales occurring in high-income countries and in Europe, particularly in the Baltic States [19].

Vogler and colleagues [20] examined pharmaceutical policies implemented in Europe during 2010-2011 and found that countries significantly affected by the crisis (the Baltic countries, Greece, Spain and Portugal) abruptly implemented multiple policy measures, including price cuts, changes in reimbursement rates and value-added taxes on medicines. In other European countries (e.g. Italy), with cost-containment measures already in place when the crisis began, ongoing policy changes were accelerated [21].

Because countries were affected differently by the recession and used different responses to overcome budgetary constraints, we planned to analyze in a systematic way how the European pharmaceutical policy environment changed during the recession by describing pharmaceutical pricing and reimbursement policy changes and comparing them between economically stable and less stable countries. Further, we described changes in sales of products in major therapeutic classes prior to and after the recession in these two country groups. We expected that some cost-containment policies would shift financial burden for medicines to patients and hypothesized that pharmaceutical sales would decline during this period, especially in less economically stable countries.

METHODOLOGY

Data sources

We used data from two sources to derive information on pharmaceutical policies. Information collected by the Pharmaceutical Pricing and Reimbursement Information (PPRI) Network comes from experts in national pharmaceutical pricing and reimbursement authorities who provide regular pharmaceutical policy updates [22]. We also obtained data on pharmaceutical policies from PharmaQuery provided by IMS Health [23]. We added information on policy changes from published literature and grouped changes into six-month implementation periods from January 2008 until December 2011. We categorized policy foci in three main groups: 1) pricing, 2) reimbursement, and 3) generics. Table 1 lists and defines policy measures by foci.

Further, we analyzed quarterly pharmaceutical sales data from January 2006 to December 2011. Sales data from IMS MIDAS Quantum (Multinational Integrated Data Analysis System) were provided by IMS Health and are generated from reports by multinational and national pharmaceutical companies to IMS Health [24].

We received sales data in standard units (volume) and in constant dollars (value). A standard unit, as defined by IMS Health, is the smallest dose of a product, equivalent to one tablet or capsule for an oral dosage form, one teaspoon (i.e. 5ml) for a syrup and one ampoule or vial for an injectable product. Sales in constant dollars are captured at the price level that is deemed most accurate for the country, (in most countries, the ex-factory price level; in Estonia, Finland, Greece, and Ireland, wholesale prices were calculated back to ex-factory level). IMS Health applies average standard conversion factors to estimate prices at various price levels along the distribution chain, e.g. ex-factory, wholesaler-to-pharmacy, public. Average conversion factors are determined with the co-operation of the pharmaceutical industry and for each country, the data reflect local market conditions. IMS Health prices do not account for discounts between manufacturers, wholesalers or payers. Constant dollars are local currency sales converted to US Dollars at a constant exchange rate. They are calculated by multiplying the local currency value in each time period by the US Dollar exchange rate for the latest study quarter (4th quarter 2011). Inflation was not taken into account.

Data included prescription-only medicines (on-patent as well as off-patent) limited to the retail market. We received data for the 10 highest-selling therapeutic classes across the eight study countries. Therapeutic classes are based on the European Pharmaceutical Research Association (EphMRA) classification of Anatomical Therapeutic Chemical (ATC) classification [25]. The highest-selling therapeutic classes across the eight countries were identified among those with total sales of products by volume accounting for at least 50% of sales in each of the eight countries from 2008 to 2011 (Table 2). Data were aggregated by therapeutic class in each country; we did not have access to product-level data.

Selection and grouping of countries

We chose eight European countries (Austria, Estonia, Finland, Greece, Ireland, Portugal, the Slovak Republic and Spain) with social security systems or national health services for the majority of their populations, which were intended to represent a cross-section of geographic

regions, economic wealth and stability, and different severity of the recession. To group the selected countries, we followed the categorization of countries defined by the Organization for Economic Co-operation and Development (OECD) with regard to fiscal consolidation in 2012. OECD defined fiscal consolidation according to concrete policies aimed at stabilizing general government gross debt or targeting a long-term 60% debt-to-GDP ratio. They defined four categories of countries: 1) countries with International Monetary Fund / European Union / European commission programs (e.g. Greece, Ireland and Portugal), 2) countries under distinct market pressure (e.g. Belgium, Hungary, Italy, Slovak Republic, and Spain), 3) countries with substantial deficits and/or debts, but less market pressure (e.g. Austria, Denmark, Finland, France, Germany, and United Kingdom), and 4) countries with no or marginal consolidation needs (e.g. Norway, Sweden and Switzerland) [26]. For the purpose of this study, we defined economically less stable countries as countries belonging to category 1 or 2 (Greece, Ireland, Slovak Republic, Spain, Portugal) and economically stable countries as those belonging to category 3 or 4 (Austria, Finland and Estonia).

Data analysis

We first categorized the pharmaceutical policy measures implemented by each country in each six-month study period, and described the number of policy measures implemented per year, per country group and per policy category. Next, we depicted pharmaceutical sales by volume (in standard units) and by value (in constant dollars) from the first quarter of 2006 to the last quarter of 2011. In a first step we looked at the data per country and per therapeutic class separately and then per country but combined for all 10 therapeutic classes. As the picture was similar for individual and total therapeutic classes, we only present the results for all therapeutic classes combined.

For the analysis we divided sales volume and sales value by size of the national population to control for population growth, using annual populations estimated from the Organization for Economic Co-operation and Development (OECD) [27]. Taking pharmaceutical sales per capita both by volume and value, we calculated:

*Annual growth rate = ((per capita sales in year / per capita sales in previous year) -1) * 100*

*Average growth rate = (∑ annual growth rates / the number of years) * 100*

Because of the varying starting points for the recession in each country and the complexity of the array of pharmaceutical policies implemented during this period, we were unable to estimate the changes in sales value or volume attributable to any specific policy or set of policies.

RESULTS

Pharmaceutical policy context during the recession

A number of changes in pharmaceutical policies occurred after the crisis began. Table 3a-c and Table 4 outline the policy changes that were implemented during the observation period (2008-2011). We identified a total of 88 policy changes; the economically stable countries

Table 1. Overall policy foci, specific policy measures and definitions

Policy focus	Policy measure	Definition
Pricing	Price cuts	A cost-containment measure where the set price of a medicine is reduced by the authorities.
	External price referencing (EPR)	**External price referencing:** The practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country. **Changes in EPR** include the introduction or abolishment of this pricing policy as well as changes in the methodology (e.g. changes of the basket of reference countries, in the ways of calculating the price to benchmark with etc.)
	Distribution remuneration (mark-ups / margins/ dispensing fee/fee-for-service remuneration	**Distribution remuneration:** The payment of a health care provider (individual or organization) for the services provided. In the case of pharmaceutical distribution, wholesalers and pharmacies are remunerated by linear mark-ups, regressive margin schemes or, in the case of pharmacies, a fee-for-service remuneration. In case of a mark-up a defined (linear or percentage) amount is added on to the cost of a good to create a profit (at the wholesale and/or retail levels), whereas a margin is expressed as percentage of the selling price. **Changes in distribution remuneration:** A decrease or increase in wholesale or pharmacy mark-ups or margins, or a change of type of distribution remuneration for a defined actor. Changes may also regard to the scope of medicines (e.g. reimbursable medicines, prescription-only medicines) to which the distribution remuneration applies to.
	Value added tax (VAT) on medicines	**VAT:** A sales-tax on products collected in stages. It is a wide-ranging tax usually designed to cover most or all goods and services, including medicines. **Changes in VAT**: Introduction or abolishment of VAT on medicines, or increase or decrease in VAT rates on medicines.
	Extraordinary price review	**Price reviews:** Review process of the decision on the previously set price of a medicine. Price reviews may, or may not, be performed in combination with reimbursement reviews. Price reviews can be done systematically (e.g. once a year) for all reimbursed medicines or a group (e.g. specific indication), or out-of-schedule.

Reimbursement	Reference price system (RP, also referred to as internal or therapeutic reference pricing)	**Reference price system:** The third party payer determines a reference price to be reimbursed for medicines with a given active ingredient or in a given therapeutic class. If the price of the medicine exceeds the reference price, the insured must pay the difference between the reimbursed fixed amount (reference price) and the actual pharmacy retail price, in addition to any co-payments (e.g. prescription fees, percentage co-payment rates). **Changes in RPS:** Introduction or abolishment of a RPS, change in the methodology on how to build clusters (grouping by identical or similar medicines, to determine the reference price
	Out-of-pocket payments	**OOP:** Payments made by a health care consumer that are not reimbursed by a third party payer. They include cost-sharing, fixed or percentage co-payments and informal payments to health care providers.
	Delisting	Exclusion of a medicine from a reimbursement list (e.g. positive list), often resulting in exclusion from reimbursement.
Generics	International non-proprietary name (INN) (generic) prescribing	**INN prescribing:** Requirements for prescribers (e.g. physicians) to prescribe medicines by INN, i.e. the active ingredient name instead of the brand name. **Changes in INN prescribing:** Introduction or abolishment, change in the way how INN prescribing is organized (imposing/eliminating financial incentives), change from indicative to obligatory INN prescribing
	Generic substitution	**Generic substitution:** Practice of substituting a medicine, whether marketed under a trade name or generic name (branded or unbranded generic), with a less expensive medicine (e.g. branded or unbranded generic), often containing the same active ingredient(s). Generic substitution may be allowed (indicative generic substitution) or required (mandatory generic substitution). **Changes in generic substitution:** Introduction or abolishment, change in the way how generic substitution is organized (imposing/eliminating financial incentives), change from indicative to obligatory generic substitution
	Public campaigns	**Generic policies:** Policies, regulation, measures and initiatives, typically undertaken by the government authorities, to promote the use of generics and/or (licensed) off-patent medicines. Generic policies may be targeted at prescribers, pharmacists, patients/consumers and other stakeholders.

Source: WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies. Glossary of pharmaceutical terms. Update 2013 (in print). Accessible at http://whocc.goeg.at/Glossary

Table 2. Ten highest-selling therapeutic classes, accounting for 50% of product sales volumes across the countries under investigation

ATC 3 level[1]	Therapeutic class[1]
A10C,H,J,K,L,M,N,S,X	Anti-diabetes products
A2B	Anti-ulcer products
B1C	Platelet aggregation inhibitors
C10A,C,C11A	Lipid regulators
C9A,B	ACE Inhibitors, single ingredient as well as in combination with other antihypertensives
M1A, M2A	Anti-rheumatics
N2A	Non-narcotic analgesics
N6A	Anti-depressants
R1A6, R1B, R6A	Allergy, systemic and nasal preparations, topical products
R3 A,B,C,D,E,F,G,H, I,J,X	Respiratory agents

ATC = Anatomical Therapeutic Chemical classification
[1] ATC classification according to European Pharmaceutical Research Association EphMRA, http://www.ephmra.org/classification/anatomical-classification.aspx

(Austria, Estonia and Finland) implemented fewer policy changes (n=<10 each) with Finland having the fewest (n=2), while the less economically stable countries (Greece, Ireland, Spain, Slovak Republic and Portugal) implemented between 10 and 22 changes per country. Portugal (n=22) and Spain (n=17) were the countries with the most changes. Most policy adjustments occurred in 2010 (n=33) and 2011 (n=40), with changes in out-of-pocket payments (n=16), changes in mark-up regulations (n=13) and price cuts (n=11) being the most frequently used policy measures. No changes were implemented with regard to generic substitution. Pricing policies were implemented multiple times per country during the observation period, with Spain enacting price cuts four times during 2008-2011. Most changes targeted reimbursable medicines, as the aim was to contain public spending on medicines, and built on existing policies; only a few changes represented newly implemented policies such as the introduction of internal reference pricing in Finland [20].

Changes in medicines sales

During the observation time all countries showed positive growth in per capita medicines sales volume for the 10 highest-selling therapeutic classes (Figure 1 and Table 5). However, in all countries average sales volume growth rates during the study period were marginal, ranging from 1% (Greece and Portugal) to 3% (in Estonia, Ireland and Slovak Republic). No differences were observed between economically stable versus unstable countries. When looking at annual growth rates the picture is more diverse: from 2006 to 2007 all countries had growth rates above 4%, with Estonia highest at 12%. In 2008 and 2009 growth rates remained fairly stable in Austria and Finland, but sharply decreased in Estonia (0% and −9%, respectively) and more gradually decreased in all economically unstable countries. After the severe year-on-year decline in 2009, Estonia experienced increased a positive sales growth rate of 17% in 2010, whereas economically

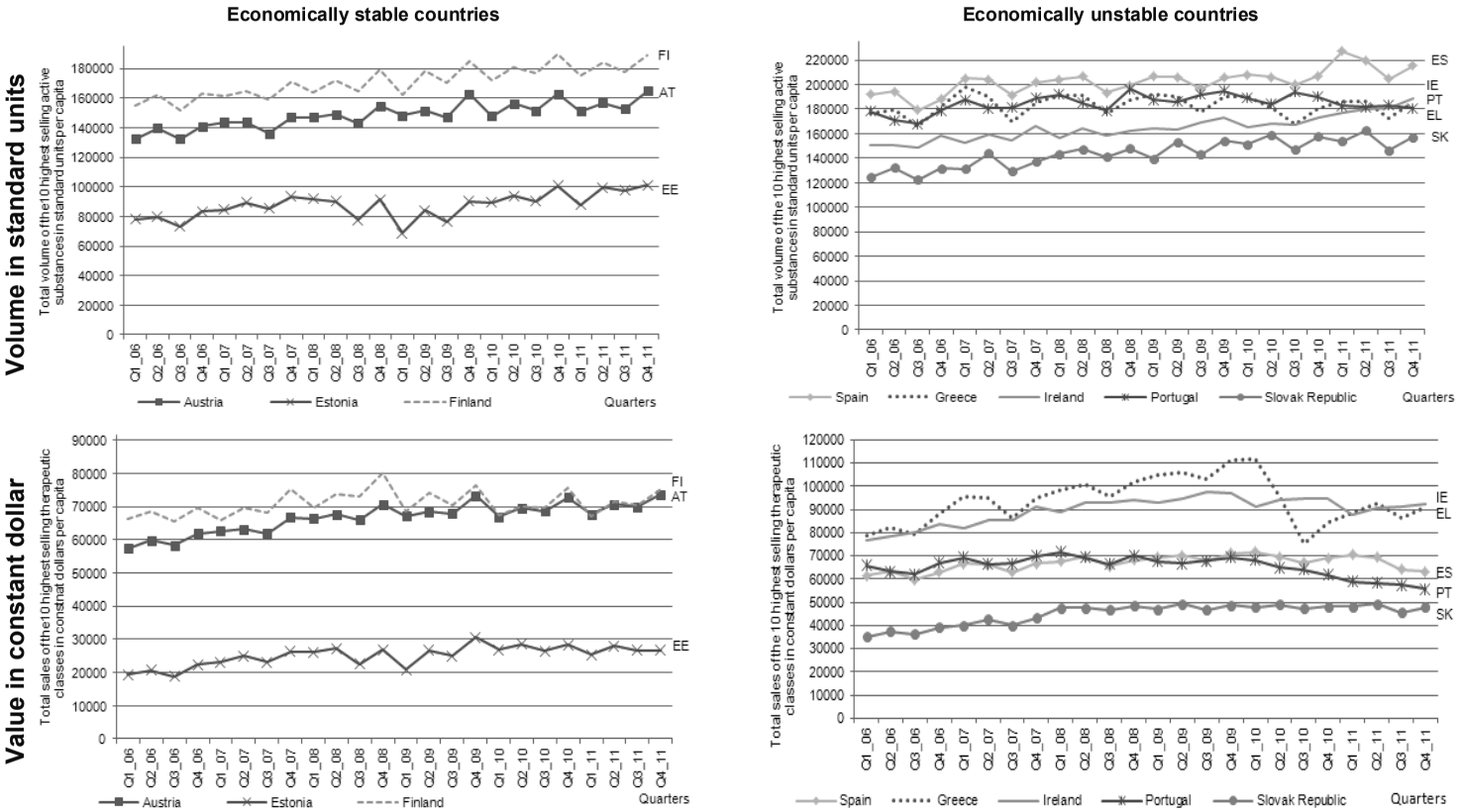


Figure 1. Total pharmaceutical sales by volume (in standard units) and value (in constant dollar) per capita of products in the 10 highest-selling therapeutic classes in economically stable and unstable countries.

Table 3a. Overview of pharmaceutical pricing policy changes implemented from 2008 until 2011

Policy measure	1st half 2008	2nd half 2008	1st half 2009	2nd half 2009	1st half 2010
Price cuts	-	**PT:** 30% price cuts for generics	**PT:** 5-12% price cuts on generics	-	**IE**: by 40% for off-patent medicines **EL:** emergency price cuts of up to a maximum of 27% on all reimbursed medicines (except orphan drugs); for off-patent medicines priced at 90% below original **ES:** 1st price cut for generics up to 30% **ES:** 2nd price cut 7.5% for health care products, including original medicines), imposed in the form of a discounts shared by all actors in the supply chain, and 20% for incontinence products
External price referencing (EPR)	-	-	-	**EL:** changes in calculation method **SK:** changes in reference countries	**ES:** changes in calculation method **PT:** changes in calculation method
Distribution remuneration	-	-	-	**IE:** changes in wholesale remuneration	**ES:** changes in wholesale remuneration **PT:** changes in wholesale remuneration **PT:** changes in pharmacy remuneration
Value-added tax	-	-	**AT:** decrease from 20% to 10% **EE:** increase from 5% to 9%	-	**IE:** increase non-oral preparations to 21% **PT:** increase from 5% to 6%
Extraordinary price review	-	**IE:** reimbursed medicines			**ES:** price review took price cuts into account **PT:** additional active substances

AT = Austria, EE = Estonia, EL = Greece, ES = Spain, EPR = external price referencing, FI = Finland, IE = Ireland, PT = Portugal, SK = Slovak Republic, VAT = value added tax

Policy measure	2nd half 2010	1st half 2011	2nd half 2011
Price cuts	**ES:** price increase for amoxicillin-containing medicines by 10-20% to avoid their withdrawal from the market **PT:** 7,5% price cut for biologicals and HIV products	**IE:** price cuts	**ES:** gradual price decreases **EL:** 35% of originators upon patent expiry, and 15% for generics
External price referencing (EPR)	-	**EL:** changes of calculation method **SK:** changes of calculation method	**EL:** changes in calculation method **PT:** changes in reference countries
Distribution remuneration	-	**EE:** changes in wholesale remuneration **EL:** changes in wholesale remuneration **EL:** abolishment of supply chain discounts **ES:** changes in wholesale remuneration **ES:** changes in pharmacy remuneration **IE:** changes in wholesale remuneration for high-cost medicines ("High Tech Scheme") **IE:** changes in wholesale remuneration for general scheme of low-income patients	**EL:** changes in pharmacy remuneration **PT:** regressive remuneration (in effect in February 2012)
Value-added tax	-	**EL:** decrease from 11% to 6.5% **ES:** increase from 8-10% for healthcare products	-
Extraordinary price review	**EL:** based on new price lists including price cuts **IE:** brands and parallel imports **SK:** reimbursed medicines	-	**EL:** resulting in new price list with price reduction of on average 10.23%

Table 3b. Overview of pharmaceutical reimbursement policy changes implemented from 2008 until 2011

Policy measure	1st half 2008	2nd half 2008	1st half 2009	2nd half 2009	1st half 2010
Reference price system	-	-	**FI:** introduction of internal reference pricing	-	**PT:** price volume agreement specified
Out-of-pocket payment	**AT:** increase prescription fee	-	**AT:** increase prescription fee **PT:** increase in reimbursement rate (from 95% to 100%) for generics for low income pensioners **PT:** increase in reimbursement rate for infertility drugs from 37% to 69%	-	**AT:** increase in prescription fee **PT:** abolishment of OOP for organ, tissue and stem cell transplant procedures
Delisting	-	-	**FI:** Seroquel	-	-

AT = Austria, EE = Estonia, EL = Greece, ES = Spain, FI = Finland, IE = Ireland, OOP = out-of-pocket payments, OTC = over the counter medicines, PT = Portugal, SK = Slovak Republic

Table 3c. Overview of pharmaceutical generics policy changes implemented from 2008 until 2011

Policy measure	1st half 2008	2nd half 2008	1st half 2009	2nd half 2009	1st half 2010
Generic prescribing	-	-	-	-	-
Generic substitution	-	-	-	-	-
Public campaigns and other generic policies	**AT:** generics information campaign	-	-	-	**EE:** generic campaign

AT = Austria, EE = Estonia, EL = Greece, ES = Spain, FI = Finland, HTA = Health Technology Assessment, IE = Ireland, PT = Portugal, SK = Slovak Republic

	2nd half 2010	1st half 2011	2nd half 2011
	EE: calculation method **SK:** Greece price cuts are taken into account	**ES:** price calculation based on lowest daily treatment costs **PT:** price calculation method and new generic group **SK**: new clusters	**EL:** pricing at or below reference price
	IE: introduction of €0.50 per medicine on prescription **ES:** Madrid: underprivileged patients will be given free access to products for seven rare diseases **PT:** changes in reimbursement rates (including antipsychotic medicines)	**AT:** increase in prescription fee **EE:** elimination of co-payment limit **ES:** co-payment linked to income **SK:** cost-sharing agreements	**PT:** shorter reimbursement reviews **SK**: limitation of certain reimbursement categories **SK:** frequency of publishing the reimbursement list
	-	**EL:** introduction of negative list (including contraceptives, lifestyle medicines) **ES:** delisting of selected medicines **PT:** delisting of OTC (16 branded non-prescription medicines, including paracetamol, omeprazole oral, contraceptives and antihistamines)	**EL:** in the course of price review 49 medicines delisted

	2nd half 2010	1st half 2011	2nd half 2011
	EE: change from optional to compulsory generic prescribing	**SK:** optional generic prescribing	**ES:** introduction of optional generic prescribing **PT:** specifications to compulsory generic prescribing
	-	-	-
	IE: rebates for generics abolished **EE:** e-prescribing **ES:** nation-wide generic campaign **PT:** Campaign to promote rational medicines use; unit dose dispensing; display of prices on packs **SK:** establishment of HTA institute	**ES:** unit dose dispensing for four substances	**PT:** e-prescribing and opening hours of pharmacies **PT:** Faster market entry for generics subject to patent disputes (25 active substances)

Table 4. Summary of policy changes from 2008 until 2011

Policy focus and measures		Stable countries			Less stable countries					Total per policy
		AT	EE	FI	SK	EL	ES	IE	PT	
Pricing	Price cuts	0	0	0	0	2	4	2	3	11
	External reference pricing	0	0	0	2	3	1	0	2	8
	Mark-up regulation	0	1	0	0	3	3	3	3	13
	Value-added tax	1	1	0	0	1	1	1	1	6
	Extraordinary price review	0	0	0	1	2	1	2	1	7
Reimbursement	Internal reference pricing	0	1	1	2	1	1	0	2	8
	Out-of-pocket payment	4	1	0	3	0	2	1	5	16
	Delisting	0	0	1	0	2	1	0	1	5
Generics	Generic prescribing	0	1	0	1	0	1	0	1	4
	Generic substitution	0	0	0	0	0	0	0	0	0
	Public campaigns and other generic policies	1	2	0	1	0	2	1	3	10
Total number of policy changes by country		6	7	2	10	14	17	10	22	88
Total number of policy changes by group			15				73			
Total number of policy changes by year		2008=4		2009=11		2010 =33		2011=40		

AT = Austria, EE = Estonia, EL = Greece, ES = Spain, FI = Finland, IE = Ireland, PT = Portugal, SK = Slovak Republic

unstable countries continued to decline (for example, -4% in Greece and -1% in Portugal in 2010). In 2011, two less economically stable countries experienced high growth in sales volume (6% in Spain and 8% in Ireland), while most other countries had a growth rate between 1% and 3%; Portugal was the exception as it still had a negative growth rate of -4% in 2011.

With respect to sales value in constant dollars, the picture is more divergent. Average annual growth rates in sales value over the whole study period varied between -2% in Portugal to 5% in Estonia. However, from 2009 onwards all countries experienced decreases in sales value. The largest declines were observed in Greece (negative year on year growth rate of -14% in 2010) and Portugal (-11% in 2011). Negative growth rates predominated in the economically unstable countries in 2010 and 2011.

DISCUSSION

Countries adjust their pharmaceutical policy framework continuously, but a concentration of policy changes took place during the economic recession in 2010 and 2011, especially in less economically stable European countries. Changes in out-of-pocket payments and mark-ups were the most frequently implemented policies. Both economically stable and less stable study countries experienced slight increases in medicine consumption (in standard units per capita) of the 10 highest-selling therapeutic classes during this period; however, economically less

Table 5. Country-specific growth rates of total pharmaceutical sales volume in standard units and sales value in constant dollars per capita of the ten highest selling therapeutic classes from 2006 – 2011

Volume in standard units per capita							
		Annual growth rates					Ø annual growth rate
Country		'06 vs. '07	'07 vs. '08	'08 vs. '09	'09 vs. '10	'10 vs. '11	2006-2011
Stable countries	AT	4.6%	4.0%	2.7%	1.5 %	1.1 %	2.3%
	EE	12.2%	-0.5%	-9.0%	17.1 %	3.1 %	3.5%
	FI	3.7%	3.8%	2.3%	3.4 %	1.0 %	2.3%
Less stable countries	EL	5.6%	0.3%	0.7%	-4.1 %	1.5 %	0.6%
	ES	6.4%	0.2%	1.5%	0.7 %	5.5 %	2.4%
	IE	4.1%	1.4%	4.3%	0.8 %	7.8 %	3.0%
	PT	6.1%	1.8%	1.1%	-0.5%	-3.7 %	0.8%
	SK	6.1%	7.1%	1.7%	4.1%	1.0 %	3.3%
Value in constant dollar per capita							
		Annual growth rate					Ø annual growth rate
Country		'06 vs. '07	'07 vs. '08	'08 vs. '09	'09 vs. '10	'10 vs. '11	2006-2011
Stable countries	AT	7.3%	6.3%	2.2%	0.4%	1.5%	2.9%
	EE	20.5%	5.2%	0.3%	7.0%	-3.2%	4.7%
	FI	3.1%	6.3%	-2.2%	-2.6%	0.7%	0.9%
Unstable countries	EL	13.3%	7.0%	6.8%	-13.5%	-2.4%	1.5%
	ES	6.1%	3.1%	2.7%	**-0.4%**	-3.7%	1.3%
	IE	7.6%	7.2%	3.6%	-1.9%	-3.4%	2.1%
	PT	5.4%	2.0%	-2.2%	-4.6%	-11.1%	-1.9%
	SK	12.0%	14.6%	0.6%	0.5%	-0.9%	4.3%

Ø = average, AT = Austria, EE = Estonia, EL = Greece, ES = Spain, FI = Finland, IE = Ireland, PT = Portugal, SK = Slovak Republic

stable countries showed decreases in annual growth rates of medicines sales measured in value per capita in 2010 and 2011, which could however be partially attributed to inflation as it was not taken into account in our study.

Our study showed that economically stable countries (Austria, Estonia and Finland) implemented fewer policy measures compared to less economically stable countries (especially Spain and Portugal) during the study period. The most frequently implemented policy changes were in patient out-of-pocket payments. Previous studies have shown that increases in co-payments such as prescription fees tend to lead to decreases in medicine utilization, especially in times of economic recession and increased unemployment [29-37]. Policy measures like the strict medicine price cuts implemented in Greece, Spain and Portugal could have had negative effects on the availability of medicines if they caused pharmaceutical companies to withdraw their products from national reimbursement lists [38]. However, contrary to our expectation,

we did not find major declines in pharmaceutical consumption during the recession in the therapeutic categories studied as most countries except for Greece and Portugal continued to have moderate positive annual growth in pharmaceutical sales volumes. But in line with media reports on drug shortages in Greece and Portugal, our data showed that sales volumes of important medicines for chronic diseases, such as ACE inhibitors or anti-depressants, dropped drastically in Greece and in Portugal in 2010 [38-39]. Despite positive growth, there nevertheless appears to have been a downturn in sales growth compared to pre-recession rates, which ranged from 5% to 12%. In contrast, pharmaceutical sales by value experienced declines during the recession, especially in less economically stable countries. The pharmaceutical policies implemented in less economically stable countries may have had the desired effect of lowering public spending while maintaining access to study medicines at relatively stable levels. However, some of the policies, e.g. increases in out-of-pocket payments for patients, may have shifted financial burden to patients.

The case of Estonia needs to be discussed separately. After a decade of rapid growth prior to the recession, during which public sector expenditures grew 6.5 times [26], Estonia experienced a major decline of gross domestic product (GDP) in 2009. Public sector spending was cut by 6.6%, a reduction of 100 million Euro compared with 2008, with € 50 million cut from health insurance expenditures [7]. A previous study detected severe declines in pharmaceutical consumption of -18% in 2008/2009 in Estonia [19], a finding mirrored by our data. In response, Estonia implemented strict cost-saving measures, including changes in out-of-pocket payments, increases in VAT rates on medicines and changes in mark-ups for medicines. In addition, regulators introduced reductions in coverage of sick leave and increases in clinical staff workload without increases in salary [7,19]. Our data show that by 2010, pharmaceutical consumption had returned to a similar level as prior to the recession, paralleling Estonia's relatively quick recovery from the recession overall [26]. Interestingly, early in the recession, none of the countries implemented policies targeting consumption by specific patient groups or in specific therapeutic areas; countries rather adjusted and enforced existing policies. More recently, several countries have explored alternative policies for sharing the financial risk of selected new, high-cost medicines including value-based pricing models (e.g. the UK) or risk-sharing agreements (e.g. Italy) [40-44]. The effects of these new approaches will need to be determined.

Our study had several limitations. All study countries had different pharmaceutical policy frameworks prior to the economic recession and adjusted their policies in different ways and at different times following the recession. Even within countries, regional differences in pharmaceutical policies exist (e.g. in Italy or Spain), which we disregarded in our study of national policies. It was not always clear whether countries implemented policies as a short-term reaction to recession-related budgetary constraints or if policies were long-term planned system changes. For instance, in Finland, the implementation of internal reference pricing in 2009 was planned long before the recession [45]. The implementation of major policy changes such as reference price systems may take several years, since many stakeholders are involved [46]. Most of the observed policy changes related to the recession were adjustments of existing policies (e.g. changing the countries in the basket for external price referencing), which could be implemented

relatively quickly. While leading to desired short-term cost-containment, these policies might have substantial long-term effects on access to, use, and affordability of medicines and negative impacts on health [47-50]. We focused our analyses of sales on products that accounted for the majority of pharmaceutical sales by volume. It is possible that policy changes had differential impacts on sales of less frequently used products, including those used by patients with rare diseases, although at least one price cut in Greece exempted orphan drugs for rare diseases.

Further, IMS sales data in constant dollars disregard discounts and rebates and do not reflect actual spending of third party payers. In addition, each country's data might include different products within a therapeutic class.

Other market dynamics such as patent expiries may also influence medicines sales. During this period, there were highly-used products with expiring patents among antidiabetes medications, antiulcerants, platelet aggregation inhibitors, lipid regulators, ACE inhibitors, and anti-depressants. The accompanying price reductions may have been one factor reducing sales value while buffering declines in sales volume.

Finally, the rapid implementation of policies during the economic recession and the different timing of policies in different countries precluded attribution of observed changes to any single policy or statistical comparisons of responses between countries. We suggest that future prospectively designed research studies focus on the impacts of policy changes in systems.

CONCLUSIONS

The ways in which countries responded to the recession differed greatly, as less economically stable countries tended to implement a larger number of policies that affected the pharmaceutical sector. Our evidence shows that despite numerous policy changes, overall pharmaceutical consumption in the top 10 selling therapeutic classes studied continued to increase in most countries, with no clear difference between economically stable and less stable countries. However, many of these policies were designed to shift a greater financial burden to patients. Future research needs to determine impacts of the observed changes on access to, use, and household affordability of needed medicines and on health outcomes.

REFERENCES

1. Habl C, Antony K, Entleitner M, Fröschl B, Leopold C, Stürzlinger H, Vogler S, Weigl M. Surveying, Assessing and Analyzing the Pharmaceutical Sector in the 25 EU Member States. Commissioned by the European Commission, Directorate-General Competition. July 2005.
2. Mossialos E, Mrazek M, Walley T. Regulating pharmaceuticals in Europe: striving for efficiency, equity, and quality. European Observatory on Health Care Systems Series. Maidenhead (UK): Open University Press; 2004.
3. Docteur E, Paris V. Pharmaceutical pricing policies in a global market. Paris: OECD Health Policy Studies; 2007. Available from: http://www.oecd.org/fr/els/systemes-sante/pharmaceuticalpricingpoliciesinaglobalmarket.htm. Accessed on 14 August 2012.
4. Seiter A. Access to medicines and the innovation dilemma – Can pharmaceutical multinationals be good corporate citizens? Business Ethics of Innovation Ethics of Science and Technology Assessment. 2007;31:89–100.
5. Shelburne R, Trentini C. Public Health in Europe: the 2007-2009 financial crisis and UNECE activities. Discussion paper of the United Nations Economic Commission For Europe. November 2009. Available from: http://www.unece.org/fileadmin/DAM/oes/disc_papers/ECE_DP_2009-2.pdf. Accessed 10 February 2013.
6. United Nations Economic and Social Council. The economic situation in the Economic Commission for Europe region: Europe, North America and the Commonwealth of Independent States in 2008-2009. Substantive session of 2009. Available from: http://www.un.org/regionalcommissions/crisis/ececis.pdf. Accessed 10 February 2013.
7. Läänelaid, Siret, Aaviksoo. Economic slowdown shaping healthcare system - Estonia. Health Policy Monitor, April 2009.
8. Nagpal S. Latvian health minister quits over big budget cuts 2009 17 September 2009 [cited 21 September 2009]; Available from: http://www.topnews.in/latvian-health-minister-quitsover-big-budget-cuts-2179023. Accessed 10 February 2013.
9. Bailey M. Latvia makes healthcare budget cuts as economic crisis bites. Scrip News; 2009.
10. Schrader K, Laaser CF. Die Krise in Südeuropa oder die Angst vor dem Dominoeffekt. Griechenland, Portugal und Spanien im Krisentest. Institut fuer Weltwirtschaft. Kiel. 2012. Available from: http://www.ifw-kiel.de/. Accessed 10 February 2013.
11. The World Bank. Averting a human crisis during the global downturn: policy options from the World Bank's Human Development Network. April 2009.
12. Stuckler D, Basu S, Suhrcke M, Coutts A, McKee M. The public health effect of economic crises and alternative policy responses in Europe: an empirical analysis. Lancet. 2009;374:315-23.
13. Holahan J. The 2007-09 recession and health insurance coverage. Health Aff (Millwood). 2011 Jan;30(1):145-52. doi: 10.1377/hlthaff.2010.1003. Epub 2010 Dec 6.
14. Lusardi A, Schneider D, Tufano P. The economic crisis and medical care usage. NBER Working Paper. 2010.
15. Fronstin P. The impact of the recession on employment-based health coverage. EBRI Issue Brief 2010;342:1-22.
16. Truffer CJ, Keehan S, Smith S, Cylus J, Sisko A, Poisal JA, Lizonitz J, Clemens MK. Health spending projections through 2019: The recession's impact continues. Health Aff (Millwood). 2010 Mar-Apr;29(3):522-9. doi: 10.1377/hlthaff.2009.1074. Epub 2010 Feb 4..
17. Mc Kee M, Stuckler D, Martin-Moreno JM. Protecting health in hard times. BMJ. 2010 Sep 29;341:c5308. doi: 10.1136/bmj.c5308.
18. Kentikelenis A, Karanikolos, Papanicolas I, et al. Health effect of financial crisis: omens of a Greek tragedy. Lancet October 2011;378(9801):1457-1458. doi:10.1016/S0140-6736(11)61556-0. Available from: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2811%2961556-0/fulltext#aff2. Accessed 10 May 2013.
19. Buysse IM, Laing RO, Mantel-Teeuwisse AK. Impact of the economic recession on the pharmaceutical sector. Utrecht University. WHO Collaborating Centre for Pharmacoepidemiology and Pharmaceuticals Policy Analysis. February 2010. Available from: http://apps.who.int/medicinedocs/en/m/abstract/Js17419e/. Accessed 10 February 2013.
20. Vogler S, Zimmermann N, Leopold C, de Joncheere K. Pharmaceutical policies in European countries in responds to the global financial crisis. South Med Rev. December 2011;4(2):22-32.
21. Belvis AG, Ferre A, Specchia MA. The financial crisis in Italy: Implications for the Healthcare sector. Health Policy. June 2012;106(1):10-16.
22. WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies. Pharmaceutical policy information 2008 – 2011.

23. IMS Institute for Healthcare Informatics. PharmaQuery 2006 – 2011. Unpublished information.
24. IMS Health MIDAS. 2007-2011.
25. European Pharmaceutical Market Research Association (EphMRA). Anatomical Classification [Internet]. 2012 [cited 2012 August 6]. Available from: http://www.ephmra.org/classification/anatomical-classification.aspx. Accessed 10 February 2013.
26. OECD. Restoring Public Finances, 2012 Update. Executive summary. OECD Publishing. 2012. DOI: 10.1787/9789264179455-4-en.
27. OECD Health data. Population data. Extracted 2 October 2012.
28. Haugh D, Mourougane A, Chatal O. The automobile industry in and beyond the crisis. OECD Economics Department working paper No. 745. 2010. Available from: http://search.oecd.org/officialdocuments/displaydocumentpdf/?doclanguage=en&cote=eco/wkp%282010%291. Accessed 10 July 2013.
29. Horton R. The global financial crisis: an acute threat to health. Lancet. 2009; 373(9661):355-356.
30. Marmot MG, Bell R. How will the financial crisis affect health? BMJ. 2009;338:b1314.
31. Leyland AH. Alcohol, financial crisis and reform: learning from the Russian experience. Eur J Public Health. 2012;22(3):300.
32. Polyzos N. Health and the financial crisis in Greece. Lancet. 2012;379(9820):1000.
33. Kaitelidou D, Kouli E. Greece: the health system in a time of crisis. Euro-health. 2012;18(1):12-14.
34. Yang BM, Prescott N, Bae EY. The impact of economic crisis on health-care consumption in Korea. Health Policy Plan. 2001;16(4):372-385.
35. Parry J, Humphreys G. Health amid a financial crisis: a complex diagnosis. Bull World Health Organ. 2009;87(1):4-5.
36. Catalano R. Health, medical care, and economic crisis. N Engl J Med. 2009;360(8):749-751.
37. Navarro V. Crisis and fiscal policies in the peripheral countries of the Euro-zone. Int J Health Serv. 2012;42(1):1-7.
38. Ornelas A. Recession-hit nations owe pharma firms billions. Swissinfo.ch. 25 February 2012. Available from: http://www.swissinfo.ch/eng/business/Recession-hit_nations_owe_pharma_firms_billions.html?cid=32185254. Accessed 10 July 2013.
39. Pharmaceutical Group of European Union (PGEU). Medicine shortages in European Community Pharmacies. PGEU. May 2013. Available from: http://www.pgeu.eu/en/library/2-position-papers/154-pgeu-statement-on-medicine-shortages-in-european-community-pharmacies.html. Access 10 June 2013.
40. Kanavos P, Nicod E, Espin J, van den Aardweg S. Short- and long-term effects of value-based pricing vs. External Price Referencing. EMINET 2010.
41. Husereau D, Cameron C. Value-based pricing of pharmaceuticals in Canada: Opportunities to expand the role of Health Technology Assessment? CHSRF Series of Reports on Cost Drivers and Health Systems Efficiency: Paper 5, 2011.
42. Espín J, Rovira J, García L. Experiences and Impact of European Risk-Sharing Schemes Focusing on Oncology Medicines. January 2011; Commissioned by the European Commission, Directorate-General Enterprise.
43. Kanavos P, Seeley E, Vandoros S. Tender systems for outpatient pharmaceuticals in the European Union: Evidence from the Netherlands, Germany and Belgium. EMINet 2010.
44. Kanavos P. Ferrario A. Managed entry agreements for pharmaceuticals: The European experience. EMINet. April 2013; Commissioned by the European Commission, Directorate-General Enterprise.
45. Pohjolainen L. Reference price and price competition – evidence from the Finnish pharmaceutical market. Master's thesis. Aalto University, School of Economics, Department of Economics. February 2012. Available: https://aaltodoc.aalto.fi/handle/123456789/3456. Accessed 20 August 2012.
46. Habl C, Vogler S, Leopold C, Schmickl B, Fröschl B. Referenzpreissysteme in Europa. Analyse und Umsetzungsvoraussetzungen für Österreich. Vienna: ÖBIG Forschungs- und Planungsgesellschaft mbH; 2008.
47. Wladysiuk M, Araszkiewicz A, Godman B, et al. Influence of patient co-payment on atypical antipsychotic choice in Poland: implications once generic atypical are available. Appl Health Econ Health Policy. 2011 March; 9(2):101-110. doi: 10.2165/11318840-000000000-00000.
48. Andersson K, Petzol MG, Sonesson C, Lönnroth K, Carlsten A. Do policy changes in the pharmaceutical reimbursement schedule affect drug expenditures? Interrupted time series analysis of cost, volume and cost per volume trend in Sweden 1986-2002. Health Policy. 2006;79:231-243.
49. Soumerai SB, Zhang F, Ross-Degnan D, Ball DE, LeCates RF, Law MR, Hughes TE, Chapman D, Adams AS. Use of atypical antipsychotic drugs for schizophrenia in Maine Medicaid Following a policy change. Health Aff (Millwood). 2008 May-

Jun;27(3):w185-95. doi: 10.1377/hlthaff.27.3.w185. Epub 2008 Apr 1..

50. Ong M, Catalano R, Hartig T. A time-series analysis of the effect of increased copayments on the prescription of antidepressants, anxiolytics, and sedatives in Sweden from 1990 to 1999. Clin Ther. 2003 Apr;25(4):1262-75.

CHAPTER 3.2

Impact of pharmaceutical policy interventions on utilization of antipsychotic medicines in Finland and Portugal: interrupted time series analyses

Submitted

Christine Leopold, Fang Zhang,
Aukje Mantel-Teeuwisse, Sabine Vogler,
Silvia Valkova, Dennis Ross-Degnan, Anita Wagner

ABSTRACT

Objectives: To analyze the impacts of two different pharmaceutical policies – the implementation of a reference price system in Finland and a mix of policies including changes in reimbursement rates, a generic promotion campaign and discounts granted to the public payer in Portugal – on the utilization of antipsychotic medicines.

Methodology: We obtained monthly IMS sales data in standard units of antipsychotic medicines in Portugal and Finland for the period January 2007 to December 2011. We used an interrupted time series design to estimate changes in overall use and generic market shares by comparing pre-policy and post-policy levels and trends.

Results: Both countries' policy approaches were associated with slight, likely unintended, decreases in overall use of antipsychotic medicines and to increases in generic market share of major antipsychotic products. In Finland quetiapine and risperidone experienced substantially increased generic market shares (estimates one year post-policy compared to before, quetiapine: 6.80% [3.92%, 9.68%]; risperidone: 11.13% [6.79%, 15.48%]. The policy interventions in Portugal resulted in a substantially increased generic market share for amisulpride (estimate one year post-policy compared to before: 22.95% [21.01%, 24.90%]; generic risperidone already dominated the market prior to the policy interventions.

Conclusions: Different policy approaches to contain pharmaceutical expenditures in the study countries had different intended – increased use of generics – and likely unintended – slightly decreased overall sales possibly consistent with decreased access to needed medicines – impacts. The latter finding stresses the importance of monitoring and evaluating the effects of pharmaceutical policy interventions.

INTRODUCTION

European social security systems face the difficult task of guaranteeing their citizens sustainable access to medicines. Innovative, specialized, often costly medicines as well as the recession have put enormous pressure on public budgets. European countries have chosen different strategies to contain costs [1-5]. Changes in co-payments and increases in value-added taxes (VAT) on medicines were among the most frequently implemented cost-containment measures in 2010 [6]. Pharmaceutical cost-containment policies do not necessarily achieve the intended financial savings and may have unintended effects on medicines utilization [7-12].

Antipsychotic medications are essential for treatment of severe chronic mental illness, such as schizophrenia, which are among the leading major chronic diseases in Europe [13,14]. The World Health Organization describes schizophrenia as a severe form of mental illness affecting about 7 per thousand of the adult population; about 24 million people worldwide mostly between 15-35 years old [15]. Due to their high cost, antipsychotic medications represent a large component of public spending on medicines and are therefore a frequent target of cost-containment. Reimbursement restrictions may, however, force patients to forego treatment in light of increased out-of-pocket payments [16] or to shift to other possibly less appropriate or more costly treatments [17]. For example, Wladysiuk et al. showed that the utilization of risperidone for schizophrenia in Poland decreased with increased patient co-payments, while olanzapine use increased once co-payments were reduced when generic olanzapine became available [18]. Andersson et al. determined that introduction of a tiered co-payment schedule was associated with decreased cost and volume for all groups of acetic acid derivates and selective serotonin reuptake inhibitors while introduction of therapeutic reference pricing was associated with reduced cost per defined daily dose of these medications [19]. Soumerai et al. found that implementation of a policy that required prior approval for reimbursement of specific atypical antipsychotics to control expenditures in one US state public insurance program resulted in increased rates of discontinuity of antipsychotic drug treatment [20]. These results are consistent with an earlier study of the effects of other policies on discontinuation of antipsychotic agents among patients with severe mental illness [21].

Our intent was to assess the impacts of different cost-containment policies in Finland and Portugal on medicines utilization within each country and to compare the magnitude of effects. We focus on antipsychotic medicines because they are included in the public reimbursement systems in both countries and because of the public health relevance of antipsychotic disorders and their treatment. The recent recession has put additional pressure on both countries to implement already planned policy changes. The recession affected both countries differently. Finland did not experience major declines in gross domestic product (GDP) during the recession. Portugal, however, suffered a 2.9% decline in GDP growth between 2008 and 2009 and another decline of 1.7% between 2010 and 2011 [22] leading to a strict three year public budget savings plan between the Portuguese Ministry of Finance and the Troika (consisting of representatives of the European Commission, the European Central Bank and the International Monetary Fund) [23].

On April 1, 2009, Finland implemented a reference price system whereby all medicines with therapeutic alternatives on the National Social Security's reimbursement list were clustered

according to therapeutic similarity based on each medicine's indication and pharmacology. Medicines in clusters were considered substitutable. For each substitution group a reference price was set at the price of the least expensive medicine in the cluster with patients having to pay the difference for higher cost medications out-of-pocket. Danzon et al. highlighted that a hoped for effect of reference pricing is that manufacturers, anticipating shifts to less expensive (mostly generic) products, decrease prices to not lose customers [24]. According to Pohjolainen et al., the average price level for all medications decreased significantly in the first four quarters after the implementation of the reference price system in Finland, which led to € 109 million savings [25,26]. In addition to establishing reference pricing, the National Social Security Scheme delisted the antipsychotic brand product Seroquel (quetiapine) from its reimbursement scheme on January 1, 2009, because the manufacturer did not decrease its price to that of the 40% less expensive generics when it became available [27,28].

In contrast, Portugal introduced several contemporaneous cost-containment policies: on October 15, 2010, the Portuguese National Authority for Medicines and Health Products (INFARMED) harmonized the reimbursement rates for antipsychotic medicines to 90% of charges [29,30]. Prior to the change, antipsychotic medicines were reimbursed at 37%, but in reality all patients received antipsychotic medicines for free as physicians could state certain pathologies (as listed in legislation) on the prescription for which antipsychotic medicines were dispensed to the patient without co-payment [31]. Following the change in reimbursement rates, no indication-specific co-payment exemptions were allowed. In addition, from September 15 to October 8 2010, INFARMED launched a television and radio campaign to promote generics ("you save, we all save") to inform the public about the use of generics and to alert consumers to the lower price of generics as compared to originals [32]. Finally, on October 15, 2010 a 6% deduction of the maximum retail price took effect for medicines that had not already lowered prices earlier; this deduction did not affect the final consumer price and is a statutory discount granted by industry and supply chain actors to the public payer [33]. In the beginning of 2013 this deduction was still applied.

We hypothesized that the implementation of the reference price system and delisting of the brand product Seroquel in Finland would lead to an increase in sales (by volume) of generics, but no reduction in overall utilization. We also hypothesized that the change in reimbursement rates in Portugal would lead to an unintended decrease in sales by volume of antipsychotic medications as many patients had to pay higher co-payments after the policy changes. Finally, we expected an increase in the generic market share in Portugal as a result of the generic campaign.

METHODOLOGY

Data source

We analyzed monthly pharmaceutical sales in Finland and Portugal between January 2007 and December 2011 provided by IMS Health [34]. Data are generated through audits of aggregated purchases of registered medicines by retail pharmacies from wholesalers in each country. IMS audits cover 812 pharmacies or 100% of the retail market in Finland and 2,910 pharmacies or 99% of the retail market in Portugal [35]. IMS MIDAS combines national audits into a globally consistent view of

pharmaceutical markets. Documentation on the IMS data collection and validation process is available upon request from the authors. Antipsychotic medicines were those in Anatomical Therapeutic Chemical (ATC) category N5A of the European Pharmaceutical Research Association (EphMRA) [36].

We extracted information on policy changes in each country from the WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies [37] and the IMS PharmaQuery databases [38]. In addition, information on policy changes was verified by national experts from Finland and Portugal through written communication.

Outcomes

We used two outcome measures: total volume of antipsychotic medicines per capita and percentage market share by volume in a therapeutic class. For the total volume analyses, we divided the total volume, which is the number of standard units (SU) per month, by size of the national population to control for population growth, using annual populations estimated from the Organization for Economic Co-operation and Development (OECD) [39]. Our analyses included prescription-only antipsychotic medicines limited to the retail market, which represented 98% of medicines sales by volume in Portugal and 87% in Finland in 2011. A standard unit, as defined by IMS Health, is the smallest dose of a product, equivalent to one tablet or capsule for an oral dosage form, one teaspoon (i.e. 5 ml) for a syrup and one ampoule or vial for an injectable product. Percent market share is the percent of total volume in the retail market for each active substance in two categories – originator brand products, which can be protected or no-longer-protected by patents depending on their exclusivity status in each period and country, and generic products which are not subject to patent protection.

Study design and data analysis

We used an interrupted time series design, the strongest quasi-experimental design [40], to estimate changes in sales attributable to the policies by comparing sales after the interventions to estimated sales based only on pre-policy levels and trends (the counterfactual). We used segmented regression models to statistically estimate aggregate changes in levels and trends of monthly sales by volume from the pre-policy period to the post-policy period. Each model included a term to estimate the baseline trend, a binary indicator for all post-policy months to estimate the immediate level change in the outcome measure following the policy change, and a term indicating the number of months after policy implementation to estimate the change in trend (slope) during the post-policy period. The combined change in level and trend at a given month after the policy represented the full policy effect. To allow for the possibility of an anticipatory response to implementation of the policy, we considered a phase-in period of four months prior to the policy intervention in both countries and excluded these four data points from the time-series model [41-44]. We also performed a sensitivity analysis by comparing results from interrupted times series models without a phase-in period, but as the results were similar we display only the results from the models with a phase-in period. Further, we estimated absolute changes from the counterfactual one year after the policy intervention, giving detail on the difference between the actual and predicted values. We performed the

analyses in SAS 9.3 and used a stepwise selection approach, which removed non-significant predictors (p >= 0.2) from the model in order of least significance.

RESULTS

The antipsychotic market in Finland was dominated by three leading active substances: quetiapine (31%), clozapine (12%) and risperidone (12%), based on aggregated sales by volume from 2007 to 2011. In Portugal risperidone (17%), quetiapine (17%) and amisulpride (12%) were the top three active substances sold in the class during that period.

Figure 1 and Table 1 show the total monthly sales of antipsychotics in standard units per capita in both countries. In Finland, prior to the implementation of the reference price system, antipsychotic sales were increasing by 704 SU (95% CI: 519, 889) per 100,000 people per month; after the policy intervention sales growth decreased by 273 SU (95% CI: -572, 26) per 100,000 people per month compared to pre-policy sales growth. There was no discontinuity in level of sales at the time of intervention. This resulted in an estimated reduction of 3,550 SU (95% CI: -7,354, 254) per 100,000 people in actual sales compared to predicted sales (or around 2.3% of predicted sales) one year after the implementation of the reference price system. In Portugal sales remained constant prior to the policies; however after the policy interventions, there was an estimated decrease in level of antipsychotic sales of 4,686 SU (95% CI: -8,913, -458) per 100,000 people (or 4.5% of predicted sales), which remained constant in the year after the policy.

Table 1. Estimates of baseline trend, level and trend changes, and absolute changes one year after the policy interventions for total antipsychotic sales and for generic market share of major active substances in Finland and Portugal

	Variable (unit)	Monthly baseline trend pre-policy (95% CI)	Level change post-policy (95% CI)	Monthly trend change post-policy (95% CI)	Absolute estimated change one year post-policy (95% CI)
Finland	Total sales growth per 100,000 population (SU)	704 (519, 889)	-	-273 (-572, 26)	-3550 (-7354, 254)
	Quetiapine generic market share (%)	2.07 (1.97, 2.17)	33.61 (31.61, 35.61)	-2.06 (-2.18, -1.95)	6.80 (3.92, 9.68)
	Risperidone generic market share (%)	2.19 (2.03, 2.34)	37.65 (34.60, 40.69)	-2.04 (-2.20, -1.88)	11.13 (6.79, 15.48)
	Clozapine generic market share (%)	0.07 (-0.02, 0.17)	2.22 (0.30, 4.14)	-0.25 (-0.36, -0.13)	-0.97 (-3.75, 1.81)
Portugal	Total sales growth per 100,000 population (SU)	-	-4686 (-8913, -458)	-	-4686 (-8758, -613)
	Risperidone generic market share (%)	-0.08 (-0.15, 0.01)	2.16 (0.76, 3.57)	0.19 (0.06, 0.31)	4.59 (2.67, 6.51)
	Amisulpride generic market share (%)	-	12.23 (9.61, 14.85)	0.82 (0.56, 1.09)	22.95 (21.01, 24.90)

CI = confidence interval, SU = standard unit

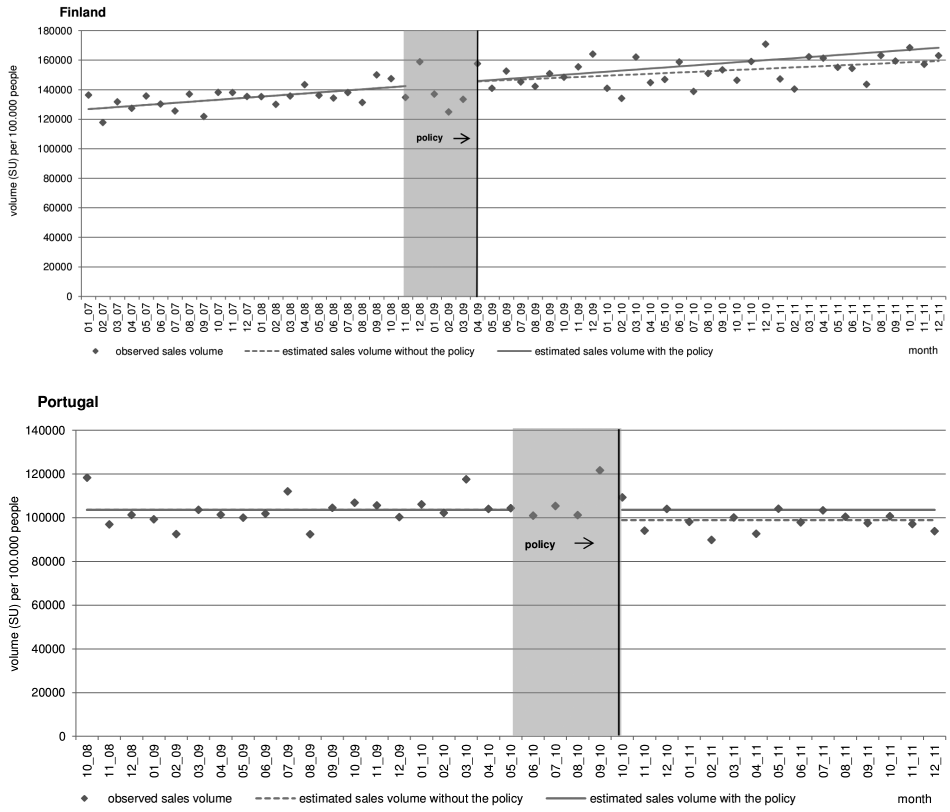


Figure 1a & b. Interrupted time series of the total retail antipsychotic markets in Finland and Portugal. Observed values and interrupted time series estimates of the total retail antipsychotic market volume (standard unit per 100,000 persons per month) before and after the phase-in period of the policy interventions in Finland and Portugal. Data source: IMS MIDAS®, January 2007 and December 2011, IMS Health Incorporated. All Rights Reserved.

Figure 2 displays the time series of generic market shares as percentage of total standard units for the three leading antipsychotic substances in each country. We examined quetiapine, clozapine and risperidone in Finland and amisulpride and risperidone in Portugal; there were no generic quetiapine products on the market in Portugal at the time of the intervention.

In Finland, retail generic market share of all three antipsychotic substances was around 20% prior to the implementation of the reference price system with rapidly increasing generic market shares of risperidone (2.19% (95% CI: 2.03%, 2.34%) per month) and quetiapine (2.07% (95% CI: 1.97%, 2.17%) per month), while the increase in clozapine generic market share remained low (0.07% per month (95% CI: -0.02, 0.17)). After the implementation of the reference price system and the delisting of Seroquel, the generic market share of quetiapine increased abruptly by 33.61% (95% CI: 31.62%, 35.61%); accompanied by a decrease in market share growth of 2.06% (95% CI: -2.18%, -1.95%) per month, which resulted in an estimated increase of 6.80% (95% CI: 3.92%, 9.68%) generic market share one year after the policy implementation period. A similar

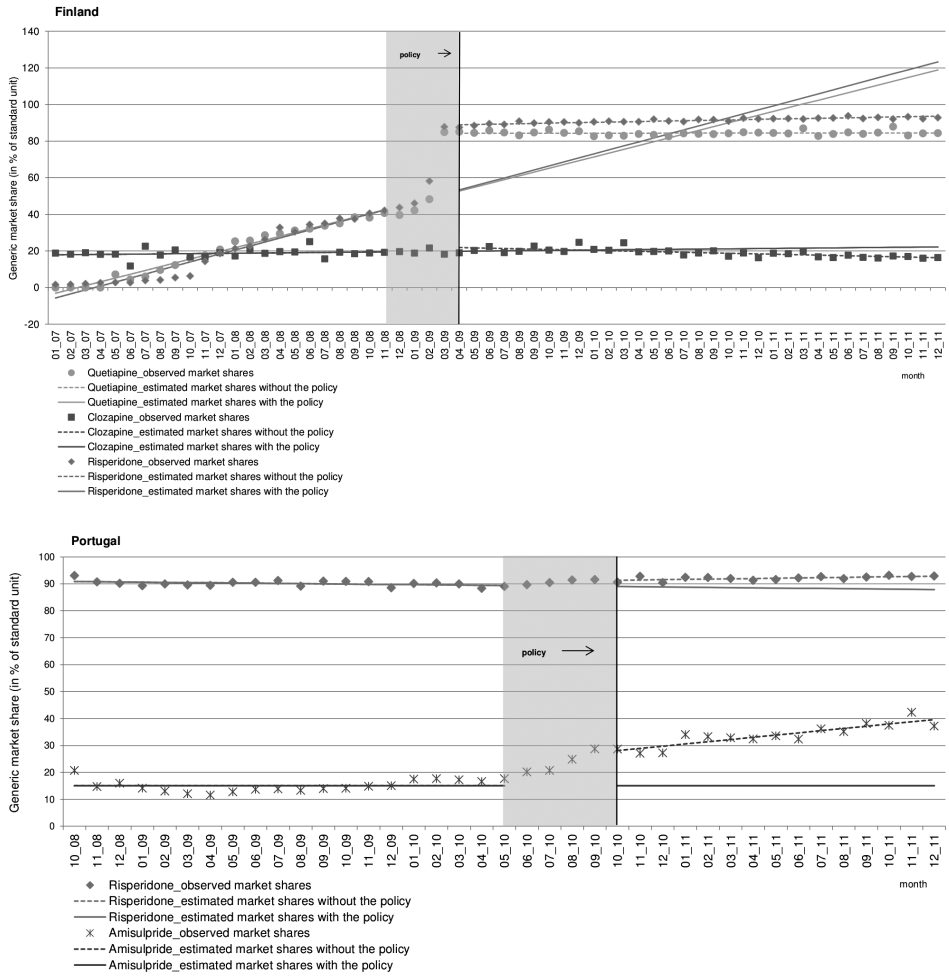


Figure 2 a & b. Interrupted time series of retail generic market shares in Finland and Portugal. Observed values and interrupted time series estimates of the retail generic market shares (percentage, standard units of generics per month) of the three top active substances in the antipsychotic market before and after the phase-in period of the policy interventions in Finland and Portugal. Data source: IMS MIDAS®, January 2007 and December 2011, IMS Health Incorporated. All Rights Reserved.

abrupt shift to generics was seen for risperidone. After the introduction of the reference price system, there was an immediate increase of 37.65% (95% CI: 34.60%, 40.69%) in generic market share accompanied by a decrease in slope of 2.04% (95% CI: -2.20%, -1.88%) per month, which resulted in a generic market share that continued to increase slightly during the post-policy period. One year after implementation, we estimated an increase of 11.13% (95% CI: 6.79%, 15.48%) in generic market share due to the policies. Post-policy changes in generic market shares for clozapine were relatively minor compared to the other two active substances. After the introduction of the reference price system, there was a slight increase of 2.22% (95% CI:

0.30%, 4.14%) in generic market share accompanied by a slight decrease in slope of 0.25% (95% CI: 0.36%, -0.13%) per month, resulting in an estimated decrease of 0.97% (95% CI: -3.75%, -1.81%) generic market share one year post-policy.

In Portugal, the generic market prior to the multifaceted policy changes looked quite different from that in Finland. Generic market shares for amisulpride remained between 10% and 20% throughout the pre-policy period with no increasing trend, while the generic market share of risperidone was already around 90% prior to the policy. After implementation of the policies, there was an immediate increase in generic market share of 12.23% (95% CI: 9.61%, 14.85%) for amisulpride and an increase in market share trend of 0.82% (95%: 0.56%, 1.09%) per month, resulting in an estimated increase of 22.95% (95% CI: 21.01%, 24.90%) in total generic market share one year after the policy intervention. The market for risperidone had already been almost entirely generic prior to the reimbursement policy. After the policy, there was an estimated increase in generic market share of 2.16% (95% CI: 0.76%, 3.57%) and an increase in trend of 0.19% (95% CI: 0.06%, 0.31%) per month, resulting in an estimated increase of 4.59% (95% CI: 2.67%, 6.51%) in total generic market share one year after the policy mix. Details of the time series estimates and confidence intervals are summarized in Table 1.

DISCUSSION

Our analyses showed that both countries' policy approaches were associated with an increased market share of generics as expected, but also to a likely unintended slight decrease in overall use of antipsychotic medicines. The decrease in overall use was expected in Portugal, but somewhat unexpected in Finland. In Finland two of the three leading active substances in the antipsychotic class (quetiapine and risperidone) experienced substantial increases in generic market share, but not the third substance (clozapine). In contrast, in Portugal the combination of policies which included statutory discounts granted to public payers, changes in reimbursement rates, and a generic campaign resulted in a major increase in generic market share only for one molecule (amisulpride); generic risperidone already dominated the market prior the policy interventions.

The two countries' policy trajectories differed. The reference price system in Finland was prepared well in advance of implementation. In April 2003 Finland introduced mandatory generic substitution, requiring pharmacists to substitute higher-priced branded medicines with less-costly generic versions. The mandatory generic substitution at the time decreased average prices of substitutable medicines by more than 10% [45,46]. Among the key elements of guaranteeing a successful implementation of a generic policy is a transparent implementation process accompanied by early involvement of all stakeholders, such as doctors and pharmacists, as well as a detailed methodology and positive perceptions of patients towards generics [47,48]. System changes such as reference price systems are intended to facilitate changes in behaviors of patients and health providers by encouraging them to be more price-sensitive; in a reference price system patients have to pay out-of-pocket the difference between the reference price and the actual price, generating an incentive for patients to request a medicine that is priced at or below the reference price. We demonstrated that Finland achieved the reference price

policy goal of greater generic utilization. We also observed a reduction in utilization post-policy, which was gradual, not statistically significant and relatively smaller compared to Portugal.

In Portugal, we found that the mix of cost-containment measures that were ongoing before and after October 2010 led to a sudden, slight, statistically significant overall decrease of retail antipsychotic use – assuming a three tablet per day oral treatment, policy changes may have resulted in 6 to 97 fewer treatment days among 100,000 people per month in Portugal. We cannot disentangle which of the policies may have exerted most influence on utilization. At the end of 2010, Portugal was urgently seeking ways to cut public spending on medicines as the Portuguese economy had not recovered from the recession in 2009. Some of the policy measures shifted costs to patients by lowering reimbursement levels and requiring higher co-payments [19]. Shortly after the change in co-payment rates in 2010, public concerns in Portugal emerged that higher co-payments would have a negative impact on utilization of essential medicines including antipsychotic medicines [49]. Our findings present a different picture than the study by Ong et al., who did not find permanent decreases in use of psychotropic medicines after a co-payment increase in Sweden in 1995, although the use of antidepressants among women was later found to decrease after a co-payment increase in 1997 [50].

In both countries, one of the most frequently sold active substances did not increase in generic market share (in Finland clozapine and in Portugal risperidone), which we attribute to different circumstances. Many countries have implemented strict prescription guidelines for clozapine by limiting prescriptions only to treatment-resistant schizophrenia patients as potentially life-threatening, side effects are associated with clozapine [51]. Clinicians may be reluctant to switch patients from clozapine to generic alternatives due to reports of worsening clinical status associated with generic substitution [52]. Further, the originator manufacturer of clozapine lowered its price to the reference price quite soon after the introduction of the reference price system, so there might not have been any financial incentive for patients to ask for a lower priced generic. Prescribing guidelines for the treatment of schizophrenia in Portugal recommended the use of risperidone and generic risperidone already had 90% of the market share in Portugal prior to the policy interventions [53]. Due to the severity of the illness and strict prescribing guidelines the generic campaign in Portugal probably did not lead to increases in generic market share of this therapeutic group. Under these circumstances, the policies did not have an observable additional effect.

Adherence to therapies is especially challenging in this patient group, and changes in cost-sharing or reimbursement benefits put additional pressure on vulnerable populations of low-income and chronically ill patients that may lead to lower utilization and worse health outcomes [54]. Soumerai et al. demonstrated that limits on coverage for the costs of outpatient prescription medicines can increase use of acute mental health services among low-income patients with chronic mental illnesses and result in increased costs to payers. He suggested that policy changes that pose substantial risks to vulnerable populations should undergo careful evaluation before their widespread adoption [55]. More research is needed on the potential unintended effects of reductions in reimbursement rates on utilization and long-term health outcomes.

IMS data represent country pharmaceutical markets consistently over time. They allow application of the strongest quasi-experimental research design for evaluating system-wide

policy interventions. Nevertheless, the data pose some limitations. They do not allow us to determine the actual number of prescriptions issued or the actual amounts that third-party payers or patients pay for each medicine. We also did not have access to actual numbers of patients receiving antipsychotics. Lastly, we were not able to determine the conditions for which antipsychotics were prescribed, since these medications are used for other indications in addition to schizophrenia, policy-induced decreases in antipsychotic use for some indications may be considered appropriate. We suggest expanding future research to patient-and indication-specific assessments of the impacts of the policy changes on access to antipsychotics and other therapeutic classes.

CONCLUSIONS

Different policy approaches to contain pharmaceutical expenditures in the study countries had different intended – increased use of generics – and likely unintended – slightly decreased overall sales possibly consistent with decreased access to needed medicines – impacts. Especially the latter finding stresses the importance of examining the long-term effects of policy measures as increases in cost-sharing may have beneficial short-term impacts on public spending, but might also entail unintended long-term reductions in utilization and shifting of costs to other types of health care.

ACKNOWLEDGEMENTS

We would like to express our gratitude to Ms. Hanna Koskinen from the Finnish Social Insurance Institution (KELA) for providing feedback on the Finnish antipsychotic data. Further, we are especially thankful for the input from Ms. Sónia Caldeira from the Portuguese Medicines Agency (INFARMED) as well as Ms. Ceu Mateus from the Portuguese National School of Public Health for sharing with us details on the different policy interventions in Portugal. Finally, we would like to thank Peter Stephens from IMS Health for critically reviewing the data.

The statements, findings, conclusions, views, and opinions contained and expressed in this article are based in part on data obtained under license from the following IMS Health Incorporated information service(s): MIDAS™ (January 2007 and December 2011), IMS Health Incorporated. All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

REFERENCES

1. WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies. PHIS Database. Vienna: Pharmaceutical Health Information System (PHIS), 2011. Available from: http://phis.goeg.at/index.aspx?alias=phisDatabase.
2. Seiter A. A Practical Approach to Pharmaceutical Policy. The World Bank. 2010.
3. European Commission. Pharmaceutical Sector Inquiry. 2009. Available: http://ec.europa.eu/. Accessed 20 June 2012.
4. Carone G, Schwierz C, Xavier A. Cost-containment policies in public pharmaceutical spending in the EU. Economic Papers 461. European Commission, Directorate-General for Economic and Financial Affairs (Ed.). September 2012. Available from: http://whocc.goeg.at/Literaturliste/Dokumente/FurtherReading/DGEconomy_Finance_CostcontainmentPharmaceutical_ecp_46.pdf. Accessed 8 February 2013.
5. Docteur E, Paris V. Pharmaceutical pricing polices in a global market. Paris: OECD Health Policy Studies; 2007.
6. Vogler S, Zimmermann N, Leopold C, de Joncheere K. Pharmaceutical policies in European countries in response to the global financial crisis. South Med Rev. December 2011;4(2):22-32.
7. Green CJ, Maclure M, Fortin PM. Pharmaceutical policies: effects of restrictions on reimbursement. Cochrane Database Syst Rev. 2010 Aug 4;(8):CD008654. doi: 10.1002/14651858.CD008654.
8. Barbui C, Campomori A, Mezzalira L. Psychotropic drug use in Italy, 1984-99: the impact of a change in reimbursement status. Int Clin Psychopharmacol. 2001;16(4):227-233.
9. Bambauer KZ, Sabin JE, Soumerai SB. The exclusion of benzodiazepine coverage in medicare: simple steps for avoiding a public health crisis. Psychiatr Serv. 2005;56(9):1143-1146.
10. Hoebert JM, Souverein PC, Mantel-Teeuwisse AK, et al. Reimbursement restriction and moderate decrease in benzodiazepine use in general practice. Ann Fam Med. 2012 Jan-Feb;10(1):42-9.
11. Vogt WB, Joyce G, Xia J. Medicaid cost control measures aimed at second-generation antipsychotics led to less use of all antipsychotics. Health Aff (Millwood). 2011 Dec;30(12):2346-54.
12. Lu CY, Soumerai SB, Ross-Degnan D. Unintended impacts of a Medicaid prior authorization policy on access to medications for bipolar illness. Med Care. 2010 Jan;48(1):4-9.
13. WHO Regional Office for Europe. Policies and Practices for mental health in Europe: meeting the challenges. 2008;115-124.
14. European Commission DG Health and Consumers. Major and chronic diseases. Available: http://ec.europa.eu/health/major_chronic_diseases/diseases/index_en.htm. Accessed 9. August 2012.
15. World Health Organization. Mental Health: Schizophrenia. Available: http://www.who.int/mental_health/management/schizophrenia/en/. Accessed 9 August 2012.
16. Zeber J, Grazier KL, Valenstein M. Effect of a medication copayment increase in veterans with schizophrenia. Am J Manag Care. 2007;13:335-46.
17. Wagner AK, Ross-Degnan D, Gurwitz JH. Effect of New York State regulatory action on benzodiazepine prescribing and hip fracture rates. Ann Intern Med. 2007;146(2):96-103.
18. Wladysiuk M, Araszkiewicz A, Godman B. Influence of patient co-payment on atypical antipsychotic choice in Poland: implications once generic atypical are available. AAppl Health Econ Health Policy. 2011 March; 9(2):101-110. doi: 10.2165/11318840-000000000-00000.
19. Andersson K, Petzol MG, Sonesson C, Lönnroth K, Carlsten A. Do policy changes in the pharmaceutical reimbursement schedule affect drug expenditures? Interrupted time series analysis of cost, volume and cost per volume trend in Sweden 1986-2002. Health Policy. 2006;79:231-243.
20. Soumerai SB, Zhang F, Ross-Degnan D, Ball DE, LeCates RF, Law MR, Hughes TE, Chapman D, Adams AS. Use of atypical antipsychotic drugs for schizophrenia in Maine Medicaid Following a policy change. Health Aff (Millwood). 2008 May-Jun;27(3):w185-95. doi: 10.1377/hlthaff.27.3.w185. Epub 2008 Apr 1.
21. Ray WA, Daugherty JR, Meador KG. Effect of a Mental Health 'Carve-Out' Program on the Continuity of Antipsychotic Therapy. N Engl J Med. 2003 May 8;348(19):1885-94.
22. OECD Health Data 2012. GDP per capita. Data extracted 1 October 2012.
23. Letter of Intent, Memorandum of Economic and Financial Policies, and Technical Memorandum of Understanding between Portugal and the International Monetary Fund. May 17, 2011. Available: http://www.imf.org/external/np/loi/2011/prt/051711.pdf. Accessed 10 January 2013.

24. Danzon P, Ketcham J. Reference Pricing of Pharmaceuticals for Medicare: Evidence from Germany, the Netherlands, and New Zealand. Front Health Policy Res. 2004;7:1-54.
25. Pohjolainen L. Reference price and price competition – evidence from the Finnish pharmaceutical market. Master's thesis. Aalto University, School of Economics, Department of Economics. February 2012. Available: https://aaltodoc.aalto.fi/handle/123456789/3456. Accessed 20 August 2012.
26. Finnish Social Insurance Institute KELA. Medicine costs and their reimbursement according to medicine group. 2010. Available: http://www.kela.fi/in/internet/liite.nsf/NET/280611165826PB/$File/laakeryh.pdf?OpenElement. Accessed 9 August 2012.
27. Helsingin Sanomat. Orion sued by AstraZeneca over patent dispute: Finnish pharmaceutical company takes advantage of loopholes in patent legislation. 30.7.2007. Available: http://www.hs.fi/english/print/1135229098411. Accessed 16 August 2012.
28. London South East. AstraZeneca takes Finland's Orion to court over copy medicines - report. 30.July 2007. Available: http://www.lse.co.uk/FinanceNews.asp?ArticleCode=4y78lyw3iacyj2t&ArticleHeadline=AstraZeneca_takes_Finlands_Orion_to_court_over_copy_medicines__report. Accessed 16 August 2012.
29. Gomes M. Medicines policy: surviving the crisis – an example from Portugal. PPRI conference. 30 September 2011. Available: https://whocc.goeg.at/Downloads/Conference2011/PraesentationenPPRIKonferenz/Day1_afternoon_Festsaal_1300_Gomes.pdf. Accessed 9 August 2012.
30. Order N.º 924-A/2010, 17th September amended by Order N.º 994-A/2010, 29th September 2010.
31. Written communication with representative of INFARMED. 20 November 2012.
32. INFARMED. Novo Pacote do Medicamento 2010. Available: http://www.infarmed.pt/portal/page/portal/INFARMED/IMPRENSA/CAMPANHAS/PACOTE_MEDICAMENTO. Accessed 10 November 2012.
33. Order Nr. 1041-A/2010, 7th October 2012.
34. IMS Health. Available: http://www.imshealth.com/portal/site/ims?CURRENT_LOCALE=de_at. Accessed 30 January 2013.
35. IMS MIDAS. 2007-2011. Unpublished.
36. European Pharmaceutical Market Research Association (EphMRA). Anatomical Classification [Internet]. 2012 [cited 2012 August 6]. Available: http://www.ephmra.org/classification/anatomical-classification.aspx. Accessed 9 August 2012.
37. Pharmaceutical Pricing and Reimbursement Information Network. Bi-annual pharmaceutical policy monitoring queries. WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies. Unpublished.
38. IMS Pharma Query. 2007-2011. Unpublished.
39. OECD Health data. Population data. Extracted 2 October 2012.
40. Cook TD, Campbell DT. Quasi-experimentation: Design and Analysis Issues for Field Settings. 1979. Chicago: Rand McNally.
41. Wagner AK, Soumerai SB, Zhang F. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002;27:299-309.
42. Kleinbaum DG, Kupper LL, Muller KE. Applied regression Analysis and Other Multivariable Methods. Pacific Grove, CA: Duxbury Press: 1998.
43. Zhang F, Wagner AK, Soumerai SB. Methods for estimating confidence intervals in interrupted time series analyses of health interventions. J Clin Epidemiol. 2009;62:143-148.
44. Gillings D, Makuc D, Siegel E. Analysis of interrupted time series mortality trends: an example to evaluate regionalized prenatal care. Am J Public Health. 1981;71:38-46.
45. Aalto-Setälä V. The impact of generic substitution on price competition in Finland. Eur J Health Econ. May 2008;9(2):185-91. Epub 2007 May 17.
46. Aalto-Setälä V, Kanerva R, Bell J. Drug Cost Development of Citalopram and Fluoxetine Following the Introduction of Generic Substitution in Finland. International Journal of Pharmaceutical Medicine. 2007;21(5):363-368.
47. Habl C, Vogler S, Leopold C, Schmickl B, Fröschl B. Referenzpreissysteme in Europa. Commissioned by the Main Association of Austrian Social Security Institutions. February 2008.
48. Simoens S. Creating sustainable European health-care systems through the increased use of generic medicines: a policy analysis. Journal of Generic Medicines. April 2010;7(2):131-137.
49. Campos A. Esquizofrénicos passam a pagar uma parte dos medicamentos antipsicóticos. Publico. 28.09.2010. Available: http://publico.pt/sociedade/noticia/esquizofrenicos-passam-a-pagar-uma-parte-dos-medicamentos-antipsicoticos-1458258. Accessed 10 January 2013.
50. Ong M, Catalano R, Hartig T. A time-series analysis of the effect of increased copayments on

the prescription of antidepressants, anxiolytics, and sedatives in Sweden from 1990 to 1999. Clinical Therapeutics. 2003;25(4):1262–75.

51. Nielsen J, Dahm M, Lublin H, Taylor D. Psychiatrists' attitude towards and knowledge of clozapine treatment. J Psychopharmacol. 2010 Jul;24(7):965-71. doi: 10.1177/0269881108100320. Epub 2009 Jan 22.

52. Kluznik JC, Walbek NH, Farnsworth MG, Melstrom K. Clinical effects of a randomized switch of patients from clozaril to generic clozapine. J Clin Psychiatry. 2001;62(Suppl 5):14–17.

53. Order Nr. 024/2011 of 29 September 2011. Utilização Clínica de Antipsicóticos.

54. Soumerai SB, Ross-Degnan D, Fortess EE, Abelson J. A critical analysis of studies of state drug reimbursement policies: research in need of discipline. Milbank Q 1993;71:217-252.

55. Soumerai SB, McLaughlin TJ, Ross-Degnan D, CasterisPaola CS, Bollin P. Effects of Limiting Medicaid Drug-Reimbursement Benefits on the Use of Psychotropic Agents and Acute Mental Health Services by Patients with Schizophrenia. N Engl J Med 1994; 331:650-655September 8, 1994DOI: 10.1056/NEJM199409083311006.

CHAPTER 4

Personalized medicine as
a challenge for policy makers

CHAPTER 4.1

Personalized medicine as a challenge for public pricing and reimbursement authorities – a survey among 27 European countries (including Iceland and Norway) on the example of trastuzumab

Health Policy. 2013 Oct 25. [Epub ahead of print]

Christine Leopold, Sabine Vogler, Claudia Habl,
Aukje Mantel-Teeuwisse, Jaime Espin

ABSTRACT

Objectives: To survey possible funding models and pricing practices as well as prices for the treatment package of trastuzumab and its accompanying diagnostic test in European countries, as an example of personalised medicines.

Methods: Qualitative descriptive data on national pharmaceutical pricing and funding policies applied to trastuzumab and its accompanying diagnostic test were obtained from a survey among competent authorities from 27 European countries as of August 2011. Further, price data (for the years 2005 to 2013) of trastuzumab in the respective European countries were surveyed and analysed.

Results: In 2011, testing and treatment mainly took place in hospitals or in specific day-care ambulatory clinics. In the European countries either both trastuzumab and the accompanying diagnostic test were funded from hospital budgets (n=13) or only medicines were funded from the third party payers such social insurances and the test from hospital budgets (n=14). Neither combined funding of both medicine and diagnostic test by third party payers was identified in the surveyed countries nor did the respondents from the competent authorities identify any managed entry agreements. National pricing procedures are different for trastuzumab versus its diagnostic test, as most countries apply price control policies for trastuzumab but have free pricing for the diagnostic test. The ex-factory price is, on average, € 609 per 150 mg vial with powder in 2013; in nine countries the price of trastuzumab went down from 2005 till 2013.

Conclusion: The example of trastuzumab and its accompanying diagnostic test highlights some problems of the interface between different funding streams (out-patient and hospital) but also with regard to the interface between the medicine applied in combination with a medical device. The findings suggest a need for further developing and refining policy options to address the identified interface issues.

INTRODUCTION

Personalised medicines, also known as co-dependent or stratified technologies, are defined as the treatment plan based on molecular screening and other tests that suggest which regime will be most effective in specific patients [1-3]. It is an approach to improve the use of (often high-cost) medicines by using diagnostic testing (including genetic testing) to maximise clinical benefits and cost-effectiveness. It is forecasted that the cost of these new co-dependent technologies may be higher at first, but their predictive potential could avert unnecessary costs as it provides precise diagnostic results leading to effective and targeted therapies [4]. In some cases these treatment packages are for a large group of patients such as for the treatment of breast cancer, in other cases it is relevant for smaller patient groups as it is the case with rare diseases [5-7]. Table 1 gives three examples of approved personalised medicines and their diagnostic tests [8].

However, there is growing disappointment from industry and health professionals but also from public pricing and reimbursement authorities that personalised medicines do not live up to their expectations including expected savings [9]. This suggests that there are quite a few challenges in appraising treatment packages in personalised medicine. The first challenges are related to the evidence package available at time of market authorisation. Drug development for cancer treatments follows an established pathway from pre-clinical research followed by early-then late-phase trials. The regulation for diagnostic tests have been less rigorous due to a lower risk of direct harm. This results in an unbalanced level of evidence on the time of admission [10]. In addition, personalised medicine requires predictive markers as opposed to prognostic markers, requiring additional and different types of research to that provided by conventional trial programmes [11].

Secondly, there are challenges related to the health care system. Personalised medicines are often used at the interface between the hospital and the out-patient sector, therefore requiring different funding streams [12]. An additional concern is the difficulty of enforcing standard protocols to ensure physicians follow through with appropriate patient care based on the test result. Furthermore a major point of concern is how the different regulatory entities involved in the assessment of either the medicine or the test may align their review process in order to facilitate a swift and reliable approval [13-14]. Not only Australia recognised that co-dependent technologies are problematic to assess in its recent review of Health Technology Assessment [15], but also at the European Union level public authorities are struggling to find appropriate procedures to take pricing and reimbursement decisions for these 'treatment packages'.

In literature personalised medicine is often discussed from the point of pharmacogenomics or genetic information used in clinical trials [16-19]. The question on how national public authorities assess the value of co-dependent technologies as a 'treatment package' has only recently been addressed by a few publications as well as at European conferences. Merlin et. al. presented how Australia recently developed a national framework for reviewing and assessing co-dependent technologies [20]. Lu and Ward compared differences in assessment processes of co-dependent health technologies between the United Kingdom (UK) and Australia with the conclusion that still important lessons need to be learned with respect to assessing the whole 'treatment package' including the test and the medicine [21]. A recent report published by the Personalised Medicine Coalition (PMC) analysed the European reimbursement systems in terms of factors that

Table 1. Examples of approved medicine and companion diagnostic

Approved medicine	Mechanism	Approved companion diagnostic
Herceptin (trastuzumab)	Targets HER2 to treat metastatic breast cancer	HER2 immunohistochemistry tests, HER2 gene-amplifications tests
Erbitux (cetucimab)	Targets EGFR to treat metastatic colorectal cancer	EGFR immunohistochemistry test
Gleevec (imatinib)	Targets the cell-surface tyrosine kinase receptor c-kit in gastrointestinal stromal tumours	c-kit immunohistochemistry test

Source: Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med. 2010. 363:301-304. DOI: 10.1056/NEJMp1006304.

support or impede market access to personalised medicine. Conclusions of the report were that countries such as Germany, the UK and France were ranked high with respect to other European countries due to their current reimbursement systems for combined diagnostic and therapeutic, previous support and investments in personalised medicine technologies. Conversely, countries such as the Netherlands, Finland and Norway were ranked lower due to lack of clear pathways for evaluation and funding of personalised medicine [22]. Meckley and Neumann came to the conclusion that in order to achieve favourable coverage and reimbursement and to support premium prices for personalised medicines, manufacturers will need to bring better clinical evidence to the marketplace and better establish the value of their products [11]. In addition, a panel session at the 2012 conference of the International Society for Pharmacoeconomics and Outcome research (ISPOR) discussed how to assess the value of co-dependent technologies [23].

Against this background of discussions at national and international level about ways of dealing with the 'treatment package' or 'joint product', this study explores the current practices of European countries with regard to pricing and funding of the 'treatment package' on the example of trastuzumab and its accompanying diagnostic test. The study aims to survey possible patterns of national funding models with regard to different settings (out patient or in-patient care) and payers. Additionally, we will survey prices and look at the price development during recent years of trastuzumab and its accompanying diagnostic test as an illustrative example. The reasons for selecting trastuzumab for the treatment of breast cancer as an example for personalised medicine are multifaceted:

1. breast cancer is among the leading diseases in women worldwide with an incidence rate (newly diagnosed cases per 100,000 females) that ranges from 50 in Estonia to 109.4 incidences in Belgium, in 2008 [24];
2. trastuzumab is among the first line therapies targeting at the human epidermal growth factor Receptor 2 (HER-2) protein which is over-expressed in some women with breast cancer. A therapy with trastuzumab is only prescribed if the cancer has been shown to overexpress' HER-2 [24-27], thus ensuring that (public) expenditures are not wasted on ineffective pharmaceutical care. The two main methods used for HER-2 testing are immunohistochemistry (IHC) and fluorescence in-situ hybridization (FISH) [28].
3. trastuzumab is one of the first well known personalised medicines which require prior testing to being prescribed [29] and therefore European public pricing and reimbursement authorities have many years of experience in assessing this 'treatment package'.

METHODOLOGY

This study presents the results of two major parts: the first part is an assessment of the current practices of pricing and funding of trastuzumab and its accompanying diagnostic test as well as a price survey of the diagnostic test. Data was received from an European survey, which was undertaken by the Gesundheit Österreich GmbH / Austrian Health Institute and commissioned by the European Commission Directorate-General Enterprise under the European Medicines Information Network on Pricing and Reimbursement (EMINet) project [30]. The timeframe of the survey was 1st of July to 30st of September 2011; the survey was sent via mail to selected staff of public authorities for pharmaceutical pricing and reimbursement (members of the Pharmaceutical Pricing and Reimbursement Information (PPRI) network [31] as well as to the network of Competent Authorities of Pricing and Reimbursement (CAPR) [32]). In September 2011 a reminder was sent to all countries and if needed individual answers were clarified through telephone conversations with country representatives. The outcomes of the survey were circulated to the CAPR network in November 2011 and then presented and discussed with national representatives at the CAPR meeting in Warsaw in December 2011, leading to some final clarifications of the results.

The survey was based on a structured questionnaire asking for information as of August 2011 on:

- setting of treatment (in- versus outpatient sector)
- eligibility criteria for public coverage of the treatment (accessibility for all female patients and whether co-payment has to be paid)
- the process of funding the medicine versus diagnostic (which institutions, national or regional decision-making)
- pricing procedure of trastuzumab and its companion diagnostic
- and about the funding and procurement procedure of trastuzumab and the accompanying diagnostic.

In total 29 European countries were approached to participate in the survey. These countries included all 27 European Union (EU) Member States plus the European Economic Area (EEA) Norway and Iceland as represented in the above mentioned networks. Out of the 29 European countries 27 countries (all except Luxembourg and Greece) replied; hence resulting in a high response rate of 93%.

The second part presents the results of a price survey on trastuzumab. Price data were provided by the research institute Gesundheit Österreich GmbH / Austrian Health Institute, which has been running the Pharmaceutical Price Information Service (PPI) for many years [33]. Reasons for choosing price data from the Austrian Health Institute were: 1) accessibility of the data by the authors, 2) reliability as the data are / have been collected as part of legal obligations [34] for the Austrian Pricing Committee [35] and 3) the PPI service became a point of reference for the European Commission and for many EU Member States.

For trastuzumab they could provide historic price data for the period from 2005 till 2013 (no price data were available for 2009) for 14 countries, i.e Austria, Belgium, Denmark, France, Finland, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland and United Kingdom (= England and Wales). We received price data of one vial 150 mg trastuzumab for all three price levels - ex-factory, pharmacy purchasing and pharmacy retail price level -

for all fourteen countries (if available). Prices referred to June of each year (except in 2005, 2006 and 2010 prices refer to December) and were mainly applied to for public hospitals, no information on official or commercial discounts and rebates were available. Prices in non-Euro-countries (Denmark, Norway, Sweden, Switzerland and England and Wales) were converted to the monthly exchange rate of May 2013 as published by the European Central Bank. In order to eradicate exchange rate fluctuations, we converted the exchange rate to the level of 2013.

Descriptive statistics were performed on the data collected by the survey as well as on the price data.

RESULTS

Point of care

In 2011, all replying countries granted access to trastuzumab and its diagnostic to female patients with demonstrated HER2-postive breast cancer. With respect to the point of care with the treatment of HER2-positive breast cancer medicines in thirteen countries it took place in the in-patient sector, i.e. in hospitals. The remaining fourteen countries indicated that the treatment was provided in the out-patient sector, specifically in day-care ambulatory clinics under the supervision of oncology/chemotherapy specialists as for instance in Sweden. However, in the majority of countries the diagnostic test was provided in hospital settings. These different settings of care lead to differences in funding systems.

National funding models of the treatment package trastuzumab and its diagnostic test

As of 2011, in all European countries trastuzumab was only prescribed if HER2-positive breast cancer was diagnosed on the basis of prior testing. In addition, a number of countries stated specific eligibility criteria for public funding of trastuzumab: in Belgium according to the national reimbursement rules prior approval of the sickness fund was required before the treatment with trastuzumab was funded by social insurance (so-called restricted reimbursement); in Latvia reimbursement of the diagnostic procedure was granted to all patients when required, whereas the medicinal treatment was only reimbursed for a limited number of patients due to budgetary limitations. In Poland patients had to be included in the respective therapeutic programmes, which offered public funding for specific diseases including their treatment; and in Portugal patients with the HER-2 test results of 3+ were considered positive and eligible for treatment with trastuzumab whereas patients with 2+ results required re-evaluation by a more sensitive technique (a biopsy is sent to an Oncology Institute and Roche pays the additional test).

Figure 1 illustrates four possible national funding models of the treatment package whose use in practice we surveyed. The data refers to 2011:

In *model 1* the diagnostic test as well as the medicine was funded through the hospital budget. Here the hospital had the opportunity to either buy one of the commercially available diagnostic tests or perform its own test. In this model funding was linked to the national funding system of hospitals and the decision on funding was taken within the scope of the hospital; this was the

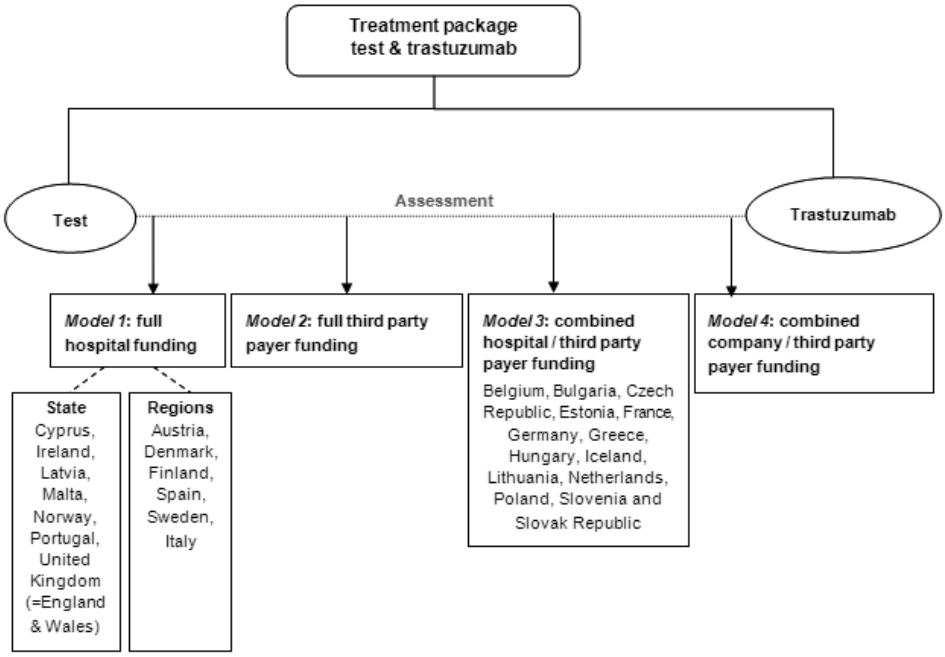


Figure 1. Funding models of trastuzumab and its companion diagnostic, 2011.

case in thirteen European countries (Austria, Cyprus, Denmark, Finland, Ireland, Italy, Latvia, Malta, Norway, Portugal, Spain, Sweden and United Kingdom). National funding of hospitals was either provided by the state (the National Health Service or the Ministry of Health), which was the case in Cyprus, Ireland, Latvia, Malta, Norway, Portugal and the United Kingdom, or hospitals were funded through regions/counties/municipalities, which was the case in Austria, Denmark, Finland, Spain and Sweden. In Italy, however, the National Medicine Agency was responsible for deciding on the reimbursement of trastuzumab whereas the reimbursement of the diagnostic was established at a regional level. As trastuzumab impacted hospital budgets considerably some countries foresaw an extra funding code in their national hospital funding system, e.g. in the Austrian DRG-based scheme, meaning that extra money was allocated for hospitalisation costs in case of patients who were treated with trastuzumab.

In *model 2* the third party payer (which can either be a social security institution or a national health service) was responsible for funding the treatment package. None of the surveyed countries applied this model as the diagnostic test was always provided and therefore funded in hospital settings.

Model 3 foresees a combination of funding sources from hospitals as well as from third party payers. Here the test was funded by hospitals, as it was performed in hospitals, and the medicine was funded by the third party payer; this was the case in most European countries (Belgium, Bulgaria, Czech Republic, Estonia, France, Germany, Greece, Hungary, Iceland, Lithuania, the Netherlands, Poland, Slovenia and Slovak Republic). However in this model there was no

common assessment of the treatment package; each item was assessed and funded separately. To encounter this gap Hungary for example established national prescribing guidelines as well as advising committees for evaluating trastuzumab and its diagnostic test as a package taking into account an economic evaluation with a special emphasis on cost-effectiveness analyses. In addition, some countries applied specific funding schemes for a defined group of high-cost medicines to which trastuzumab belongs to. For instance, at the time of the survey, in the Netherlands the hospital received 80% reimbursement from the health insurer for medicines on the list of high-cost medicines, such as trastuzumab. The remaining 20% as well as the extra costs for the diagnostic was paid by the hospital out of its own budget.

In *model 4* funding is split between pharmaceutical industry and third party payers; this concept is known as risk-sharing agreements, in recent times summarized as managed entry agreements. Here the financial risk due to uncertainty of new medicines is shared between manufacturers and payers. In some cases industry provides the diagnostic test for free to hospitals, in other cases manufacturers grant either discounts to third party payers or only receives payment in case the treatment was successful. According to the official information received none of the respondents reported that this model was applied for trastuzumab in their country in 2011.

Pricing practices

With respect to pricing policies a major difference between trastuzumab and its diagnostic test could be observed: in 2011 trastuzumab was subject to national pricing rules but for the diagnostic test European countries had not elaborated similar pricing policies resulting in free pricing (cf. Table 2). Medicine prices can be controlled at ex-factory, pharmacy purchasing or pharmacy retail level. Most European countries (except Denmark, Germany, Sweden and United Kingdom) applied price control mechanisms either for all medicines or limited to reimbursable medicines. These price control mechanisms were set based on laws or enactments; in a few countries (Italy, France and Spain) prices were negotiated between manufacturer and third party payers. In 2011, external price referencing is the most commonly used price control procedure (all countries except Denmark, Germany, Sweden and UK), where the price of a medicine is set on the basis of the price in one or several countries. As trastuzumab is mainly administered in hospitals many countries do not apply wholesale or pharmacy

Table 2. Overview of pharmaceutical pricing policies in European countries, 2011

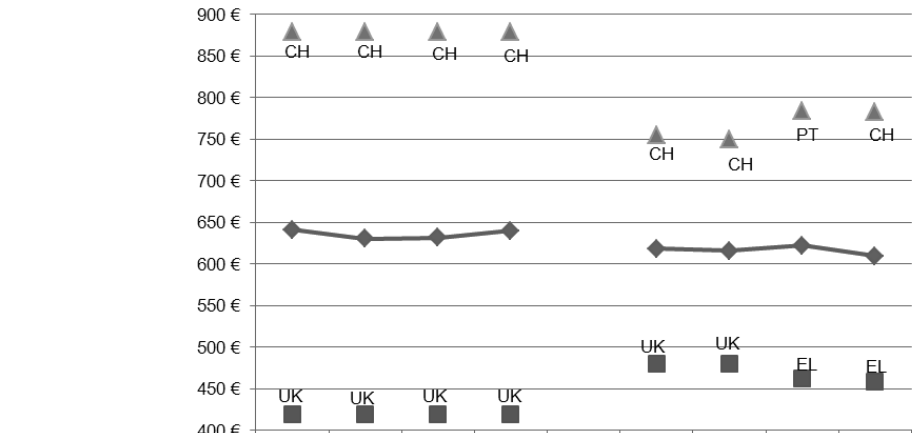
Price level	Free pricing	Negotiations	Statutory pricing
Ex-factory	Denmark, Germany, Finland, Latvia, Netherlands, Poland, Sweden and United Kingdom	Italy, France, Spain	All other EU-countries, Iceland and Norway
Pharmacy purchasing (linear or regressive mark-ups)	-	Denmark, Finland, Netherlands, Norway, Sweden	All other EU-countries, Iceland
Pharmacy retail (linear or regressive mark-ups)	-	-	All EU-Member countries plus Iceland and Norway

EU = European Union

margins. However, as shown in Figure 4, if margins are applied huge differences can be seen (as high as up to 30% as it is the case in Italy and as low as 2% in Sweden).

Price developments

Trastuzumab belongs to the group of high-cost cancer medicines: on average the included European countries have to pay € 609 per 150 mg vial with powder of trastuzumab (year 2013). Figure 2 shows the price development of one vial trastuzumab 150 mg from 2005 until 2013. In 2005 the average price was € 641. Since 2005 the average price gradually decreased with some increases in specific years (i.e. 2008 and 2012) to € 609 in 2013. It is visible that there were great differences between the countries: in 2005 the lowest priced country (the United Kingdom) paid € 420 and the highest priced country (Switzerland) paid € 878; while in 2013 the difference between the highest (Switzerland € 782) and the lowest priced country (United Kingdom € 458) diminished. As illustrated in Figure 3 the decrease of the average price was mainly driven by Greece, Norway, France and Switzerland. The average price increase was driven by Germany and Austria. With regard to the price of a diagnostic test information is only from the European survey, where two countries reported prices: Austria reported an approximate price of € 110 for the diagnostic test and Estonia a price of € 418 for a FISH test and € 29 for an IHC test.



	2005	2006	2007	2008	2009	2010	2011	2012	2013
Ø unit ex-factory price €	641 €	631 €	632 €	640 €		618 €	616 €	622 €	609 €
Min	420 €	420 €	420 €	420 €		480 €	480 €	463 €	458 €
Max	878 €	878 €	878 €	878 €		755 €	750 €	784 €	782 €

Figure 2. Price development of the average ex-factory prices per unit in € of 1 vial, 150 mg trastuzumab, 2005 - 2013. The average ex-factory price was calculated based on a basket of 14 countries: Austria, Belgium, Denmark, France, Finland, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland and UK (= England & Wales). Prices refer to June of each year (except in 2005, 2006 and 2010 prices refer to December) and are mainly applied to for public hospitals. Prices in non-Euro-countries (Denmark, Norway, Sweden, Switzerland and the UK) were converted to the monthly exchange rate of May 2013 as published by the European Central Bank (http://www.oenb.at/de/stat_melders/datenangebot/zinssaetze/wechselkurse/wechselkurse.jsp). Ø = average, CH = Switzerland, EL = Greece, PT = Portugal, UK = only England and Wales, UK: price paid by the National Health Service France: 2006, 2007, 2008 no price available Belgium: 2008 no price available. Source: [33]

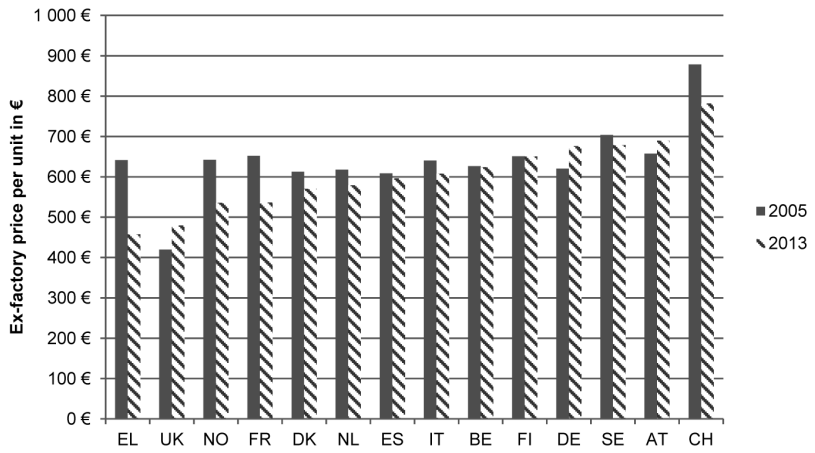


Figure 3. Unit ex-factory prices in € of 1 vial, 150 mg trastuzumab in fourteen European countries, 2005 and 2013. The countries were scaled in increasing order for 2013 prices. UK: price paid by the National Health Service. Prices refer to June of each year (except in 2005, 2006 and 2010 prices refer to December) and are mainly applied to for public hospitals. Prices in non-Euro-countries (Denmark, Norway, Sweden, Switzerland and the UK) were converted to the monthly exchange rate of May 2013 as published by the European Central Bank (http://www.oenb.at/de/stat_melders/datenangebot/zinssaetze/wechselkurse/wechselkurse.jsp). AT = Austria, BE = Belgium, CH = Switzerland, DE = Germany, DK = Denmark, EL = Greece, ES = Spain, FI = Finland, FR = France, IT = Italy, NL = Netherlands, NO = Norway, SE = Sweden, UK = only England and Wales. Source: [33]

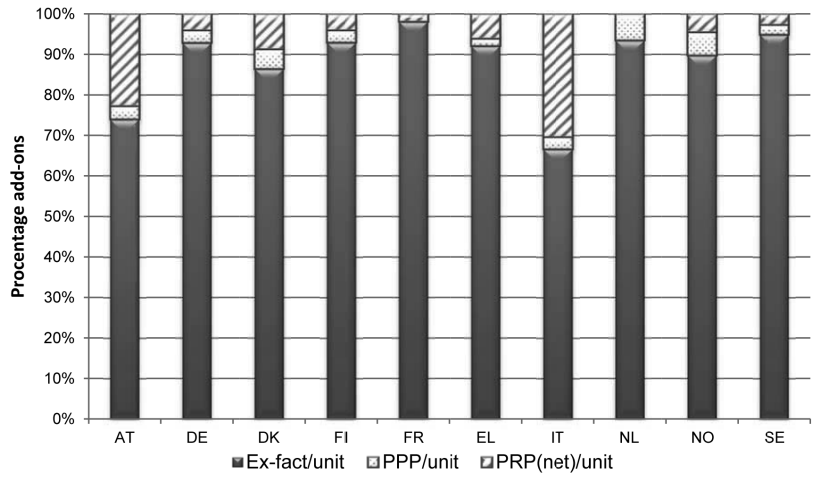


Figure 4. All price levels of 1 vial, 150 mg trastuzumab in € in ten European countries, June 2013. PPP = pharmacy purchasing price, PRP = pharmacy retail price. AT = Austria, DE = Germany, DK = Denmark, EL= Greece, FI = Finland, FR = France, IT = Italy, NL = Netherlands, NO = Norway, SE = Sweden. No price information for pharmacy purchasing and pharmacy retail prices were available in Beglium, Spain, Switzerland and the United Kingdom, as trastuzumab is applied in hospitals and therefore mark-ups are not regulated. Prices refer to June of each year (except in 2005, 2006 and 2010 prices refer to December) and are mainly applied to for public hospitals. Prices in non-Euro-countries (Denmark, Norway, Sweden, Switzerland and the UK) were converted to the monthly exchange rate of May 2013 as published by the European Central Bank (http://www.oenb.at/de/stat_melders/datenangebot/zinssaetze/wechselkurse/wechselkurse.jsp). Source: [33]

DISCUSSION

This study showed that depending on the place of treatment – in most countries it is the hospital and in a few countries it is out-patient day-clinics under the supervision of specialists – the funding sources but also the pricing procedures are different for the diagnostic test and the medicine. In 2011, two predominant funding models for the 'treatment package' trastuzumab and its diagnostic test were identified: 1) funding by hospitals for both the medicine and the test and 2) a combination of funds between hospital and third party payer. With respect to pricing the study displayed that there is free pricing for the diagnostic test in Europe; whereas the price of trastuzumab is regulated according to national pricing policies resulting in differences in the ex-factory price and a slight decline in overall price between 2005-2013.

The results of the survey confirm previous perceptions of the challenge of assessing the treatment package of personalised medicine. The main reason for this challenge is that trastuzumab and its diagnostic test are applied at the interface of different funding streams (as shown in the four models) which leads to multiple areas of conflicts:

1. In model 1 the test as well as the medicine is funded by the hospital, which is in principal an ideal situation as the funding decision is taken by one institution. However, in practice there is a split in responsibilities between authorities in some countries. For instance, in Italy the decision of funding of trastuzumab is taken at national level, whereas the decision of funding the test is taken at hospital level, which is often the regional level. Or in other countries different departments within the Ministry of Health are responsible for the funding decisions (e.g. in Cyprus the Pharmaceutical Services Department of the Ministry of Health is responsible for funding of the medication and the Medical Services Department for the diagnostic procedure). In a worst case scenario it could happen that e.g. the hospital takes the decision to fund the test, but at national level the decision on reimbursing trastuzumab is not permitted due to budgetary constraints.
2. In model 2 both the test and the medicine is paid for by the third 265 party payer. This would be another ideal model as both elements would have to be assessed by the same institution, which could apply a common assessment tool for the 'treatment package'. However, none of the responding countries had this model as the diagnostic test was always administered in hospitals and therefore also funded through the hospital budget.
3. In model 3, which is the most commonly used model, funding was split between the hospital and the third party payer. Here the different funding streams of the in- and the out-patient sector are often not well coordinated as proven by the Pharmaceutical Health Information System (PHIS) project, a project funded by the European Commission [36]. This might lead to shifting of costs between the different sectors which could have as a consequence that tests are performed by hospitals but the eligibility of reimbursement in the out-patient sector is not given. Our study confirmed these outcomes as some of the respondents of our study had difficulties to answer questions on funding or pricing of the diagnostic test as this is part of the medical service in hospitals and no nationwide information is available. This lack of knowledge is particularly critical since trastuzumab as well as other medicines

used in a 'personalised medicines package' are often among high-cost medicines. This puts great pressure on hospital budgets, as these high costs are often not covered by the DRG systems, but require additional funding from third party payers (e.g. in the Netherlands). Hence, there is a great need for a common assessment tool for the treatment package as well as across sectors. The PHIS project mentioned some national initiatives such as coordinating the hospital formulary with the list of the out patient sector as a possible way forward (e.g. in the Stockholm County Council) [37], and in a seminar to learn about improving the interface management for medicines held in Stockholm in September 2012, further country examples were presented [38].

4. Finally, the last model suggests splitting funding between third party payers and manufacturers. This concept, known as managed entry agreements or risk-sharing schemes, gains more and more popularity especially for innovative and often high-cost medicines. Especially Germany, Italy, the Netherlands and the United Kingdom are known for being pioneers in this field [39]. However, according to the information from the European public authorities no such agreements were in place for trastuzumab and its diagnostic test at the time of the survey. As this information on such agreements is considered as confidential and thus not shared, the picture might not be complete. Ferrario and Kanavos point out that risk-sharing or further managed entry agreements are on the rise in some European countries [40].

Other funding models e.g. funding by patients were not considered as in Europe – despite the high price of trastuzumab – use is always covered by public funds.

The challenge of the interface is not only relevant for funding but also for pricing as different procedures are applied in the in- and the outpatient sector. In hospital settings no formal pricing procedures are foreseen as the hospital price of the diagnostic or the medicine is often negotiated between hospital owners and suppliers on a confidential basis, leading to non-publication and lacking of price information. For reimbursable medicines, in our case trastuzumab, it is initially priced according to general national pricing rules often followed by price negotiations in hospitals. In the case of trastuzumab the actual hospital price is expected to be identical to the list price (= ex-factory price) as there are no therapeutic alternatives for which discounts might be negotiated [36]. Vogler and co-authors illustrated that in five European countries selected hospitals nearly never granted discounts for trastuzumab [41]. Nevertheless, it was interesting to see, that our study showed that the unit ex-factory price of trastuzumab decreased over time in most countries. One of the reasons for this price decrease is that pharmaceutical pricing policies are dynamic as public authorities adjust pricing regulations regularly. Especially in times of limited budgets, as it is the case in the current economic recession, countries (e.g. Greece, Portugal and Spain) are forced to implement strict price cuts [42]. But also traditionally economically stable countries are opting to regulate medicine prices, e.g. Germany used to be a free pricing country for medicines but in 2011 it implemented regulations linking pharmaceutical pricing to added therapeutic benefit scores, the so called AMNOG [43]. Further, in 2013 the Netherlands changed its policy of sharing the financial burden between hospitals and third party payers for high cost medicines. These medicines are now fully reimbursed by third party payers [31].

A limitation of our study is that no country specific information on the price of the diagnostic test could be provided. Many countries replied that they had no information on the diagnostic test as it is under the supervision of hospitals. This outcome is in line with the findings of Meckley and Neumann, as they described that the existing pricing and reimbursement systems present challenges for diagnostics, because if cumbersome coding systems and the lack of value-based arrangements [11]. Information on pricing of the diagnostic test is scarce, but the price of a HER2-positve breast cancer test was studied by the Institute for Prospective Technological Studies. This study indicated that the cost of immunohistochemistry (IHC) test (including IVD and personnel costs) as of 2006 differed significantly in Europe, ranging from € 103 in the United Kingdom to € 190 in Ireland, with Germany around € 127 (public social health insurance) and € 167 (private health insurance). The same differences were observed in the costs of the FISH test: The reported costs (including material and personnel costs) varied between € 220 (UK) to € 495 in the Netherlands. The reported costs from Ireland (€ 250) and Germany (€ 257, public social health insurance and € 398, private health insurance) were within this interval [28]. Even though we only had prices of two countries (Austria and Estonia), we came to the same conclusion that there are huge price differences for the same test in different countries (Austria a price of € 110 for the diagnostic test and Estonia a price of € 418).

This study adds to existing discussions on personalised medicines by raising the challenging point of dual funding systems including resulting data gaps as well as of missing or limited policies for the treatment package 'medicine and test'. Our study not only confirms the results of the PHIS project, which displayed the knowledge gap between the in- and the out-patient sector, but also provides an illustrative example. In terms of pricing but also of funding the medicine and the test are very often considered as separate items. Only a few countries have started to address this challenge by establishing advising committees with experts from different disciplines ('boards'), national guidelines guaranteeing cost-effective and targeted prescribing of personalised medicine as well as economic evaluation. Norway, Sweden and Denmark as well as the United Kingdom might be mentioned as good practice examples. They have developed well defined guidelines or procedures for funding these medicines and the diagnostic procedures. The European Commission recommended in its 2011 conference on European perspectives in personalised medicine a close cooperation among Health Technology Agencies in Europe to establish appropriate assessment tools [44-45]. The discussions need to continue as personalised medicines will also in future play an important role. As a result, some of the responding countries (e.g. Ireland) specifically mentioned that in future changes in relation to the funding of high-cost medicines such as personalized medicine and companion diagnostics will have to be made.

CONCLUSION

The study highlights that European countries have opted for different funding models to reimburse the treatment package of trastuzumab and its accompanying diagnostics. In the case of trastuzumab and its diagnostic test, all funding models are exclusively based on public funding - might this be the state, a third party payer such social insurance or a public hospital

- and do not require a contribution of the manufacturer or the patient. Since trastuzumab is a high-cost medicine, this confirms the challenge of this treatment package for public payers.

Further, the study provided additional knowledge to an area where information is scant: funding of care across sectors (a problem of the interface between in- and out-patient care) but also regarding the interface of medicines and medical devices. Traditionally pharmaceutical policies were focused on medicines alone and were often limited to the out patient sector. The example of how European countries deal with the treatment package of trastuzumab and its accompanying diagnostic test illustrates how competent authorities for pharmaceutical pricing and reimbursement have addressed this challenge and have progressed by developing solutions. Yet, a lot still needs to be done to refine these approaches.

ACKNOWLEDGEMENTS

Acknowledgements are given to the European Medicines Information Network on Pricing and Reimbursement of pharmaceuticals (EMINet) project, a project co-funded by the European Commission (DG Enterprise and Industry) for providing the results of the survey. Further, we would like to thank the members of the Pharmaceutical Pricing and Reimbursement Information (PPRI) network and the network of Competent Authorities of Pricing and Reimbursement (CAPR), who provided answers to the survey as well as took their time to answer clarifications. Thanks also go to the Austrian Health Institute for providing price data on trastuzumab from their Pharma Price Information (PPI) service.

In addition, we would like to thank Prof. Anke Hövels from Utrecht University, Division of Pharmacoepidemiology and Clinical Pharmacology, for giving input to the introduction of this paper.

REFERENCES

1. Coggi PT. A European view on the future of personalised medicine in the EU. Eur J Public Health. 2011 Feb;21(1):6-7. doi: 10.1093/eurpub/ckq202.
2. Ginsburg GS, Willard HF. The foundations of genomic and personalized medicine. Essentials of Genomic and Personalized Medicine. Academic Press, Elsevier Inc., San Diego, USA. 2010; 1-10.
3. Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med. 2010 Jul 22;363(4):301-4. doi: 10.1056/NEJMp1006304. Epub 2010 Jun 15.
4. Sullivan R, Peppercorn J. Delivering afforable cancer care in high-income countries. Lancet Oncol. 2011; 12(10):933-980.
5. Brewer G. Drug development for orphan diseases in the context of personalized medicine. Transl Res. 2009 Dec;154(6):314-22. doi: 10.1016/j.trsl.2009.03.008. Epub 2009 Apr 23.
6. Tambuyzer E. Towards a framework for personalized healthcare: lessons learned from the field of rare diseases. Personalized Medicine. September 2010; 7(5):569-586. doi: 10.2217/pme.10.52.
7. Habl C, Bachner F. Initial investigation to assess the feasibility of a coordinated system to access orphan medicines. 2011; European Commission, Directorate-General Enterprise; Available from: http://whocc.goeg.at/Publications/BooksReports. (accessed 10 September 2012).
8. Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med. 2010. 363:301-304. DOI: 10.1056/NEJMp1006304.
9. Laksman Z, Detsky AS. Personalized medicine: understanding probabilities and managing expectations. J Gen Intern Med. 2011;26(2):204–6.
10. Hall PS, McCabe C. What Evidence is there for reimbursement of personalized medicine? PharmacoEconomics. 2013;31:181-183. DOI 10.1007/s40273-013-0025-x.
11. Meckley LM, Neumann PJ. Personalized medicine: factors influencing reimbursement. Health Policy. 2010;94(2):91–100.
12. Schmitt F. HER21 breast cancer: how to evaluate? Adv Ther. 2009;26(1):1–8.
13. Jepards S. Personalized Medicine: Progress in regulating companion diagnostics. Applied & Translational Genomics. 2013. DOI: 10.1016/j.atg.2013.05.003.
14. Cohen JP. Overcoming regulatory and economic challenges facing pharmacogenomics. New Biotechnology. 6 September 2012. 29(6):751-756.
15. Australian Government Department of Health and Ageing. Review of Health Technology Assessment in Australia: A Discussion Paper. Canberra, Australis: Commonwealth of Australia; 2009.
16. Terzic A, Waldman SA. Translational medicine: path to personalized and public health. Biomark Med. 2010 Dec;4(6):787-90. doi: 10.2217/bmm.10.101.
17. Thomas A, Phillips A, Donnelly R, Piech CT. Comparative effectiveness, personalized medicine and innovation: the path forward. Pharmacoeconomics. 2010;28(10):923-30. doi: 10.2165/11539030-000000000-0000010.2165/11537370-000000000-00000.
18. Waldman SA, Terzic A. Widening the path to personalized medicine. Clin Transl Sci. 2011; 4(5):392-4. Epub 2011/10/28.
19. Snyderman R, Yoediono Z. Prospective care: a personalized, preventative approach to medicine. Pharmacogenomics. January 2006; 7(1):5-9. doi: 10.2217/14622416.7.1.5.
20. Merlin T, Farah C, Schubert C, Mitchell A, Hiller JE, Ryan P. Assessing Personalized Medicines in Australia: A National Framework for Reviewing Codependent Technologies. Medical decision making. August 2012. doi: 10.1177/0272989X12452341.
21. Lu CY, Ward R. A comparatice study of the multiple technology assessment process in the UK and Australia. Value Health. November 2012; 15(7): PHP155.
22. Garfield S. Advancing Access to Personalized Medicine: A Comparative Assessment of European Reimbursement Systems. Personalized Medicine Coalition. Bridgehead International. 2011. Available from: http://www.personalizedmedicinecoalition.org/sites/default/files/files/PMC_Europe_Reimbursement_Paper_Final.pdf. (accessed 26 December 2012).
23. 15th European Annual European Congress of the International Society for Pharmacoeconomics and Outcome research (ISPOR). 3-7 November 2012. IP7: How do you assess the value of co-dependent technologies? Available from: http://www.ispor.org/congresses/Berlin1112/Issue_Panels.aspx. (accessed 26 December 2012).
24. Organisation for Economic Co-operation and Development. OECD Health Data 2011 Version. June 2012 [updated September 2012]; Available from: http://dx.doi.org/10.1787/data-00540-en. (accessed 26 December 2012).

25. NICE technology appraisal guidance 107 Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer. National Institute for Health and Clinical Excellence. 2006; Available from: ttp://www.nice.org.uk/nicemedia/pdf/TA107guidance.pdf. (accessed 26 December 2012).

26. Joensuu H, Kellokumpu-Lehtinen PL, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006; 354:809-820February 23, 2006DOI: 10.1056/NEJMoa053028

27. Piccart-Gebhart MJ, Procter M, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.N Engl J Med 2005; 353:1659-1672October 20, 2005DOI: 10.1056/NEJMoa052306

28. Enzing C, et al. Case studies and cost-benefit analysis of HER2 and TPMT in four EU Member States. European Commission Directorate-General Joint Research Centre, Institute for Prospective Technological Studies. 2006; Technical Report EUR 22214 EN.

29. European Medicine Agency. European Public Assessment Report (EPAR) for Herceptin. 2011 [cited EMA/350167/2011]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/0002 78/human_med_000818.jsp&mid=WC0b01ac058001d124. (accessed 26 December 2012).

30. European Commission, General Directorate Enterprise and Industry. Grants work plan 2009. Action ENT/IMA/1.1.10.3.7. Studies/network/meetings and conferences in the context of the pricing and reimbursement of pharmaceutical products in the EU. Available from: http://ec.europa.eu/enterprise/contracts-grants/files/call-for proposals/gwp_2009_en.pdf. (accessed 26. December 2012).

31. WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies. Pharmaceutical Pricing and Reimbursement (PPRI) network. Available from: http://whocc.goeg.at/. (accessed 26 December 2012).

32. European Commission, General Directorate for Enterprise and Industry. Pharmaceutical forum working group on pricing and reimbursement. Available from: http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/pharmaceutical forum/wg_pricing_en.htm. (accessed 26 December 2012).

33. Pharma Price Information (PPI) service. Gesundheit Österreich GmbH (Austrian Health Institute); 2013.

34. General Social Insurance Act § 351c, Federal Law No. 189/1955, latest change by Federal Law I No. 398/2011 [in German]. 2012.

35. Bundesministerium für Gesundheit. Regelung für die Vorgehensweise der Preiskommission bei der Ermittlung des EU-Durchschnittspreises gemäß § 351c Abs. 6 ASVG. 1 January 2008.

36. Vogler S, Habl C, Leopold C, et al. PHIS Hospital Pharma Report. Pharmaceutical Health Information System. Commissioned by the Executive Agency for Health and Consumers and the Austrian Federal Ministry of Health. 2010. Available from: http://whocc.goeg.at/Literaturliste/Dokumente/BooksReports/PHIS_Hospital%20Pharma _Report.pdf. (accessed 20 December 2012).

37. Gustafsson LL, Wettermark B, et al. The 'Wise List'- A Comprehensive Concept to Select, Communicate and Achieve Adherence to Recommendations of Essential Drugs in Ambulatory Care in Stockholm. Basic Clin Pharmacol Toxicol. 2011 ; 108(4):224-33.

38. Björkhem-Bergman L, Andersén-Karlsson E, Laing R, Diogene E, Melien O, Jirlow M, Malmström R, Vogler S, Godman B, Gustafsson LL. Interface management of pharmacotherapy. Joint hospital and primary care drug recommendations.Eur J Clin Pharmacol. 2013; 69(1):73-8.

39. Espin J, Rovira J, Garcia L. Experiences and Impact of European Risk-Sharing Schemes. Focusing on Oncology Medicines. Andalusian School of Public Health commissioned by the European Commission General Directorate Enterprise. January 2011. Available from: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/risksharing_oncology_01201 1_en.pdf. (accessed 20 December 2012).

40. Ferrario A, Kanavos P. Managed entry agreements for pharmaceuticals: The European experience. London School of Economics commissioned by the European Commission General Directorate Enterprise. April 2013. Available from: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/mea_report_en.pdf (accessed 20 May 2013).

41. Vogler S, Zimmerman N, Piessnegger J, Bucsics A. Discounts and rebates granted to public payers for medicines in European countries. South Med Rev. 2012 July;5(1):38- 46.

42. Vogler S, Zimmermann N, Leopold C, de Joncheere K. Pharmaceutical policies in European countries in responds to the global financial crisis. South Med Rev. December 2011;4(2):22-32.

43. Henschke C, Sundmacher L, Busse R. Structural changes in the German pharmaceutical market: Price setting mechanisms based on the early benefit evaluation. Health Policy 2013; 109:263-269.

44. Lenz C, Girek O, Schmitt D. Advancing health technology assessment (HTA) and reimbursement processes to promote access to personalized medicine. Journal fur Pharmakologie und Therapie 2011. 20(5):150-152.

45. Health Directorate of the European Commission's DG Research and Innovation. Conference on European Perspectives in Personalised Medicine. 2011. Burssel. Available from: http://ec.europa.eu/research/health/events-06_en.html. (accessed 20 December 2012).

CHAPTER 5

General discussion

DISCUSSION

This concluding chapter discusses the benefits and limitations of research on pharmaceutical pricing and reimbursement policy interventions to understand health policy. In specific, the critical question why there is a need to analyze pharmaceutical pricing and reimbursement policies is addressed. Further, methodological challenges of comparing medicines prices and consumption as well as policy data are described and the policy implications of all study findings are presented. Finally, areas for future research are identified.

PHARMACEUTICAL PRICING AND REIMBURSEMENT POLICY ANALYSIS – WHY IS IT STILL NEEDED?

Even though in recent years an increasing number of descriptions of national pharmaceutical systems, especially in developed countries such as Europe, Canada, Australia and the USA, are being published [1-10], there is still a need for regular up-to-date pharmaceutical policy analysis to take account of the rapidly changing environment. Reasons are multifaceted and four of them have led to the studies in this thesis and are discussed in the following paragraphs:

Firstly, despite efforts of exchanging best practice experiences among European countries, policy-making in the field of pharmaceutical pricing and reimbursement - as it is the case for health care in general - is still a national competence. Even if countries apply the same policy many differences exist, which influence medicine prices and other outcome measures in other European countries. For this reason, we compared one of the most commonly used pricing policies in Europe - external price referencing (EPR) - across European countries in chapter 2.1 and analyzed in chapter 2.2 how national medicine prices may be affected by this policy. EPR is defined as the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiation of the price of the product in a given country [11]. In chapter 2.1 we reviewed the country-specific PPRI (Pharmaceutical Pricing and Reimbursement Information) Pharma Profiles written by representatives of the PPRI Network[1]. The Profiles were analyzed according to predefined criteria such as methodological differences in Europe with respect to the national legal framework, the countries included in the reference basket and the method of calculation of the reference price. As expected, many differences were found between countries as the way of implementing EPR is a national competence. We found that of 28 analyzed European countries 24 applied EPR in 2010. Most countries had less than 10 countries in their reference baskets, but this number ranged from one country to 26 countries. Higher income countries tended to include higher income countries in their basket, whereas lower income countries generally referred to lower income regional countries. Taking the average price of all countries in the basket as the basis to calculate the national price was the most common strategy (n = 8).

[1] The Pharmaceutical Pricing and Reimbursement (PPRI) network is a sustainable, self-funded network for public authorities in pricing and reimbursement in Europe and other countries [32].

The methodology of EPR which impacts price determination has changed in most European countries over the past 10 years (n = 19), showing that EPR is still widely used and a dynamic policy in contrast to what some people believe [12].

In chapter 2.2 we looked at whether EPR leads to the desired effects of lower and stable medicine prices. The study aimed at examining the impact of EPR on on-patent medicine prices, adjusting for other factors that may affect price levels such as sales volume, exchange rates, gross domestic product (GDP) per capita, total pharmaceutical expenditure (TPE), and the size of the pharmaceutical industry in 14 European countries in 2007 and 2008. Based on the unit ex-factory prices in the European region (in €), scaled ranks per country and per product were calculated. The study showed that on average EPR as a pricing policy is associated with lower prices. However, the large variation in price levels among countries using EPR confirmed that the price level is not only driven by EPR. This study however also raised methodological questions on price comparisons, which will be discussed below.

Secondly, the field of pharmaceuticals is an innovative, dynamic and rapidly changing area, which requires regular adjustments and re-evaluations of existing policies. Hence, findings of previous policy analyses might already be outdated a few of years after their publication, as it occurred for example in the case of medicine price convergence in Europe. Various reports showed that EU price convergence for medicines was more rapid in the second half of the 1990s as a result of the process of EU monetary convergence [13-15]. Starting from 2000 two clusters of countries were identified: the core EU countries (such as France, Italy, Benelux[2] countries) with a 15% average price gap; and the cluster of newer EU Member States and Spain, Portugal and Greece, which had average prices almost 40% lower than the EU-15 level[3] [13-15]. However, due to policy changes such as price cuts as a consequence of the economic recession in many countries, the picture of medicine price convergence in Europe may have changed. Therefore, in chapter 2.3, we analyzed prices of ten on-patent medicines in five years (2007-2011) of 15 European countries. The unit of analysis was the ex-factory price in € per defined daily dose (exchange rate indexed to 2007). We found that the prices between countries and selected products varied to a great extent. In the study period, a price divergence was seen which was driven only by two countries, Germany (up to 27% more expensive than the average) and Greece (up to 32% cheaper than the average). All other countries had relatively stable prices and centered around the average of the countries included in the study. Prices of less expensive medicines remained relatively stable or decreased over time, while prices of expensive medicines tended to increase. It is therefore crucial for policy makers to keep in mind that the European policy environment is diverse and changing over time, requiring regular monitoring of the effects, and that these policy changes do have an impact on national medicine prices.

Thirdly, overall national economic trends such as the current economic recession in Europe require adjustments of existing policies. Short-term measures needed to be implemented to

[2] Benelux countries: Belgium, the Netherlands and Luxembourg

[3] EU-15 countries = EU Member States as of 1 January 1995: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Spain, Sweden, United Kingdom, Portugal.

control public spending on medicines. As this is a very timely topic, we explored in chapter 3.1 which pharmaceutical pricing and reimbursement policies were implemented by countries during the time of the economic recession and evaluated the correlation with medicines sales in eight European countries. Based on a literature review, we described pharmaceutical policy changes and used IMS Health data to analyze quarterly sales of products in the 10 highest-selling therapeutic classes in eight European countries, in IMS standard units (volume) and constant dollars (value). We presented sales growth rates, comparing economically stable versus less stable countries classified based on 2012 fiscal consolidation plans of OECD member countries. Our study showed that economically stable countries (Austria, Estonia, Finland) implemented between two and seven policy changes each, whereas economically less stable countries (Greece, Ireland, Slovak Republic, Spain, Portugal) implemented between 10 and 22 policy changes. Most policy changes occurred in 2010/2011 and included changes in out-of-pocket payments, price mark-up schemes and price cuts. All countries showed moderate increases in sales volumes (except Portugal and Greece, both showing slight declines after 2009), while sales value decreased in both country groups, with greater declines in economically less stable countries.

In chapter 3.2 we performed a detailed evaluation of the impact of different policy measures on the consumption of antipsychotic medicines in Portugal and Finland during the time of the economic recession. We obtained monthly IMS sales data in standard units of antipsychotic medicines in Portugal and Finland for the period January 2007 to December 2011. We used an interrupted time series design to estimate changes in overall use and generic market shares by comparing pre-policy and post-policy levels and trends. We found that both countries' policy approaches were associated with slight, likely unintended, decreases in overall use of antipsychotic medicines and increases in generic market share of major antipsychotic products. These findings clearly indicate that the implementation of new policies or the adjustment of existing policies can have positive effects on controlling public spending in a short time period, but sometimes these policy changes may have unintended consequences such as higher out-of-pocket payments for patients which may lead to a decrease in use. Therefore, there is a need to continuously monitor intended and possibly unintended effects of new policies or policy changes.

Fourthly, new technologies such as highly specialized treatments including diagnostic tests - often referred to as personalized medicines - are being developed and are among the highest priced medicines putting additional pressure on public funding of medicines. Hence, policy-makers are confronted with essential ethical questions such as how much is a society willing to pay for new and innovative medicines if the available funds remain the same. We analyzed this European trend towards personalized medicines in chapter 4.1, by looking at how European pricing and reimbursement authorities deal with the common challenge of how to evaluate new and often expensive medicines which include medical devices. We analysed qualitative descriptive data on national pharmaceutical pricing and funding policies applied to trastuzumab and its accompanying diagnostic test as an example of personalized medicines as part of the treatment package. Data were obtained from a survey among competent authorities from 27 European countries as of August 2011. Further, price data (for the years 2005 to 2013) of trastuzumab in the respective European countries were surveyed and analyzed. We

found that in 2011 testing and treatment mainly took place in hospitals or in specific day-care ambulatory clinics. In the surveyed European countries either both trastuzumab and the accompanying diagnostic test were funded from hospital budgets or medicines were funded from the third party payers such social insurances and the test from hospital budgets. Neither combined funding of both medicine and diagnostic test by third party payers was identified in the surveyed countries nor did the respondents from the competent authorities identify any managed entry agreements. National pricing procedures are different for trastuzumab versus its diagnostic test, as most countries apply price control policies for trastuzumab but have free pricing for the diagnostic test. In nine countries the price of trastuzumab went down from 2005 till 2013. The move to health technology assessment (HTA) that is occurring in many countries may have addressed some aspects of the problems occurring in this complex area. But other decisions, such as whether these medicines and diagnostics should be paid for from hospital or primary care budgets, may have a devastating effect on access.

For these four reasons as well as possible other reasons, e.g. new evolving price mechanisms such as managed entry agreements, there is a continuous need for pharmaceutical policy analysis. Consequently, pharmaceutical policy discussions will remain a hot political topic in all countries and will be part of the agenda of international organizations such as the World Health Organization (WHO), the Organization for Economic Co-operation and Development (OECD), the European Commission (EC) and the World Bank. Evidence is needed to fuel their discussions and the public debate, and therefore evidence based decision-making in the pharmaceutical policy area is advocated [12,16,17].

METHODOLOGICAL CHALLENGES IN PHARMACEUTICAL PRICING AND REIMBURSEMENT POLICY ANALYSIS

As outlined in the introduction, pharmaceutical pricing and reimbursement policies are embedded in a framework with many different interests of the actors involved as well as legal provisions, leading to possible economic as well as information asymmetries and contradicting policy objectives. Hence, assessment tools and research methods used to inform pharmaceutical policy decision-makers should be neutral, based on evidence, and no preempting conclusion should be drawn by limiting the scope of questions to one problem area. Such a research method needs to verify, describe, and - as much as possible - quantify the research question. The analytical process is one that requires expert knowledge in interpreting data and dialogue with insightful stakeholders to reach meaningful conclusions. As data could be incomplete and opinions on the results could be divergent between stakeholders, final recommendations of such research should therefore be guided by political sensitivity and supported by experiences and studies from other countries [18].

Pharmaceutical policy analysis often studies the impact of implemented policies or policy changes. Verifying and quantifying the impact of such policy reforms is only possible if researchers have access to reliable quantitative and qualitative data over time. In this thesis three major data sets were used: medicine price data, medicine sales data and pharmaceutical pricing and reimbursement policy data. We encountered several methodological challenges, which we summarized in Table 1 and discuss in the following paragraphs.

Table 1. Summary of methodological challenges with respect to pharmaceutical pricing and reimbursement policy analysis

Methodological challenges	Examples
Data availability and transparency of data	Sources of medicine price data Sources of medicine consumption data Collection of up-to-date policy data Sharing of information
Validity and comparability of data	Price levels Unit of comparison Exchange rates Weighing of prices by volume
Understanding the policy context	Impact of timing of policy implementation on study design Collection of data on the policy context

The ability to compare medicine prices and consumption data across populations, geographic locations and over time requires standardized information from reliable sources [19,20]. We identified two major medicine price databases for European countries: the EURIPID database [21], which is only accessible for public authorities of EU Member States, and the publicly available Pharmaceutical Price Information (PPI) service by the Austrian Health Institute [22], which offers its service for free to the Austrian authorities and with costs to all other interested parties. In the studies in chapters 2.2, 2.3 and 4.1 we used medicine price data from the Austrian Health Institute. Reasons for choosing this source of data were 1) accessibility of the data by the authors, 2) reliability as the data have been collected as part of legal obligations [23] for the Austrian Pricing Committee [24] and 3) the PPI service became a point of reference for the European Commission and for many EU Member States.

Another source of information would be to directly search for medicine price data in national positive lists, which vary greatly as there are no common European requirements on which information needs to be provided. To comply with the EU Transparency Directive EU Member States have to publish and provide public access to prices of reimbursable medicines [25,26]. Most EU Member States provide their positive list either as publicly available database, links to downloadable xls-files or in book formats. These lists vary however in level of detail, are published in the national language with national specifications, national currency, differences in price levels (e.g. the NHS price in the United Kingdom), and frequency of updating ranging from daily to annually or irregularly [20].

Using an international database such as the PPI service provides advantages over individually searching national price lists: data was provided in a comparable and structured way across European countries not only for originators but also for all available generics in national currency or converted to the €, additional information on exchange rates and reimbursement limits were delivered, and historic price data were available which was important for our research looking at price trends over time (chapters 2.2 and 2.3). Constraints were that no information was provided on confidential discounts and rebates as well as that these data mainly cover the out-patient sector as medicines in the in-patient sector are often funded directly by regions or

individual hospitals [27,28]. For these reasons it remains a "black box" what hospitals and also in some cases third party payers actually pay for certain medicines [28].

With respect to medicine consumption (prescription, dispensing or medicine sales) data no EU regulations are in place to foresee transparent availability. Sources vary from databases that are commercial (e.g. IMS Health), administrative (e.g. databases containing claims, prescription or dispensing records), or publicly operated by regulatory agencies, suppliers or third party payers [29]. For prescription and dispensing data, great differences exist between EU Member States with respect to public availability of anonymous data. The Nordic countries traditionally provide more information in the public domain, while other countries such as Eastern European countries are not as used to transparency and public data availability [30]. National structures and definitions of prescribing data may differ to a great extent hampering cross-national analyses [29]. In addition, quantitative data on medicine consumption is often expensive and difficult to obtain. For the purpose of the studies included in this thesis, we received data from IMS Health. IMS data are generated from reports by multinational and national pharmaceutical companies, wholesalers and retailers to IMS Health [31]. We found that the IMS data was a very suitable source for international comparisons, despite the fact that it is aggregated data. IMS data may therefore not be useful to assess effects of policies on the individual patient or prescription level, but research questions such as in chapter 3.1 and 3.2 can be assessed with these data (depending on the level of aggregation).

An important aspect of all studies included in this thesis was to understand the dynamics of the pricing and reimbursement policy environment including the numerous national policy changes. For this reason high-quality data on pricing and reimbursement policies as well as on policy changes were of key relevance for the performance of the studies. Potential sources for policy information range from peer-reviewed articles, to grey literature and country profiles published by international organizations such as the World Health Organization or commercial consultancy companies. However, these sources often do not provide insightful information to understand the national pharmaceutical policy context. Therefore, the main policy data source for all the studies included in this thesis was the Pharmaceutical Pricing and Reimbursement Information (PPRI) Network [32]. The PPRI network started as an EU-funded project from 2005 until 2007 and continues as a sustainable network for public authorities in pricing and reimbursement in Europe and other countries. Within the scope of the PPRI network country-specific reports, PPRI Pharma Profiles, on national pricing and reimbursement systems of the European Member States and associated countries were published. This approach of collecting and sharing information is unique as the PPRI Pharma Profiles were written in a common structure with common terminology by representatives of public authorities, such as Ministries of Health or third party payers, which are responsible for pricing and reimbursement. In addition, the PPRI secretariat has established the possibility to confidentially exchange and share information between PPRI members on ad-hoc policy questions reflecting up-to-date national policy discussions. Although this information may further enhance the understanding of the policy context and the decision-making process, it is only available for members of the PPRI network.

The capacity to perform cross-national medicine prices and medicine consumption comparisons depends not only on the availability of reliable high-quality data but also on the

validity and comparability of these data [33-35]. For this reason, we compared medicine prices at ex-factory price level to guarantee comparability of different medicines in a basket of countries as distribution margins and taxes vary to a great extent not only in Europe but worldwide [34]. Only in chapter 4.1 the prices of all three price levels were presented as the prices of only one sample medicine was compared. Limitations of price data are that these data do not include information on confidential discounts or rebates after price negotiations between manufacturers and third party payers or hospitals. There is still the belief that transparency, through publishing the results of confidential price negotiations between manufacturers and third party payers or hospitals, would hamper the outcome of the negotiation process [36]. This does not only hamper cross-national research on medicine price comparison, but it is also an important aspect for policy-makers for countries applying EPR and referencing to the 'artificial' high list prices.

Further, it is especially crucial that an exact definition of the price per unit is given. In the studies included in this thesis, we collected the medicine price for the same product, the same strength, the same pharmaceutical form and, if available, the same pack size to ensure comparability. Crucial for cross-national comparisons is the exchange rate as fluctuations exist over time and may bias the results. For this reason, in case a country did not use the €, we used the monthly conversion rate of the European Central Bank for all studies; only in chapter 2.3 we indexed the exchange rate to the year 2007 to account for exchange rate fluctuations. In chapter 2.2 we followed suggestions from literature to weigh medicine prices according to their sales volume to account for medicines with high volume which have lower prices according to economics of scale [37]. This approach requires access to medicine sales data which is challenging as data is difficult to obtain and linking two different data sets can create problems of matching the exact same medicine with each other. Another approach is to calculate the unit price per defined daily dose (DDD), which we did in chapter 2.3. The DDD is the WHO defined average dose per day for a medicine used for its main indication in adults [38] and does not necessarily reflect the recommended or actual dose used [39]. A challenge that occurs when calculating the price per DDD is, that DDDs have not been assigned for some medicines, which we therefore had to define and calculate ourselves based on the product information.

To examine the impact of implemented policies or changes of existing policies on health outcomes or on other parameters such as medicine prices or consumption requires information on the exact time of the implementation of a policy or a policy change. However, this is not always clear as political discussions on the implementation of a policy, which often implies adjustments of existing laws and regulations, may take up to several years. Among the key elements of guaranteeing a successful implementation of a policy is a transparent implementation process accompanied by early involvement of all stakeholders, such as doctors and pharmacists, as well as a detailed methodology and positive perceptions of patients towards the policy [40,41]. System changes such as the implementation of a reference price system are intended to facilitate changes in behaviors of patients and health providers by encouraging them to be more price-sensitive; in a reference price system patients have to pay the difference between the reference price and the actual price out-of-pocket, generating an incentive for patients to request a medicine that is priced at or below the reference price. Such behavioral and also cultural changes happen gradually and often start before the actual implementation of a law [42].

We encountered this methodological challenge in chapters 3.1 in which we studied the impact of the recent economic recession. First of all, it was difficult to define when the economic crisis started. Therefore, we looked at developments in gross domestic products (GDP) per capita as well as unemployment rates over time. From these data it was evident that the European countries were hit by the economic recession at different times. We therefore then decided that it was impossible to take the start of the economic recession as one point in time for all countries assessing the impact on medicines sales. In addition, the rapid implementation of policies during the economic recession and the different timing of policies in different countries precluded attribution of observed changes to any single policy or statistical comparisons of responses between countries. Therefore, a sophisticated statistical analysis such as a pre / post interrupted time series analysis could not be performed in chapter 3.1; we decided to use descriptive analysis to understand trends of consumption over time.

Finally, it was not always clear whether countries implemented policies as a short-term reaction to recession-related budgetary constraints or if policies were long-term planned system changes. For instance, in Finland, the implementation of internal reference pricing in 2009 was planned long before the recession [42]. Most of the observed policy changes related to the recession were adjustments of existing policies (e.g. changing the countries of the basket for external price referencing), which could be implemented relatively quickly. While leading to desired short-term cost-containment, these policies might have substantial long-term effects on access to, use, and affordability of medicines and negative impacts on health [43-45].

For this reason, it is especially important to have access to insightful national information on the 'heart of the policy reform'. We found the qualitative data provided by the PPRI network to be very helpful. Of great value was the communication with PPRI members to verify certain policy details and to understand a country's characteristics, in order to interpret a policy or also a medicine price correctly. In addition, we received insight information from PPRI members on the country's culture, history and the "political temperature". We recognize the value of such networking activities, as especially face-to-face meetings or exchange of ad-hoc questions via e-mail give room for discussion of challenges policy-makers face in their daily working routine.

In summary, methodological challenges in pharmaceutical policy analysis are often related to availability and transparency of reliable and high-quality data. In addition, validity and comparability of data are necessary when performing pharmaceutical policy analysis. Another key aspect when performing cross-national pharmaceutical policy analysis is to understand the policy context which requires insight information on policy dynamics.

POLICY IMPLICATIONS OF FINDINGS AND AVENUES FOR FUTURE RESEARCH

In July 2013 the Priority Medicines Report for Europe and the World, a publication of the World Health Organization and commissioned by the European Commission, identified research priorities for planning the Horizon 2020 combined research program for the EU [46]. The report highlighted among other topics the importance of investigating in cross-national research

of pharmaceutical pricing and reimbursement policies. The report suggests several research priorities which focus on the broader environment of pricing and reimbursement policies and the specific 'tools' that are used. Among those are the effects of external price referencing, the impact of the economic recession on medicine utilization and issues around pricing and reimbursement of new medicines such as personalized medicines for a small group of population.

All studies included in this thesis already represent a first step in answering several of the above mentioned research priority areas. While performing these studies we identified two critical factors for future successful studies in cross-country comparisons of pharmaceutical pricing and reimbursement policies. The first important point concerns the *improvement of publicly available, transparent and comparable data* on medicine prices and utilization data as discussed above. Inclusion of utilization data in a European price database has not been planned nor are there other plans to establish a European database on medicine utilization including prescription data. It remains the responsibility of each EU Member State to play an important role in data collection and harmonization; every national pharmaceutical policy should ideally contain a comprehensive plan to collect reliable medicine consumption and medicine price data [47].

The second important point is the availability of *adequate information on the pharmaceutical policy context*. We already elaborated on the importance of availability of insightful national pharmaceutical pricing and reimbursement policies, but further we see of key relevance additional information such as the wealth of a country or the size or strength of the pharmaceutical industry. We illustrated for instance in chapter 2.2, that the size of pharmaceutical industry and the level of gross domestic product had an influence on the price level. Much has been done in the last ten years to improve the situation of availability of insightful policy data: some large-scale European projects were launched to foster exchange between public authorities but also to the public by publishing reports or articles. However, even though the benefits of such transparent initiatives are recognized at national as well as at European level, the sustainability of several of these networks is at stake due to limited funding [46].

With respect to methodologies, much can be learned from international comparative studies in other research areas, such as sociological and economic studies, which might require qualitative methods such as interviews with national stakeholders, so as to put results of research into context and to better understand variations of outcomes.

The ultimate goal of studying pharmaceutical pricing and reimbursement policies is to understand issues of high prices and/or of poor affordability in the context of public systems to then develop policies and interventions that can be applied to rectify these problems and ultimately improve access [33]. Keeping this in mind several policy implications and avenues for future research can be formulated resulting from the experiences of this thesis.

We have shown that prices of the same medicine still vary to a great extent among European countries. Instead of the conventional wisdom that medicine prices of European countries may converge [48], we observed a price divergence driven by price changes in only two of the 15 countries. This could have been caused by the several pricing policy measures that were implemented as a consequence of the recent economic recession. These developments and the fact that the ability to pay for medicines vary greatly in Europe [21] trigger discussions on

the need for differential pricing mechanisms and policies for Europe. The concept of Ramsey optimal pricing states that prices should differ across markets according to the demand elasticity: more price-sensitive users are charged a lower price than users that are less sensitive [49]. If applied in practice, this would mean that users in lower income countries should be reqiured to pay a lower price as they are more sensitive to price than high-income users [50]. However, the concept of differential pricing limits the value of transparency, as it depends on confidential agreements within countries.

In this thesis the focus has been on analyzing well-established and widely applied policies such as external price referencing. Recently, several countries have explored alternative policies that link pricing and reimbursement decisions with sharing the financial risk of selecting new, high-cost medicines including value-based pricing models taking into account societal costs when evaluating the value of a treatment (e.g. the United Kingdom) or risk-sharing agreements between payers and industry (e.g. Italy) [51-55]. The effects of these new approaches will need to be determined and appropriate policy analysis methodologies including measurements e.g. on societal aspects will need to be defined. But also the growing importance of HTA bodies including their methodologies, procedures and knowledge on the access to market of novel medicines offers another interesting opportunity for research in this field, especially at EU level where harmonization of licensing and reimbursement requirements is being attempted to overcome disparities of access across Europe. It will be important to investigate the effects of these initiatives (such as parallel HTA-EMA, scientific advice) and their actual impact on access to medicines [56].

Another point is how the role of patients can be strengthened in pharmaceutical pricing and reimbursement policy making. In other parts of the pharmaceutical policy field, e.g. regulatory science, civil society representatives are already formally involved in the decision-making process. Whether it actually represents an added value to involve patients in pricing and reimbursement decisions is open to question [46], but the implementation of policies which require patients to be more price-sensitive and therefore more self-determined would be desirable. An example could be a reference price system, where patients have to pay out-of-pocket the difference between the reference price and the actual price, which generates an incentive for patients to request a medicine that is priced at or below the reference price. Another possibility could be to explicitly indicat the price of the medicine on the package, which was done in Portugal, to make patients aware of the actual price of the product [32]. Another aspect is that some policy changes such as increases of patient co-payments may have considerable consequences for patients to the point of unaffordability of medicines. In chapter 3.2 we found a decrease in use of antipsychotic drugs in Portugal due to the implementation of various policies including changes in co-payments. On the other hand in chapter 3.1 we could not find any real effects on use of the ten top-selling active substances as too many policy changes occurred during the observation period.

The final point, which we would like to highlight for future research, is the trend towards more specialized and personalized medicines – either orphan medicinal products for patients with rare diseases or stratified medicines which include prior testing for targeted therapies. These medicines serve only a small group of patients and are often among the highest

priced medicines. An additional aspect is that these treatments often require prior genetic testing or other screening methods which add to the overall cost of treatment [20]. These pharmacotherapies are often applied at the interface of the out-patient and hospital sectors which imply questions of funding responsibilities between the two sectors. At the moment, in many countries, these sectors operate as separate worlds from a pricing and reimbursement perspective [28]. Legal and organizational needs have to be addressed in order to reduce the duality in the system and to remove existing incentives for stakeholders to transfer treatments and patients between the two sectors. All stakeholders should be incentivized to define the best point of care, including pharmacotherapy, for patients from a therapeutic perspective. Research is needed to explore the possibility of an implementation of policies applicable to both sectors, such as joint reimbursement lists and joint therapeutics committees as occurs in Scotland [57]. The introduction of policies to improve interface management should be accompanied by sound evaluations [58].

FINAL CONCLUSIONS

The findings of pharmaceutical pricing and reimbursement policy analysis play a key role in helping to understand, interpret and evaluate the rapidly changing pharmaceutical policy environment. Many stakeholders find that these studies are of importance as the results are used to guide the more efficient use of scarce public health care resources. The studies included in this thesis have shown that the current available data on pricing and reimbursement policies and medicine prices and consumption provide ample opportunities for studying cross-national variations in pharmaceutical policies. Analyzing pharmaceutical policy, pricing and consumption data can be used as a "lens" to understand and evaluate broader health policy and systems issues

.

REFERENCES

1. Barbui C, Campomori A, Mezzalira L, Lopatriello S, Cas RD, Garattini S. Psychotropic drug use in Italy, 1984-99: the impact of a change in reimbursement status. Int Clin Psychopharmacol. 2001 Jul;16(4):227-33.
2. Bambauer KZ, Sabin JE, Soumerai SB. The exclusion of benzodiazepine coverage in Medicare: simple steps for avoiding a public health crisis. Psychiatr Serv. 2005 Sep;56(9):1143-6.
3. Hoebert JM, Souverein PC, Mantel-Teeuwisse AK, Leufkens HGM, van Dijk L. Reimbursement restriction and moderate decrease in benzodiazepine use in general practice. Ann Fam Med. 2012;10(1):42-9. doi: 10.1370/afm.1319.
4. Vogt WB, Joyce G, Xia J, Dirani R, Wan G, Goldman DP. Medicaid cost control measures aimed at second-generation antipsychotics led to less use of all antipsychotics. Health Aff (Milwood). 2011 Dec;30(12):2346-54. doi: 10.1377/hlthaff.2010.1296.
5. Lu CY, Soumerai SB, Ross-Degnan D, Zhang F, Adams AS. Unintended impacts of a Medicaid prior authorization policy on access to medications for bipolar illness. Med Care. 2010 Jan;48(1):4-9. doi: 10.1097/MLR.0b013e3181bd4c10.
6. Zeber JE, Grazier KL, Valenstein M, Blow FC, Lantz PM. Effect of a medication copayment increase in veterans with schizophrenia. Am J Manag Care. 2007 Jun;13(6 Pt 2):335-46.
7. Wagner AK, Ross-Degnan D, Gurwitz JH, Zhang F, Gilden DB, Cosler L, Soumerai SB. Effect of New York State regulatory action on benzodiazepine prescribing and hip fracture rates. Ann Intern Med. 2007 Jan 16;146(2):96-103.
8. Wladysiuk M, Araszkiewicz A, Godman B, Szabert K, Barbui C, Haycox A. Influence of patient co-payment on atypical antipsychotic choice in Poland: implications once generic atypical are available. Appl Health Econ Health Policy. 2011 Mar 1;9(2):101-10. doi: 10.2165/11318840-000000000-00000.
9. Andersson K, Petzol MG, Sonesson C, Lönnroth K, Carlsten A. Do policy changes in the pharmaceutical reimbursement schedule affect drug expenditures? Interrupted time series analysis of cost, volume and cost per volume trend in Sweden 1986-2002 Health Policy. 2006;79:231-243.
10. Green CJ, Maclure M, Fortin PM, Ramsay CR, Aaserud M, Bardal S. Pharmaceutical policies: effects of restrictions on reimbursement. The Cochrane Database of Systematic Reviews. 2010;(8):CD008654. doi: 10.1002/14651858.CD008654.
11. WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies. Pharmaceutical Pricing and Reimbursement glossary. Updated version as of July 2013. Available from: http://whocc.goeg.at/Glossary/. Accessed 14 August 2013.
12. Seiter A. A Practical Approach to Pharmaceutical Policy. Directions in Development. The World Bank, Washington 2010. Available from: http://www-wds.worldbank.org/external/default/WDSContentServer/WDSP/IB/2010/06/22/000334955_20100622050742/Rendered/PDF/552030PUB0Phar10Box349442B01PUBLIC1.pdf. Accessed 14 August 2013.
13. European Commission. European Competitiveness Report 2006: Economic reforms and competitiveness. Key messages from the European Competitiveness Report. 2006. Available from: http://ec.europa.eu/enterprise/sectors/ict/files/euro_comp_report_2006_en.pdf
14. Kyle MK, Allsbrook JS, Schulman KA. Does Reimportation Reduce Price Differences for Prescription Drugs? Lessons from the European Union. Health Serv Res. 2008 Aug;43(4):1308-24. doi: 10.1111/j.1475-6773.2008.00838.x. Epub 2008 Mar 12.
15. Cambridge Pharma Consulting. Pricing and Market Access Review 2005. IMS Intelligence 2006
16. Docteur E, Paris V. Pharmaceutical pricing policies in a global market. Paris: OECD Health Policy Studies; 2007. Available from: http://www.oecd.org/fr/els/systemes-sante/pharmaceuticalpricingpoliciesinaglobalmarket.htm. Accessed on 14 August 2013.
17. Paris V, Belloni A. Value in Pharmaceutical Pricing. OECD Health Working Paper. 2013. No. 63. Available from: http://www.oecd-ilibrary.org/social-issues-migration-health/value-in-pharmaceutical-pricing_5k43jc9v6knx-en. Accessed on 14 August 2013.
18. Almarsdottir AB, Traulsen JM. Studying and evaluating pharmaceutical policy – becoming a part of the policy and consultative process. Pharm World Sci. 2006 Feb;28(1):6-12. Epub 2006 Jun 30.
19. Sjöqvist F, Birkett D. Chaper 10. Drug Utilization. Introduction to Drug Utilization Research. First ed. Geneva, Switzerland: World Health Organization 2003: 76-84.
20. Rosian I, Vogler S, Stürzlinger H. Internationale Arzneimittelpreisvergleiche: Meta-Analyse. Commissioned by Pharmig. Vienna 2004; Available from: http://whocc.goeg.at/

Publications/BooksReports. Accessed 20 July 2012.

21. Bouvy J, Vogler S. Pricing and Reimbursement Policies: Impacts on Innovation. Background paper to chapter 8.3 of the WHO Priority Medicines for Europe and the World 2013. World Health Organization 2013. Available from: http://www.who.int/medicines/areas/priority_medicines/BP8_3_pricing.pdf. Accessed on 12 July 2013.
22. Pharma Price Information (PPI) service. Gesundheit Österreich GmbH (Austrian Health Institute); 2012.
23. General Social Insurance Act § 351c, Federal Law No. 189/1955, latest change by Federal Law I No. 398/2011 [in German]. 2012.
24. Bundesministerium für Gesundheit. Regelung für die Vorgehensweise der Preiskommission bei der Ermittlung des EU-Durchschnittspreises gemäß § 351c Abs. 6 ASVG. 1 January 2008.
25. Council Directive of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems (89/105/EEC). http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31989L0105:en:HTML. Accessed 12 August 2013.
26. European Commission. Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of public health insurance systems. 2012. Available from: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/transpadir_finalprop01032012_en.pdf. Accessed on 12 July 2013.
27. Vogler S, Zimmermann N, Mazag J. Procuring medicines in hospitals: results of the European PHIS survey. European Journal of Hospital Pracitice 2011;(2):21.
28. Vogler S, Habl C, Leopold C, Morak S, Mazag J, Zimmermann N. PHIS Hospital Pharma Report 2010. Pharmaceutical Health Information System. Available from: http://phis.goeg.at/downloads/hospitalPharma/PHIS_Hospital%20Pharma_Report.pdf. Accessed on 12 July 2013.
29. Hoebert JM, Mantel-Teeuwisse Ak, van Dijk L, Laing RO, Leufkens HGM. Quality and completeness of utilization data on biological agents across European countries: Tumor Necrosis Factor alpha inhibitors as a case study. Pharmacoepidemiol Drug Saf. 2011 Mar;20(3):265-71. doi: 10.1002/pds.2093. Epub 2011 Jan 10.
30. Vogler S, Schmickl B. Rationale Arzneimitteltherapie in Europa [in German]. Vienna: Gesundheit Österreich GmbH, 2010. Available from: http://whocc.goeg.at/Literaturliste/Dokumente/BooksReports/GOeG_OeBIG_Rationale%20Arzneimitteltherapie%20in%20Europa.pdf. Accessed 20 June 2012.
31. IMS Health MIDAS. 2007-2013.
32. PPRI network. PPRI / PHIS Pharma Profiles. Available from: http://whocc.goeg.at/Publications/CountryReports. PPRI (Pharmaceutical Pricing and Reimbursement Information), 2007-2013.
33. Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R. Medicine prices, availability, and affordability in 36 developing countries: a secondary analysis. Lancet 2009;373(9659):240-249.
34. Waning B, Maddix J, Soucy L. Balancing medicine prices and business sustainability: analyses of pharmacy costs, revenues and profit shed light on retail medicine mark-ups in rural Kyrgyzstan. BMC Health Serv Res. 2010;10(1):205.
35. van Mourik M, Cameron A, Ewen M, Laing R. Availability, Price and affordability of cardiovascular medicines: a comparison across 36 countries using WHO /HAI data. BMC Cardiovascular Disorders 2010;10:25.
36. Vogler S, Zimmermann N, Leopold C, Habl C, Mazag J. Discounts and rebates granted for medicines for hospital use in five European countries. The Open Pharmacoeconomics & Health Economics Journal 2013;5:1-10.
37. Danzon PM, Chao LW. Cross-national price differences for pharmaceuticals: how large, and why? J Health Econ. 2000 Mar;19(2):159-95.
38. World Health Organization. ATC/DDD Methodology 2009. Available: http://www.whocc.no/atc_ddd_methodology/purpose_of_the_atc_ddd_system/. Accessed 20 August 2013.
39. Heerdink ER, Urquhart J, Leufkens HG. Changes in prescribed drug doses after market introduction. Pharmacoepidemiol Drug Saf. 2002 Sep;11(6):447-53.
40. Habl C, Vogler S, Leopold C, Schmickl B, Fröschl B. Referenzpreissysteme in Europa. [in German]. Commissioned by the Main Association of Austrian Social Security Institutions 2008. Available from: http://whocc.goeg.at/Literaturliste/Dokumente/BooksReports/EB_RPS_31_3_08.pdf. Accessed 11 June 2012.
41. Simoens S. Creating sustainable European health-care systems through the increased use of generic medicines: a policy analysis. Journal of Generic Medicines 2010;7(2):131-137.
42. Pohjolainen L. Reference price and price competition – evidence from the Finnish

pharmaceutical market. Master's thesis. Aalto University, School of Economics, Department of Economics. 2012. Available: https://aaltodoc.aalto.fi/handle/123456789/3456. Accessed 20 August 2012.

43. Andersson K, Petzol MG, Sonesson C, Lönnroth K, Carlsten A. Do policy changes in the pharmaceutical reimbursement schedule affect drug expenditures? Interrupted time series analysis of cost, volume and cost per volume trend in Sweden 1986-2002 Health Policy 2006;79:231-243.
44. Soumerai SB, Zhang F, Ross-Degnan D, Ball DE, Le Cates RF, Law MR, Hughes TE, Chapman D, Adams AS. Use of atypical antipsychotic drugs for schizophrenia in Maine Medicaid Following a policy change Health Aff (Millwood). 2008 May-Jun;27(3):w185-95. doi: 10.1377/hlthaff.27.3.w185. Epub 2008 Apr 1.
45. Ong M, Catalano R, Hartig T. A time-series analysis of the effect of increased copayments on the prescription of antidepressants, anxiolytics, and sedatives in Sweden from 1990 to 1999. Clinical Therapeutics 2003;25(4):1262-75.
46. Kaplan W, Writz VJ, Mantel-Teuwisse A, Stolk P, Duthey B, Laing R. Priority Medicines Report for Europe and the World Update 2013. World Health Organization 2013. Available from: http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf. Accessed 20 August 2013.
47. Hoebert J, van Dijk L, Mantel-Teeuwisse A, Leufkens H.G.M, Laing R. National medicines policies – a review of the evolution and development process. Journal of Pharmaceutical Policy and Practice 2013;6:5. doi:10.1186/2052-3211-6-5.
48. Kanavos P, Vandoros S, Irwin R, Nicod E, Casson M. Differences in costs of and access to pharmaceutical products in the EU 2011; IP/A/ENVI/ST/2010-12. European Parliament, Brussels. Available from: http://www.europarl.europa.eu/document/activities/cont/201201/20120130ATT36575/20120130ATT36575EN.pdf. Accessed 20 June 2013.
49. Danzon PM, Towse A. Differential pricing for pharmaceuticals: reconciling access, R&D, and patents. Int J Health Care Finance Econ. 2003 Sep;3(3):183-205.
50. Danzon PM, Towse A, Mulcahy AW. Setting cost-effectiveness thresholds as a means to achieve appropriate drug prices in rich and poor countries. Health Aff (Millwood). 2011 Aug;30(8):1529-38. doi: 10.1377/hlthaff.2010.0902.
51. Kanavos P, Nicod E, Espin J, van den Aardweg S. Short- and long- term effects of value-based pricing vs. External Price Referencing. EMINET 2010. Available from: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/valuebased_pharmapricing_012010_en.pdf. Accessed 20 June 2012.
52. Husereau D, Cameron C. Value-based pricing of pharmaceuticals in Canada: Opportunities to expand the role of Health Technology Assessment? CHSRF Series of Reports on Cost Drivers and Health Systems Efficiency: Paper 5, 2011. Available from: http://www.cfhi-fcass.ca/publicationsandresources/researchreports/ArticleView/11-12-16/8eeaf655-b2b6-4c39-a909-6854acfea850.aspx. Accessed 20 April 2013.
53. Espín J, Rovira J, García L. Experiences and Impact of European Risk-Sharing Schemes Focusing on Oncology Medicines. January 2011; Commissioned by the European Commission, Directorate-General Enterprise. Available from: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/risksharing_oncology_012011_en.pdf. Accessed 12 May 2013.
54. Kanavos P, Seeley E, Vandoros S. Tender systems for outpatient pharmaceuticals in the European Union: Evidence from the Netherlands, Germany and Belgium. EMINet 2010. Available from: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/study_pricing_2007/tendering_systems_en.pdf. Accessed 15 May 2013.
55. Kanavos P. Ferrario A. Managed entry agreements for pharmaceuticals: The European experience. EMINet. April 2013; Commissioned by the European Commission, Directorate-General Enterprise. Available from: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/mea_report_en.pdf. Accessed 15 April 2013.
56. Tafuri G, Stolk P, Trotta F, Putzeist M, Leufkens HGM, Laing R, De Allegri M. How do the EMA and FDA decide which anticaner drugs make it to the market? A comparative qualitative study. Submitted for publication.
57. Herms S, Rutledge P. The Lothian Joint Formulary: overcoming the barriers to formulary success. Pharmacy in Practice 2002;12(6):279-85.
58. Gustafsson LL, Wettermark B, Godman B, Andersén-Karlsson E, Bergman U, Hasselström J, Hensjo LO, Hjemdahl P, Jägre I, Julander M, Ringertz B, Schmidt D, Sjöberg S, Sjögvist F, Stiller CO, Törnqvist E, Tryselius R, Vitols S, von Bahr C. The 'Wise List'– A Comprehensive Concept to Select, Communicate and Achieve Adherence to Recommendations of Essential Drugs in Ambulatory Care in Stockholm. Basic Clin Pharmacol Toxicol. 2011 ;108(4):224-33. doi: 10.1111/j.1742-7843.2011.00682.x.

CHAPTER 6

Summary, Samenvatting,
and Zusammenfassung

CHAPTER 6.1

Summary

SUMMARY

The pharmaceutical policy environment is dynamic as new medicines are being developed and different medical needs arise, while diverse interests by stakeholders influence policy making. Tensions are especially noticeable with respect to pricing and reimbursement of medicines; what health care plans may view as necessary to maintain equitable access to medicines, industry may view as inimical to research and development (R&D) and innovation. As public health care budgets – including pharmaceutical expenditure – are limited policy makers have to constantly adjust and implement pharmaceutical policies to cope with the changing pharmaceutical environment. This financial pressure even increased during the last years of the economic recession.

The goal of this thesis is to understand pharmaceutical pricing and reimbursement policies and their impact on medicines prices and consumption in Europe. The underlying basis for this thesis is pricing and reimbursement policy data in European countries, which are analyzed in descriptive as well as through statistical methods by evaluating the impact of these policies on medicine prices and consumption, especially during the economic recession.

In the introduction (**chapter 1**) we explain the pharmaceutical policy framework in which policy makers have to take decisions and give reasons why pharmaceutical policy analysis is constantly needed. Raising pharmaceutical expenditure as well as a changing pharmaceutical environment lead to the need for adjusting and implementing pharmaceutical policies. As policy making is a national competence, the pharmaceutical policy environment in Europe is diverse showing a variety of pricing and reimbursement policy methodologies. Investigating the impact of (differences in) national policies and policy changes is crucial for policy makers to understand whether public affordability and accessibility to medicines is still guaranteed.

Chapter 2 addresses the question as to how national pharmaceutical policies aim at controlling public pharmaceutical spending by regulating medicine prices. In particular, **chapter 2.1** gives a descriptive overview of one of the most commonly used pricing policies in Europe: external price referencing (EPR). EPR is defined as the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country. In this chapter we reviewed the country-specific PPRI (Pharmaceutical Pricing and Reimbursement Information) Pharma Profiles written by representatives of the PPRI Network. The PPRI network is a sustainable, self-funded network for public authorities in pricing and reimbursement in Europe and other countries. The profiles were analyzed according to predefined criteria such as methodological choices in Europe with respect to the national legal framework, the countries included in the reference basket and the method of calculation of the reference price. As expected, many differences were found between countries as the way of implementing EPR is a national competence. We found that of 28 analyzed European countries 24 applied EPR in 2010. Most countries had less than 10 countries in their reference baskets, but this number ranged from one country to 26 countries. Higher income countries tended to include higher income countries in their basket, whereas lower income countries generally referred to lower income regional countries, as there is a relationship between a country's gross domestic product (GDP) per capita rank and the average rank of the reference countries in the basket

(Kendall's rank correlation tau: 0.556263, p=0.0005331). Taking the average price of all countries in the basket as the basis to calculate the national price was the most common strategy (n = 8). The methodology of EPR which impacts price determination has changed in most European countries over the past 10 years (n = 19), showing that EPR is still widely used and a dynamic policy in contrast to what some people belief.

In **chapter 2.2** we assessed whether EPR leads to the desired effect of lower and more stable medicine prices. The study aimed at examining the impact of EPR on on-patent medicine prices, adjusting for other factors that may affect price levels such as sales volume, exchange rates, GDP per capita, total pharmaceutical expenditure (TPE), and size of the pharmaceutical industry in 14 European countries between 2007 and 2008. We received for 14 on-patent products medicine price data (unit ex-factory prices level in €) from the Austrian Health Institute, which we used to calculate scaled ranks per country and per product. We analyzed the relationship between the scaled ranks and several explanatory variables (such as EPR, TPE per capita and GDP per capita) by a linear regression model. The median of the scaled ranks of the countries varied from as low as 0.23 in Italy to 0.83 in Denmark. Two of the countries that did not apply EPR (Germany and Denmark) had the highest scaled ranks. The unadjusted linear regression model confirmed that applying EPR in a country was associated with a lower scaled rank (p=0.002). This association persisted after inclusion of total pharmaceutical expenditure per capita and GDP per capita in the final model. The assessment of the relationship between pharmaceutical employment per 100,000 inhabitants and the scaled ranks per country and product showed a statistically significant correlation (p=0.0063). We therefore concluded that the price level is not only driven by EPR but also by pharmaceutical industry size. Substantial price differences among countries that apply EPR may be explained by different methodologies with respect to the selection of countries in a reference basket or the method for calculating the price.

The aspect of how national policies affect the overall medicine price level in European countries and whether these policies lead to price convergence across Europe is addressed in **chapter 2.3**. Previous reports showed that European Union (EU) price convergence for medicines was more rapid in the second half of the 1990s as a result of the process of EU monetary convergence. Starting from 2000 two clusters of countries were identified: the core EU countries (such as France, Italy, Benelux countries) with a 15% average price gap; and the cluster of newer EU Member States and Spain, Portugal and Greece, which had average prices almost 40% lower than the EU-15 level[1]. However, due to policy changes such as price cuts as a consequence of the economic recession in many countries, the picture of medicine price convergence in Europe may have changed. We received medicine price data from the Austrian Health Institute for ten on-patent medicines in five years (2007-2011) of 15 European countries. The unit of analysis was the ex-factory price in € per defined daily dose (DDD, exchange rate indexed to 2007). We found that the prices between countries and selected products varied to a great extent from as

[1] EU-15 countries = EU Member States as of 1 January 1995: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, United Kingdom.

low as an average price of € 1.3/DDD for sitagliptin in 2010-2012 to an average of € 221.5/DDD for alemtuzumab in 2011. During the study period, a price divergence was seen which was only driven by two countries, Germany (up to 27% more expensive than the average) and Greece (up to 32% cheaper than the average). All other countries had relatively stable prices and centered around the average of the countries included in the study. Prices of less expensive medicines remained relatively stable or decreased over time, while prices of expensive medicines tended to increase. It is therefore crucial for policy makers to keep in mind that the European policy environment is diverse and changing over time, requiring regular monitoring of the effects, and that these policy changes do have an impact on national medicine prices.

Chapter 3 focuses on how countries re-evaluate and adjust national policies in times of economic recession. **Chapter 3.1** analyses which pharmaceutical pricing and reimbursement policies were implemented by countries during the time of the economic recession and evaluates the correlation with medicines sales in eight European countries. Based on a literature review, we described pharmaceutical policy changes and used IMS Health data to analyze quarterly sales of products in the 10 highest-selling therapeutic classes, in IMS standard units (volume) and constant dollars (value). We presented sales growth rates, comparing economically stable versus less stable countries classified based on 2012 fiscal consolidation plans of OECD member countries. Our study showed that economically stable countries (Austria, Estonia, Finland) implemented between two and seven policy changes each, whereas economically less stable countries (Greece, Ireland, Slovak Republic, Spain, Portugal) implemented between 10 and 22 policy changes. Most policy changes occurred in 2010 (n=33/88) and 2011 (n=40/88) and included changes in out-of-pocket payments (n=16/88), changes in price mark-up schemes (n=13/88) and price cuts (n=11/88). All countries showed moderate increases in sales volumes ranging from 1% (Greece and Portugal) to 3% (in Estonia, Ireland and Slovak Republic); while average annual growth rates in sales value varied between -2% in Portugal to 5% in Estonia. However, from 2009 onwards all countries experienced decreases in sales value. The largest declines were observed in Greece (negative year on year growth rate of -14% in 2010) and Portugal (-11% in 2011). We concluded that countries' responses to the recession differed. We observed a higher density of policy changes implemented by less economically stable countries. Unexpectedly almost all countries showed moderate increases in pharmaceutical sales volume despite declines in sales value, especially in the less economically stable countries.

Chapter 3.2 presents a detailed evaluation of the impact of different policy measures on the consumption of antipsychotic medicines in Portugal and Finland during the time of the economic recession. We obtained monthly IMS sales data in standard units of antipsychotic medicines in Portugal and Finland for the period January 2007 to December 2011. We used an interrupted time series design to estimate changes in overall use and generic market shares by comparing pre-policy and post-policy levels and trends. We found that both countries' policy approaches were associated with slight, likely unintended, decreases in overall use of antipsychotic medicines and to increases in generic market share of major antipsychotic products. In Finland quetiapine and risperidone experienced substantially increased generic market shares (estimates one year post-policy compared to before, quetiapine: 6.80% [95% confidence intervals (CI) 3.92%,

9.68%]; risperidone: 11.13% [95% CI 6.79%, 15.48%]. The policy interventions in Portugal resulted in a substantially increased generic market share for amisulpride (estimate one year post-policy compared to before: 22.95% [95% CI 21.01%, 24.90%]; generic risperidone already dominated the market prior to the policy interventions. These findings clearly indicate that the implementation of new policies or the adjustment of existing policies can have positive effects on controlling public spending in a short time period, but sometimes these policy changes may have unintended consequences such as higher out-of-pocket payments for patients which may lead to a decrease in use. Therefore, there is a need to continuously monitor intended and possibly unintended effects of new policies or policy changes.

In Europe, there is an increasing use of personalized medicines which require prior genetic testing to guide their use which entail new challenges to policy makers with respect to pricing and reimbursement. In specific, **chapter 4.1** describes how European pricing and reimbursement authorities deal with the increasing and common challenge of how to evaluate and assess these 'treatment packages' which included both new and often expensive medicines as well as medical devices such as diagnostics. We analysed qualitative descriptive data on national pharmaceutical pricing and funding policies applied to trastuzumab and its accompanying diagnostic test as an example of personalized medicines. Data were obtained from a survey among competent authorities from 27 European countries as of August 2011. Further, we received medicine price data (for the years 2005 to 2013) of trastuzumab in the respective European countries from the Austrian Health Institute. We found that in 2011 testing and treatment mainly took place in hospitals or in specific day-care ambulatory clinics. In the surveyed European countries either both trastuzumab and the accompanying diagnostic test were funded from hospital budgets (n=13) or medicines were funded by third party payers such social insurances and the test was funded from hospital budgets (n=14). Neither combined funding of both the medicine and diagnostic test by third party payers was identified in the surveyed countries nor did the respondents from the competent authorities identify any managed entry agreements. National pricing procedures were different for trastuzumab versus its diagnostic test, as most countries applied price control policies for trastuzumab but had free pricing for the diagnostic test. Since 2005 the average price gradually decreased from € 641 with some increases in specific years (i.e. 2008 and 2012) to € 609 in 2013. We concluded that the example of trastuzumab and its accompanying diagnostic test highlights some problems of the interface between different funding streams (out-patient and hospital) but also with regard to the interface between the medicine applied in combination with a medical device. The move to health technology assessment (HTA) that is occurring in many countries may have addressed some aspects of the problems occurring in this complex area. But other decisions, such as whether these medicines and diagnostics should be paid for from hospital or primary care budgets may have a devastating effect on access.

The concluding **chapter 5** contains a general discussion of the benefits and limitations of research on pharmaceutical pricing and reimbursement policy interventions. In specific, we advocate firstly for an improvement of data availability and transparency with respect to publicly available medicine price and consumption data sources as well as of up-to-date

policy data; secondly for better validity and comparability of data in specific with regard to price levels, the unit of comparison, exchange rates and weighing of prices by volume; and for a transparent access to adequate information on national policies (e.g. with respect to the impact of timing of policy implementation on the study design as well as the collection of data on the policy context) to understand the context in which they are being implemented. Finally, avenues for future research such as exploring assessment methodologies with respect to new technologies such as personalized medicines and patient involvement are identified to eventually improve access to and affordability of medicines. The studies included in this thesis have shown that the current available data on pricing and reimbursement policies and medicine prices and consumption provide ample opportunities for studying cross-national variations in pharmaceutical policies. Analyzing pharmaceutical policy, pricing and consumption data can be used as a "lens" to understand and evaluate broader health policy and systems issues.

CHAPTER 6.2

Samenvatting

SAMENVATTING

Farmaceutisch beleid wordt vormgegeven in een dynamische geneesmiddelenmarkt. Nieuwe geneesmiddelen worden ontwikkeld en verschuivingen in medische noodzaak treden op, terwijl de verschillende belangen van betrokken partijen het beleid beïnvloeden. Met name ten aanzien van prijsstelling en vergoeding van geneesmiddelen treedt spanning op; wat vanuit het oogpunt van de volksgezondheid wordt gezien als noodzakelijk om toegang tot geneesmiddelen te waarborgen, kan door de farmaceutische industrie worden beschouwd als nadelig voor onderzoek, ontwikkeling en innovatie. Publieke budgetten voor de gezondheidszorg – inclusief farmaceutische zorg – zijn beperkt. Daarom moeten beleidsmakers hun beleid continu bijstellen en nieuw beleid ontwikkelen om in te spelen op deze veranderende omgeving. De financiële druk hiertoe is in de afgelopen jaren toegenomen door de economische recessie.

Het doel van dit proefschrift is om op basis van beschikbare gegevens in Europa inzicht te krijgen in het beleid rondom prijsstelling en vergoeding van geneesmiddelen en de invloed van dit beleid op prijzen en consumptie van geneesmiddelen. Deze gegevens zijn zowel op een beschrijvende manier als met behulp van statistische methoden geanalyseerd. De invloed van het beleid is vooral bestudeerd ten tijde van de recente economische recessie.

In de introductie (**hoofdstuk 1**) wordt het kader beschreven waarbinnen beleidsmakers beslissingen moeten nemen en worden redenen aangegeven waarom het nodig is het farmaceutisch beleid continu te analyseren. De toegenomen uitgaven aan geneesmiddelen en de veranderende omgeving vragen om bijstelling en implementatie van farmaceutisch beleid. Omdat beleidsvorming ten aanzien van prijsstelling en vergoeding van geneesmiddelen onder de nationale verantwoordelijkheid van lidstaten valt, is er in Europa een grote verscheidenheid aan beleid en methoden op dit gebied. Onderzoek naar de impact van (verschillen in) nationale beleidsmaatregelen is cruciaal voor beleidsmakers om vast te kunnen stellen of publieke betaalbaarheid van en toegang tot geneesmiddelen voldoende is gewaarborgd.

Hoofdstuk 2 gaat in op de vraag hoe nationale beleidsmaatregelen pogen de publieke uitgaven voor geneesmiddelen te controleren door prijsstelling van geneesmiddelen te reguleren. **Hoofdstuk 2.1** geeft een overzicht van één van de meest toegepaste beleidsinstrumenten op het gebied van prijsvorming in Europa: externe prijsreferentie (EPR). EPR is het gebruik van de prijs van een geneesmiddel in een of meerdere landen om zo een benchmark- of referentieprijs te verkrijgen voor de prijsstelling of prijsonderhandeling in een ander land. Voor dit hoofdstuk zijn zogenaamde landenprofielen, geschreven door vertegenwoordigers van het PPRI ('Pharmaceutical Pricing and Reimbursement Information') netwerk, bestudeerd. Het PPRI netwerk is een zichzelf in stand houdend netwerk van publieke autoriteiten op het gebied van prijsstelling en vergoeding van geneesmiddelen in Europa en enkele andere landen. De profielen zijn onderzocht op gegevens met betrekking tot EPR aan de hand van vooraf vastgestelde criteria, waaronder het wettelijk kader en methodologische keuzes zoals het aantal referentielanden en de wijze waarop de referentieprijs wordt berekend. Zoals verwacht werden vele verschillen tussen Europese landen gevonden, omdat dit beleid

een nationale verantwoordelijkheid is. In 24 van de 28 onderzochte Europese landen was EPR in 2010 ingevoerd als beleidsmaatregel. De meeste landen gebruikten prijzen van minder dan 10 andere landen om de referentieprijs te bepalen, maar dit aantal varieerde van één tot 26 landen. Dat hogere inkomenslanden vooral prijzen van andere hogere inkomenslanden gebruikten en lagere inkomenslanden van andere lagere inkomenslanden, bleek uit de gevonden relatie tussen de plaats van een land op basis van rangschikking van het bruto binnenlands product (BPP) en de gemiddelde plaats van de referentielanden in deze rangschikking (Kendall's rank correlation tau: 0.556263, p=0.0005331). De meeste landen bepaalden de referentieprijs door het gemiddelde van de prijzen in de referentielanden te berekenen (n=8). In de afgelopen 10 jaar is de gebruikte methodologie in 10 landen aangepast wat aangeeft dat EPR een dynamische beleidsmaatregel is, in tegenstelling tot wat sommigen geloven.

In **hoofdstuk 2.2** hebben we bestudeerd of EPR leidt tot het gewenste effect van lagere en stabielere geneesmiddelprijzen. Het onderzoek had tot doel de impact van EPR op de prijzen van gepatenteerde geneesmiddelen te bepalen in 14 Europese landen tussen 2007 en 2008, waarbij er gecorrigeerd werd voor andere factoren die het prijsniveau kunnen bepalen als verkoopvolume, wisselkoersen, BPP per hoofd van de bevolking, totale uitgaven aan farmaceutische zorg en omvang van de farmaceutische industrie. Geneesmiddelprijzen (fabrieksprijzen in € per eenheid) werden van het Oostenrijkse gezondheidsinstituut ('Austrian Health Institute') verkregen voor 14 gepatenteerde geneesmiddelen. Deze prijzen zijn gebruikt om een geschaalde rangorde per land en per product te berekenen. De relatie tussen deze rangorde en mogelijke verklarende variabelen zoals EPR en totale uitgaven aan farmaceutische zorg en BPP per hoofd van de bevolking is onderzocht met behulp van een lineair regressiemodel. De mediaan van de rangorde varieerde van 0.23 voor Italië tot 0.83 voor Denemarken. Twee van de landen zonder EPR (Duitsland en Denemarken) hadden de hoogste plaats in de rangorde. Het ongecorrigeerde lineaire regressiemodel bevestigde dat het toepassen van EPR in een land was geassocieerd met een lagere rangorde (p=0.002). Deze associatie hield stand na correctie voor totale uitgaven aan farmaceutische zorg en BPP per hoofd van de bevolking in het uiteindelijke model. Ook werd een statistisch significante relatie (p=0.0063) gevonden tussen het aantal werknemers in de farmaceutische industrie per 100,000 inwoners en de rangorde per land en per product. Daarom werd er geconcludeerd dat het prijsniveau niet alleen door EPR wordt bepaald, maar ook door de omvang van de farmaceutische industrie in een land. De grote verschillen in prijsniveau tussen landen die EPR hebben ingevoerd wordt mogelijk verklaard door verschillen in methodologie, zoals de selectie van referentielanden en de wijze waarop de referentieprijs wordt berekend.

De vraag hoe nationale beleidsmaatregelen het prijsniveau in Europese landen beïnvloeden en of dit beleid leidt tot prijsconvergentie in Europa wordt beantwoord in **hoofdstuk 2.3**. Eerdere rapporten hebben aangetoond dat prijsconvergentie in de Europese Unie (EU) het snelst optrad in de tweede helft van de jaren negentig als gevolg van het proces van monetaire convergentie. Vanaf 2000 kunnen twee clusters van landen worden onderscheiden: het cluster met de "oude" EU landen (o.a. Frankrijk, Italië en de Benelux) voor wie het verschil in prijs gemiddeld 15% was en het cluster van de nieuwe lidstaten en Spanje, Portugal en Griekenland, voor wie prijzen

bijna 40% lager waren dan het EU-15[1] gemiddelde. Door nieuwe beleidsmaatregelen zoals prijsverlagingen tijdens de economische recessie kan dit beeld echter zijn veranderd. Voor dit onderzoek zijn prijsgegevens ontvangen van het Oostenrijks gezondheidsinstituut van tien gepatenteerde geneesmiddelen voor een periode van vijf jaar (2007-2011) in 15 Europese landen. De in dit onderzoek gebruikte prijs was de fabrieksprijs in € per 'defined daily dose' (DDD), waarbij de wisselkoersen op 2007 waren geïndexeerd. Er werden grote prijsverschillen gevonden tussen landen en producten. De gemiddelde prijs varieerde van €1.3/DDD voor sitagliptine in 2010-2012 tot €221.5/DDD voor alemtuzumab in 2011. De prijsconvergentie die optrad gedurende de onderzoeksperiode werd door slechts twee landen bepaald; Duitsland (meer dan 27% hogere prijzen dan het gemiddelde) en Griekenland (tot 32% goedkoper dan het gemiddelde). De overige landen hadden relatief stabiele geneesmiddelprijzen die rond het gemiddelde prijsniveau lagen. Prijzen van de goedkopere geneesmiddelen bleven relatief stabiel of namen af in de tijd, terwijl prijzen van dure geneesmiddelen omhoog leken te gaan. Dit onderzoek laat zien dat het voor Europese beleidsmakers van groot belang is om zich te realiseren dat de vorming van beleid plaatsvindt in een diverse en dynamische omgeving en dat veranderingen in beleid een effect hebben op nationale prijsstellingen. Dit maakt het monitoren van de effecten van beleidsmaatregelen noodzakelijk.

Hoofdstuk 3 richt zich op de vraag hoe landen hun nationale geneesmiddelenbeleid herevalueren en bijstellen tijdens de economische recessie. **Hoofdstuk 3.1** bestudeert welke beleidsmaatregelen rondom prijsstelling en vergoeding van geneesmiddelen door acht Europese landen zijn geïmplementeerd tijdens de economische recessie en of er een correlatie is met geneesmiddelenconsumptie. Gegevens over de veranderingen in het beleid zijn op basis van literatuuronderzoek verkregen en IMS Health data zijn gebruikt om verkoopcijfers per kwartaal in standaard units (volume) en dollars (uitgaven) van de tien meest verkochte productgroepen (therapeutische klassen) te analyseren. De groeipercentages werden vergeleken tussen economisch stabiele (Estland, Finland en Oostenrijk) en minder stabiele landen (Griekenland, Ierland, Slowakije, Spanje, Portugal), waarbij stabiliteit werd bepaald op basis van de fiscale consolidatieplannen van de OECD lidstaten in 2012. Economisch stabiele landen bleken twee tot zeven veranderingen in het farmaceutisch beleid te hebben doorgevoerd, terwijl de minder stabiele landen elk tussen de 10 en 22 veranderingen doorvoerden. De meeste veranderingen vonden plaats in 2010 (n=33/88) en 2011 (n=40/88) en behelsden veranderingen in de eigen bijdrage (n=16/88), veranderingen in het systeem van 'mark ups' (n=13/88) en prijsverlagingen (n=11/88). In alle landen werden kleine stijgingen in de jaarlijkse verkoopvolumes waargenomen, variërend van 1% in Griekenland en Portugal tot 3% in Estland, Ierland en Slowakije. De jaarlijkse verkoopcijfers in dollars varieerden daarentegen van -2% in Portugal tot +5% in Estland. Vanaf 2009 lieten alle landen echter een daling in uitgaven zien. De grootste dalingen werden waargenomen in Griekenland (negatief groeipercentage van -14% in 2010) en Portugal (-11% in

[1] EU-15 = de 15 EU lidstaten op 1 januari 1995: België, Denemarken, Duitsland, Finland, Frankrijk, Griekenland, Ierland, Italië, Luxemburg, Nederland, Oostenrijk, Portugal, Spanje, Verenigd Koninkrijk, Zweden

2011). Dit onderzoek toonde aan dat landen verschillend reageren op de economische recessie, waarbij economisch minder stabiele landen meer beleidsmaatregelen implementeerden. De lichte stijging van het geneesmiddelengebruik in volume was een onverwachte bevinding, die in vrijwel alle landen werd waargenomen en die plaatsvond ondanks een daling in uitgaven aan geneesmiddelen, vooral in de economisch minder stabiele landen.

Hoofdstuk 3.2 geeft een gedetailleerde analyse weer van de impact van verschillende beleidsmaatregelen op het gebruik van antipsychotica in Portugal en Finland gedurende de economische recessie. Gegevens over het maandelijks gebruik van deze middelen in standaard units werden verkregen van IMS Health voor de periode januari 2007 tot en met december 2011. Een 'interrupted time series' analyse werd uitgevoerd om veranderingen in het niveau van en de trend in gebruik van antipsychotica en veranderingen in het marktaandeel van generieke antipsychotica voor en na de introductie van beleidsmaatregelen te bepalen. Er werd gevonden dat de gekozen beleidsmaatregelen in beide landen leidden tot kleine, vermoedelijk ongewenste, dalingen in het gebruik van antipsychotica en een stijging in het generieke marktaandeel van de meest gebruikte antipsychotica. In Finland werden aanzienlijke stijgingen in het generieke marktaandeel van quetiapine (6.80%, 95% betrouwbaarheidsinterval (BI) 3.92%-9.68%) en risperidon (11.13%, 95% BI 6.79-15.48%) waargenomen als de periode voor de invoering van de beleidsmaatregelen werd vergeleken met het jaar erna. De beleidsmaatregelen in Portugal leidden tot een behoorlijke stijging van het generieke marktaandeel van amisulpride (22.95%, 95% BI 21.01%-24.90%) maar niet van risperidon, omdat voor dat antipsychoticum de generieke versies de markt al domineerden. Deze bevindingen laten zien dat dergelijke maatregelen een positief effect kunnen hebben op de korte termijn uitgaven aan geneesmiddelen, maar dat deze maatregelen tegelijkertijd onbedoelde neveneffecten kunnen hebben zoals hogere eigen bijdragen die tot een daling in het gebruik kunnen leiden. Daarom is het noodzakelijk de bedoelde en onbedoelde effecten van nieuwe of aangepaste beleidsmaatregelen continue te monitoren.

In Europa wordt een toename gezien van de zogenaamde individualisering van geneesmiddelen ('personalised medicine'), waarbij de toepassing van het geneesmiddel wordt bepaald door het (genetische) profiel van de patiënt. Deze 'personalised' geneesmiddelen brengen bijzondere uitdagingen met betrekking tot prijsstelling en vergoeding voor autoriteiten met zich mee. **Hoofdstuk 4.1** beschrijft daarom hoe Europese autoriteiten omgaan met deze uitdagingen en hoe zij de behandelcombinaties van een vaak nieuw en duur geneesmiddel en een medisch hulpmiddel zoals een diagnostische test beoordelen. Hierbij zijn gegevens over de prijsstelling en vergoeding van trastuzumab en het bijbehorende diagnosticum als voorbeeld genomen. Deze gegevens zijn verkregen via een onderzoek onder de bevoegde autoriteiten van 27 Europese landen in augustus 2011. Daarnaast zijn gegevens over de bijbehorende prijsstelling van trastuzumab verkregen via het Oostenrijks gezondheidsinstituut voor de periode 2005-2013. Uit dit onderzoek bleek dat het testen en behandelen van patiënten in 2011 vooral binnen ziekenhuizen en gespecialiseerde dagcentra plaatsvond. In de onderzochte landen werden zowel trastuzumab als het bijbehorende diagnosticum vanuit het ziekenhuisbudget gefinancierd (n=13) of werd het geneesmiddel gefinancierd door een derde partij als de zorgverzekeraar terwijl het diagnosticum werd gefinancierd vanuit

het ziekenhuisbudget (n=14). In geen enkel land werden zowel het geneesmiddel als het diagnosticum door de zorgverzekeraar gefinancierd en ook werden zogenaamde 'managed entry agreements' niet gerapporteerd. De nationale procedures voor prijsstelling verschilden voor trastuzumab en het bijbehorende diagnosticum; de meeste landen kenden mechanismen om de prijs van trastuzumab te reguleren, terwijl voor het diagnosticum een vrije prijsstelling gold. De gemiddelde prijs van trastuzumab was vanaf 2005 geleidelijk gedaald van €641 tot €609 in 2013, waarbij er kleine verhogingen zichtbaar waren in sommige jaren (bijvoorbeeld 2008 en 2012). Dit voorbeeld van trastuzumab en het bijbehorende diagnosticum belicht verscheidene problemen die kunnen optreden bij het vaststellen van de prijs en de vergoeding van een geneesmiddel en een bijbehorend medisch hulpmiddel, maar ook problemen in de 'interface' tussen verschillende geldstromen binnen de gezondheidssector (intramuraal en extramuraal). Het toepassen van 'health technology assessment' (HTA), zoals in een toenemend aantal landen gebeurt, komt tegemoet aan sommige aspecten van de problemen die in dit complexe veld optreden. Maar andere beslissingen, zoals uit welk budget deze geneesmiddelen en bijbehorende diagnostica moeten worden betaald, kunnen mogelijk een vernietigend effect hebben op de toegang tot 'personalised' geneesmiddelen.

Het afsluitende **hoofdstuk 5** bevat een algemene bespreking van de voordelen en beperkingen van onderzoek naar interventies op het gebied van prijsstelling en vergoedingen van geneesmiddelen. We roepen ten eerste op tot een betere (publieke) beschikbaarheid en transparantie van gegevens over prijsstelling en consumptie van geneesmiddelen en up-to-date gegevens ten aanzien van genomen beleidsmaatregelen; ten tweede tot betere validiteit en vergelijkbaarheid van dergelijke gegevens, met name met betrekking tot gebruikte prijsniveaus en eenheden, wisselkoersen en het wegen van prijzen om te corrigeren voor verschillen in verkoopvolumes; en tenslotte tot transparantie van en toegang tot adequate informatie over nationale beleidsmaatregelen (bijvoorbeeld over de exacte timing in verband met het mogelijke effect op de onderzoeksopzet) om zo de nationale context waarbinnen deze maatregelen worden genomen beter te begrijpen. Daarnaast worden mogelijkheden voor toekomstig onderzoek geïdentificeerd, zoals het verkennen van beoordelingsmethoden voor nieuwe technologieën waaronder 'personalised' geneesmiddelen en de rol van patiënten in dit proces, wat uiteindelijk kan leiden tot een betere toegang tot en betaalbaarheid van geneesmiddelen. De onderzoeken in dit proefschrift laten zien dat de momenteel beschikbare gegevens over beleidsmaatregelen ten aanzien van prijsstelling en vergoeding van geneesmiddelen, geneesmiddelprijzen en gebruiksgegevens vele mogelijkheden bieden om variaties in farmaceutisch beleid tussen landen te bestuderen. Het analyseren van dergelijke gegevens kan fungeren als een "venster" om algemene aspecten van beleid en systemen in de gezondheidszorg te kunnen begrijpen en evalueren.

CHAPTER 6.3

Zusammenfassung

ZUSAMMENFASSUNG

Das arzneimittelpolitische Umfeld ist dynamisch: Laufend werden neue Arzneimittel entwickelt, um den Bedarf am medizinischen Fortschritt zu decken, während sich die kontroversiellen Interessen der Akteure auf die Ausgestaltung der Arzneimittelsysteme auswirkt. Spannungen treten vor allem im Bereich Arzneimttelpreisfestsetzung und Erstattung auf: Maßnahmen, welche die öffentliche Verwaltung für grundlegend erachten, um einen gerechten Zugang zu Arzneimitteln zu gewährleisten, mag die pharmazeutische Industrie als negativ für Forschung und Entwicklung sowie für Innovation einschätzten. Aufgrund dieser Dynamik und der Tatsache, dass die öffentlichen Gesundheitsausgaben – inklusive der Arzneimittelausgaben – limitiert sind, müssen Entscheidungsträger ständig Anpassungen und Neueinführungen von politischen Maßnahmen vornehmen. Durch die Finanzkrise, während der letzten fünf Jahre, hat sich dieser finanzielle Druck auf die öffentlichen Budgets sogar noch verstärkt.

Zielsetzung dieser Dissertation ist es arzneimittelpreis- sowie erstattungspolitische Maßnahmen und deren Einfluss auf Arzneimittelpreise und –verbrauch in Europa zu erfassen. Informationen zu Maßnahmen der Arzneimittelpreisbildung und –erstattung, Arzneimittelpreise und -verbrauch in den europäischen Ländern wurden dazu deskriptiv aufbereitet und mittels statistischer Methoden analysiert.

In der Einleitung (**Kapitel 1**) beschreiben wir den arzneimittelpolitischen Rahmen, in welchem Entscheidungsträger agieren, und begründen, warum es einen fortwährenden Bedarf an der Analyse des arzneimittelpolitischen Umfelds gibt. Steigende Arzneimittelausgaben sowie ein sich schnell veränderndes arzneimittelpolitisches Umfeld erfordern neue bzw. geänderte Maßnahmen. Die Ausgestaltung der Arzneimittelsysteme liegt in der Europäischen Union in der Verantwortung der EU-Mitgliedstaaten, und die unterschiedliche Ausgestaltung der Arzneimittelpreisbildungs- und –erstattungssysteme ist eine Folge davon. Die Untersuchung des Einflusses der Einführung und Anpassung von Maßnahmen in diesem Bereich ist von zentraler Bedeutung für Entscheidungsträger/innen, um die öffentliche Finanzierung von und den Zugang zu Arzneimitteln langfristig zu gewährleisten.

Kapitel 2 beschäftigt sich mit der Frage, ob die Regulierung von Arzneimittelpreisen eine Dämpfung der öffentlichen Arzneimittelausgaben bewirken kann. Dazu wird einführend in **Kapitel 2.1** ein deskriptiver Überblick über eine der am häufigsten verwendeten Preisfestsetzungsmaßnahmen in Europa gegeben: der internationale Preisvergleich (in englischer Literatur als external price referencing, EPR bekannt); bei dieser Methodik wird der Preis eines Arzneimittels auf Basis der Preise in anderen Referenzländern festgesetzt. In diesem Kapitel analysierten wir die PPRI-Länderberichte (PPRI = Pharmaceutical Pricing and Reimbursement Information), welche von Vertreter/innen des PPRI-Netzwerkes geschrieben wurden, auf Informationen hinsichtlich des Einsatzes von EPR. Das PPRI-Netzwerk ist ein nachhaltiges, selbstfinanziertes Netzwerk von Behörden, die für die Arzneimittelpreisfestsetzung und -erstattung in Europa zuständig sind. Die PPRI-Länderberichte wurden anhand von definierten Kriterien, wie etwa Informationen über die Vorgangsweise hinsichtlich der nationalen gesetzlichen Rahmenbedingungen, der gewählten Referenzländer und des gewählten Preisfestsetzungsverfahrens analysiert. Wie erwartet, wurden unzählige Unterschiede in der Ausgestaltung und der Umsetzung von EPR in

den Ländern gefunden. Von 24 der 28 untersuchten Länder wenden EPR an (im Jahr 2010). Die meisten Länder hatten weniger als 10 Vergleichsländer, wobei sich hier eine große Bandbreite von einem Land bis zu 26 Länder zeigte. Wir konnten nachweisen, dass einkommensstarke Länder dazu tendierten, andere einkommensstarke Länder in ihrem Referenzländerkorb aufzunehmen, wohingegen einkommensschwache Länder umgekehrt zu einkommensschwachen Länder referenzierten. Dies ist auf den Zusammenhang zwischen Bruttoinlandsprodukt (BIP) pro Kopf und der durchschnittlichen Anzahl der Referenzländer zurückzuführen (Kendall's rank Korrelation tau: 0.556263, p-value = 0.0005331). Am häufigsten (n = 8) wurde der Preis in einem Land als Durchschnitt des Preises in allen Vergleichsländern ermittelt. Die EPR-Methodik, welche sich auf die Arzneimittelpreise in anderen Ländern auswirkt, hat sich in den letzten 10 Jahren kontinuierlich verändert (n = 19). Trotz manch gegenteiliger Meinung bleibt EPR eine stark verbreitete und zugleich sehr dynamische Methodik zur Preisfestsetzung.

In **Kapitel 2.2** untersuchen wir, ob EPR den erwünschten Effekt, niedrigere und stabilere Preise zu erzielen, bewirkt. Ziel der Studie war es, die Auswirkungen von EPR auf die Preise patentgeschützter Arzneimittel unter Berücksichtigung von zusätzlichen Faktoren wie Umsatzvolumen der untersuchten Produkte, Wechselkurs, BIP pro Kopf, Arzneimittelausgaben und Größe der pharmazeutischen Industrie in 14 europäischen Ländern in den Jahren 2007 und 2008 zu analysieren. Wir erhielten dafür Preisdaten von 14 patentgeschützten Arzneimitteln (auf Ebene des Fabrikabgabepreises in €) von dem wissenschaftlichen Institut Gesundheit Österreich GmbH, mit welchen wir eine Skalierung pro Land und pro Produkt errechneten. Wir analysierten die Beziehung zwischen den Skalierungen und den verschiedenen beschriebenen Faktoren mittels eines linearen Regressionsmodells. Der Median der Skalierungen der Länder reichte von 0,23 in Italien bis 0,83 in Dänemark. Zwei der Länder, die nicht EPR anwenden (Deutschland und Dänemark), wiesen den höchsten Wert auf. Dank des linearen Regressionsmodells konnten wir nachweisen, dass EPR zu einem tendenziell niedrigerem Preisniveau ($p = 0.002$) führt. Der statistische Zusammenhang blieb nach Einschluss der variablen Arzneimittelausgaben pro Kopf und BIP pro Kopf bestehen. Die Auswertung im Hinblick auf einen möglichen Zusammenhang zwischen der Anzahl der pharmazeutischen Unternehmen pro 100.000 Einwohner/innen und der Skalierung pro Land und Produkt zeigte eine statistisch signifikante Korrelation ($p = 0.0063$). Daraus folgerten wir, dass das Preisniveau nicht nur von EPR, sondern auch von der Relevanz der pharmazeutischen Industrie in einem Land beeinflusst ist. Die erheblichen Preisunterschiede zwischen den Ländern, welche EPR anwendeten, könnten auf die unterschiedlichen methodischen Ansätze, welche die Länder wählten (z. B. hinsichtlich der Vergleichsländer oder der Berechnung des Preises), zurückzuführen sein.

Der Aspekt, wie nationale politische Maßnahmen das Arzneimittelpreisniveau in den europäischen Ländern beeinflussen und ob sie zu einer Preiskonvergenz in Europa führen, wurde in **Kapitel 2.3** analysiert. Frühere Studien zeigten eine Preiskonvergenz bei Arzneimitteln in Europa in der ersten Hälfte der 1990er-Jahre als Konsequenz der gesamteuropäischen Währungspreiskonvergenz. Seit 2000 verlief die Preiskonvergenz unterschiedlich zwischen der Gruppe der ersten EU-Mitgliedstaaten (wie Frankreich, Italien und die Beneluxländer) mit einer durchschnittlichen Preisschere von 15% und der Gruppe der neueren EU-Mitgliedsländer sowie

Spanien, Portugal und Griechenland, welche einen durchschnittlichen Preis von fast 40% unterhalb des EU-15-Durchschnittspreises[1] aufwiesen. Jedoch das Muster der europäischen Preiskonvergenz könnte sich, aufgrund der durch die Finanzkrise eingeführten Maßnahmen wie Preiskürzungen geändert haben. Um dieser Frage nachzugehen, haben wir Preise von zehn patentgeschützten Arzneimitteln aus 15 Ländern über fünf Jahre hinweg (2007-2011) analysiert. Die Preise erhielten wir vom wissenschaftlichen Institut Gesundheit Österreich GmbH; untersucht wurde der Fabriksabgabepreis in € pro definierter Tagesdosis (in englischer Literatur als defined daily dose, DDD bezeichnet) und einem auf das Jahr 2007 bezogenen Wechselkurs. Der Preis variierte erheblich zwischen den Ländern und den ausgewählten Produkten: vom niedrigsten Durchschnittspreis von € 1,3/DDD für Sitagliptin in 2010-2012 zu einem Höchstdurchschnittspreis von € 221,5/DDD für Alemtuzumab in 2011. Die Preisabweichungen während des Untersuchungszeitraums wurden durch nur zwei Länder – Deutschland mit fast 27% teureren Preisen als der Durchschnitt und Griechenland mit fast 32% niedrigeren Preisen als der Durchschnitt – getrieben. Alle anderen Länder wiesen relativ stabile Preise auf und waren um den Durchschnittswert aller in der Studie aufgenommenen Länder angesiedelt. Preise von preiswerteren Produkten blieben relativ stabil bzw. sanken mit der Zeit, während Preise von hochpreisigen Produkten eher stiegen. Aus diesem Grund ist es für politische Entscheidungsträger/innen sehr wichtig, sich in Erinnerung zu rufen, dass das politische Umfeld sehr divers ist und sich mit der Zeit verändert; dies erfordert eine regelmäßige Überprüfung der Auswirkungen der Maßnahmen, etwa auf die Arzneimittelpreise.

Kapitel 3 beschäftigt sich mit der Frage, wie Länder während der Finanzkrise ihre nationalen Maßnahmen im Bereich Arzneimittelpolitik angepasst haben. **Kapitel 3.1** analysiert, welche Arzneimittelpreisfestsetzungs- und -erstattungsmaßnahmen während der Finanzkrise eingeführt wurden und untersucht deren möglichen Einfluss auf den Arzneimittelverbrauch in acht europäischen Ländern. Die Auflistung der Maßnahmen basierte auf einer Literaturrecherche; den Arzneimittelkonsum analysierten wir mittels IMS Health-Daten über den quartalsweisen Verbrauch aller Produkte in den 10 meistverkauften therapeutischen Klassen (in der IMS-Messgröße „Standards Units" / standardisierte Einheiten, sowohl mengenmäßig als auch wertmäßig in konstant gehaltenen Dollar). Dabei stellten wir die Steigerungsraten der Arzneimittelumsätze in wirtschaftlich stabilen Ländern denen in wirtschaftlich weniger stabilen Ländern gegenüber – die Kategorisierung in diese beiden Gruppen erfolgte auf Basis der OECD-Finanzplanung 2012. Unsere Studie zeigte, dass wirtschaftlich stabile Länder (Estland, Finnland, Österreich) zwischen zwei bis sieben Änderungen der poltischen Maßnahmen vornahmen, während wirtschaftlich weniger stabile Länder (Griechenland, Irland, Slowakei, Spanien und Portugal) weitaus mehr, zwischen 10 und 22 Maßnahmen, einführten. Die meisten Maßnahmen wurden 2010 (n = 33/88) und 2011 (n = 40/88) gesetzt und inkludierten Änderungen bei den Zuzahlungen (n = 16/88), Änderungen der Abgeltung der Vertriebsakteure (n = 13/88) und Preiskürzungen (n = 11/88). Alle Länder wiesen einen moderaten Anstieg des Arzneimittelumsatzes in der Bandbreite von 1% (Griechenland und Portugal) bis 3% (Estland, Irland und Slowakei) auf, während die jährliche durchschnittliche Wachstumsrate zwischen -2% in Portugal

1 EU-15 Länder = EU Mitgliedschaft seit 1. Jänner 1995: Belgien, Dänemark, Deutschland, Finnland, Frankreich, Griechenland, Großbritannien, Irland, Italien, Luxemburg, Niederlande, Portugal, Spanien, Schweden, Österreich.

und 5% in Estland schwankte. Seit 2009 erfahren allerdings alle Länder Rückgänge des wertmäßigen Absatzes. Die größten Rückgänge wurden in Griechenland (eine negative jährliche Wachstumsrate von 14% in 2010) und Portugal (-11% in 2011) beobachtet. Die Länder reagierten somit – so schließen wir – unterschiedlich auf die Finanzkrise. Tendenziell mehr Maßnahmen wurden von wirtschaftlich weniger stabilen Ländern eingeführt. Unerwartet war jedoch, dass fast alle Länder einen moderaten Anstieg des mengenmäßigen Arzneimittelumsatzes aufwiesen, während der wertmäßige Absatz sank (v. a. in den wirtschaftlich weniger stabilen Ländern).

Kapitel 3.2 stellt eine detaillierte Analyse der Auswirkungen der unterschiedlichen im Rahmen der Finanzkrise eingeführten Maßnahmen auf den Verbrauch von Antipsychotika in Portugal und Finnland dar. Wir erhielten von IMS-Health monatliche Umsatzdaten in „standardisierten Einheiten" (wiederum die von IMS-Health verwendete Maßeinheit der „Standard Units") von Antipsychotika in Portugal und Finnland in der Zeit von Jänner 2007 bis Dezember 2011. Wir wendeten ein statistisches Zeitfolgenmodell an, um mögliche Änderungen beim mengenmäßigen Gesamtverbrauch und den Generikaanteilen zu analysieren und insbesondere die Entwicklung vor und nach der Einführung von Maßnahmen zu vergleichen. Die Ergebnisse zeigten, dass die Herangehensweisen beider Länder zu einem geringen, wenngleich unerwarteten Rückgang des Gesamtverbrauchs von Antipsychotika sowie einem Anstieg des Generikaanteils führten. In Finnland stiegen die Generikaanteile der Wirkstoffe Quetiapine und Risperidone (Schätzungen vom im Jahr vor der Einführung der Maßnahme verglichen mit einem Jahr danach: Quetiapine: 6,80% [95% Konfidenzintervall (KI) 3,92%, 9,68%]; Risperidone: 11,13% [95% KI 6,79%, 15,48%]). Die Interventionen in Portugal führten zu einem erheblichen Anstieg des Generikaanteiles von Amisulpride (Schätzungen vom im Jahr vor der Einführung der Maßnahme verglichen mit einem Jahr danach: 22,95% [95% KI 21,01%, 24,90%]); das Generikum von Risperidone hat bereits vor der Intervention den Markt dominiert. Diese Ergebnisse zeigten deutlich, dass die Einführung bzw. Anpassung von politischen Maßnahmen einen kurzfristig positiven Einfluss auf Kostendämpfung haben kann, jedoch diese manchmal zu unerwarteten und möglicherweise unerwünschten Auswirkungen, wie höheren Zuzahlungen für Patienten/Patientinnen führen kann, welche sich wiederum in einem sinkenden Verbrauch auswirkten können. Aus diesem Grund besteht ein kontinuierlicher Bedarf an regelmäßigen Überprüfungen der erwünschten sowie der unerwünschten Konsequenzen der eingeführten politischen Maßnahmen.

In den letzten Jahren verzeichnet Europa eine steigende Nutzung von personalisierten Arzneimitteln, welche einen genetischen Test zur Entscheidung über die Therapie als Voraussetzung vorsehen. Dies bringt neue Herausforderungen im Hinblick auf Arzneimittelpreisfestsetzung und -erstattung für Entscheidungsträger/innen. **Kapitel 4.1** widmet sich daher insbesondere der Frage, wie Behörden in europäischen Ländern mit der oft schwierigen Evaluierung und Bewertung des „Behandlungspakets" der personalisierten Arzneimittel, welches häufig hochpreisige und neue Arzneimittel sowie Medizinprodukte umfassen, umgehen. Dazu zeigten wir für Trastuzumab und die dabei eingesetzten diagnostischen Tests als ein Beispiel für personalisierte Medizin auf, welche Strategien zur Arzneimittelpreisfestsetzung und Erstattung in den europäischen Ländern eingesetzt werden. Daten wurden einer Umfrage bei den zuständigen Behörden in allen damals 27 EU-Mitgliedstaaten vom August 2011 entnommen. Zusätzlich erhielten wir Preisdaten (von den Jahren 2005-2013) von Trastuzumab in den jeweiligen Ländern vom wissenschaftlichen

Institut Gesundheit Österreich GmbH. Die Ergebnisse zeigten, dass im Jahr 2011 sowohl der Test als auch die Therapie hauptsächlich im Spital bzw. in Tagesklinken verabreicht wurden. In den untersuchten europäischen Ländern wurden entweder sowohl Test als auch Medikament aus dem Krankenhausbudget finanziert (n = 13), oder die Kosten für das Medikament wurden von den öffentlichen Zahlern (entweder Sozialversicherung oder nationaler Gesundheitsdienst) und die Kosen für den Test aus dem Krankenhausbudget (n = 14) getragen. Eine gemeinsame Finanzierung für Medikament und Test seitens der öffentlichen Hand ist aus keinem der untersuchten Länder bekannt; ebenso wenig neue Finanzierungsmodelle wie „Managed Entry Agreements". Ein weiteres Ergebnis der Studie war, dass für das Medikament eine unterschiedliche Preisregulierung als für den Test zum Einsatz kam: so setzten die meisten Länder Preiskontrollmaßnahmen für Trastuzumab, erlaubten jedoch freie Preisbildung für den Test (d. h. die Unternehmen konnten den Preis selbst festlegen). Seit 2005 sank der durchschnittliche Preis von Trastuzumab in den meisten untersuchten Ländern, wenngleich es in wenigen Jahren (2008 und 2012) Preiserhöhungen gab. Im Schnitt sank er von € 641 im Jahr 2005 auf € 609 in 2013. Die Ergebnisse dieser beispielhaft für Trastuzumab und seinem diagnostischen Test durchgeführten Studie zeigten erhebliche Schwierigkeiten der Finanzierung an der Nahtstelle niedergelassener Sektor und Spitalsbereich sowie auch zwischen Arzneimittel und Medizinprodukt auf. Eine verstärkte Bewertung von Gesundheitsleistungen (in englischer Literatur als Health Technology Assessment, HTA bezeichnet) kann einen Beitrag leisten, um diese Herausforderungen anzugehen. Dennoch bleibt die Gefahr bestehen, dass bestimmte Finanzierungsmodelle (z. B. eine ausschließliche Finanzierung von Arzneimittel und diagnostischer Tests aus dem Krankenhausbudget oder seitens der Zahler für den niedergelassenen Bereich) sich negativ auf den Zugang zu diesem personalisierten Arzneimittel auswirken könnte.

Das **Schlusskapitel 5** beinhaltet eine Diskussion der Vor- und Nachteile der Erforschung von arzneimittelpolitischen Trends. Wir empfehlen einerseits die eingeschränkte Datenverfügbarkeit und die damit verbundene geringe Transparenz von Arzneimittelpreisen, Verbauchsdaten und aktuellen Informationen über die Politikmaßnahmen zu verbessern. Des weiteren sehen wir die Notwendigkeit für eine bessere Datenvalidität und der damit verbundenen Datenvergleichbarkeit v. a. im Hinblick auf Arzneimittelstufen, vergleichbarer Maßgrößen, der Wechselkursproblematik und einer möglichen mengenmäßigen Gewichtung von Preisen. Darüber hinaus setzen wir für eine Verbesserung des Zugangs zu entsprechenden Länderinformationen über Politikmaßnahmen (z. B. um die zeitliche Dimension sowie den politischen Rahmen bei der Einführung einer Maßnahme beim Studiendesign bestmöglich zu berücksichtigen) ein. Schlussendlich skizzierten wir mögliche zukünftige Forschungsgebiete, wie zum Beispiel einerseits die Erforschung neuer Bewertungsmethoden im Hinblick auf personalisierte Medizin und andererseits eine aktivere Beteiligung von Patienten/Patientinnen, um damit den Zugang und die Leistbarkeit von Arzneimitteln zu verbessern. Die Studien dieser Dissertation zeigen, dass die derzeitig verfügbaren Daten über Arzneimittelpreisfestsetzungs- und Erstattungsmaßnahmen sowie über Arzneimittelpreise und –verbrauch eine Vielzahl an Möglichkeiten für länderübergreifende Analysen bieten. Desweiteren kann die Erforschung von arzneimittelpolitischen Maßnahmen, Arzneimittepreisen sowie Verbrauch auch dazu dienen, um das Gesundheitssystem im Allgemeinen besser zu verstehen und zu evaluieren.

CHAPTER 7

Addendum

CHAPTER 7.1

Acknowledgements

ACKNOWLEDGEMENTS

I would like to express my sincere thanks to Bert Leufkens (Utrecht University), Richard Laing (WHO) and Aukje Mantel-Teeuwisse (Utrecht University) for their guidance and support throughout the PhD program. It was Richard's enthusiasm for pharmaceutical policy analysis that inspired me to start with my professional PhD and Bert's inspiration "to think out of the box" while writing my PhD thesis as well as Aukje's faith in me and my work and her positive motivation, which gave me the courage to finalize this achievement. I therefore feel honored that I had the privilege of working with and learning from you.

Further, I am deeply thankful for the support of Sabine Vogler (Gesundheit Österreich GmbH). Learning from her as a co-worker and throughout the PhD program as well as her dedication of leading the Pharmaceutical Pricing and Reimbursement Information (PPRI) network has been an inspiration to me.

I am deeply grateful to Kees de Joncheere (WHO) for his encouragement and guidance throughout the PhD program as well as for his valuable contributions to the research papers.

I would also like to express my thanks to Claudia Habl (Gesundheit Österreich GmbH). Her critical mind and her enthusiasm for policy analysis have shaped this work. In her position as head of the Department of Health Economics she also supported me by enabling a flexible and supportive work environment.

Another major inspiration of my work was the professional discussions I had with the members of the Pharmaceutical Pricing and Reimbursement Information (PPRI) network. The PPRI network meetings with the opportunity to present my work were of great value. I would therefore like to express my sincere thanks to all members of the PPRI network.

During my PhD program I had the extraordinary opportunity to complete an academic fellowship at Harvard Medical School with Anita Wagner and Dennis Ross-Degnan. Their professional mentorship has inspired me deeply and will shape my future career.

I am grateful for all the contributions of my collaborators and co-authors to the body of this work. In particular, I would like to thank the IMS Health Institute for providing me with pharmaceutical sales data as well as for giving me the opportunity to complete an academic fellowship at the IMS Institute for Healthcare Informatics.

Finally, I want to express my deep gratitude to my family and friends for sharing the joy of my achievements as well as the unavoidable problems and frustrations of this professional and personal journey. In particular, I would like to thank my father for his continuous support and strength.

CHAPTER 7.2

List of co-authors

AFFILIATIONS DURING THE CONDUCTANCE OF THE RESEARCH

Kees de Joncheere
Department of Essential Medicines and Pharmaceutical Policies, World Health Organization, Geneva, Switzerland (since May 2012)
Regional Office for Europe, World Health Organization, Copenhagen, Denmark

Jaime Espin
Andalusian School of Public Health / Escuela Andaluza de Salud Pública, Granada, Spain

Claudia Habl
Department of Health Economics, Gesundheit Österreich GmbH / Austrian Health Institute, Vienna, Austria

Richard O. Laing
Department of Essential Medicines and Pharmaceutical Policies, World Health Organization, Geneva, Switzerland

Bert G.M. Leufkens
Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands

Aukje K. Mantel-Teeuwisse
Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands

Dennis Ross-Degnan
Department of Population Medicine, Harvard Medicine School and Harvard Pilgrim Health Care Institute, Boston, USA

Leonhard Seyfang
Department of Health Economics, Gesundheit Österreich GmbH / Austrian Health Institute, Vienna, Austria

Silvia Valkova
IMS Institute for Healthcare Informatics, Pennsylvania, USA

Sabine Vogler
Department of Health Economics, Gesundheit Österreich GmbH / Austrian Health Institute, Vienna, Austria

Anita K. Wagner
Department of Population Medicine, Harvard Medicine School and Harvard Pilgrim Health Care Institute, Boston, USA

Fang Zhang
Department of Population Medicine, Harvard Medicine School and Harvard Pilgrim Health Care Institute, Boston, USA

CHAPTER 7.3

List of publications

SCIENTIFIC PUBLICATIONS INCLUDED IN THIS THESIS

Leopold C, Vogler S, Mantel-Teeuwisse AK, de Joncheere K, Leufkens HG, Laing R. Differences in external price referencing in Europe: a descriptive overview. Health Policy. 2012;104(1):50-60. DOI: 10.1016/j.healthpol.2011.09.008.

Leopold C, Mantel-Teeuwisse AK, Seyfang L, Vogler S, de Joncheere K, Laing RO, Leufkens HG. Impact of external price referencing on medicine prices – a price comparison among 14 European countries. South Med Rev. 2012;5(2):34-41.

Leopold C, Mantel-Teeuwisse AK, Vogler S, de Joncheere K, Leufkens HGM, Laing RO. Is Europe heading to a common price level for on-patent medicines? A price comparison among 15 Western European countries. Health Policy. 2013;112(3): 209-216 http://dx.doi.org/10.1016/j.healthpol.2013.08.012.

Leopold C, Vogler S, Habl C, Mantel-Teeuwisse AK, Espin J. Personalized medicine as a challenge for public pricing and reimbursement authorities – a survey among 27 European countries (including Iceland and Norway) on the example of trastuzumab. Health Policy 2013 Oct 25. DOI:10.1016/j.healthpol.2013.09.018. [Epub ahead of print].

Leopold C, Mantel-Teeuwisse AK, Vogler S, Valkova S, de Joncheere, Wagner AK, Ross-Degnan D, Laing RO. Impact of pharmaceutical policy measures implemented in respond to the 2008 recession on medicine consumption in Europe. Submitted for publication.

Leopold S, Zhang F, Mantel-Teeuwisse AK, Vogler S, Valkova S, Ross-Degnan D, Wagner AK. Impact of pharmaceutical policy interventions on sales of antipsychotic medicines in Finland and Portugal: interrupted time series analyses. Submitted for publication.

SCIENTIFIC PUBLICATIONS NOT INCLUDED IN THIS THESIS

Leopold C, Vogler S, Piesnegger J, Bucsics A. Aktuelle Heilmittelausgaben und arzneimittelpolitische Trends in Europa. Soziale Sicherheit. 2013;9:414-429.

Vogler S, Zimmermann N, Leopold C, Habl C, Mazag J. Discounts and Rebates Granted for Medicines for Hospital Use in Five European Countries. The Open Pharmacoeconomics & Health Economics Journal. 2013;5:1-10.

Vogler S, Zimmermann N, Leopold C, de Joncheere K. Pharmaceutical policies in European countries in response to the global financial crisis. South Med Rev. 2011;4(2):22-32.

Leopold C, Vogler S, Habl C. Was macht ein erfolgreiches Referenzpreissystem aus – Erfahrungen aus internationaler Sicht. Soziale Sicherheit. 2008;11:614-23.

Vogler S, Habl C, Leopold C. Arzneimittel – wer zahlt? Erstattung und Selbstbeteiligung in der erweiterten EU. Soziale Sicherheit. 2006;9:411-8.

Vogler S, Leopold C, Zuidberg C, Habl C. Medicines discharged in household garbage. Analysis of a pharmaceutical waste sample in the city of Vienna. Submitted for publication.

Vogler S, Leopold C, Zimmermann N, Habl C, de Joncheere K. The Pharmaceutical Pricing and Reimbursement Information (PPRI) initiative – experiences from engaging with pharmaceutical policy makers. Submitted for publication.

CHAPTER 7.4

About the author

ABOUT THE AUTHOR

Christine Leopold obtained a master degree in International Business Relations from the Austrian University of Applied Science in 2002. She then specialized in health care by completing a postgraduate master degree in International Health Care Management, Economics and Policy from Bocconi University in Milan, Italy, in 2004. Since 2005 she works for the Austrian Health Institute, Department of Health Economics. Her work focuses on pharmaceutical system analysis at national, European and international level. She is a leading member of the European Pharmaceutical Pricing and Reimbursement Information (PPRI) network and she co-leads the WHO Collaborating Centre for Pharmaceutical Policy Analysis at the Austrian Health Institute. Further, she is the co-leader of the National Centre for Rare Diseases at the Austrian Health Institute, which is in charge of developing a national action plan for rare diseases in Austria.

In September 2009 Christine started her professional PhD under the umbrella of the Utrecht World Health Organization (WHO) Collaborating Centre for Pharmaceutical Policy and Regulation, which is based at the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, the Netherlands. In 2012 she had the opportunity to take sabbatical leave from her position at the Austrian Health Institute to further enhance on her PhD. For this reason she completed an academic fellowship in Global Health Research at the IMS Institute for Healthcare Informatics in Pennsylvania (July – August 2012) as well as a Harvard Medical School Fellowship in Pharmaceutical Policy Research at the Department of Population Medicine in Boston (September – November 2012).

Upon graduation of her PhD thesis in January 2014, she will continue her academic interest in pharmaceutical policy analysis by working as a post-doctoral Pharmaceutical Policy Research fellow at Harvard Medical School in the Department of Population Medicine in Boston. The planned project will focus on assessing the processes and impacts of regional strategies to facilitate Health Technology Assessments (HTA) of innovative, expensive medicines in Latin American countries.