Study on enhanced cross-country coordination in the area of pharmaceutical product pricing

Final Report

DISCLAIMER

This document does not represent the position of the European Commission and does not represent European Commission's recommendations. The interpretations and opinions contained in it are solely those of the authors.

Contract number: 2014 73 03 for the implementation of Framework Contract
№ EAHC/2013/Health/01 'Health economic reports – analysis and forecasting' (Lot 2)

Funded by the Health Programme of the European Union

Written by Gesundheit Österreich
Forschung- und Planungs GmbH
December – 2015

EUROPEAN COMMISSION

Directorate-General for Health and Food Safety
Directorate B — Health systems, medical products and innovation
Unit B1: Performance of national health systems

Email: SANTE-ACCESS-TO-MEDICINES@ec.europa.eu

European Commission
B-1049 Brussels

EUROPEAN COMMISSION

Study on enhanced cross-country coordination in the area of pharmaceutical product pricing

Final Report

Directorate-General for Health and Food Safety
Health systems, medical products and innovation

2015

EW-01-15-894-EN-N

Europe Direct is a service to help you find answers to your questions about the European Union.

Freephone number (*)**:**

00 800 6 7 8 9 10 11

(*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

Disclaimer

Luxembourg: Publications Office of the European Union, 2015

ISBN 978-92-79-53462-1
doi: 10.2875/631265

For questions about the report, please contact Dr Sabine Vogler (email: sabine.vogler@goeg.at).

Authors

Sabine Vogler (GÖ FP)
Lena Lepuschütz (GÖ FP)
Peter Schneider (GÖ FP)
Verena Stühlinger (UMIT)

Supported by

Christina Oedl (GÖ FP)
Nina Zimmermann (GÖ FP)

Copy-editing

Geoffroy Fisher (SOGETI)
Jelle Bosch (SOGETI)

Project assistant

Brigitte Marsteurer (GÖ FP)

Table of contents

List of tables

List of figures

List of abbreviations

AAI	Accelerated Access Initiative
AESGP	Association Européenne des Spécialités Pharmaceutiques Grand Public / Association of the European Self-Medication Industry
AIC	Akaike information criterion
AIFA	Agenzia Italiana del Farmaco / Italian Medicine Agency
AIM	Association Internationale de la Mutualité / International Association of Mutual Benefit Societies
ANS	Air Navigation Services
ANSP	Air Navigation Services Provider
ARV	Anti-retroviral(s)
ASAQ	Adapted Simple Accessible Quality
ASMR	Amélioration du service médical rendu / added therapeutic value (France)
ATM	Air Traffic Management
BEUC	Bureau Européen des Unions de Consommateurs / European Consumer Organisation
CAP	Common Agricultural Policy
CAPR	Competent Authorities for Pharmaceutical Pricing and Reimbursement
CDM	Clean Development Mechanism
CEPS	Comité Economique des Produits de Santé / Economic Committee for Health Care Products (France)
Chafea	Consumers, Health, Agriculture and Food Executive Agency
CPME	Comité permanent des médicins européens / Standing Committee of European Doctors
DDD	Daily Defined Dose
DES	Discrete-event simulation
DNDi	Drugs for neglected diseases initiative
DP	Differential pricing
EAHC	Executive Agency for Health and Consumers
EAHP	European Association of Hospital Pharmacists
EASA	European Aviation Safety Agency
EASP	Escuela Andalucia de Salúd Pública / Andalusian School of Public Health
EATMN	European Air Traffic Management Network
EB	Executive Board
EC	European Commission
ECJ	European Court of Justice
EEA	European Economic Area

EFPIA	European Federation of Pharmaceutical Industries and Associations
EFTA	European Free Trade Association
EGA	European Generic and Biosimilar Medicines Association
EMA	European Medicines Agency
EMBASE	Excerpta Medica Database
EMINet	European Medicines Information Network
EPF	European Patient Forum
EPHA	European Public Health Alliance
EPR	External price referencing
ERU	Emission Reduction Units
ESIP	European Social Insurance Platform
ETG	Emission Trading Group
EU	European Union
EU ETS	EU Emission Trading System
EUROPABIO	European Association for Bioindustries
FAB	Functional Airspace Block
FDC	Fixed-Dose Combination
G-BA	Gemeinsamer Bundesausschuss / Federal Joint Committee (Germany)
GA	General Assembly
GAVI	Global Alliance for Vaccination and Immunisation
GDP	Gross Domestic Product
GMP	Good Manufacturing Practice
GNI	Gross National Income
GÖ FP	Gesundheit Österreich Forschungs- und Planungs GmbH (subsidiary of GÖG to serve public clients)
GÖG	Gesundheit Österreich GmbH / Austrian Public Health Institute
HAI	Health Action International
HAS	Haute Autorité de Santé / High Authority for Health (France)
HIV	Human immunodeficiency virus
HTA	Health Technology Assessment
HSE	Health Service Executive (Ireland)
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheits-wesen / Institute for Quality and Efficiency in Health Care
JI	Joint Implementation
JPA	Joint Procurement Agreement
JPASC	Joint Procurement Agreement Steering Committee
LDC	Least-developed country/ies

Lif	Lægemiddelindustriforeningen / Danish Association of the Pharmaceutical Industry
LMIC	Low- and middle- income country/ies
LSE	London School of Economics
MAH	Marketing Authorisation Holder(s)
MCDA	Multi-Criteria Decision Analysis
MEA	Managed-entry agreement(s)
Medev	Medicine Evaluation Committee
MoCA	Mechanism of Coordinated Access to Orphan Medicinal Products
MS	Member State(s)
MSF	Médecins sans frontières
NAP	National Allocation Plan
NGO	Non-Governmental Organisation
NM	Network Manager
NSA	National Supervisory Authority
OECD	Organization for Economic Co-operation and Development
OEP	Országos Egészségbiztosítási Pénztár / National Health Insurance Fund (Hungary)
OLS	Ordinary least squares
OMC	Open Method of Coordination
OTC	Over-the-Counter medicine(s)
PAHO	Pan-American Health Association
PFC	Perflourocarbons
PGEU	Pharmaceutical Group of the European Union
PHIS	Pharmaceutical Health Information System
POM	Prescription-only medicine(s)
PPI	Pharma Price Information (medicine price service of the Austrian Public Health Institute)
PPP	Purchasing power parity/ies
PPRI	Pharmaceutical Pricing and Reimbursement Information
PPRS	Pharmaceutical Pricing Regulation Scheme (UK)
PRB	Performance Review Body
QALY	Quality adjusted life years
QoL	Quality of life
R&D	Research and Development
SBC	Schwarz-Bayesian Criterion
SES	Single European Sky
SESAR	Single European Sky Air Traffic Management Research
SMR	Service médical rendu / therapeutic value (France)

SNF	Samfunns- og næringslivsforskning / Institute for Research in Economics and Business Administration (Norway)
SPPSC	Specific Procurement Procedure Steering Committee(s)
STAMP	Safe and Timely Access to Medicines for Patients
SÚKL	Státní ústav pro kontrolu léčiv / State Institute for Drug Control (Czech Republic)
SWOT	Strengths, weaknesses, opportunities and threats
TB	Tuberculosis
TEU	Treaty on the European Union
TFEU	Treaty on the Functioning of the European Union
TLV	Tandvårds- och läkemedelsförmånsverket / Dental and Pharmaceutical Benefits Agency (Sweden)
TPE	Total pharmaceutical expenditure
TRIPS	Trade Related Aspects of Intellectual Property Rights
TVF	Transparent Value Framework
UMIT	University for Health Sciences, Medical Informatics and Technology (Austria)
UN	United Nations
UNFPA	United Nations Population Fund
UNICEF	United Nations International Children's Emergency Fund
VAT	Value added tax
VBP	Value based pricing
VPAAG	Vaccine Presentation and Packaging Advisory Group
WG	Working Group
WHO	World Health Organization
WTO	World Trade Organization

List of country abbreviations

AT	Austria
BE	Belgium
BG	Bulgaria
CH	Switzerland
CY	Cyprus
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
EL	Greece
ES	Spain
FI	Finland
FR	France
HR	Croatia
HU	Hungary
IE	Ireland
IS	Iceland
IT	Italy
LT	Lithuania
LU	Luxembourg
LV	Latvia
MT	Malta
NL	The Netherlands
NO	Norway
PL	Poland
PT	Portugal
RO	Romania
SE	Sweden
SI	Slovenia
SK	Slovak Republic
TR	Turkey
UK	United Kingdom
USA	United States of America

Acknowledgements

We would like to express our sincere gratitude to several people who contributed to this study by providing inputs on their country, sharing experience on pricing policy practice and offering comments on draft versions of this study.

First, we would like to thank staff from competent authorities for pharmaceutical pricing and reimbursement who provided and validated information on their country's EPR system by responding to the country survey (see list in Annex 4).

Further, we would like to acknowledge all experts who were generously available to provide their expertise on differential pricing during expert interviews, as listed in Annex 7 of this report. Moreover, we would like to thank the EURIPID team for providing valuable information.

This report has been subject to and benefitted from an extensive stakeholder review and peer review process. We thank all stakeholders for their excellent inputs; stakeholder institutions are acknowledged in Annex 15. In addition, our sincere thanks go to Zaheer-Ud-Din Babar (University of Auckland, New Zealand), Reinhard Busse and Dimitra Panteli (University of Technology Berlin, Germany), Elizabeth Docteur (Elizabeth Docteur Consulting, USA), Dermot Glynn (Europe Economics, UK), Jaime Espin (Andalusian School of Public Health, Spain), Aidan Hollis (University of Calgary, Canada), Margaret Kyle (Toulouse School of Economics, France), Steve Morgan (University of British Colombia, Canada) and Joan Rovira (University of Barcelona, Spain) who provided valuable peer reviews and suggestions on how to strengthen the study.

Last but not least, we are grateful to the European Commission for commissioning this report. We particularly thank Dirk van den Steen, Corina Vasilescu and Dimitrios Florinis for their guidance and detailed comments during the course of the project.

Executive Summary

European patients and citizens need access to safe, effective and affordable medicines while the health care system should be financially sustainable, and innovation should be encouraged. This is perhaps the key challenge for the national competent authorities and public payers as pharmaceutical pricing and reimbursement remains the competence of EU Member States. In the light of increasing financial pressure while further new high-priced medicines are expected to come to the market, new approaches to achieve the above-mentioned objectives might be required. Without disregarding the subsidiarity principle, possible benefits of cooperative approaches should be studied and discussed.

In this context, a consortium of Gesundheit Österreich Forschungs- und Planungs GmbH, SOGETI Luxembourg S.A. and the University for Health Sciences, Medical Informatics and Technology was commissioned by the European Commission (DG SANTÉ / Chafea) to explore the pharmaceutical pricing policies of external price referencing (EPR) and differential pricing (DP) with regard to their ability to achieve two of the three above-mentioned policy objectives: to improve patients' access to medicines and to generate savings for public payers.

In particular, this 'study on enhanced cross-country coordination in the area of pharmaceutical product pricing' aimed to survey existing EPR schemes in European countries and to develop possible improvements to the current EPR practice, as well as to analyse how DP schemes could possibly be designed for European countries, including addressing identified constraints to DP in Europe. Furthermore, it should be explored how EU-level coordination mechanisms could support the improvement of EPR systems and the establishment of a DP scheme.

To achieve these research objectives, the authors relied upon a range of methods including a literature review, a survey of competent authorities for pharmaceutical pricing, interviews with procurement experts, price simulations, a legal analysis, research of cooperation models and SWOT (strengths, weaknesses, opportunities, and threats) analyses. Extensive reviews involving the services of the EC, stakeholders and academics ('peers') were performed to ensure the high quality of the report.

External price referencing for medicines – Use and impact

External price referencing (EPR), also known under different names such as external reference pricing or international price comparison / benchmarking, 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 a medicine in a given country.

EPR is the most commonly applied pricing policy in European countries. As of 2015, apart from Germany, Sweden and the UK, all other EU Member States, as well as Iceland, Norway, Switzerland and Turkey, set the prices of (some of) their medicines based on price comparisons with other countries. In Germany, though the law provides for prices in other countries to be considered as an additional piece of information in pricing of new medicines, it is claimed that EPR is not applied in the follow-up procedure. In Denmark, EPR is only applied as a supportive pricing policy in the hospital sector. According to a survey undertaken in April/May 2015, 20 of the 29 countries that apply EPR use this policy as sole or main pricing policy. Typically, EPR is limited to specific medicines, such as originator, prescription-only or new medicines. The number of reference countries included in the basket varies between one country (Luxembourg) and 30 countries (Hungary and Poland). Countries most frequently referenced to are

France, Belgium, Denmark and Spain followed by Italy, the UK and by, to a lesser extent, Austria, Germany and Slovakia. Major criteria defining the composition of country baskets are geographic neighbourhood or a comparable economic situation in the reference countries.

The methodological specifications of how an EPR scheme is designed differ between the mentioned countries. For instance, 21 countries do the comparisons of medicine prices at the level of ex-factory prices, and eight countries at pharmacy purchasing price (wholesale price) level. The EPR applying countries refer to the officially published list prices, thus taking neither statutory nor negotiated discounts into account. Germany, though not applying EPR, specified in its law that discounted prices are to be reported by the manufacturers. The most commonly applied method to calculate a reference price is an average, or some kind of modified average, of the prices in the reference countries. The price data required for EPR are provided by the marketing authorisation holder in 23 countries, and 26 countries validate the price information provided. Though price monitoring is provided for in the legislation of 25 countries, it is actually done on a regular basis solely in 17 countries. These regular intervals vary between countries and range from three months to five years.

A literature review conducted as part of the study suggests that EPR has proven to be effective in generating, sometimes substantial, savings for public payers. The extent of savings has considerably depended on the methodology applied. There are lost opportunities due to discounts, rebates and similar arrangements in the reference countries that are not considered in EPR. As illustrated by simulations done by the authors of this study, it may be possible to achieve major impacts on price reductions by referencing to discounted prices and by performing regular EPR reviews. With regards to patient access, EPR is likely to have a negative impact since it incentivises the pharmaceutical industry to first launch in higher-priced countries and delay, and refrain from entering the market in lower-priced countries, and may also inhibit them from offering medicines at lower prices in lower-priced countries.

External price referencing – Options for improvement and cooperation mechanisms

EPR is a pricing policy that considers the prices in other countries, but it is not a cooperation tool per se. However, both changes in the methodology undertaken unilaterally by countries as well as cooperative approaches between Member States can help improve the performance of EPR which is a resource- and time-consuming activity, and thus possibly positively impact the outlined policy objectives. The report discusses four options for improvement: 1) a central price database, 2) the consideration of discounts, 3) regular price monitoring, and 4) the coordination of EPR formulae.

A major tool to facilitate price comparisons could be a European medicine price database, such as the existing Euripid database of competent authorities of EU Member States and a few further European countries. According to its users, Euripid has proven to be extremely supportive for competent authorities when they carry out technical work related to EPR (price surveys, validation and comparisons). Thus, the authors consider a centralised price database as a promising cooperation mechanism that should be continued and possibly extended in future. It would be highly recommended to have a centralised database that covers all EU Member States. However, some countries may not be able to join a European price database (e.g. no possibility to share the price data of the own country due to a lack of ownership) which would limit the effectiveness of the database. A current limitation to a European price database is the provision of undiscounted list price data only. The inclusion of discounted prices could significantly improve the relevance and quality of such a database. If the inclusion of discounted

prices is not possible, it is recommended to consider alternative approaches, such as at least an indication in the price database of whether, or not, discounts have been granted to that product.

As the analysis has shown, EPR could provide lower prices if the price comparisons were done at the level of real prices paid by payers (discounted prices) instead of list prices. As a unilateral measure, EPR applying countries could take into account, as a minimum, statutory manufacturer discounts in the reference countries (e.g. Germany) that are officially published. However, this would only cover parts, possibly small ones, of the discounts granted. Higher savings might be generated if prices actually paid by public payers are referenced to, i.e. considering also confidential discounts, rebates, and similar financial arrangements in the other countries. One option to receive this information is a sharing of these data among Member States.

Another option to improve EPR would be regular price reviews with subsequent price revisions whose impact on reducing prices has been evidenced by simulations. However, industry could also benefit from regular price revisions if price increases (e.g. due to exchange rate fluctuations) were also considered. There is room for improvement since several Member States do not seem to perform regular (i.e. bi-annually, annually or at other defined time intervals) price re-evaluations even if provided for in the legislation.

Finally, another consideration could be the adaptation of the EPR formulae. For instance, countries could adjust prices by reference countries' purchasing power parities, rather than merely by nominal exchange rates, when performing EPR. This is a step that could be taken unilaterally by any EPR applying country. If several countries consider such changes, an exchange of information and best practice on criteria and methods for adjustment, which would support capacity building is recommended. A multi-national agreement on adjusting formulae in a particular method would be similar to the implementation of differential pricing in Europe (see below).

The four options presented can support policy-makers to improve the efficiency of performing price comparisons under EPR, and can help generating further savings for public payers. However, apart from the fourth option which contains traits of differential pricing, the other three options are not necessarily expected to impact the differentiation of prices between countries along the lines of ability-to-pay and thus improve access to medicines. The four options presented are not mutually exclusive, and it is recommended to consider a combination of these options.

Differential pricing for medicines – Use and impact

Overall, differential pricing (DP) describes the strategy of having different prices for the same product charged to different customers. This study regards differential pricing which is understood as an international, governmental policy defining the prices of medicines according to the ability-to-pay, and/or the economic situation of the countries under DP. There is a difference to 'price discrimination' ('market discrimination', 'Ramsey pricing') that describes a business strategy of economic actors to segment the market according to the observed demand-elasticity of consumers and that is not the focus of this study.

Experience with DP exists with medicines for specific indications (particularly HIV/AIDS, tuberculosis, malaria, vaccines) that were procured under DP by international agencies and programmes (UNICEF, PAHO, GAVI, Global Fund, UNITAID) for low- and middle-income countries, including least-developed countries. There is no experience with DP, as defined above, applied for high-income countries, such as European countries.

The applied DP schemes aimed to ensure access to medicines that would otherwise have been unaffordable for these countries. Though the results are mixed, it was found that in some cases DP might have resulted in an improved access to medicines for low-income countries. In addition, there was some evidence that DP helped to reduce prices and thus made medicines more affordable. However, the entry of generic medicines into the market was seen to be more effective in driving prices down than DP.

It has been argued that DP may benefit manufacturers as well since they gain additional markets, and low profit margins in these markets might be out-weighted by increased unit sales.

Under specific conditions DP might serve as a, however second-best, policy option to ensure short-term access to medicines, particularly new on-patent medicines. It should be supported by other policy options including generic competition, joint procurement, voluntary licensing and compulsory licensing. A global legal framework for DP has been suggested by researchers advocating for access to medicines globally.

Differential pricing – Proposal for an EU coordination mechanism

The report discusses a possible outline of a DP scheme for medicines in Europe as requested by the project tender specifications. This possible DP framework is described for analytical purposes, to illustrate what DP could mean in practice and to be able to assess its feasibility; but it should be noted that the authors do not necessarily recommend that a DP scheme should be implemented in Europe.

Such a scheme would require the agreement on principles and mechanisms of the countries included (in case of a collaborative approach for the EU, these were all 28 Member States) which is a challenge and might not be politically feasible in the short term. Mechanisms to be agreed upon would involve a maximum or minimum entry price, one of the biggest challenges by itself, and the size of the mark-ups or mark-downs. When designing such mechanisms, economic indicators, such as the gross domestic product or the purchasing power parities, should be taken into consideration. Some would argue that a DP scheme should be designed in a way that prevents higher prices in the higher-income countries compared to a situation without DP; others that these higher price levels might be justified.

In any case, if the DP approach is chosen, it is recommended to start with a pilot project for one, or a few products, defined according to some eligibility criteria (candidate medicines could include orphan medicinal products, or other high-priced medicines, for instance). EU Member States are advised to accompany any DP pilots, and later possibly regular DP schemes, by evaluations, with the possibility to feed-in lessons learned in future mechanisms. The pilots could be launched in cooperation with pharmaceutical companies interested in marketing their product in the European Union under a DP scheme. Trust and better planning between the two parties could be ensured if both supply and purchase guarantees would be integrated into contracts for medicines procured under DP. Notwithstanding the subsidiarity principle, operationally, the DP schemes would benefit from a central coordinating structure.

A key constraint that limits any differential pricing in Europe is parallel trade. Parallel trade occurs, if a genuine product originally sold under the patent protection is traded in another country without control or permission from the original patent holder. This leads to the re-importation of medicines from lower-priced to higher-priced countries and thus contradicts the principles of DP in which prices vary according to economic parameters. From a legal perspective, medicines as such are no exception to the free mobility of goods in the internal market. Thus, though parallel trade should not be

interfered with in order to not distort competition within the Union, export bans and notification/authorisation procedures related of exports of medicines might be justified if considered suitable, proportionate and necessary for achieving health and life protection goals. However, no legally binding Commission decision or European Court of Justice rule has yet been issued on this matter, although the effects of parallel trade on health and safe access to medicines remain a matter of strong controversy.

Policy options for the future

The exact impacts of a possible DP scheme within the European market are still unclear. It is evident, however, that the implementation of a DP scheme would be extremely challenging and would require enormous political will to address legal constraints and achieve agreements between Member States on principles and mechanisms. However, the challenge of ensuring patient access to new, possibly innovative medicines has become an urgent need in the light of new high-priced medicines. Thus, while the implementation of a DP appears to be unfeasible in the EU in the short run, EU Member States could consider using DP traits in EPR schemes. In the short term, EU Member States could improve their EPR systems, particularly by doing regular price revisions and considering (statutory) discounts, but these measures primarily help generate savings, and do not necessarily improve access to medicines. Some of the latter measures can be taken unilaterally by EU Member States, and cooperation would mainly regard the exchange of good practise on the methodology to be employed.

Moreover, EU Member States could consider exploring other new pharmaceutical (pricing) policies such as joint procurement initiatives which were not within the scope of this study. It is recommended using fora, such as the stakeholder review meeting of this project, to openly discuss strategies among stakeholders on how to deal with new high-cost medicines.

Résumé

Les patients et les citoyens européens doivent avoir accès à des médicaments sûrs, efficaces et abordables financièrement tandis que le système de soins de santé devrait être financièrement viable, et les innovations encouragées. Voilà peut-être le principal défi pour les autorités nationales compétentes et les payeurs publics alors que la fixation des prix des médicaments et le remboursement relèvent de la compétence des États membres de l'UE. Compte tenu de la pression financière croissante, tandis que d'autres nouveaux médicaments couteux sont attendus sur le marché, de nouvelles approches pour atteindre les objectifs mentionnés ci-dessus pourraient être nécessaires. Dans le respect du principe de subsidiarité, les possibles avantages en terme d'approches coopératives dans l'UE devraient néanmoins être étudiés et discutés.

Dans ce contexte, un consortium composé de Gesundheit Österreich Forschungs- und Planungs GmbH (GÖ FP, Autriche), SOGETI Luxembourg SA et de l'Université des sciences de la santé, de l'informatique médicale et de la technologie (UMIT, Autriche) a été commandée par la Commission européenne (DG SANTÉ / Chafea) pour explorer les interventions ciblant la fixation des prix de la comparaison externe de prix (CEP) et la tarification différenciée (TD) à l'égard de leur capacité à atteindre deux des trois objectifs de la politique mentionnée ci-dessus: à améliorer l'accès des patients aux médicaments et à générer des économies pour les payeurs publics.

Cette «study on enhanced cross-country coordination in the area of pharmaceutical product pricing» («étude sur le renforcement de la coordination entre les pays dans le domaine de la régulation des prix des produits pharmaceutiques») visait en particulier à sonder les régimes CEP existants dans les pays européens et de développer des améliorations possibles de la pratique de CEP actuelle, ainsi que d'analyser la manière dont les régimes de TD pourraient éventuellement être conçus pour les pays européens et faire face aux contraintes identifiées à la TD en Europe. En outre, l'étude devrait développer des mécanismes de coordination au niveau de l'UE qui pourraient soutenir l'amélioration des systèmes de CEP et l'établissement d'un système de TD.

Pour atteindre ces objectifs de recherche, les autrices/auteurs de cette étude se sont appuyés sur une gamme de méthodes, y compris une recherche de la littérature, une enquête auprès des autorités compétentes de la régulation des prix des produits pharmaceutiques, des entrevues avec des spécialistes de la TD, des simulations de prix, une analyse juridique, une recherche de modèles de coopération et d'analyses SWOT (forces, faiblesses, opportunités et menaces). Des examens approfondis associant les services de la CE, les parties prenantes et les universitaires ('pairs') ont été effectués pour garantir la qualité du rapport.

Comparaison externe des prix des médicaments – utilisation et impact

La comparaison externe des prix (CEP) est définie comme la pratique d'utiliser le(s) prix d'un médicament dans un ou plusieurs pays en vue de calculer une référence ou prix de référence pour fixer ou négocier le prix d'un médicament dans un pays donné.

La CEP est l'intervention de la régulation des prix plus couramment appliquée dans les pays européens. En 2015, à l'exception de l'Allemagne, la Suède et le Royaume-Uni, tous les autres États membres de l'UE, ainsi que l'Islande, la Norvège, la Suisse et la Turquie, fixent les prix de leurs médicaments (au moins de quelques médicaments) en se basant sur des comparaisons de prix avec d'autres pays. En Allemagne, bien que la loi prévoit de prendre en considération le prix des médicaments dans d'autres pays comme un élément d'information supplémentaire dans la fixation des prix des médicaments brevetés, il est dit que la CEP n'est pas appliqué dans la procédure de

suivi. Au Danemark, la CEP est seulement appliquée comme une politique de soutien au niveau des prix dans le secteur hospitalier. Selon l'enquête réalisée en avril/mai 2015, 20 des 29 pays qui appliquent la CEP utilisent cette politique comme politique unique ou principale au niveau des prix. Les systèmes de la CEP sont typiquement limités aux médicaments spécifiques, tels que les princeps, délivrés uniquement sur ordonnance ou de nouveaux médicaments. Le nombre de pays de référence compris dans le panier varie entre un pays (Luxembourg) et 30 pays (Hongrie et Pologne). Les pays les plus fréquemment utilisés comme références sont la France, la Belgique, le Danemark et l'Espagne suivis par l'Italie, le Royaume-Uni et par, dans une moindre mesure, l'Autriche, l'Allemagne et la Slovaquie. Les principaux critères définissant la composition des paniers de pays sont le voisinage géographique ou une situation économique comparable dans les pays de référence.

Les spécifications méthodologiques de la façon dont un régime de CEP est conçu diffèrent entre les pays mentionnés. Par exemple, 21 pays font les comparaisons des prix des médicaments au niveau des prix ex-usine, et huit pays au niveau du prix de gros. Les pays appliquant la CEP se rapportent aux prix de liste officiellement publié, ne prenant ainsi en compte ni remises statutaires ni négociées. Bien que l'Allemagne n'applique pas la CEP, le pays a précisé dans sa législation que les prix réduits par remises doivent être déclarés par les entreprises pharmaceutiques. La méthode la plus couramment appliquée pour calculer un prix de référence est une moyenne, ou une sorte de moyenne modifiée, des prix dans les pays de référence. Les données sur les prix requis pour la CEP sont fournis par l'entreprise pharmaceutique dans 23 pays, et dans 26 pays les autorités compétentes de la régulation des prix valident cette information des prix. Bien que la surveillance des prix est prévue dans la législation de 25 pays, elle est en réalité effectuée sur une base régulière uniquement dans 17 pays. Ces intervalles réguliers varient entre les pays et vont de trois mois à cinq ans.

Une recherche de la littérature réalisée dans le cadre de l'étude suggère que la CEP a prouvé son efficacité dans la réalisation, parfois importante, d'économies pour les payeurs publics. L'importance des économies dépend considérablement de la méthodologie appliquée. Il y a des opportunités perdues en raison de remises et arrangements similaires dans les pays de référence qui ne sont pas pris en compte dans la CEP. Comme illustré par des simulations effectuées par les autrices/auteurs de cette étude, il peut être possible de réaliser des impacts majeurs sur les réductions de prix en se référant à des prix réduits et en effectuant des examens réguliers de CEP. En ce qui concerne l'accès des patients, la CEP est susceptible d'avoir un impact négatif car il incite les entreprises pharmaceutiques à lancer un médicament dans un premier temps sur le marché dans des pays présentant des prix plus élevés et de s'abstenir d'entrer sur le marché des pays ayant des prix moins-élevés tout en les empêchant d'offrir des médicaments à plus bas prix dans les pays présentant les prix les plus bas.

Comparaison externe des prix – Options pour les mécanismes d'amélioration et de coopération

La CEP est une politique de prix qui tient compte des prix dans d'autres pays, mais ce n'est pas un outil de coopération en soi. Toutefois, les deux changements dans la méthodologie pris unilatéralement par les pays ainsi que les approches de coopération entre les États membres peuvent contribuer à améliorer la performance des CEP, qui est une activité de ressources et de temps, et donc éventuellement avoir un impact positif sur les objectifs de la Politique. Le rapport examine quatre options d'amélioration: 1) une base de données centrale sur les prix, 2) la prise en compte des remises, 3) le suivi régulier de prix, et 4) la coordination des formules de CEP.

Un outil majeur pour faciliter les comparaisons de prix pourrait être une base de données de prix des médicaments européenne, telle que la base de données existante des autorités compétentes des États membres de l'UE et d'autres pays européens, Euripid. Selon ses utilisateurs, Euripid s'est avérée extrêmement utile pour les autorités compétentes pour des travaux techniques liés au CEP (enquêtes sur les prix, validation et comparaisons). Ainsi, les autrices/auteurs considèrent une base de données centralisée des prix comme un mécanisme de coopération prometteur qui devrait être maintenu et éventuellement étendu à l'avenir. Il serait fortement recommandé d'avoir une base de données centralisée qui couvre tous les États membres de l'UE. Toutefois, certains pays peuvent ne pas être en mesure de rejoindre une base de données de prix européen (par exemple, pas de possibilité de partager les données sur les prix de leur propre pays en raison d'un manque d'appropriation) qui limiterait l'efficacité de la base de données. L'inclusion de prix réduits par remises pourrait sensiblement améliorer la pertinence et la qualité d'une telle base de données. Si l'inclusion des prix réduits n'est pas possible, il est recommandé d'envisager d'autres approches, comme au minimum une indication dans la base de données de prix de savoir si, oui ou non, des remises sont appliquées à ce produit.

Comme l'analyse l'a montré, la CEP pourrait fournir des prix plus bas si les comparaisons de prix ont été effectuées au niveau des prix réels payés par les payeurs publics (prix réduits par remises) au lieu des prix de la liste. Comme mesure unilatérale, les pays candidats aux CEP pourraient prendre en compte, au minimum, les rabais légaux du fabricant dans les pays de référence (Allemagne, par exemple) qui sont officiellement publiés. Toutefois, cela ne ferait que couvrir une (petite) partie des remises accordées. Une épargne plus élevée peut être générée si les prix réellement payés par les payeurs publics sont référencés, par exemple, tenir compte des rabais confidentiels, des promotions, et des arrangements financiers similaires dans les autres pays. Une option possible pour recevoir ces informations est un partage de ces données entre les États membres.

Une autre option pour améliorer la CEP serait des examens de prix réguliers avec des révisions de prix ultérieures dont l'impact sur la réduction des prix a été mis en évidence par les simulations. Cependant, l'industrie pourrait également bénéficier de révisions régulières des prix si l'augmentation de prix (par exemple en raison des fluctuations des taux de change) a également été considérée. Il y a de la place pour des améliorations depuis que plusieurs États membres ne semble pas effectuer (p.ex. deux fois par an, chaque année ou à intervalles de temps défini) des réévaluations régulières des prix, même si cela est prévu dans la législation.

Enfin, une autre considération pourrait être l'adaptation des formules de CEP. Par exemple, les pays pourraient ajuster les prix par rapport aux parités de pouvoir d'achat des pays de référence, plutôt que simplement par des taux de change nominaux, lors de l'exécution de CEP. Ceci est une étape qui pourrait être prise unilatéralement par n'importe quel pays appliquant la CEP. Si plusieurs pays considèrent ces changements, un échange d'informations et de meilleures pratiques sur les critères et méthodes d'ajustement qui soutiendrait le renforcement des capacités sont recommandés. Un accord multinational sur l'ajustement des formules dans une méthode particulière serait similaire à la mise en œuvre d'une tarification différenciée en Europe (voir ci-dessous).

Les quatre options présentées peuvent aider les autorités à améliorer l'efficacité de l'exécution des comparaisons de prix en vertu des CEP, et ils peuvent aider à générer des économies supplémentaires pour les payeurs publics. Cependant, en dehors de la quatrième option qui contient des caractères de tarification différenciée, un impact des trois autres options sur la différenciation de prix n'est pas nécessairement attendu entre les pays sur les grandes lignes de la capacité de paiement, ni une amélioration de l'accès

aux médicaments. Les quatre options présentées ne sont pas mutuellement exclusives, et il est recommandé d'envisager une combinaison de ces dernières.

La tarification différenciée pour les médicaments – utilisation et impact

Dans l'ensemble, la tarification différenciée (TD) décrit la stratégie d'avoir des prix différents pour le même produit facturés à des clients différents. Dans cette étude la TD est comprise comme une politique gouvernementale internationale définissant les prix des médicaments en fonction de la capacité de payer, et/ou de la situation économique des pays inclus dans la TD. Il y a une différence de «discrimination par les prix» («discrimination sur le marché», «tarification de Ramsey») qui décrit une stratégie d'entreprise des acteurs économiques à segmenter le marché en fonction de la demande d'élasticité observée des consommateurs et qui n'est pas l'objet de cette étude.

L'expérience de la TD existe sur des médicaments pour des indications spécifiques (en particulier le VIH/SIDA, la tuberculose, la malaria, les vaccins) qui ont été acquis au titre de la TD par des organismes internationaux et des programmes (UNICEF, Organisation panaméricaine de la Santé, GAVI, Fonds mondial, UNITAID) pour des pays à revenu faible et intermédiaire, y compris les pays les moins avancés. Il n'y a aucune expérience avec la TD, telle que définie ci-dessus, appliquée pour les pays à revenu élevé, tels que les pays européens.

Les régimes de TD appliqués visent à assurer l'accès à des médicaments qui auraient autrement été inabordables pour ces pays. Bien que les résultats soient mitigés, il a été constaté que dans certains cas la TD aurait permis d'améliorer l'accès aux médicaments pour les pays à faible revenu. En outre, il y a des preuves que la TD a contribué à réduire les prix des médicaments et donc à les rendre plus abordables. Toutefois, l'entrée de médicaments génériques sur le marché a été plus efficace que la TD dans le cadre d'une baisse des prix.

Il a été dit que la TD peut également profiter aux entreprises pharmaceutiques par le gain d'autres marchés, et de faibles marges bénéficiaires dans ces marchés pourraient être contrebalancées par l'augmentation des ventes unitaires.

Dans des conditions spécifiques, la TD pourrait servir en tant qu'option stratégique (cependant en tant que 2^{e} choix) pour assurer l'accès à court terme aux médicaments, en particulier les nouveaux médicaments sous brevet. Elle devrait être soutenue par d'autres options stratégiques, y compris la concurrence des génériques, les achats groupés, les licences volontaires et obligatoires. Un cadre juridique global a été suggéré pour la TD par des chercheurs militant pour l'accès aux médicaments à l'échelle globale.

La tarification différenciée – Proposition pour un mécanisme de coordination de l'UE

Le rapport examine l'approche possible d'un système de TD pour les médicaments en Europe, comme demandé par les spécifications de l'appel d'offre du projet. Le cadre de TD possible est décrit à des fins analytiques, pour illustrer ce que la TD pourrait signifier en pratique et pour être en mesure d'évaluer sa faisabilité; mais il convient de noter que les autrices/auteurs ne recommandent pas nécessairement qu'un régime de TD devrait être mis en œuvre en Europe.

Un tel système nécessiterait l'accord sur les principes et les mécanismes des pays inclus (dans le cas d'une approche de collaboration pour l'UE, ce sont les 28 États membres), qui est un défi et pourrait ne pas être politiquement réalisable à court terme. Les mécanismes à convenir impliqueraient un prix maximum ou minimum d'entrée, l'un des

plus grands défis en soi, et la taille des majorations ou des minorations. Lors de la conception de tels mécanismes, les indicateurs économiques, tels que le produit intérieur brut ou les parités de pouvoir d'achat, devraient être pris en considération. Certains diront que la TD devrait être fait d'une manière que les prix dans les pays à revenu élevé ne sont pas plus hauts en comparaison avec la situation sans TD; d'autres que des prix élevés pour les pays plus riches pourraient être justifiées.

Dans tous les cas, si l'approche de TD est choisie, il est recommandé de commencer par un projet pilote pour un - ou plusieurs - produits, défini selon certains critères d'éligibilité (p.ex. les produits médicaux orphelins ou d'autres médicaments couteux). Les États membres de l'UE sont invités à accompagner toutes les TD pilotes, et plus tard d'éventuels régimes réguliers de TD, par des évaluations, avec la possibilité d'utiliser les leçons apprises pour les mécanismes futurs. Les pilotes pourraient être lancées en coopération avec des entreprises pharmaceutiques intéressées dans la commercialisation de leurs produits dans l'Union européenne en vertu d'un régime de TD. La confiance et une meilleure planification entre les deux parties pourrait être assurée si les garanties d'approvisionnement et d'achat seraient intégrées dans les contrats pour les médicaments achetés dans le cadre de la TD. Nonobstant le principe de subsidiarité, sur le plan opérationnel, les régimes de TD bénéficieraient d'une structure centrale de coordination.

Une contrainte principale qui limite toute tarification différenciée en Europe est le commerce parallèle. Le commerce parallèle a lieu, si un produit authentique vendu à l'origine sous la protection d'un brevet est commercialisé dans un autre pays sans contrôle ni autorisation du titulaire du brevet d'origine. Cela conduit à la réimportation de médicaments d'un prix inférieur aux pays aux prix plus élevés et contredit ainsi les principes de la TD dans laquelle les prix varient en fonction de paramètres économiques. D'un point de vue juridique, si le commerce parallèle est autorisé en Europe et ne doit pas être perturbé afin de ne pas fausser la concurrence au sein de l'Union, les interdictions d'exportation et la notification/procédures d'autorisation pourraient être justifiés si cela est jugé approprié, nécessaire et proportionné pour atteindre les buts en terme de protection de la santé et de la protection de la vie. Toutefois, aucune décision juridiquement contraignante de la Commission ou jugements de la Cour européenne de Justice n'a encore été rendue à ce sujet, bien que les effets du commerce parallèle sur la santé et l'accès sûr aux médicaments restent un sujet très controversé.

Les options politiques pour l'avenir

Les impacts précis d'un possible système de TD au sein du marché européen sont encore peu clairs. Il est cependant évident que la mise en œuvre d'un système de TD serait extrêmement difficile et exigerait une énorme volonté politique pour ce qui est de résoudre les contraintes juridiques et parvenir à des accords entre les États membres sur les différents principes et mécanismes. La mise en œuvre d'une TD semble être irréalisable dans l'UE dans le court terme. Cependant, le défi d'assurer l'accès des patients aux nouveaux - éventuellement innovants - médicaments est devenu un besoin urgent à la lumière des nouveaux médicaments couteux. Ainsi, les États membres de l'UE pourraient envisager d'utiliser des caractères de la TD dans les régimes de CEP. À court terme, les États membres de l'UE pourraient améliorer leurs systèmes de CEP, notamment en faisant des révisions régulières des prix tout en tenant compte des réductions (statutaires), mais ces mesures aideront surtout à générer des économies et non à améliorer l'accès aux médicaments. Certaines de ces dernières mesures peuvent être prises unilatéralement par les États membres de l'UE, et la coopération concernerait principalement l'échange de bonnes pratiques sur la méthodologie à employer.

En outre, les États membres de l'UE pourraient envisager d'explorer d'autres nouvelles politiques pharmaceutiques telles que des initiatives d’achat en commun qui ne sont pas comprises dans le cadre de cette étude. Il est recommandé d'utiliser des forums, tels que la réunion des examens des parties prenantes de ce projet, afin de discuter ouvertement de stratégies entre les parties prenantes sur la façon de traiter les nouvelles médecines couteuses.

Kurzfassung

Die Regierungen der europäischen Länder haben die Verantwortung, Patientinnen und Patienten den Zugang zu sicheren, wirksamen und leistbaren Arzneimitteln zu ermöglichen. Gleichzeitig muss allerdings auch die Finanzierung der Gesundheitssysteme langfristig gesichert und Innovation durch entsprechende Anreize ausreichend gefördert werden. Diese zum Teil konfliktären Ziele stellen die zuständigen Behörden für Arzneimittelpreisbildung und Erstattung in den EU-Mitgliedstaaten vor bedeutende Herausforderungen. In Anbetracht knapper finanzieller Budgets und der Markteinführung neuer, hochpreisiger Arzneimittel wird es neuer Strategien bedürfen, um die genannten Ziele zu erreichen. Eine verstärkte Kooperation in der EU könnte dabei – ohne das Subsidaritätsprinzip in Frage zu stellen – ein vielversprechender Ansatz sein.

In diesem Zusammenhang hat die Europäische Kommission (Generaldirektion Gesundheit und Lebensmittelsicherheit / Exekutivagentur für Verbraucher, Gesundheit und Lebensmittel – Chafea) ein Konsortium aus Gesundheit Österreich Forschungs- und Planungs GmbH (GÖ FP), SOGETI Luxembourg S.A. und der Privaten Universität für Gesundheitswissenschaften, Medizinische Informatik und Technik GmbH (UMIT) damit beauftragt, zwei Strategien der Arzneimittelpreisbildung zu untersuchen: den internationalen Preisvergleich (im Folgenden EPR – Abkürzung des Fachbegriffs „External Price Referencing" – genannt) und das sogenannte Differential Pricing (DP). Für diese beiden Maßnahmen der Preispolitik soll untersucht werden, ob sie dazu beitragen können, den Zugang der Patientinnen und Patienten zu Medikamenten zu verbessern und Einsparungen an öffentlichen Mitteln zu erzielen.

Die vorliegende „Study on Enhanced Cross-Country Coordination in the Area of Pharmaceutical Product Pricing", eine Studie zu verstärkter länderübergreifender Kooperation im Bereich der Preispolitik für Arzneimittel, verfolgte mehrere Ziele: Die EPR-Systeme in europäischen Staaten sollten untersucht und Verbesserungsvorschläge für die aktuelle Praxis entwickelt werden. Hinsichtlich DP galt es, die Umsetzungsvarianten dieser – bislang in Europa noch nicht angewandten – preispolitischen Maßnahme zu erheben und zu prüfen, welche Voraussetzungen für die Einführung eines DP-Systems erforderlich sind. Ein weiteres Ziel dieser Studie bestand darin, Kooperationsmechanismen auf EU-Ebene zu identifizieren, welche die bestehende EPR-Praxis verbessern und ein allfälliges DP-System unterstützen könnten.

Um diese Ziele zu erreichen, bediente sich das Autorenteam einer Reihe unterschiedlicher Methoden. Dazu gehörten eine systematische Literaturrecherche, eine Primärdatenerhebung mittels eines vorausgefüllten Fragebogens an die für Arzneimittelpreisbildung zuständigen Behörden in den europäischen Ländern, Interviews mit Expertinnen/Experten im Bereich Beschaffung und DP, Preissimulationen, eine rechtliche Analyse, die Untersuchung von Kooperationsmodellen sowie SWOT-Analysen (Strengths – Stärken, Weaknesses – Schwächen, Opportunities – Chancen und Threats – Gefahren). Die Studie durchlief mehrere Feedbackschleifen, im Zuge derer Kommentare von Dienststellen der Europäischen Kommission, von Akteuren im Arzneimittelwesen (zuständigen Behörden und Interessengruppen) sowie Wissenschaftler/innen („Peers") eingeholt und eingearbeitet wurden, um eine hohe Qualität der Studie zu gewährleisten.

EPR für Arzneimittel – Praxis und Konsequenzen

EPR (External Price Referencing) ist eine Methodik der Preisbildung, bei der die Preise desselben Medikaments in anderen Ländern herangezogen werden, um im eigenen Land den Preis eines Arzneimittels festzulegen bzw. eine Basis für Verhandlungen über den Preis bzw. die Erstattung zu schaffen.

EPR ist gängige Preisbildungspraxis in den meisten europäischen Staaten. Im Jahr 2015 legten mit Ausnahme von Deutschland, Großbritannien und Schweden sämtliche EU-Mitgliedstaaten und auch Island, Norwegen, die Schweiz und die Türkei den Preis ihrer Arzneimittel (zumindest in einem Teilmarkt) auf Basis von Preisvergleichen mit anderen Staaten fest. In Deutschland besteht zwar der rechtliche Rahmen für EPR für neue Medikamente, in der Praxis findet diese Methode der Preisbildung aber keine Anwendung. In Dänemark wird EPR nur im stationären Sektor – und zwar als ergänzende Maßnahme der Preisbildung – angewendet. Eine im Rahmen dieser Studie im April/Mai 2015 durchgeführte Erhebung bei zuständigen Behörden ergab, dass 20 der 29 Staaten, die EPR einsetzen, diese Maßnahme als ausschließliche bzw. zentrale Methode der Preisbildung verwenden. Üblicherweise wird EPR nur für ausgewählte Arzneimittel angewendet, typischerweise für Originalpräparate, verschreibungspflichtige oder innovative Produkte. Die Anzahl der zum Vergleich herangezogenen Referenzländer liegt zwischen einem Land (in Luxemburg) und 30 Ländern (in Ungarn und Polen). Staaten, auf die oft referenziert wird, sind Frankreich, Belgien, Dänemark und Spanien, gefolgt von Italien, Großbritannien, und – weniger oft – Österreich, Deutschland und Slowakei. Hauptkriterien, warum Staaten als Referenzländer ausgewählt werden, sind geografische Nähe oder eine vergleichbare wirtschaftliche Situation.

Die Methodik für EPR ist in den einzelnen Ländern unterschiedlich ausgestaltet: 21 Staaten vergleichen die Arzneimittelpreise auf Basis des Fabriksabgabepreises, während acht Staaten den Apothekeneinkaufspreis (Großhandelspreis) heranziehen. Die für EPR angewandten Preisvergleiche basieren generell auf den offiziellen, publizierten Listenpreisen und nicht auf rabattierten Preisen – seien diese durch gesetzliche Herstellerrabatte oder Verhandlungen zwischen Industrie und Zahlern zustande gekommen. Nur Deutschland, das in der Praxis EPR nicht anwendet, fordert laut gesetzlicher Grundlage von den Pharma-Unternehmen die Meldung rabattierter Preise. Der EPR-Referenzpreis wird meist auf Basis eines (oft eines adaptierten) Durchschnitts der Preise in den Referenzländern festgelegt. Die Preisinformationen, die für EPR benötigt werden, sind in 23 Ländern von den Herstellern bereitzustellen; 26 Länder validieren diese Preisangaben. Obwohl in 25 Staaten Preismonitoring gesetzlich vorgeschrieben ist, wird dieses in der Praxis nur von 17 Staaten durchgeführt. Die Zeitspannen zwischen den Preisevaluationen schwanken länderspezifisch zwischen drei Monaten und fünf Jahren.

Die im Rahmen dieser Studie durchgeführte systematische Literaturrecherche zeigte das Kostendämpfungspotenzial von EPR auf: EPR führt – wie die Literatur zeigt – in einigen Fällen zu teilweise erheblichen Einsparungen an öffentlichen Ausgaben. Die methodische Ausgestaltung von EPR hat allerdings beträchtlichen Einfluss darauf, in welcher Größenordnung Einsparungen erzielt werden können. Behörden könnten niedrigere Preise erreichen, wenn sie nicht – wie bisher – auf die Listenpreise, sondern auf rabattierte Preise in den anderen Ländern referenzierten; dies zeigten vor allem die im Rahmen der Studie durchgeführten Simulationen. Allerdings unterliegen Rabatte in vielen Fällen der Vertraulichkeit. Weiteres Sparpotenzial ergibt sich – wie ebenfalls durch Simulationen belegt –, wenn Preismonitoring regelmäßig durchgeführt würde. Hinsichtlich eines verbesserten Zugangs von Patientinnen/Patienten zu Medikamenten wird allerdings EPR in der Literatur als nicht vorteilhaft eingeschätzt; denn EPR setzt Anreize für Pharma-Unternehmen, Arzneimittel zunächst in Hochpreisländern auf den Markt zu bringen. Damit sind diese Medikamente in Niedrigpreisländern erst viel später bzw. in einigen Fällen gar nicht verfügbar.

EPR – Verbesserungsvorschläge und Kooperationsmechanismen

EPR ist eine Strategie der Preisbildung, bei der die Preise in anderen Staaten eine zentrale Rolle spielen, aber es ist kein Kooperationsmechanismus per se. Die Wirksamkeit von EPR in Hinblick auf die beschriebenen Ziele könnte mittels Änderungen in der Methodik verbessert werden; die zeit- und ressourcenaufwändige Durchführung von EPR könnte effizienter werden. Dies wäre erreichbar durch Verbesserungen in der Methodik, die entweder von einzelnen Mitgliedstaaten unilateral und/oder im Rahmen von Kooperationen zwischen den Mitgliedstaaten umgesetzt werden könnten. Die vorliegende Studie diskutiert vier Vorschläge für verbesserte Kooperation zwischen den Mitgliedstaaten in Bezug auf EPR: 1) eine zentrale Preisdatenbank, 2) die Berücksichtigung rabattierter Preise, 3) Preismonitoring und 4) einen abgestimmten Ansatz der für EPR eingesetzten Methodik.

Eine europäische Arzneimittelpreis-Datenbank ist ein zentrales Instrument, das Staaten bei der Durchführung der für EPR benötigten Preisrecherchen unterstützt. Ein Beispiel für eine solche Preisdatenbank ist die bestehende Euripid-Datenbank im Eigentum der zuständigen Behörden für Preisbildung in beteiligten EU-Mitgliedstaaten und einigen weiteren europäischen Ländern. Nationale Behörden, die Euripid nutzen, betonten gegenüber dem Autorenteam, welche Arbeitserleichterung die Verwendung von Euripid bei Preiserhebung, -validierung und -vergleich ihnen bietet. Die europäische Preisdatenbank stellt zweifellos einen vielversprechenden Kooperationsmechanismus dar, dessen Fortführung und Ausbau empfohlen wird. Hinsichtlich einer Ausweitung sprechen sich die Autorinnen/Autoren dieses Berichts für eine möglichst umfassende Datenbank aus – sie sollte im Idealfall sämtliche EU-Mitgliedstaaten abdecken. Manche Länder können sich jedoch aus rechtlichen Gründen nicht an einer europäischen Preisdatenbank beteiligen (z. B. besteht teilweise aus Urheberschutzgründen keine Möglichkeit, nationale Preisinformationen weiterzugeben). Die Tatsache, dass die europäische Preisdatenbank Euripid gegenwärtig Preisinformationen ohne Rabatte enthält, stellt eine weitere Limitation dar. Die Aufnahme rabattierter Preise könnte die Relevanz und den Wert einer europäischen Preisdatenbank erheblich steigern; allerdings können bestehende vertragliche Vereinbarungen einem Einspielen rabattierter Preisdaten in die Datenbank entgegenstehen. Angesichts dieser Hürden wird empfohlen, alternative Strategien – wie etwa eine Kennzeichnung, ob Rabatte auf ein Produkt gewährt werden oder nicht, ohne Präzisierung der Höhe – zu überlegen.

Der zweite Kooperationsmechanismus betrifft die Berücksichtigung der tatsächlich finanzierten (d. h. rabattierten) Preise anstelle der offiziellen Listenpreise beim Preisvergleich. Rabattierte Preisdaten aus vertraulichen Abkommen werden allerdings nicht zugängig sein. Als ersten Schritt könnten Behörden zumindest die Preise unter Berücksichtigung der in einigen Ländern bestehenden (veröffentlichten) gesetzlichen Herstellerrabatte für das EPR heranziehen. Monetär hätte dies jedoch wahrscheinlich nur bescheidene Auswirkungen. Wie auch die Simulationen im Rahmen dieser Studie zeigten, wären höhere Einsparungen möglich, wenn unter Berücksichtigung sämtlicher vertraulicher Rabatte oder ähnlicher vertraglicher Vereinbarungen (z. B. sogenannter Managed Entry Agreements) auf die tatsächlichen Preise referenziert würde.

Eine weitere Maßnahme, um die Wirksamkeit von EPR zu verbessern, bestünde in regelmäßigen Preisevaluationen, die sich danach in entsprechenden Preisanpassungen niederschlagen könnten. Die im Bericht präsentierten Simulationen bestätigten Einsparungen öffentlicher Gelder aufgrund dieses Preismonitorings. Die Industrie könnte ebenfalls von Preisanpassungen profitieren, wenn Preissteigerungen (etwa durch Wechselkursschwankungen) berücksichtigt würden. In der Praxis – so zeigte die Erhebung im Rahmen dieser Studie – führen mehrere Mitgliedstaaten offensichtlich

keine regelmäßigen Preisevaluationen durch, obwohl diese eigentlich gesetzlich vorgesehen wären.

Schließlich könnte eine Änderung der herangezogenen Berechnungsgrundlagen (Formeln) zur Verbesserung der EPR-Methodik beitragen. Beispielsweise könnten die Preise der Referenzländer nach Kaufkraftparitäten gewichtet werden, anstelle sie nach den nominellen Währungskursen umzurechnen. Diese Maßnahme könnte von jedem Land, das EPR anwendet, einzeln initiiert werden. Wenn mehrere Länder solche Maßnahmen planen, wäre ein Informationsaustausch über Kriterien und Methoden sowie über Good-Practice-Beispiele empfehlenswert. Eine länderübergreifende Verständigung über die Anpassung der Berechnungsgrundlagen (Formeln) nach einer bestimmten Methode käme der Einführung von Differential Pricing (DP) bereits sehr nahe (siehe unten).

Die vier aufgezeigten Verbesserungsvorschläge können einen Beitrag dazu leisten, die Preisbildungsmethode EPR effizienter zu gestalten, und zu niedrigeren Preisen von Arzneimitteln beitragen. Abgesehen von der vierten Option, die sich durch Charakteristika von DP auszeichnet, tragen die Handlungsoptionen nicht der unterschiedlichen Zahlungsfähigkeit der einzelnen Mitgliedstaaten Rechnung und sind somit nicht unbedingt darauf ausgerichtet, den Zugang zu Medikamenten verbessern. Die vier vorgestellten Verbesserungsvorschläge schließen einander nicht aus; eine Kombination dieser Handlungsoptionen wird empfohlen.

DP für Arzneimittel – Praxis und Konsequenzen

Im Falle von Differential Pricing (DP) werden für das gleiche Produkt unterschiedliche Preise für verschiedene Kunden(gruppen) verrechnet. In der vorliegenden Studie wird DP als eine länderübergreifende Maßnahme der Politik von Staaten (bzw. supranationalen Institutionen) definiert, bei der die Preise eines Arzneimittels entsprechend der Zahlungsfähigkeit und/oder der wirtschaftlichen Situation der Länder im DP-Schema festgesetzt werden. Dieser Ansatz unterscheidet sich von der „Preisdiskriminierung" (auch „Ramsey-Pricing" bezeichnet), die als eine von Unternehmen angewandte Business-Strategie darauf abzielt, den Markt gemäß der Nachfrage-Elastizität zu segmentieren. Preisdiskriminierung, die manchmal auch unter dem Begriff DP subsumiert wird, stellt eine Handlungsoption für Unternehmen und nicht für Staaten dar und ist daher nicht Gegenstand der vorliegenden Studie.

Die Erfahrungen mit DP bei Medikamenten liegen primär in einigen Indikationen (insbesondere HIV/AIDS, Tuberkulose, Malaria, Impfungen) und bei wirtschaftlich ärmeren Ländern (z. B. des globalen Südens) vor. In diesen Fällen werden Arzneimittel meist über internationale Organisationen (UNICEF, PAHO, GAVI, Global Fund, UNITAID) beschafft. Wirtschaftlich stärkere Staaten – wie die europäischen – wenden DP bei Arzneimitteln derzeit nicht an.

DP wurde eingesetzt, um den Zugang zu Medikamenten sicherzustellen, die sonst für ärmere Länder unerschwinglich wären. Dabei zeigte sich, dass in einigen – nicht allen – Fällen der Zugang zu Medikamenten verbessert werden konnte. In manchen Fällen konnten die Preise von Arzneimitteln mittels DP gesenkt und Medikamente damit erschwinglicher werden. Wenn allerdings Generika auf den Markt kamen, trug das zu deutlich niedrigeren Preisen bei als DP. Neben diesem zumindest teilweise beobachteten Nutzen von DP für ärmere Staaten und deren Bevölkerung wird diese Maßnahme als auch vorteilhaft für Pharma-Unternehmen eingeschätzt, da sie ihnen ermöglicht, neue Märkte zu erschließen. Damit können höhere Absatzzahlen den niedrigeren Gewinn auf Grund der niedrigeren Preise in ärmeren Ländern wettmachen.

DP hat Limitationen, kann aber unter gewissen Bedingungen einen Beitrag dazu leisten, kurzfristig Zugang zu neuen Arzneimitteln zu schaffen. DP sollte jedoch mit weiteren Maßnahmen kombiniert werden, wie z. B. mit Wettbewerb zwischen Generika, einem gemeinsamen Einkauf mehrerer Länder, mit Zwangslizenzen für patentgeschützte Arzneimittel („compulsory licensing") und freiwilligen Lizenzen („voluntary licensing"). Wissenschaftler/innen, die sich für einen verbesserten Zugang zu Medikamenten weltweit einsetzen, sprachen sich dafür aus, DP nicht als regionale Maßnahme zu verstehen, sondern einen globalen Rechtsrahmen dafür zu schaffen.

DP — Vorschlag für einen europaweiten Koordinationsmechanismus

Die Autorinnen/Autoren der Studie wurden beauftragt, zu skizzieren, wie ein DP-System für Arzneimittel in Europa ausgestaltet werden könnte. Daraus kann allerdings nicht der Schluss gezogen werden, dass die Autorinnen/Autoren des Berichtes Position für die Einführung von DP in Europa beziehen.

Um DP einzuführen, müssten sich sämtliche beteiligte Staaten auf die Prinzipien und Mechanismen des gemeinsamen DP-Systems verständigen. Im Falle einer Kooperation in der EU müssten sich 28 Mitgliedsstaaten einigen, was eine enorme politische Herausforderung darstellt, die nicht einfach – und schon gar nicht kurzfristig – umzusetzen ist. Kritische Punkte dabei betreffen insbesondere die Höhe der Startpreise, von denen aus die Differenzierung der Preise in den eingeschlossenen Staaten vorzunehmen sind, sowie das Ausmaß der Auf- und Abschläge für die einzelnen Länder. Zur länderspezifischen Preisdifferenzierung sind Indikatoren der Wirtschaftskraft — wie etwa das Bruttoinlandsprodukt oder die Kaufkraftparität — heranzuziehen. Je nach Ausgestaltung des DP-Mechanismus könnten die unter DP vereinbarten Preise in den reicheren Ländern höher als ohne DP sein, wozu unterschiedliche Meinungen bestehen. Manche betrachten dies als gerechtfertigt, während sich andere für die Umsetzung des DP-Systems in einer Form aussprechen, bei der das Preisniveau nicht höher würde.

Sollten sich die EU-Mitgliedstaaten für die Einführung von DP entscheiden, wird empfohlen, mit einem Pilotprojekt für ein Medikament oder ein paar wenige Produkte zu starten. Für die Auswahl der Medikamente für solche Pilotprojekte müssten entsprechende Kriterien definiert werden; geeignete Kandidaten wären z. B. Arzneimittel für seltene Krankheiten oder andere hochpreisige Medikamente. Die DP-Pilotinitiativen und auch ein späteres allfälliges DP-System soll mit einer Evaluation begleitet werden, um Erfahrungen zu sammeln, welche in die Weiterentwicklung des Systems einfließen könnten. Pilotprojekte könnten in Zusammenarbeit mit Pharma-Unternehmen durchgeführt werden, die daran interessiert sind, ihre Arzneimittel in Europa unter einem DP-System auf den Markt zu bringen. Die Aufnahme von Liefer- und Abnahmegarantien in ein DP-System würde Vertrauen zwischen den Pharma-Unternehmen und öffentlichen Zahlern schaffen und die Planungssicherheit erhöhen. Ohne das Subsidiaritätsprinzip in Frage zu stellen, wäre eine Koordinationsstelle/-struktur für die operative Abwicklung von DP hilfreich.

Eine erhebliche Herausforderung für die Einführung von DP in Europa stellt der Parallelhandel dar. Parallelhandel liegt vor, wenn ein patentgeschütztes Arzneimittel in einen anderen Staat ohne Einfluss oder Erlaubnis des Patentinhabers eingeführt wird. Dies führt zu einem Re-Import von Arzneimitteln aus Niedrigpreisländern in Hochpreisländer und konterkariert damit die Prinzipien von DP, bei dem ja die Preise entsprechend der Wirtschaftskraft der Länder festgelegt werden. Obwohl Parallelhandel im Sinne der Prinzipien des freien Wettbewerbs (welcher für Medikamente gleich wie für andere Güter gilt) nicht unterbunden werden kann, könnten Ausfuhrverbote und Genehmigungen für die Ausfuhr bestimmter Arzneimittel gerechtfertigt, angemessen und nötig sein, um die Gesundheit von Patientinnen und Patienten zu schützen. Dazu liegen bislang aber weder

von der Europäischen Kommission noch vom Europäischen Gerichtshof verbindliche Aussagen vor. Die Auswirkungen des Parallelhandels auf die Gesundheit der Bürger/innen in der EU und deren Zugang zu Arzneimitteln bleiben jedoch ein kontrovers diskutiertes Thema.

Handlungsoptionen für die Zukunft

Wie würde sich DP für Medikamente in der EU auswirken? Dies lässt sich aus derzeitiger Sicht nur schwer abschätzen. Seine Einführung wäre jedenfalls ein enormer Kraftakt und würde entsprechenden politischen Willen der EU-Mitgliedstaaten erfordern, um die rechtlichen Hürden zu bewältigen und auch ein gemeinsames Verständnis über Prinzipien und Mechanismen eines DP-Systems für Medikamente zu schaffen. Angesichts der hohen Preise einiger Arzneimittel stehen die EU-Mitgliedstaaten zunehmend vor der schwierigen Herausforderung, ihren Patientinnen/Patienten Zugang zu diesen Medikamenten zu gewähren. Ein umfassendes „echtes" DP-System scheint kurzfristig nicht politisch umsetzbar. Die EU-Mitgliedstaaten könnten allerdings überlegen, Charakteristika von DP in ihre EPR-Systeme einfließen zu lassen. Daneben bestehen kurzfristige Optimierungspotentiale für EPR mittels Preismonitoring und der Berücksichtigung rabattierter Preise in den Preisvergleichen. Diese Maßnahmen würden allerdings in erster Linie dazu beitragen, Einsparungen zu erzielen, nicht jedoch den Zugang zu Arzneimitteln verbessern.

Neben den beiden in dieser Studie untersuchten Maßnahmen könnten die EU-Mitgliedstaaten weitere neue Ansätze in der Arzneimittelpreispolitik verfolgen, wie zum Beispiel gemeinsamen Einkauf (nicht Gegenstand dieser Studie). Es wird empfohlen, Foren – wie etwa das im Rahmen dieses Projekts stattgefundene Treffen mit Akteuren zur Kommentierung des vorliegenden Berichts – zu nutzen, um Handlungsstrategien hinsichtlich hochpreisiger Arzneimittel gemeinsam zu diskutieren.

1 Introduction

This report represents the final report for the Request for Specific Services No 2014 73 03 for the implementation of Framework Contract No EAHC/2013/Health/01 'Health economic reports – analysis and forecasting' (Lot 2) for the 'Study on enhanced cross-country coordination in the area of pharmaceutical product pricing'.

1.1 Objectives

The **general objective** of this study is to examine the policy options of external price referencing (EPR) and differential pricing (DP), respectively, in terms of increased cost containment and increased accessibility of medicinal care. The study aims to gain insights into possible benefits from improving cross-country policy coordination in the area of pharmaceutical pricing, by getting a deeper understanding of EPR and DP in terms of technical, economic and legal considerations for both policy avenues in the European Union (EU). Pricing policies beyond EPR and DP were not in the scope of this study; also, reward for innovation and further policy objectives were not explicitly mentioned in the tender specifications to be considered in-depth specifically for this study.

The Request or Specific Services No Chafea/2014/Health/09 for the implementation of Framework Contract No Chafea/2013/Health/01 (Lot 2): Health economic reports – analysis and forecasting (Study on enhanced cross-country coordination in the area of pharmaceutical product pricing) lists the following **specific objectives**:

- to describe which possible improvements could be made to the currently existing EPR schemes, supported by technical analyses outlining the impact, particularly related to the cost-containment aim to optimise savings for public payers;
- to describe how differential pricing schemes could possibly be designed for European countries, and to explore which prerequisites (including addressing legal constraints) are needed to be addressed in order for differential pricing to be applied in EU Member States; again supported by technical analyses outlining possible effects, particularly related to improving access and affordability for patients;
- to explore which coordination mechanisms (EU-level cooperation) would be required to support an improved EPR system, and to outline a possible DP scheme through EU-level cooperation;
- to consult with relevant stakeholders on the draft findings and preliminary conclusions.

While in literature and policy discussions EPR and DP schemes are usually considered as mutually exclusive policy options, this study is intended to be open in considering a possible integration of typical aspects of one scheme into another. One prerequisite of the report was not to take a relative preference for either EPR or DP in the EU but to study possible approaches for improvements and implementation.

1.2 Activities and deliverables

This study was performed by a consortium composed of Gesundheit Österreich Forschungs- und Planungs GmbH (GÖ FP, project leader) and SOGETI Luxembourg S.A. (consortium leader), together with the University for Health Sciences, Medical Informatics and Technology (UMIT) as sub-contractor related to the legal analysis.

The tender specifications state seven tasks of the project. These tasks, composed of two to four activities each, are summarised in Figure 1.

Figure 1: Overview of tasks and activities

Source: The authors

Table 1 provides an overview on how the specific objectives summarised in Chapter 1.1 were linked to these tasks.

Table 1: Defined tasks and research questions

External price referencing (EPR)	Differential Pricing (DP)
Task 2: How does EPR work now (in Europe)? How can EPR be improved?	*Task 4:* How does DP work now (wherever applied, e.g. in low- and middle-income countries)? (How) can DP be implemented in the EU?
Task 3: Which EU coordination mechanisms would be required to improve EPR?	*Task 5:* Which EU coordination mechanisms would be required to implement DP in the EU?
Task 6: Stakeholder review	
Task 7: Reporting and peer review	

Source: The authors

The final report was submitted to the European Commission (EC) on 18 December 2015, as specified in the tender specifications, i.e. twelve months after the project start on 19 December 2014. This final report was produced taking into account comments from several review loops. A first draft version that summarised the preliminary findings of Tasks 2, 3, 4 and 5 had been sent to the EC on 23 June 2015. A revised version following feedback from Commission staff during a meeting and further comments in writing by some Directorates-General (SANTE, GROW, COMP) of the EC was submitted to stakeholders in August 2015 (cf. Chapter 3.5.1). Following the stakeholder review, a revised version was sent to peers for their review in October 2015 (cf. Chapter 3.5.2). A draft final report submitted to the EC on 18 November 2015 incorporated the changes of peer reviewers and EC services.

1.3 Outline of the report

This report has five further chapters which follow, to a large extent, the defined tasks and activities.

Chapter 2 – Background and context: Based on findings from preceding evidence the rationale for this study is explored.

Chapter 3 – Methodology: This methodology chapter presents, in different sub-sections, the methodological approaches adopted for the literature review, the survey of competent authorities, the expert interviews, the simulations and legal analysis, and the stakeholder and peer reviews (supplemented by Annex 15 and 16).

Chapter 4 – Results: In this chapter, the findings of Tasks 2 (EPR) and 4 (DP) are presented i.e. a survey and an analysis of the existing schemes of the two policies.

Chapter 5 – Proposals for cooperation mechanisms: This chapter provides proposals related to EU coordination mechanisms for improvements of EPR (Task 3) and for a possible implementation of DP in Europe (Task 5).

Chapter 6 – Conclusions and policy recommendations: In the concluding chapter, policy recommendations based on the findings are discussed.

The report is accompanied by 17 annexes.

2 Background and context

2.1 Challenges

Health care systems in Europe have increasingly been confronted with numerous challenges such as population ageing associated with the rise of chronic diseases and multi-morbidity, rapid spreading of new (high-cost) health technologies, increasing citizens' expectations and, at the same time, a tightening of health budgets [1-4].

Over the decade, pharmaceutical expenditure per capita has been rising. During the global financial crisis, the growth in health and pharmaceutical expenditure has slowed down and was negative in several European countries [5]. The crisis has hit some European countries particularly hard (Greece, Spain and Portugal, for instance) and led to cuts in health care investments. Beyond financial implications, first analyses of the impact of the crisis imply negative effects on the quality of health services and also on health outcomes [6-11].

However, recently updated OECD data (as of 2013) shows that pharmaceutical expenditure has been rising again and has reached pre-crisis levels in several European countries [12]. This is particularly attributable to demographic developments in the EU, the emergence of new high-cost medicines, particularly biological medicines, and an increasing use of 'personalised', or 'stratified medicines'.

The challenge of high-cost medicines has increasingly been addressed by researchers and policy-makers. The relevant literature [13, 14] highlight high prices of some medicines, in particular in the oncology area and for Hepatitis C, which lead to a situation that a considerable share of the public budget is spent on only a few medicines. At meetings and conferences this has been discussed as a major issue [15, 16], and policy papers at EU and national levels expressed concerns about high prices of medicines, as is will be shown in Chapter 2.3.

Recent studies on new medicines have shown, partially wide, differences in price across European countries which are not necessarily in line with the economic situation of the respective countries [17-19]. Among the European Union countries, Germany, Sweden and Denmark tend to be high-priced countries for new medicines, whereas Central and Eastern European countries were at the lower end [20]. In price comparisons excluding Central and Eastern European countries, Greece, Portugal and Spain tended to be at lower ranks [17, 21-23].

While possible therapeutic innovation is welcomed by patients (even if some promising medicines do not fulfil the expectations), high-priced medicines are a major challenge for many countries around the world, including European countries, in their efforts to ensure equitable access to high-quality medicines while securing long-term financial sustainability. Access to medicines is a major policy objective, which needs to be balanced with other policy objectives. In the EU, Member States are committed to balancing their policies in order to achieve the partially conflicting policy objectives of '(1) timely and equitable access to pharmaceuticals for patients all in the EU, (2) control of pharmaceutical expenditure for Member States, and (3) reward for valuable innovation within a competitive and dynamic market that also encourages Research & Development' [24]. As outlined in Chapter 1, this study aims to examine selected policies with regard to the objectives of access to medicines and cost-containment whereas the analysis of policies with regard to ensuring reward for innovation was not defined as an explicit research objective.

2.2 Pricing policies

National policy-makers have the responsibility to choose the most appropriate policy options and to implement them in a design that best achieves their policy goals. As described in a recently published WHO review on 'Access to New Medicines in Europe' [3], pharmaceutical policies may be located at different stages related to the launch of the medicines: before the launch of the medicine on the market ('pre-launch activities'), at the time of the launch of the medicine being launched ('peri-launch activities') and after launch ('post-launch activities'). Pricing, i.e. the setting of the price of a medicine [25], is, together with reimbursement, a peri-launch activity.

In the European Union, pharmaceutical pricing and reimbursement decisions are the competence of the EU Member States under the condition that EU provisions, such as the Transparency Directive [26], are respected. At country level, pricing is typically the competence of the Ministry of Health or a Medicine Agency. In some Member States, pricing and reimbursement competences are combined in one authority (e.g. the Medicine Agency in Italy), whereas in other countries there are different institutions for pricing and reimbursement (e.g. in Austria, pricing with the Ministry of Health and reimbursement with the social health insurance); for an overview see a book chapter on pricing in Europe [27].

Policy-makers have different policies to determine medicine prices. The most common pricing policy in European countries and increasingly world-wide is external price referencing (EPR) [28, 29]. EPR, which is also known under different names such as external referencing pricing (ERP) or international price comparison / benchmarking, 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' [25]. Details on the use of EPR in European countries is provided in Chapter 4.1.1, based on own survey results among EU Member States and countries beyond.

Literature and practice suggests that EPR has limitations, such as incentivizing the first launch of medicines in countries with a high price level and delayed or no launch of medicines in countries with a low price level, possibly contributing to observed medicine shortages or to price convergence, risk of overpaying of public payers due to referencing to official list prices instead of confidential discounted prices [28, 30, 31]. However, EPR was also found to be able to contribute to generating savings for public payers [21, 32-34]. A detailed discussion of benefits and limitations of EPR is undertaken further in the study (cf. Chapter 4.1.2.1).

In response to the limitations of EPR, many EU Member States have increasingly been considering value-based pricing (VBP) elements in their pricing and reimbursement decisions [35], even if VBP as an integrative fully-fledged pricing and reimbursement policy has only been implemented in Sweden. The planned VBP in the UK has not been implemented [27].

Another reaction to observed limitations of EPR has been the call for the implementation of differential pricing in the EU (see, for instance, a discussion in the European Parliament [36] or a stakeholder's position paper [37]). Differential pricing is defined as 'the strategy of selling the same product to different customers at different prices. In the case of (reimbursable) medicines prices would vary among the countries according to their ability to pay' [25]. The use of differential pricing has been limited to low- and middle-income countries (LMIC), particularly to specific therapeutic groups such as vaccines, contraceptives and anti-retrovirals (ARV) [4, 38]. Currently, differential pricing in the EU appears difficult, and possible positive effects would be undermined by

the practices of parallel trade and EPR schemes. Practice and experience with differential pricing outside the EU is outlined in this study in Chapter 4.2.1.

The pricing policies of EPR, DP and VBP particularly address new medicines and can be supplemented by specific policies targeted at generic medicines [1, 39, 40]. Neither generic policies nor VBP are the scope of this study.

2.3 Policy initiatives

2.3.1 EU processes and initiatives

On the 4th of April 2014, the European Commission published a communication on several actions to be undertaken in order to increase the effectiveness and accessibility as well as to improve the resilience of health systems of EU Member States [41]. With regard to the cost-effective use of medicines (one of the five defined objectives under the 'Reflection process - Towards modern, responsive and sustainable health systems' [42] and in order to reconcile the policy objectives of ensuring accessible healthcare for all EU citizens with the need for cost containment, it was suggested to give consideration to 'improved cooperation on building mechanisms for increased transparency and better coordination to minimise any unintended effects that current national pricing systems may have in terms of accessibility throughout the EU' [41]. On the 20th of June 2014, the 'Council conclusions on the economic crisis and healthcare' of the Council of the European Union invited the European Commission to 'support, as appropriate, exchange of information between Member States on policies related to pharmaceutical products and medical devices, with particular attention being paid to small markets' [43]. On the 1st December 2014, the 'Council conclusions on innovation for the benefit of patients' [44] noted with concern that 'due to the very high prices of some innovative medicinal products in relation to their benefit to patients and to the public health expenditure capacities of some Member States, patients do not always have access to innovative treatments'. Member States were invited to 'increase the effective sharing of information on prices of and expenditure on medicinal products, including innovative medicinal products', and, while fully respecting the Member States' competencies, the European Commission was invited to 'support the exchange of information between Member States on prices, pricing policies and economic factors determining the availability of medicinal products as well as, where appropriate, medical devices, with particular attention being paid to orphan medicinal products and small markets as they are particularly vulnerable to deferred or missed market launches, supply shortages and obstacles to achieving affordable prices of medicinal products' and to 'continue to support research and information tools that aim to provide a better understanding of how pharmaceutical pricing may be applied to maximise benefits for patients and Member States' health systems and, where relevant, to minimise possible unintended negative effects on patient access and health budgets' [44].

In the context of the sub-group on 'cost-effective use of medicines', two studies were commissioned and produced which are also of relevance for this study[1]:

- The study 'External reference pricing of medicinal products: simulation-based considerations for cross-country coordination' [45] offered a simulation model to

[1] The investigators of this study were asked by the EC to base some of their research activities incrementally on the findings achieved in the study of Toumi M, Rémuzat C, Vataire A-L and Urbinati D [45]. In particular, investigators were commissioned to run some simulations for EPR done in the other study, however with updated data.

identify and assess the main parameters impacting medicine price dynamics within external price referencing systems, and concluded that if EPR was considered as an isolate pricing policy it could lead to lower medicine price erosions than what could be observed in real life, suggesting that other pricing policies, potentially amplified by EPR, were contributing to driving prices down. Frequent price revisions, iterative price cuts, large reference country baskets, price calculation methods, genericisation impact and prices' sources were identified as major factors to impact medicine price development over time in systems using EPR.

- The 'Study of the policy mix for the reimbursement of medicinal products. Proposal for a best practice-based approach based on stakeholder assessment' [46] explored which pharmaceutical policies stakeholders (payers, competent authorities, research-oriented and generic industry, patients and consumers, health care professionals) considered as preferred. Based on the stakeholders' assessments investigated in a Multi-Criteria Decision Analysis (MCDA), the authors developed a proposal for the best practice-based approach for such a policy mix, reconciling the different, often conflictive policy objectives. The stakeholder survey showed that EPR ranked last (rank 10) when various policies' ability to achieve the different policy objectives was evaluated, whereas DP was considered as more preferred (rank 7). The analysis per stakeholder showed that the research-oriented industry had a very low preference for EPR (rank 10 = last rank) and an interest in DP (rank 4), whereas competent authorities for pharmaceutical pricing and reimbursement as well as public payers had neither preference for EPR nor for DP. Competent authorities ranked both EPR and DP last (rank 11), and public payers ranked DP last (rank 12); this was preceded by EPR and the policy of discounts/rebates/price negotiations/claw-backs (both rank 11).

During the last 10-15 years, EU processes were held in the area of the medicines: In response to the 'Pammolli report' [47], the European Union established the G10 group –ten selected Member States and stakeholder representatives– who presented recommendations on how to enhance competitiveness and innovation in the pharmaceutical sector in Europe in 2002, thus also addressing pricing issues (e.g. the scope of price control) [48]. For advancing the G10 recommendations, the European Commission adopted the Communication entitled 'A stronger European-based pharmaceutical industry for the benefit of the patient – a call for action' in July 2003 and proposed to 'provide a forum for Member States to generate and share information on common relative effectiveness issues in the context of pricing and reimbursement decisions' [49]. To follow up on these recommendations, the High Level Pharmaceutical Forum was set up in 2005 as a three-year process involving all EU Member States and stakeholders. The Pharmaceutical Forum focused on three main topics: information to patients on diseases and treatment options, pricing and reimbursement policies, and relative effectiveness. The High Level Pharmaceutical Forum recommended authorities and stakeholders of the Pharmaceutical Forum to 'strengthen their efforts in ensuring timely access to valuable innovations and in ensuring access to medicines for all citizens' [24]. With regard to an optimal use of resources, it was recommended that 'national pricing and reimbursement policies should ensure an efficient use of price control, a consistent package of supply- and demand-side measures and the right environment for price competition'. One G10 recommendation had defined the principle that EU Member States could control prices of reimbursable medicines (these are medicines purchased and/or reimbursed – at least partially - by the State), whereas for non-funded (non-reimbursed) medicines marketing authorization holders should be allowed to freely price medicines. This principle was confirmed by the High Level Pharmaceutical Forum. Also, the need for further cooperation and exchange of experiences at EU level was again expressed by the High Level Pharmaceutical Forum [24].

Based on the Pharmaceutical Forums work, the European Commission followed the recommendation for a continuation of cooperation and sharing of experiences at the EU level. The network of Competent Authorities for Pharmaceutical Pricing and Reimbursement (CAPR) was set up by EU Member States, at the initiative of the Slovenian Presidency in 2008, and in 2010 the Process on Corporate Responsibility in the field of Pharmaceuticals was launched as a voluntary multi-stakeholder process with three independent platforms. The platform 'Access to medicines in Europe' aimed at finding common non-regulatory approaches to enable timely and equitable access to medicines after their marketing authorisation. Its six working groups addressed orphan medicines, biosimilar medicines, Over-the-Counter (OTC) medicines, supply in small markets, managed-entry agreements and prioritization. The outcomes of the five first working groups of Platform on Access to Medicines in Europe were endorsed by the Steering Group in April 2003 ([50]). In July 2013, the Priority Medicines Report [2] (connected to the working group 'prioritization') was published.

In this context, two further projects should be mentioned:

- The CAPR network and the working groups of the platform 'Access to medicines in Europe' under the Process on Corporate Responsibility were supported by the European Medicines Information Network project (EMINet) consortium[2]. The EMINet study 'Short- and Long-Term Effects of Value-Based Pricing vs. External Price Referencing' [52] discussed the relative merits and limitations of the two policies VBP and EPR, particularly with regard to the impact on medicine prices and on reward for innovation (the discussion of benefits and limitations of EPR in Chapter 4.1.2.1 will refer to some of the results).
- With the support of an EU grant, the European medicines price database called Euripid was established [53]. In its report as of 25 January 2013 on the proposal for a revised Transparency Directive, the European Parliament advised the Commission and the Member States 'to examine how to continue to co-operate on the functioning of the Euripid price information database, which provides EU-wide added value in terms of price transparency' [54]. After the end of the EC funding in December 2014, Euripid was organised as a self-administered and self-funded project of EU Member States, and in 2015 its organisational format was changed again, following being awarded the project 'Statistical data for medicinal product pricing' under the 3rd Health Programme. Further information about Euripid will be provided in Chapter 5.1 as this will be explored as one of the EU's coordination options.[3]

The EU Joint Procurement Agreement (JPA) for pandemic vaccines and medical countermeasures as of April 2014 entered into force in July 2014. It determines the practical arrangements governing the joint procurement, the decision-making process, and the awarding of the contract [55]. Since the potential of the JPA was thought to reach beyond vaccines for pandemics, it is also further addressed in the discussion on the cooperation options (cf. Chapter 5.2.2).

[2] EMINet was launched in December 2008 to provide information, technical expertise and analysis on pharmaceutical pricing and reimbursement policies and related topics such as the distribution or rational use of medicines during 2009 until 2012 [51]. The EMINet consortium consisted of the project leader Gesundheit Österreich GmbH (GÖG), London School of Economics (LSE) and Andalusian School of Public Health (EASP).

[3] The consortium of this study was asked by the EC to cooperate with the contractor in charge of the project 'Statistical data for medicinal product pricing' in the 3rd Health Programme: The work performed in the framework in this study should also be considered in the other project.

In June 2014, the European Commission published a Working Document entitled 'Pharmaceutical Industry: A Strategic Sector for the European Economy' which, provides an overview about EU initiatives and activities in the field [56].

The years 2014 and 2015 have seen some new pharmaceutical activities and initiatives that, while not focusing on pricing, are of relevance, in particular with regard to new high-cost medicines. The European Medicines Agency (EMA) launched the adaptive pathways pilot project [57, 58]. The concept of adaptive pathways foresees an early approval of a medicine for a restricted patient population based on small initial clinical studies. The first approval is followed by progressive adaptations of the marketing authorisation to expand access to the medicine to broader patient populations based on data gathered from its use and additional studies. At the beginning of 2015, the Commission expert group on 'Safe and Timely Access to Medicines for Patients' (STAMP) was created. It shall provide advice and expertise to the Commission services in relation to the implementation of the EU pharmaceutical legislation, as well as programmes and policies in this field. The aim of the group is to discuss experience acquired so far with the implementation of the EU pharmaceutical legislation and national initiatives, and identify ways to optimise the use of existing regulatory tools to further improve safe and timely access and availability of medicines for patients. The work of the EMA, including the pilot project on adaptive pathways, will be part of this discussion [59, 60].

The latter initiatives are examples of collaboration between EC and Member States that bridge between regulatory issues and pricing/reimbursement policies.

2.3.2 Further initiatives

In 2013, the World Health Organization (WHO) published the WHO Guideline on Country Pharmaceutical Pricing Policies which aimed to assist national policy-makers and other stakeholders in identifying and implementing policies to manage medicine prices. The Guideline contains one section which addresses the commonly used EPR practice [31]. In 2011, a WHO/HAI review [28] looked into the practice of EPR world-wide.

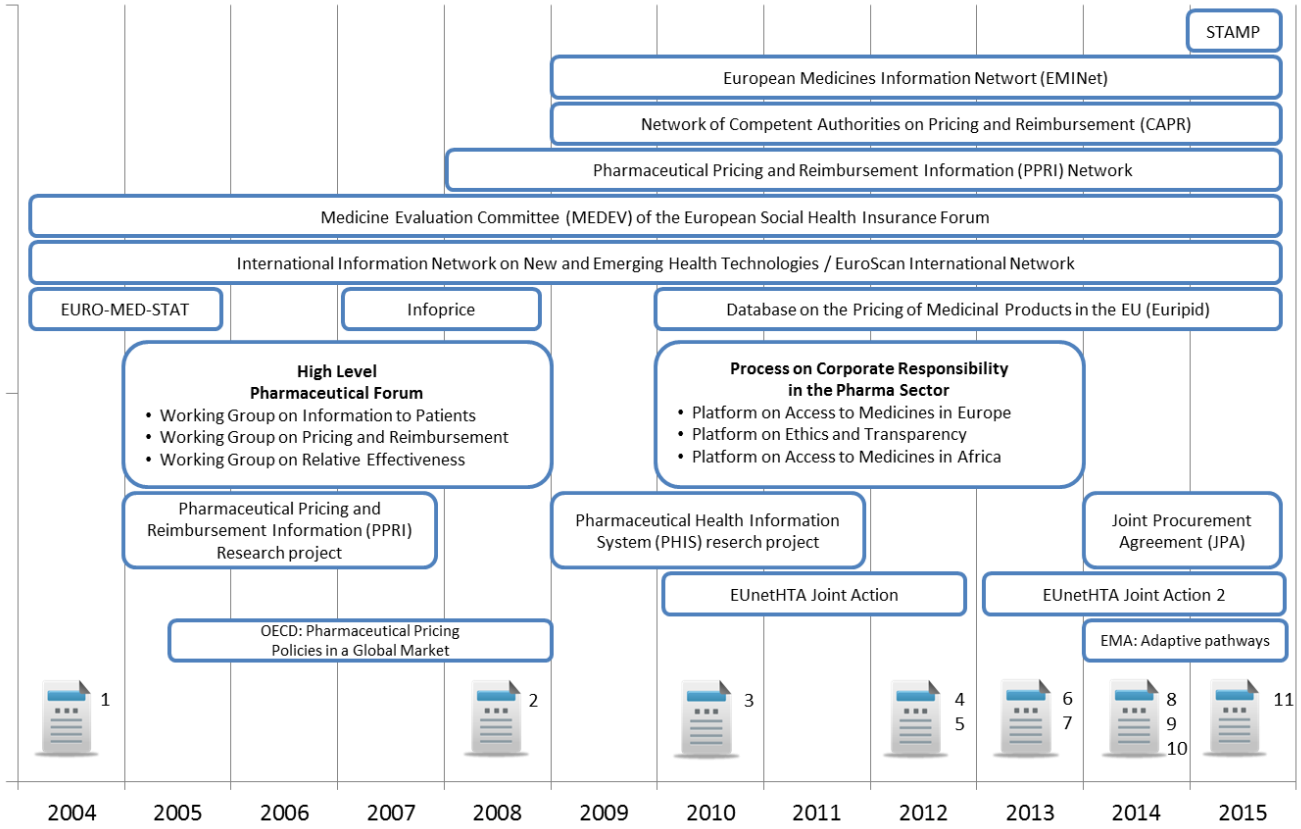
The WHO guideline followed long-term policy-advice and guiding work of WHO in Europe and other regions of the world. In 2010, the Pan American Health Organization (PAHO) published a report on 'Access to High-Cost medicines in the Americas' [61], and in 2015 the Regional Office for Europe of the WHO released a review on access to new medicines in Europe, with a particular focus on high-priced medicines [3].

For more than a decade, WHO has been calling for further exploring, implementing and analysing the concept of DP, particularly in LMIC, as an alternative to high prices when separated high- and low-to-middle-income markets exist for a medicine and when the supplier exerts significant power over pricing, such as when there is limited or no competition due to patent protection, data exclusivity, or other markets. In the Priority Medicines Report 2004, an approach with thresholds (of maximum prices per medicine as determined by economic evaluation) was proposed for each country based on the national income level as a way forward to enhance innovation and provide access to medicines, particularly for middle-income countries [62, 63].

The Organization for Economic Co-operation and Development (OECD) has also been working on pharmaceutical policies and medicine prices. The 2008 OECD report 'Pharmaceutical Pricing Policies in a Global Market' pointed at the impact of pharmaceutical policies outside borders: 'External price referencing (or international benchmarking) stands to affect the prices and availability of medicines outside the country undertaking the benchmarking practice by reducing the manufacturers' willingness to set prices according to national market conditions. This may have a

negative effect on affordability and availability of medicines in smaller markets and lower-income countries.' [64]. An OECD study about VBP [35] addressed the policy of EPR due to its given relevance and the implications of VBP in most referred countries on the other countries using EPR. On 24 June 2015, the OECD addressed the topic of high-cost medicines in a workshop entitled 'High Cost Medicines: Are New Pharmaceutical Business Models Compatible with Efficient and Sustainable Public Spending in Medicines?'.

Figure 2: Initiatives, projects and reports in the field of pharmaceutical pricing in Europe



Reports: (1) Kaplan/Laing (2003): Priority Medicines for Europe and the World [65]; (2) OECD (2008): Pharmaceutical Pricing Policies in a Global Market [64]; (3) European Commission (2010): Joint Report on Health Systems [66]; (4) Toumi et al. (2012): EU Pharmaceutical expenditure forecast [67]; (5) Carone et al. (2010): Cost-containment policies in public pharmaceutical spending in the EU [1]; (6) Kaplan et al. (2013): Priority Medicines for Europe and for the World, 2013 Update [2]; (7) Paris/Belloni (2013): Value in Pharmaceutical Pricing [35]; (8) Vogler et al. (2014): Study of the policy mix for the reimbursement of medicinal products [46]; (9) Toumi et al. (2014): External Reference Pricing for medicinal products [45]; 10) European Commission (2014): Pharmaceutical Industry: A strategic sector for the European economy [56]; (11.) WHO, Regional Office for Europe (2015): Access to new medicines in Europe [3]

Source: Overview compiled by GÖ FP, 2015

3 Methodology

The findings of this study were compiled through a range of different data collection and analysis methods.

3.1 Literature review

The literature review aimed at exploring findings related to the use, experiences with and evaluations of the EPR and DP pricing policies and their impacts on accessibility, savings and other public health goals. In addition, the literature review related to the DP also aimed at identifying DP schemes in place, theoretical (background) literature on DP and the pre-requisites required to implement such schemes.[4]

3.1.1 Literature search

The systematic literature search on EPR followed the same search strategy as in Toumi M, Rémuzat C, Vataire A-L and Urbinati D [45] since tender specifications required the literature review on EPR to be incremental to that study. The scope of the search was external price referencing (not internal reference pricing) for medicines (except vaccines) in the 28 Member States of the EU, Norway, Switzerland, Turkey and Iceland. As an incremental literature search to EPR, the period was restricted to the period from December 2012 until January 2015. In contrast, the systematic literature search on DP was not restricted to any country, and it covered the period from January 1997 until January 2015. In both searches, studies in English, German, French, Spanish and Italian were considered. The detailed search strategies are outlined in Annex 1.1.

In order to conduct an adequate incremental systematic literature review on EPR, the same international databases were searched: Medline (consulted through Ovid website), EMBASE (searched on the Ovid website) and EconLit. Additionally, a thorough hand search was conducted including a systematic search on the internet, in the reference lists of the identified studies and the websites of the international organisations (e.g. EU, WHO, OECD) and networks for relevant literature. These literature databases and sources were also used for the literature review on DP.

3.1.2 First and second selection of relevant publications

Screening and selection of the abstracts and full texts were based on criteria defined ex-ante. The selection of the studies was subdivided into a first selection of publications and a second selection of full texts.

The first selection of publications was based on available abstracts and titles (the latter in case abstracts were not available). The inclusion/exclusion of literature dealing with EPR followed criteria laid down in Toumi M, Rémuzat C, Vataire A-L and Urbinati D [45] concerning the date, language, country and context of the study (cf. Table A1 in Annex 1.1). For the second selection, full texts of all included abstracts were thoroughly read and selected using the same criteria. The selection of publications on DP followed the

[4] In order to have most up-to-date information (and to avoid the publication bias), the current existing EPR schemes in Europe were surveyed through primary research by a survey of competent authorities for pharmaceutical pricing and reimbursement that validated information of the authors (cf. Chapter 3.2.1 for the methodology).

same procedure, but different criteria for inclusion/exclusion were applied (cf. Table A2 in Annex 1.1).

3.1.3 Results of literature search and selection

In the systematic literature search for EPR a total of 1,115 abstracts were identified (duplicates were excluded). After the selection of relevant abstracts according to pre-defined criteria, 66 references qualified for further reading, of which full texts were available in 64 cases. In addition, a systematic internet search added 10 relevant publications. After reading the full texts, 45 publications proved relevant to provide further information with regard to the research question (for the graphical illustration of the selection process for literature related to EPR, please refer to Figure A1 in Annex 1.3).

Through systematic literature search for DP, the authors identified a total of 652 abstracts (duplicates were excluded). After the selection of relevant abstracts according to pre-defined criteria, 59 references qualified for further reading, of which full texts were available in 58 cases. In addition, a systematic internet search added seven relevant publications. After reading the full texts, 56 publications proved relevant to provide further information with regard to the research question (for the graphical illustration of the selection process for literature related to DP, please refer. Figure A2 in Annex 1.3).

When reading the full texts, relevant information was collected and documented in a literature matrix (for the structure of the literature matrix: Annex 1.4).

The information from the literature review was used to discuss the experiences with EPR (Chapter 4.1.2) and to back the proposal for further information included in EPR (Chapter 4.1.3) as well as to report on use and experiences (Chapter 4.2.1). Even if the literature review was sought to be incremental (e.g. only new literature), findings from literature stemming from the discussion of experiences were also included (Chapter 4.1.2) as to provide a more complete picture.

3.2 Primary and secondary data collection

3.2.1 Survey of competent authorities

Since literature tends to be slightly outdated and would thus not be able to accurately describe the current situation, it was decided to perform a survey aiming at gathering the most up-to-date information. The use and practice of EPR as of 2015, including detailed methodological information, was predominantly surveyed with competent authorities for pharmaceutical pricing and reimbursement in all 28 EU Member States, Iceland, Norway, Switzerland and Turkey.

A questionnaire composed of 16 items was designed (cf. Annex 3 for the questionnaire).

Since the authors already had in-depth knowledge on the use of EPR in the surveyed countries and wanted to ease the work load for the potential respondents, a two-step approach was chosen:

- The existing information on EPR surveyed in previous researches and continuous monitoring of countries' policies was compiled. Most of the information was obtained from the PPRI (Pharmaceutical Pricing and Reimbursement Information) network of competent authorities whose secretariat is located with the authors affiliated to GÖ FP.

- The developed questionnaire based on the existing information for the 32 selected countries was pre-filled and the competent authorities were asked for validation and for the adding of missing information relating to their country. The competent authorities addressed were, in most cases, the same respondents as in the study of Toumi M, Rémuzat C, Vataire A-L and Urbinati D [45] (for the list of respondents, see Annex 4). In case of delayed and little responsiveness, the authors used their existing contacts with the authorities to identify possible alternative respondents.

The survey with the competent authorities was launched on the 16th of March 2015 and was aimed to be finalised by the 31st of March 2015. Personalised e-mails with the survey in attachment were sent to representatives of the competent authorities in all 28 EU Member States, Iceland, Norway, Switzerland and Turkey. The survey was presented to competent authorities during a PPRI network meeting held in March 2015, with the aim to increase the response rate. Two reminders were sent per e-mail to the respondents in April and May 2015, supplemented by further personalised reminders.

Eventually, responses from all 32 countries were received. The last validated questionnaire was returned to the authors on the 17th of June 2015.

The survey results are described in Chapter 4.1.1.

3.2.2 Interviews with DP experts

In order to obtain additional information about practice and experience with current DP schemes for medicines, interviews with experts in this area, particularly from procurement agencies and international institutions such as UNICEF, UNITAID and the Global Alliance for Vaccination and Immunisation (GAVI) were carried out. We selected experts who are or were practically involved in DP schemes, since the knowledge gained from the interviews should supplement the evidence from literature. Some interview partners were recommended by other interviewees. Experts, typically from academia, who had already been selected and agreed upon with the EC as possible peer reviewers, were excluded since we aimed to get their input through the peer review.

The questionnaire and the list of interviewees can be found in Annexes 6 and 7.

Information gained from the interviews was included in the discussion about use and experiences with DP (Chapter 4.2.1).

3.2.3 Research about cooperation mechanisms

In order to obtain more information on practices, costs, benefits and limitations of a central medicine price database, which was one of the cooperation mechanisms to be investigated, the experts involved in the management of the European medicine price database Euripid were contacted and three interviews with members of the project management and Executive Board of Euripid were conducted (for the questionnaire, please refer to Annex 9). The information was used for Chapter 5.1.1.

The authors were also asked to investigate possible cooperation mechanisms beyond pharmaceutical pricing. Therefore, we conducted a desk-top research on the EU Emission Trade System, the Common Agricultural Policy (CAP) and air travel regulation. The results are presented in Annex 14.

3.3 Simulations

3.3.1 Rationale of the simulation model

A basic simulation model was built with the aim of achieving the following objectives:

- to illustrate the general workings of EPR in price setting in European countries, similar to what was achieved in Toumi M, Rémuzat C, Vataire A-L and Urbinati D [45];
- to illustrate the impact of changes in EPR mechanisms, for instance the inclusion of additional parameters;
- to expand upon analysis on EPR systems and illustrate and compare the prices of a given medicine resulting from a simple differential pricing mechanism; and
- to support policy-makers by understanding the basic impacts of DP methodologies.

Intentionally, the framework was kept simple with the aim of clearly highlighting policy trade-offs and functioning of different methodologies, rather than aiming to estimate or project real price levels.

The model uses information on the actual EPR mechanisms and characteristics of the included countries, and estimates fictitious medicine prices, and, for illustrative purposes, also examples of real prices, under these actual EPR rules as well as impact on medicine prices when some of these mechanisms or rules are modified.

3.3.2 Model approach

The model is structured as a discrete-event simulation (DES) which is flexible and allows the tracking of different agents, in this case countries, through a number of defined events. The occurrence of events and their consequences depend on the country's attributes, such as EPR methodology, GDP, exchange rate and others. This study is an incremental analysis built on previous EU-commissioned work and the structure of the model is heavily based on Toumi M, Rémuzat C, Vataire A-L and Urbinati D [45] who simulated EPR mechanisms and impacts of changes in EPR policies. However, the focus here is on the use of fictitious scenarios to highlight specific features of EPR and inform the discussion on EPR policies compared to the concept of differential pricing.

In this model, at every discrete point in time, countries that are at a point of re-evaluation, update their medicine prices. This is done depending on the country's characteristics and EPR methodology and based on the prices of the previous time period of countries within the country basket.

Country attributes

The model uses up-to-date information on country characteristics and EPR methodologies collected through the country survey undertaken as part of the project (cf. Annex 10 for inputs used).

Country attributes included in the model are:

- EPR (Yes/No); No EPR: UK, Sweden, Denmark[5];
- Re-evaluation period in months;
- Minimum number of reference prices available;
- Method of calculation (average, minimum, average of 3 lowest, 3rd lowest);
- Country basket[6];
- Exchange rates;
- Type of price used (ex-factory, pharmacy purchasing price)[7].

As an example, Cyprus updates its EPR price every 12 months using a country basket of four countries and calculates the average pharmacy purchasing price. That means that within the model every 12 months after an initial price was set a re-evaluation occurs with the new price being the average of the reference countries' prices in the month prior to re-evaluation.

Time horizon

The basic time periods of the model are taken to be one month, with no re-evaluations taking place within one month. Most scenarios are run over a 10 year (120 months) horizon.

Country sample

Similarly to Toumi M, Rémuzat C, Vataire A-L and Urbinati D [45] the statistical scenarios ran for 28 EU Member States plus Switzerland, Norway and Iceland.

Limitations

The simple model aims at illustrating an exemplary medicine price across Europe under different policy rules. The model made several simplifying assumptions as clearly outlined above, and thus cannot, and does not aim to, perfectly forecast or predict the price of certain pharmaceuticals. Indeed, the purpose is to illustrate and explain the general workings of EPR. For instance, it was assumed that EPR was the only price determining criterion, ignoring other aspects such as negotiation, thus the model did not incorporate all aspects affecting medicine prices.

Further, no distinction is made between different types of medicines, and an exemplary (fictitious) product, rather than the overall price level, is illustrated. Annex 11 shows simulations using the same model for real current medicine prices for two products. Further, the model did not incorporate any volumes or demand elasticity information and thus can only provide judgements on price developments, but no conclusions on changes in turnover or overall savings of different stakeholders.

---

[5] Since EPR is applied in the hospital sector only in Denmark, the assumption of no EPR in Denmark was built into the model. Germany, on the other hand, was included in the model as EPR applying country even though EPR is not used systematically. However, it is provided for in the legislation, and with this assumption it was in line with the study of Toumi M, Rémuzat C, Vataire A-L and Urbinati D [45] which classified Germany as an EPR country.

[6] The Greek response to the country survey was received on the day of the deadline of submission of the draft interim report. Since it could not be clarified in the course of the project when exactly the extensions of the Greek country basket took place, this change in EPR methodology in Greece was not considered in the model input.

[7] Types of prices are converted using average wholesale margin information from Vogler S and Schneider P [68]

The model is static in nature, i.e. considers the development of prices under certain defined country attributes and policy rules. Dynamic effects, such as companies reacting to lower or higher profits, or countries adapting their rules based on overall spending, are not incorporated. This is relevant since, as is discussed in this report, pharmaceutical industry may respond strategically to EPR schemes.

These limitations mean that model results need to be interpreted carefully. The model aims at illustrating the workings of current EPR systems and the impacts of different methodological changes; it was, however not designed to perfectly predict medicine prices.

Data management and presentation

The model was calculated using Stata 13.1.

The findings of the simulations are presented in Chapter 4.1.4 (EPR) and Chapter 4.2.3 (DP), as well as in Annex 11.

3.4 Legal analysis

The legal analysis aimed at identifying legal constraints in EU law that prevent the introduction of an EU-wide coordinated DP scheme and the conditionalities of a legal framework that might serve to allow such an EU-wide policy. It is based on traditional legal research methods. When referring to 'traditional legal research methods' a theoretical, dogmatic approach is meant: for the analysis, EU law has been assessed and interpreted by using traditional methods of interpretation, including systematic interpretation (e.g. interpretation of secondary law in compliance with primary law), principle of primacy of EU law application, principle of uniformity and effectiveness of EU law and by analysing relevant European Court of Justice (ECJ) case law[8]. Legal documents as well as case law were obtained through the official EU law website (eur-lex.europa.eu/) and through the official website on case law of the ECJ (curia.europa.eu/juris/). Relevant case law was identified through basic legal documents of EU Institutions, literature and ECJ keyword search.

3.5 Reviews

In addition to internal reviews within the consortium and consideration of comments of the European Commission to ensure high quality of the report, a stakeholder review and a peer review were conducted for draft versions of this report.

3.5.1 Stakeholder review

The stakeholder review consisted of two components:

1) A written stakeholder review: On 8 August 2015, the authors sent the draft report to a total of 51 institutions, among which 13 stakeholders (associations / interest groups), 32 Member State institutions (pricing authorities), and six DP experts. Written comments were collected during August and September 2015.

[8] For current debates related to methods in European Legal Scholarship see Riesenhuber K [69], Gestel R and Micklitz HW [70], Hervey T, Cryer R, Sokhi-Bulley B and Bohm A [71].

2) A stakeholder review meeting, held with the participation of 34 representatives from EU Member States and interest groups in Brussels on 17 September 2015.

The methodology of the stakeholder review is described in the stakeholder review report in Annex 15.

3.5.2 Peer review

We identified academic experts with excellence in pharmaceutical pricing. It was aimed to balance representativeness with regard to geographic regions and expertise in EPR and/or DP.

The methodology of the peer review, including the selected peer reviewers, was agreed upon with the EC at the kick-off meeting in December 2014. In August 2015, 17 selected peer reviewers were contacted to announce the peer review and ask for cooperation. On 9 October 2015, the authors submitted a draft report to 16 potential peer reviewers (one candidate reviewer already declined when he had been contacted in August 2015) and asked for comments by 20 October 2015 at the latest. The deadline was extended until 9 November 2015. We received comments from 9 peer reviewers (counted per institution) between 11 October and 8 November 2015. All peer reviewers did the review pro bono. For further information on the peer review, including the list of peer reviewers, please refer to Annex 16.

4 Results

4.1 External price referencing

4.1.1 Use of EPR in Europe

This following overview about the use and practice of EPR refers to 32 European countries, including all 28 EU Member States, Iceland, Norway, Switzerland and Turkey. Information is based on a survey with competent authorities for pricing and reimbursement (for the methodology see Chapter 3.2.1).

4.1.1.1 Implementation of EPR

In the majority of European countries EPR is applied in one or the other way during the pricing process. EPR is in use in 29 countries whereas different approaches are applied in three countries: Germany, Sweden and the United Kingdom.

The system in Germany combines elements of free pricing, EPR and VBP following a reform act that the Parliament passed in November 2010, which aimed to strengthen the assessment of the benefit of medicines. Medicines with a new active ingredient are subject to an early benefit assessment which is conducted in the first year after market launch. At launch, marketing authorisation holders (MAH) have the right to set prices – which are entirely reimbursed–, and after one year the prices are re-negotiated taking into account the results of the assessment. For this early benefit assessment, manufacturers have to submit a scientific dossier to the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) demonstrating the added therapeutic benefit compared to treatment alternatives. The G-BA then authorises the Institute for Quality and Efficiency in Health care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWIG) to review the dossier and the price application. Together with expert hearings the G-BA decides on the added value and whether price negotiations are opened. During these price negotiations international prices are also taken into consideration [72].

In Sweden the price of medicines is determined through value-based pricing (VBP), in which the price is decided by the Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket, TLV) with respect to three key principles: (1) societal perspective, which bases on the principles of human value, need and solidarity and cost effectiveness[9], (2) threshold value, based on the individuals' maximum willingness-to-pay for a quality-adjusted life year (QALY) gained, and (3) marginal decreasing utility of treatments, which considers that the benefits of a treatment vary by indication or by degree of severity.

In the UK, MAH have the right to freely set their prices for branded medicines with a new active ingredient subject to the so-called Pharmaceutical Pricing Regulation Scheme (PPRS) which regulates the maximum profit of manufacturers. Even if there is freedom of pricing, the Department for Health has to agree to the price prior to launch.

[9] The human value principle states that health care should respect the equal value of all human life. The need and solidarity principle ensure that those with the most pressing medical needs have more of the health care system's resources than other patient groups. This principle interacts with the cost effectiveness principle, meaning that the cost of using a medicinal product should be reasonable from a medical, humanitarian and socioeconomic perspective.

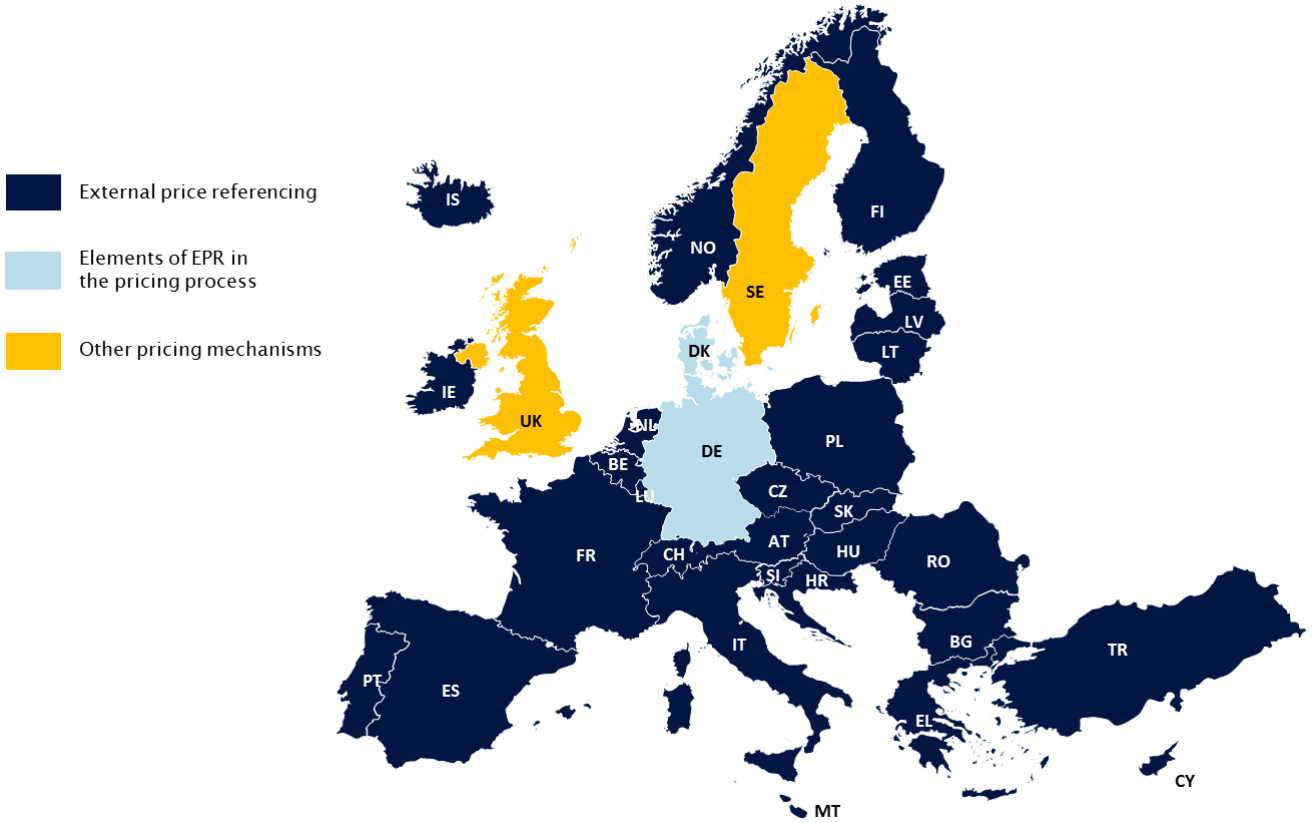
4.1.1.2 Relevance of EPR

Out of the 29 countries that apply EPR, 20 use EPR as the sole or main pricing policy. However, in some countries, EPR is limited to specific sectors and/or medicines. In Denmark, EPR was reintroduced in 2009 as a result of an agreement between the Danish Association of the Pharmaceutical Industry (Lægemiddelindustriforeningen, Lif), the Danish regions and the Ministry of Health that stipulated that EPR should act as price ceiling for new medicines in the hospital sector and contribute to cost-containment. In the out-patient sector in Denmark, prices of medicines are still set by the pharmaceutical manufacturer (free pricing). In Slovenia, the price of medicines determines how EPR is applied: EPR is the main policy for setting the maximum allowed prices, but is only a supportive policy for setting extraordinary higher prices or for lower prices agreed between the MAH and the purchaser/payer. In Ireland, EPR is used as a supportive policy to set prices for new single source on-patent medicines, whereas it is the main criterion for re-alignment of existing prices.

In ten countries EPR is used as a supportive criterion in the decision process, and prices in other countries are jointly considered together with other criteria. In these countries pricing authorities often take a broad range of factors into account when determining the prices for medicines that should be 'reasonable'. Other factors which are taken into account include (1) the cost of the therapy cycle, (2) benefits to be gained from the medicine use from the patients' perspective, (3) relative benefits compared to treatment alternatives, (4) budget impact i.e. analysis of the effects on the health care system, (5) funds available for reimbursement, (6) reward for innovation (provided that sufficiently detailed information about the research and development cost structure of the manufacturer has been submitted). The measurement of absolute benefits is done in QALYs gained and the level of the threshold values differ from country to country, often reflecting economic differences and the ability-to-pay.

The price application might undergo a thorough assessment. In France, for instance, a medicine is evaluated by the Economic Committee for Health Care Products (Comité Economique des Produits de Santé, CEPS) if the pharmaceutical manufacturer wants to launch the product in the reimbursement market. Before granting a price, the transparency commission of the French High Authority for Health (Haute Autorité de Santé, HAS) assesses the therapeutic value (Service médical rendu, SMR) and the added therapeutic value (Amélioration du service médical rendu, ASMR) of the medicine compared to treatment alternatives. The ASMR is rated on a scale ranging from ASMR I (major improvement, new therapeutic area, reduction of mortality) to ASMR V (no improvement). Based on this evaluation, CEPS enters into price negotiations with the MAH. However, only medicines with ASMR I-III are eligible for EPR and they are subject to Health technology assessment (HTA) evaluation.

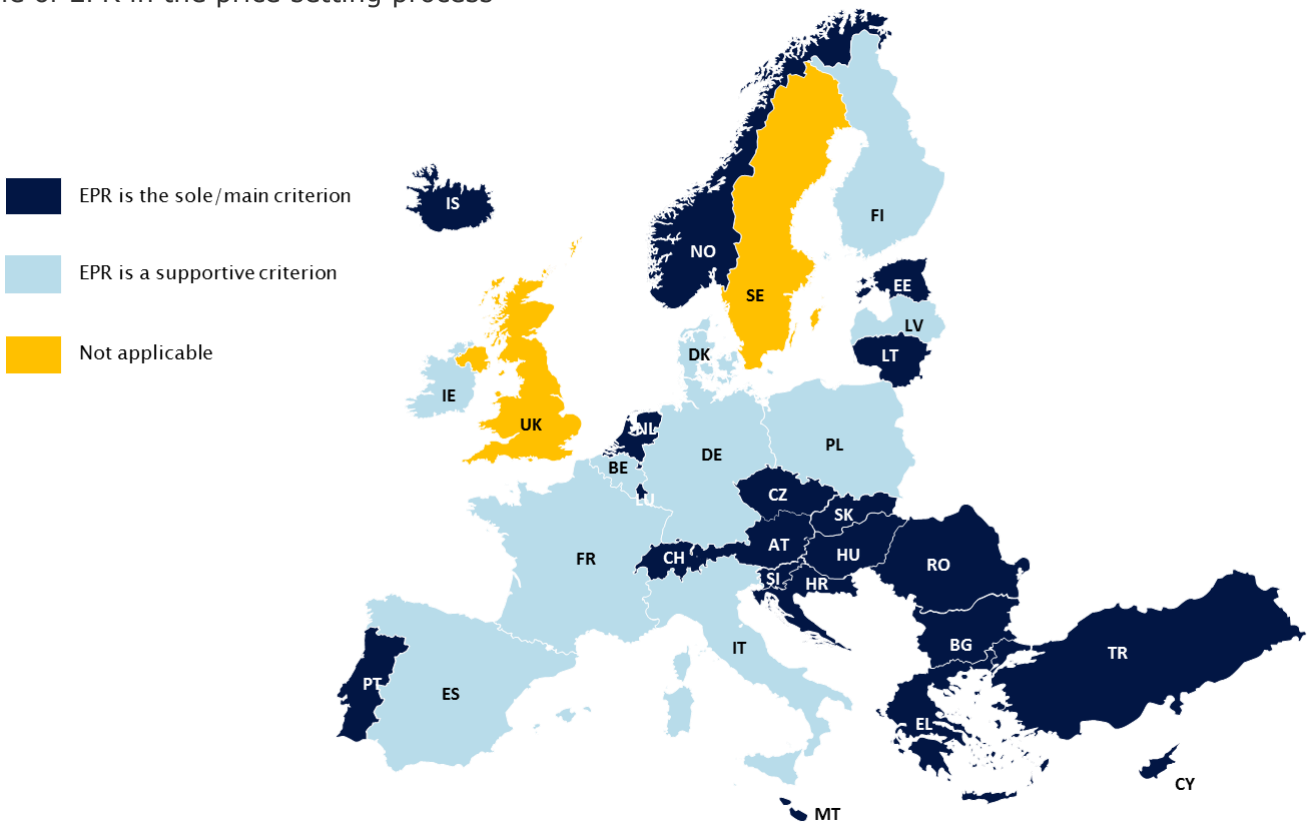
Figure 3: Use of external price referencing (EPR) in European countries



DK: EPR is used to set the price cap for new medicines in the hospital sector. In the out-patient sector the pharmaceutical manufacturer can freely set the price. DE: elements of EPR are – together with elements of free pricing and VBP – applied in the pricing process.

Source: GÖ FP, based on bi-annual surveys with competent authorities represented in the PPRI network and a survey as of spring 2015

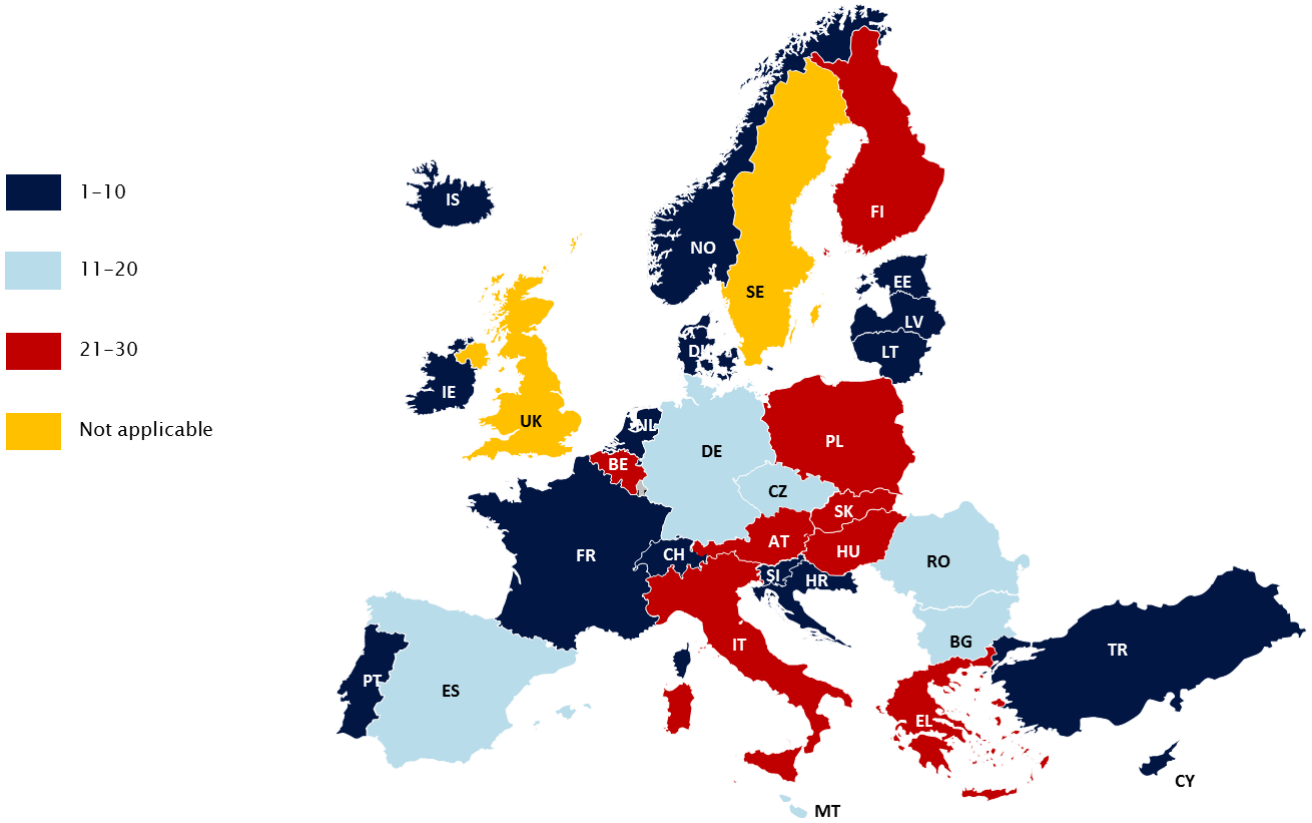
Figure 4: Role of EPR in the price setting process



DE: EPR is provided for in law but not used in practice.
DK: EPR is used to set the price cap for new medicines in the hospital sector; in the out-patient sector the manufacturer can freely set the prices.
IE: EPR is used as a supportive policy to set prices for new single source on-patent medicines, and as a main criterion for realignment of existing prices. SI: EPR is used as the main policy for setting maximum allowed prices, and it is applied as a supportive policy for medicines with extraordinary higher prices and for medicines with lower prices agreed between the manufacturer and the purchaser/payer.
SE and UK (and in DK in the out-patient sector): other pricing policies are in place.

Source: GÖ FP, based on bi-annual surveys with competent authorities represented in the PPRI network and a survey as of spring 2015

Figure 5: Number of reference countries in the basket for the comparison in EPR



ES: the number of countries has not been defined, mainly Euro zone countries are taken into account. IT: the countries are not defined, but prices from countries which participate in the Euripid database are considered.
SE and UK (and in DK in the out-patient sector): other pricing policies are in place. DE: EPR is not applied in practice.

Source: GÖ FP, based on bi-annual surveys with competent authorities represented in the PPRI network and a survey as of spring 2015

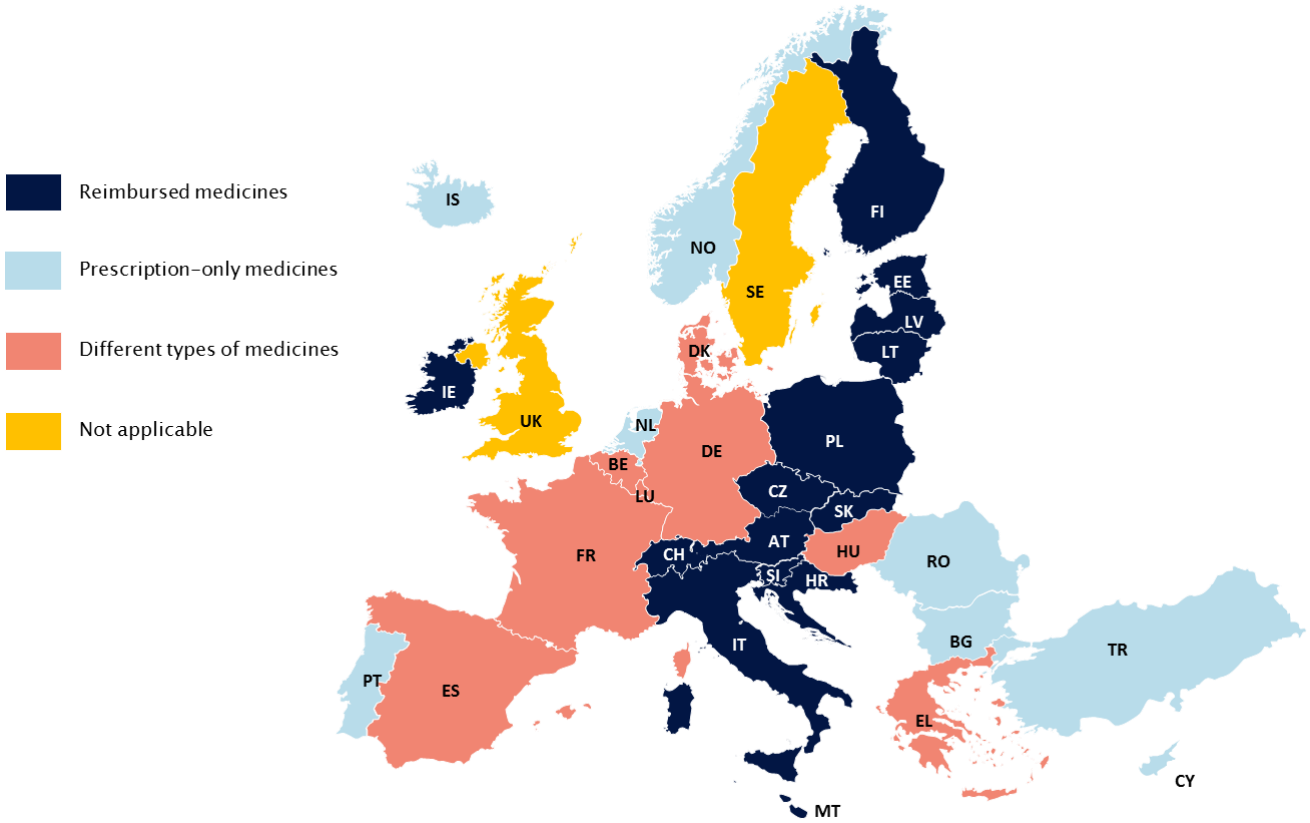
Table 2: Composition of country baskets used in EPR

C	AT	BE	BG	CH	CY	CZ	DE	DK	EE	EL	ES	FI	FR	HR	HU	IE	IS	IT	LT	LU	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK	UK	TR
AT		■	■		■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■		■	■	■	■	■	■	■	
BE	■		■		■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■		■	■	■	■	■	■	■	
BG		■				■		■	■	■	■	■	■		■			■	■		■				■	■	■		■	■		
CH	■	■					■	■				■	■										■								■	
CY	■	■					■	■		■			■					■							■		■		■			
CZ		■						■		■	■	■	■	■	■	■		■	■		■		■		■	■	■		■	■	■	
DE	■	■				■		■		■	■	■	■			■		■					■			■			■		■	
DK	■	■					■					■				■							■	■					■			
EE																			■		■									■		
EL	■	■	■		■	■	■	■	■		■	■	■	■	■	■		■	■	■	■	■	■		■	■	■	■	■	■	■	
ES	■	■			■		■		■	■		■	■			■		■	■	■	■	■	■				■			■		
FI	■	■	■		■		■	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
FR							■				■							■													■	
HR						■					■		■					■												■		
HU	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
IE	■	■					■	■			■	■	■											■							■	
IS								■				■												■					■			
IT	■	■			■	■		■	■	■	■	■	■		■	■	■		■		■		■	■	■	■	■	■	■	■	■	
LT			■			■			■						■							■				■		■			■	
LU	reference to the country of origin																															
LV						■		■	■						■				■								■			■		
MT					■	■			■		■				■			■	■						■	■			■	■	■	
NL		■					■						■																		■	
NO	■	■					■	■				■				■							■					■			■	
PL	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	
PT											■		■																■			
RO	■	■	■			■	■			■	■				■			■	■						■					■		
SE	not applicable																															
SI	■						■						■																			
SK	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■		■	■	■	■	■	■		
UK	not applicable																															
TR										■	■		■					■								■						
	16	18	9	2	10	15	16	18	13	14	18	15	20	8	13	13	4	17	15	8	13	8	15	6	12	15	11	14	14	16	17	0

C. = Countries. Countries in the basket are indicated for the countries listed in the first column.

Source: GÖ FP, based on bi-annual surveys with competent authorities represented in the PPRI network and a survey as of spring 2015

Figure 6: Types of medicines regulated by EPR



BE, EL: originator medicines. DK: new medicines in the hospital sector that are marketed by members of the Danish Association of the Pharmaceutical Industry. ES: New reimbursed medicines when no comparator in Spain is available. HU: EPR applies in case if one of the six conditions is met: (1) new active substance, (2) new indication, (3) new formulation and new route of administration, (4) new combination if any of the components is not yet reimbursed, (5) price increase, (6) changes of category of reimbursement. LU: All types of medicines.
SE and UK (and in DK in the out-patient sector): other pricing policies are in place. DE: EPR is not applied in practice.

Source: GÖ FP, based on bi-annual surveys with competent authorities represented in the PPRI network and a survey as of spring 2015

4.1.1.3 Reference countries in the basket

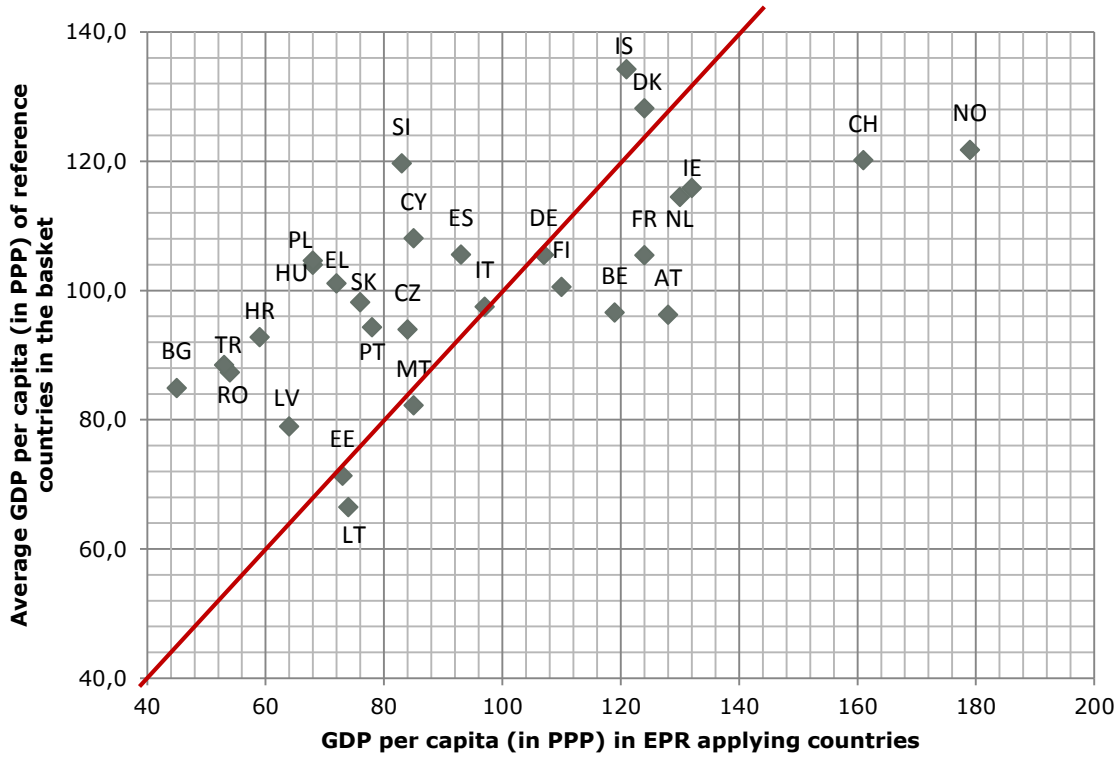
Table 2 provides an overview of the reference countries (indicated in rows) of the European countries that apply EPR. The number of reference countries ranges between 1 (Luxembourg) and 30 (Hungary and Poland). Two countries do not clearly define their reference baskets: The Medicines Agency in Italy consults the Euripid database (cf. Chapter 5.1.1), and available prices are used for referencing, and in Spain prices are referenced mainly to countries in the Euro zone, giving priority to neighbouring countries such as France, Italy and Portugal. In both countries, Italy and Spain, EPR is a supportive criterion in the pricing process, and the obtained information is used as guidance for a reasonable price in the negotiations with the pharmaceutical manufacturers.

The composition of country baskets aims to reflect geographic proximity or comparable economic conditions in reference countries. For instance, the three Baltic countries, Estonia, Latvia and Lithuania, have each other in their reference baskets. A similar pattern can also be observed among Northern and Southern European countries. Figure 7 shows the relationship between gross domestic product (GDP) per capita (in power purchasing parities/PPP) of the EPR applying countries and the average GDP per capita of the reference countries in the basket. If countries in the basket on average reflect comparable economic situations, then the points lie closer to the red 45° line. Indeed, this is the case for only few countries. Especially lower-income countries (e.g. Bulgaria) tend to include higher-income countries in their basket.

Among the countries in the survey, Luxemburg is the only country that includes the country of origin in its reference basket. In some countries (e.g. Lithuania), the country of origin is used as a 'default option' when it is not possible to obtain price information from reference countries. However, this does not occur too often, since countries have implemented different mechanisms to deal with missing information (cf. Chapter 4.1.1.6 on methodological challenges). The countries which are most often stated as reference countries are France (20), Denmark, Belgium and Spain (18), Italy, and UK (17) and Austria, Germany and Slovakia (16).

Three countries define 'first line' or highly prioritised countries and 'back-up' or alternative countries. Thus, should prices not be available in 'first line' countries, price information from a back-up country (or more countries) is searched. For instance, Cyprus defines country groups according to the level of medicine prices (high-, medium and low-priced countries) from which price information of four countries is collected. If in one country no price information is available, then price information is searched sequentially in the two back-up countries per country group.

Figure 7: Relationship between gross domestic product (GDP) per capita (in power purchasing parities/PPP) of the EPR applying countries and the average GDP per capita of the reference countries



Source: Based on authors' calculation with data on GDP per capita (in PPP) from Eurostat

4.1.1.4 Scope of medicines under EPR

EPR typically covers two types of medicines: reimbursable medicines (i.e. medicines that are, at least partially, funded by the state) and prescription-only medicines (POM) that require a medical prescription. However, the scope of coverage varies between the 13 countries which apply EPR to reimbursable medicines. In Finland, medicines that are immediately included in the reference price system (internal price referencing) are not eligible for EPR, whereas in Slovenia medicines that are candidates for public financing are included. Differences in coverage are also found in the seven countries which apply EPR for POM. The range of EPR can be extended to include generics with no corresponding originator in the reimbursement list, parallel imported products, hospital products or reimbursed Over-the-Counter (OTC) medicines. EPR can even be applied to all types of medicines as this is the case in Luxemburg. In six countries specific defined types of medicines are covered by EPR: Originator medicines in Belgium and Greece, new medicines in the hospital sector in Denmark, new reimbursed medicines in Spain and innovative medicines in Germany and France. Hungary has a list of six types of medicines for which the price is set by EPR.

4.1.1.5 Calculation of the reference price

21 countries take the ex-factory price (manufacturer price) into account when referencing to other countries. In Latvia, usually ex-factory prices are compared, but wholesale prices can be considered in cases when (1) one of the three lowest prices in the basket is from Denmark, or (2) the ex-factory price is not available or (3) the MAH

indicates a reduced (or no) wholesale margin to the ex-factory price in the application process. Luxembourg refers, in principle, to the ex-factory price of the country of origin, and also to the pharmacy purchasing price and pharmacy retail price. Germany is the only country whose legislation provides for taking into account real prices of medicines, i.e. manufacturers are required to provide the actual ex-factory price after deducting any discounts that are granted in the reference countries. However, since EPR does not play a major role in practice (see above), this provision is of less importance in practice. Eight countries regulate pharmacy purchasing prices (wholesale prices), often these countries do not have a regulation of pharmaceutical wholesale remuneration in place. In the case of Cyprus and Malta, this relates to central procurement of pharmaceuticals dispensed in the public sector.

For the calculation of the reference price, 15 countries use the average price or a slightly modified method such as the average of the three lowest prices of reference countries or a formula where negotiated prices shall not exceed 95% of the average price of reference countries. In six countries the reference price is calculated through the lowest price. Iceland and Slovenia are the only countries applying two calculation methods. In Iceland the average price is used for out-patient medicines, and the lowest price method is applied to hospital only medicines. Similarly, in Slovenia, elements of both approaches are combined, but a more ample calculation method is in place.[10] Four countries indicated no specific formula, since price information from other European countries is only used as supportive criterion in price negotiations with the marketing authorisation holder. Three countries reported calculation methods distinctive from other European countries. In Estonia, determined prices cannot exceed the highest valid prices in the reference countries, and in Latvia the reference price is the third lowest price in the country basket but shall not be higher than the price in Lithuania or Estonia. In France prices should be similar to those in the reference countries and should not be lower than the lowest price in one of the four reference countries.

Germany was the only country to report that a formal weighting of prices by the estimated yearly turnover of a pharmaceutical[11] and purchasing power parities (PPP) of other countries could be applied [73]. In all other countries weighting is formally not applied to the prices from the reference countries, but due to the focus of reference countries with similar GDP implicitly a kind of weighting can be achieved.

4.1.1.6 Approaches to deal with methodological challenges

Concerning methodological issues in the calculation of reference prices, countries reported a broad range of measures on how to deal with the non-availability of price (information) in reference countries. In countries where EPR serves as a supportive policy, missing price information is not considered as a major issue since policy-makers use other criteria and policies in price setting, and they thus are not, or less, dependent on the price data from the other countries. In contrast, countries having EPR as the main criterion for pricing need to take such situations into account. Some countries simply use the available prices for calculation whereas others have defined a minimum

[10] Published prices from the reference countries are corrected for pertinent wholesale and/or pharmacy margins and – if necessary – also for pack size and strength. This calculation yields a value which is called the administratively 'projected manufacturer's element of price'. For originator medicines the lowest 'projected manufacturer's element of price' among the reference countries is taken as reference price. For generics, the reference price is the average of the highest priced and the lowest priced generics and can amount up to 72% of the average.

[11] MAH are required to provide information about the estimated yearly turnover in the application process.

requirement when setting prices. Both methodologies can go along with the reassessment of prices. For instance, in Ireland, medicines are on the market relatively early but due to the basket composition and the calculation method, prices are comparably high. Therefore the legal framework allows Ireland's Health Service Executive (HSE) to review domestic prices later at any point in time, subject to consideration of a range of criteria. In some countries, alternative pricing criteria come into play, when prices data from an insufficient number of reference countries is available: (1) Official documentation from the country of origin is used instead of the missing prices[12]; (2) Consideration of prices from other EU Member States except the reference countries; (3) a pharmaco-economic analysis carried out by the MAH or by the competent authorities; (4) an algorithm which adjusts for the missing prices.

When a generic version of a product is available, the choice of the comparator in a reference country constitutes another fundamental methodological question. This is of relevance for countries that apply EPR also for generics. In seven countries prices are referenced only to the price of the same pharmaceutical specialities (i.e. generics to generics, originators to originators), in ten countries the price of the originator is used for referencing and in three countries the price of the generic is considered. The methodology in four countries includes the prices of both. In Hungary, it is part of the process of calculating the average comparative price of any medicine, which takes into account all medicines in similar pack size with the same dose, independently of generic or originator.[13]

Another methodological question is whether or not the medicine is reimbursed in the reference countries. 18 countries refer to the price of a medicine in the reference countries regardless of the reimbursement status, whereas nine countries exclude medicines that are not reimbursed in the other countries. In some countries, the exclusion of non-reimbursed medicines is done rather implicitly: In Croatia, the Ordinance for the calculation of the wholesale price stipulates the national sources to be used, and these lists only contain reimbursed pharmaceuticals. Spain, applying EPR as supportive pricing policy, has not specified how to deal with such a situation. France has no official regulation for such scenarios either and decides on a case by case basis.

The choice of the most appropriate pharmaceutical presentation (i.e. defined by pharmaceutical form, pack size and strength) is another methodological challenge. In response, most countries introduced rules as follows (one or several rules may apply): (1) When medicines are available in different pack sizes, with different prices in the reference countries, the closest pack size of the assessed medicine is used as reference. The divergence of package sizes can be defined in a percentage band as done in the Czech Republic or in absolute limits as this is the case in Bulgaria. (2) When different dosages are available at different prices, the same dosage of the assessed medicine is used as reference. This could be either done by comparing the price per unit (Austria), the price per Daily Defined Dose, DDD (Poland) or the price per course of treatment (France). (3) When the pharmaceutical form in the reference countries is different from the one of the assessed medicine, then some countries use the comparable pharmaceutical form as reference whereas others do not allow referencing to other pharmaceutical forms. Again, the options chosen by the countries to deal with these methodological issues strongly depend on whether the countries use EPR as main or

[12] In the survey competent authorities of countries which use these criteria stated that this occurred in very rare cases.

[13] However this happens in very exceptional cases, as EPR is overwhelmingly applied to innovative products.

supportive policy and which scope of medicines EPR is applied for. In Estonia, all available pack sizes are taken into account.

Reference baskets are frequently composed of countries which are not part of the Euro zone. For instance, Denmark (18 times in a country's reference basket), the UK (17 times) and Czech Republic (15 times) are among the most frequently referenced countries in Europe. The question of which exchange rates to apply in EPR is another methodological challenge since exchange rates fluctuations can have major implications. 15 countries source the exchange rates from their national central banks or the European Central Bank (ECB). There is a widespread variation between the choices of exchange rate type: Daily, 3-month-average, 6-month average and 12-month average are applied in European countries. All countries, however, take the application date to determine the exchange rate. In seven countries, the exchange rate, together with price information, is provided by the MAH and randomly checked by the national authority. Three countries make use of the already converted prices indicated in the Euripid database: In Estonia and Spain, it is used when no price is available in the reference countries and the prices have to be compared to EU Member States that are not part of the Euro zone, and Italy prices from Euripid are used as supportive criterion in price negotiations.

4.1.1.7 Data provision and validation

In 23 countries, information about prices in the reference countries is provided by the marketing authorization holder. Thus, competent authorities benefit from the fact that MAH should know best at which price their product is sold in other countries. In Cyprus and the Czech Republic, the competent authorities for pricing additionally conduct an independent price search. In the Czech Republic this is done in parallel to the application procedure in order to speed it up as, according to the law, the State Institute for Drug Control (státní ústav pro kontrolu léčiv, SÚKL) as competent authority for pricing has 21 days to present prices as basis of the pricing and reimbursement decision. In seven countries, prices are searched independently by the competent authorities either from official sites or are requested from the reference countries. In Spain three sources are consulted to obtain price information[14]: 1) MAH through the application form, 2) available national sources such official websites and databases, or 3) the Euripid database (cf. Chapter 5.1.1).

26 countries validate price information in one or the other form. For competent authorities that conduct an independent price search, validation is done during the search procedure. Some of the latter consider the prices found to be correct unless the MAH proves the contrary through valid evidence (e.g. invoices). In countries, in which the MAH provides the price information, prices are validated either through national databases, official sites or Euripid database, and can be done either on a regular basis or randomly. In Austria, according to the Austrian General Social Insurance Law, the competent authority for pricing, the Austrian Federal Ministry of Health, can ask the Austrian Public Health Institute to check the price data submitted by the MAH. For this purpose, the Austrian Public Health Institute has established the Pharma Price Information (PPI) service that provides medicine price data at all price types (ex-factory price, pharmacy purchasing price, pharmacy retail price net and gross) of all 28 EU

[14] An independent price search also serves to validate and complete data provided by MAH. During the pricing procedure, manufacturers are required to provide information about the prices in other European countries and information about similar products from other companies.

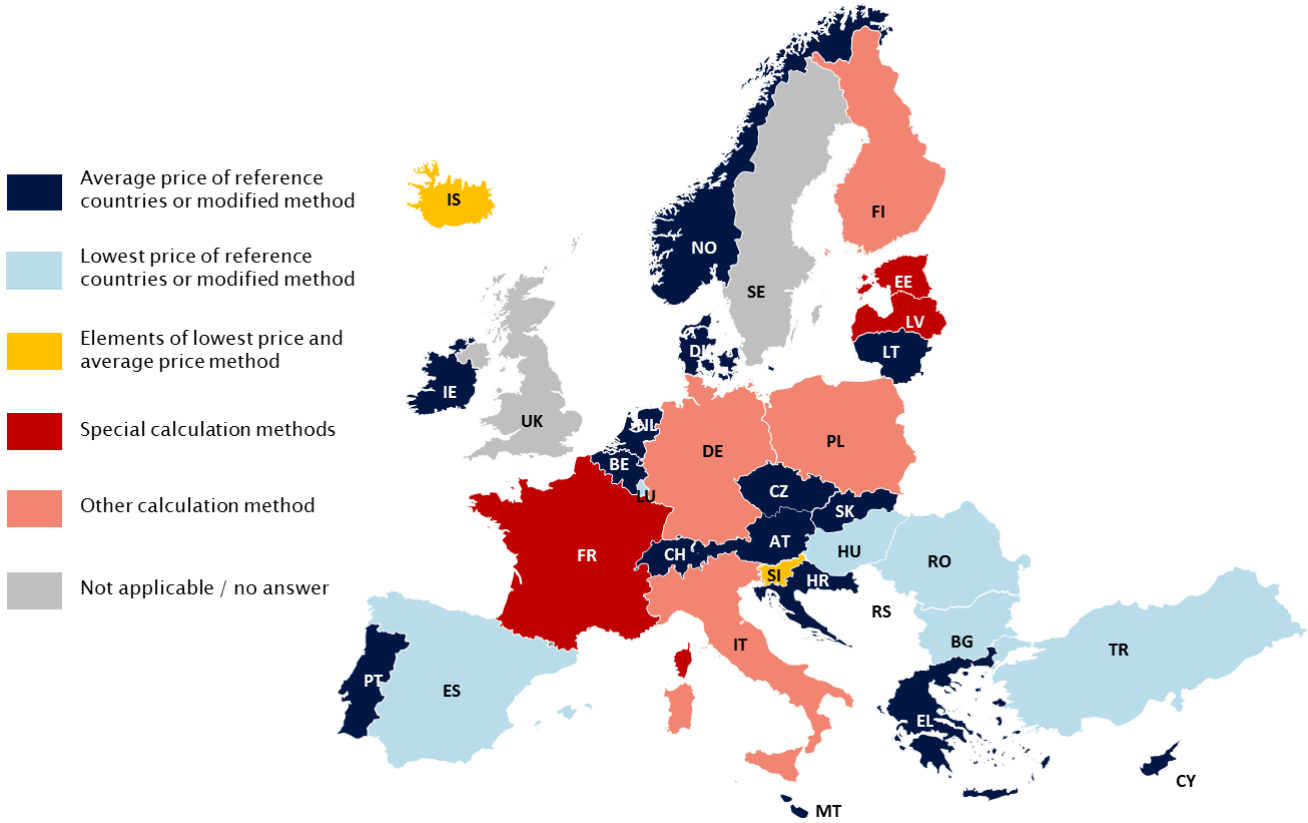
Member States, Norway and Switzerland. Two countries, Finland and Germany, do not validate price information. In both countries EPR is solely a supportive policy and, additionally, in the case of Germany, manufacturers are requested to submit information about real prices (not list prices) in other countries, information which cannot be obtained through the three mentioned above sources.

4.1.1.8 Price monitoring and revisions

In 25 countries, the legal framework provides for regular revision of the EPR-based prices. Some countries have either fixed dates or fixed intervals, ranging from one month to five years. A special form of 'tiered intervals' is implemented in Poland, where prices and reimbursement status are valid for a 2-2-3-5 year's period and being evaluated at the end of each period. In seven countries no regular revision of EPR-based prices is undertaken. In Ireland, price re-evaluations are an important element of the pricing policies. In Ireland, the law allows to review prices at any point in time, subject to consideration of a range of criteria. Croatia plans the introduction of a legal framework for regular revision, and Hungary passed a law paving the way for regular external price reviews.

Out of the 25 countries with price monitoring and price revisions, 17 do it on a regular basis and the remainder on certain occasions. The regularity of price monitoring is sometimes linked to price revisions required by law but does not necessarily coincide. The duration of the intervals can range between from three months to even five years. In some cases regular price monitoring or revisions are linked to certain types of medicines. This is, for instance, the case in Norway where the prices of the 250 substances with the highest turnover are annually revised, or in Spain and Ireland where the prices of off-patent medicines are regularly updated once a year. 7 countries reported no regular price monitoring nor price revisions, which are in some cases related to a later availability of price information in reference countries or the terms of the price agreement. 3 countries answered that they do not monitor or revise the prices of pharmaceuticals. However, price monitoring and price revisions can help public payers to economically benefit from EPR: In the survey countries reported that because of monitoring and revisions annual savings between EUR 71 and 200 million and 8% lower prices of pharmaceuticals were achieved.

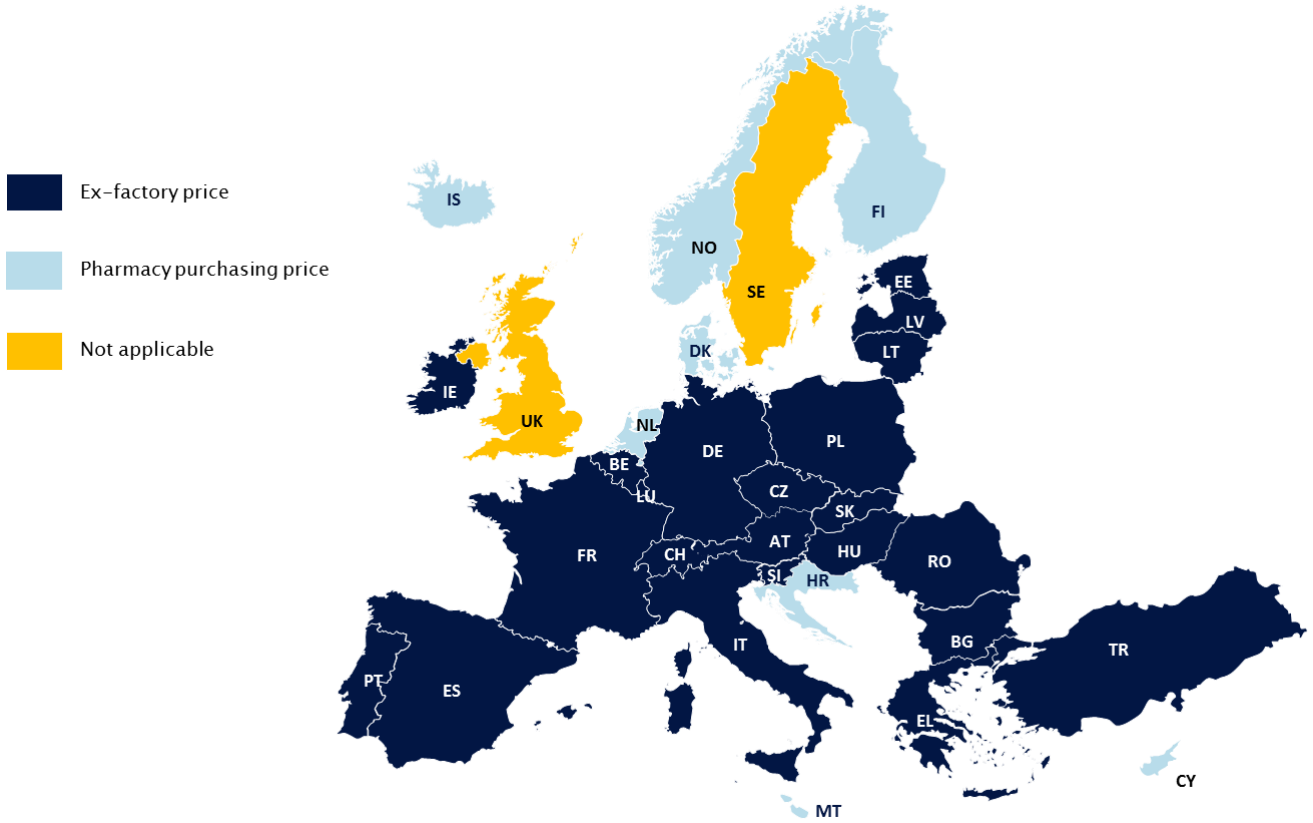
Figure 8: Calculation method of reference prices in EPR



CZ, EL, NO & SK: Average of the three lowest prices of reference countries in the basket. EE: Prices cannot exceed the highest valid price in reference countries. FR: prices should be similar to those in the reference countries and should not be lower than the lowest price in one of the four reference countries. IS: The average price of reference countries is used for out-patient medicines while the lowest price of reference countries is used for in-patient medicines. LT: The reference price shall not exceed 95% of the average price of reference countries. LV: The third lowest price in the country basket, but not higher than the price in LT & EE. SI: The lowest price is used for original medicines and the average price for generics. SE and UK (and in DK in the out-patient sector): other pricing policies are in place. DE: EPR is not applied in practice.

Source: GÖ FP, based on bi-annual surveys with competent authorities represented in the PPRI network and a survey as of spring 2015

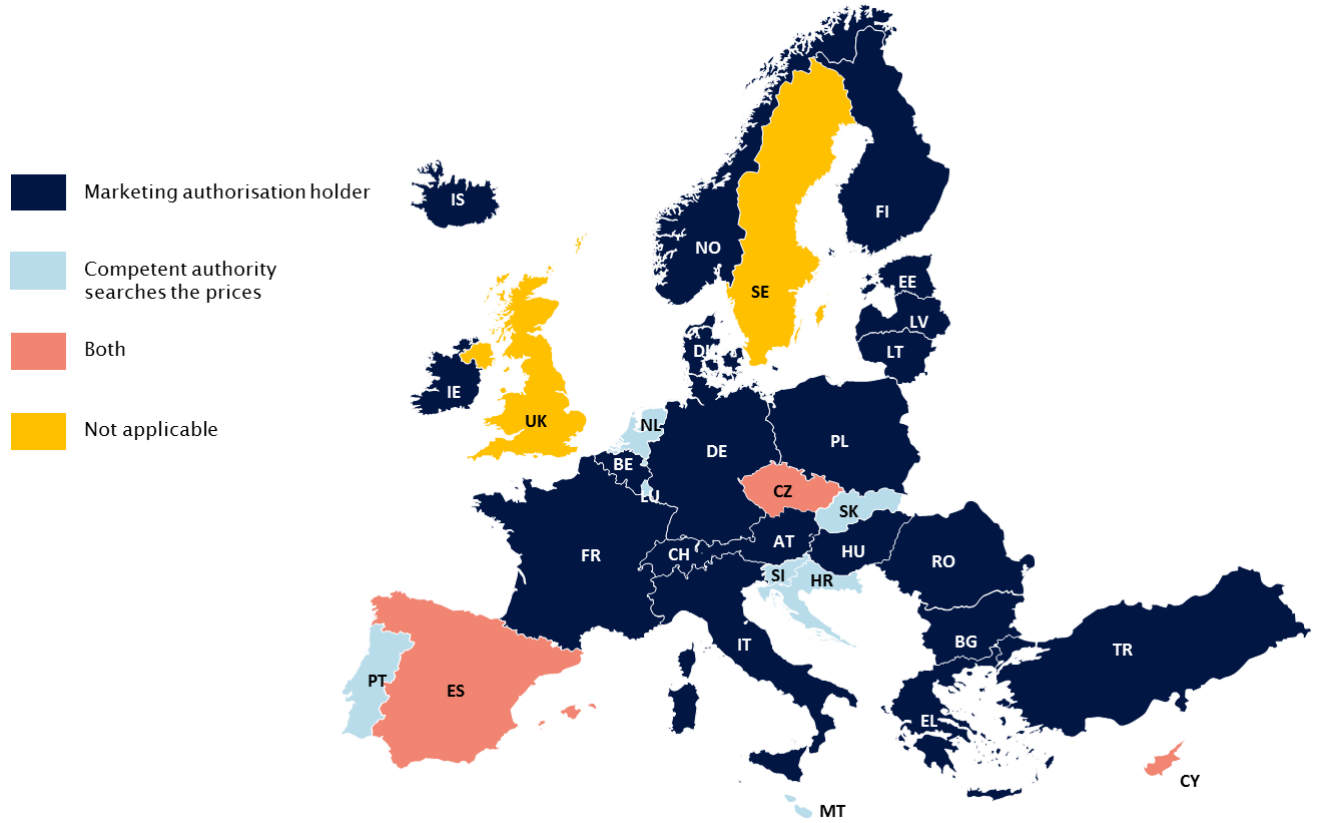
Figure 9: Price type which is taken into account for EPR purposes



DE: the actual ex-factory price (after deducting any discounts that the manufacturer has to grant) is taken into account. LV: ex-factory prices are usually compared but in some cases the pharmacy purchasing prices are taken into account. LU: takes into account ex-factory prices, but does not have specific regulations for wholesale and pharmacy margins and thus also considers pharmacy purchasing prices and pharmacy retail prices in the reference country. Therefore technically all price types are considered. SE and UK (and in DK in the out-patient sector): other pricing policies are in place. DE: EPR is not applied in practice.

Source: GÖ FP, based on bi-annual surveys with competent authorities represented in the PPRI network and a survey as of spring 2015

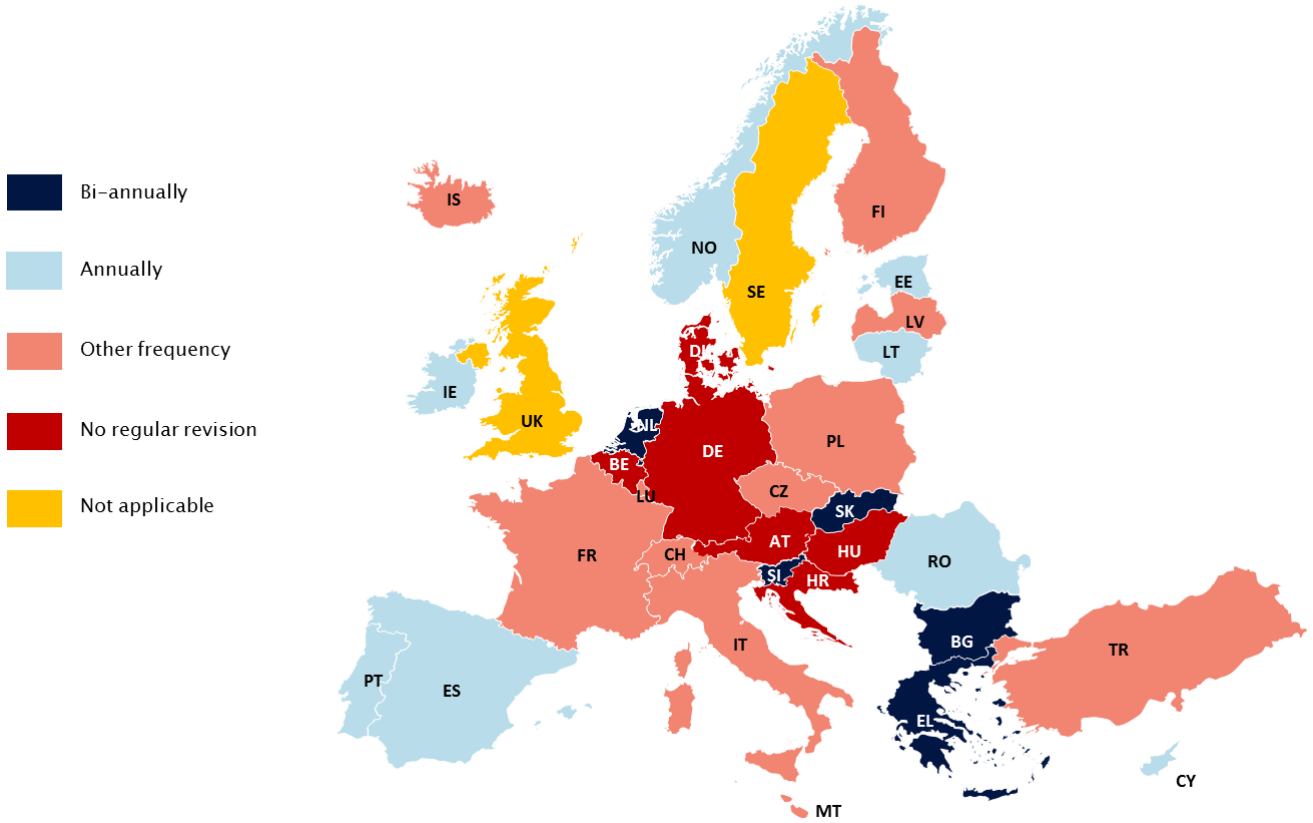
Figure 10: Sources of price information for EPR



SE and UK (and in DK in the out-patient sector): other pricing policies are in place. DE: EPR is not applied in practice.

Source: GÖ FP, based on bi-annual surveys with competent authorities represented in the PPRI network and a survey as of spring 2015

Figure 11: Regular revisions required by law in EPR



BG: bi-annual revision for reimbursed medicines with no alternative at ATC 5 level, all other reimbursed medicines are revised annually. ES: the law requires regular revisions only for off-patent medicines. For those medicines to which EPR is applied to i.e. new reimbursed medicines, revisions are made on a case by case basis. IE: yearly price re-alignments apply to medicines in the reference price system. SE and UK (and in DK in the out-patient sector): other pricing policies are in place. DE: EPR is not applied in practice.

Source: GÖ FP, based on bi-annual surveys with competent authorities represented in the PPRI network and a survey as of spring 2015

4.1.1.9 Discounts and financial arrangements

The practice of lowering list prices through discounts, rebates and similar financial arrangements[15] between public payers and the MAH is wide-spread. 22 countries reported that discounts, rebates or similar financial arrangements (e.g. managed-entry agreements such as risk sharing schemes) – either statutory (i.e. based on a law) or confidential (based on agreements) – are in place. As will be discussed later in more detail (cf. Chapter 4.1.2), the widespread use of the discounts and similar provides financial benefits to the country using it, but the other countries referencing to that country do not benefit from the lower prices since they refer to undiscounted higher prices.

4.1.1.10 Changes in EPR

With regard to changes in the EPR methodology / process since 2010, a change in the basket of the reference countries was most frequently reported. In the last four years nine countries changed their reference countries, and in two further countries such a change is still under discussion. In the survey, authorities did not specify in which direction this change was, but there seems to be a slight tendency towards increasing basket as three countries reported that the number of reference countries has been extended. However, this has to be taken cautiously because in some cases this was due to the accession of Croatia to the European Union in 2013. Countries in which the price is calculated by the average price of all EU countries (e.g. Slovakia) had to adjust their baskets. The second most frequent change is in the methodology of the calculation method, which was indicated by four countries. In 13 countries no major changes in the EPR methodology / process have occurred since 2010.

4.1.2 Experiences with EPR

As shown in the previous Chapter 4.1, EPR is a very common policy in Europe. Moreover, as more and more countries world-wide have been moving towards aiming for universal coverage and managing medicine prices through price regulation, EPR has become a more common practice world-wide [28].

While the policy has become more commonly applied, the limitations of EPR have increasingly been discussed in recent years. Despite methodological issues questions about the underpinning philosophy have also arisen as EPR tends to import relative value judgements. Decisions about pricing and reimbursement reflect a country's social preferences in the health system. Additionally, differences in national health settings stoke the discussions about comparability of prices. A study of Vogler S, Zimmermann N and Habimana K [46] commissioned by the European Commission highlighted that external price referencing was ranked low with regard to its ability to achieve the policy objectives not only preferred by stakeholders such as pharmaceutical industry but also by competent authorities and payers (for detailed results cf. Chapter 2.3.1). A discussion with members of the PPRI network showed that authorities who recently

[15] A discount is a price reduction granted to specified purchasers under specific conditions prior to purchase. In contrast, a rebate is a payment made to the purchaser after the transaction has occurred. Purchasers (either hospitals or pharmacies) receive a bulk refund from a wholesale, based on sales of a particular product or total purchases from the wholesaler or manufacturer over a period of time [25].

introduced EPR considered the policy effective to achieve their goals, whereas authorities with longer-term experiences with EPR said that the benefits of the beginning have increasingly been foiled by limitations arising after some time (personal communication from a focus group discussion with competent authorities).

The evidence presented in the following Chapters 4.1.2.1 and 4.1.2.2 is based on the findings of the systematic literature review (for the methodology and included references see Chapter 3.1 and Annexes 1 and 2).

4.1.2.1 Benefits and limitations

According to the literature review, EPR practice has shown the following benefits and limitations.

Savings

There is evidence from some studies in Europe that EPR can lead to substantial savings for the public payers (cf. Table 3 for some studies on this issue).

Table 3: Studies about the possible savings of EPR

Study	Results
Windmeijer et al. (2006)	In 1996 the Pharmaceutical Prices Act was introduced and resulted in considerably lower medicine prices. The study measured the effects of the implementation of EPR in the Netherlands and came to the conclusion that this pricing practice resulted in lower prices. The decrease was on average by about 15%. Prices of products without a reimbursement price were affected most by the new act, but also many clustered medicines (i.e. medicines of identical and/or similar therapeutic benefit, including generics) were forced to lower their prices.
Merkur/Mossialos (2007)	The study simulated the effect of EPR on medicine prices in Cyprus. The conclusion was that it would lower prices and contain costs after identifying Cyprus as a high priced country for medicines. The simulation was done for two classes of medicines: For the list of the most expensive products, the pharmacy retail prices were lowered by between 33% and 39% and for the most sold products, the average relative change in Cypriot prices was a lowering between 26% and 33%.
Brekke et al. (2009)	In 2000, Norway introduced the EPR system based on prices in nine other European Economic Area (EEA) countries as the main pricing principle for prescription-only medicines, both on-patent and off-patent, except for those which are already included in the (internal) reference price system. The study analysed how the two regulatory regimes EPR and reference price system affected the company's pricing strategies. The price reduction for originator medicines was about 18%, while generics faced price reduction of about 8%.
Filko/Szilagyiova (2009)	Slovak pharmaceutical prices had been subject to price cuts by 6.6% in 2007 and by 7.4% 2008 based on the fluctuation of the Slovak koruna. In 2008, Slovakia introduced an EPR system, which was changed one year later towards higher transparency. Following the change of the EPR methodology the proportion of pharmaceutical expenditure as share of total health care spending declined to approximately 25%.
Håkonsen et al. (2009)	The study looked at medicines prices development from 1994 till 2004 in Norway, which had introduced EPR in 2000. It concluded that consistent use of EPR and subsequent price revisions led to substantial price reductions on many medicines. In the year of its introduction, EPR resulted in medicine price reduction by 2.0%. By comparison, the consumer price index increased on 3.1% in that respective year.

Study	Results
Leopold et al. (2012)	Price data of 14 on-patent products, in 14 European countries in 2007 and 2008 were obtained and translated into scaled ranks. Afterwards the scaled ranks were weighted by running a regression on scaled ranks, medicine prices were in general lower in cases where the country applied EPR compared to countries which did not.
Toumi et al. (2014)	The study simulated the effects of EPR on medicine prices in all European countries. It concluded that when EPR is applied as the sole criterion it decreases medicines prices by about 15% after 10 years. In the simulations the price differentials between countries remained substantial over 10 years (about 30%) suggesting a limited impact of EPR in price convergence. For countries applying EPR, periodic price revision is the main requirement for price decreases.

Source: Brekke KR, Dalen DM and Strøm S [32], Filko M and Szilagyiova P [74], Håkonsen H, Horn AM and Toverud E-L [33], Leopold C, Mantel-Teeuwisse AK, Seyfang L, et al. [21], Merkur S and Mossialos E [34], Toumi M, Rémuzat C, Vataire A-L and Urbinati D [45], Windmeijer F, De Laat E, Douven R and Mot E [75]

A few remarks should be considered in this context:

- The way an EPR system is designed in technical terms appears to be of fundamental reference to its ability to achieve savings [30, 76]. The impact of methodology specifications (e.g. country basket, frequency of updates, calculation of reference price) will be tested in Chapter 4.1.4.
- Part of the technical design of EPR is also to build capacity of staff to do EPR in the most appropriate way (issues of capacity-building, access to data, see also below administrative efforts).
- However, the incremental effect decreases over time as there are no continuous large reductions in price: Member States applying EPR reported about high savings shortly after the introduction of the measure but these were reduced over time (personal communication). This might, among others, be attributable to the 'fade-out' effect. This means that initially EPR proved successfully, but then it appeared to have lost effectiveness. Such a 'fade-out effect' has been observed with other policies as well, and adjustments of a policy are required after some time (therefore also called 'pendulum effect' [77]. Still, the cumulative effects can be expected to be higher compared to non-EPR or non-price control.
- Price reductions in reference countries are not automatically translated into price decreases in referencing countries since prices are not regularly monitored [1, 30, 45]. A study concluded that an annual systematic price revision for all countries almost doubled the price decrease compared to price revisions every three years [45]. In addition, due to the referencing to higher undiscounted prices (see below), the benefit of savings generated in one country needs to be seen in the light of higher prices, or even limited access, in the other referencing countries.
- A combination of EPR with other strategies (e.g. price negotiations following EPR) proved to lead to lower prices than EPR as a stand-alone policy [32, 78].
- There is some evidence that lower-income countries might have to pay higher prices whereas they might benefit from lower prices in the absence of the EPR applied by other countries and referring to them [28, 52].

Launch delays and accessibility issues

A key issue in the debate about limitations of EPR is its potential to contribute to accessibility problems: Though EPR does not necessarily restrict access, it incentivises marketing authorisation holders to launch first in countries with a high medicine price level in order to have the list prices in these countries referenced to by others, and to delay market entry, or not market at all, in low-priced countries in order not to negatively impact the international benchmark. In addition, it may also inhibit

manufacturers from offering medicines at lower prices in lower-priced countries [1, 19, 30, 45, 52, 64, 76, 79-82].

The OECD considered EPR as a policy that is 'readily gameable by the pharmaceutical industry and – by reducing firms' willingness to price to market – contributes to access and affordability problems' [64]. It has been argued that medicine shortages or the discontinuation of medicine supply are partially also attributable to pricing and reimbursement practices such as EPR [19, 30, 83, 84]. In one case, the investigations of a national antitrust authority have revealed that the temporary unavailability was due to price alignments across EU countries [85]. Some low-priced countries face medicine shortages following extensive parallel exports [84, 86]. Some Member States have reacted by imposing parallel exports ban for specific medicines (cf. Chapter 4.2.2).

Transparency concerns and risk of overpaying

As shown in the survey (cf. Chapter 4.1.1), countries do not consider discounts granted to public payers, even not statutory manufacturer discounts (i.e. based on a law) that are publicly available. Germany is the only country that has a legal provision on this matter: Discounted price information can be asked from the manufacturers.

In fact, statutory manufacturer discounts granted to public payers are not very frequent, but they exist (e.g. in Germany, Spain). In Ireland manufacturer discounts are not statutory but are embedded in the national framework agreement. In addition, confidential discounts, rebates or similar arrangements negotiated and agreed by manufacturers and payers are known to be in place in several European countries [87]. The increasing use of managed-entry agreements has a similar negative effect on transparency and undermines the effect of EPR ([28, 88], comments of a peer reviewer).

By referencing to official list prices instead of discounted prices, countries risk overpaying [28, 30, 45]. One peer reviewer phrased it as follows: 'Official prices to which comparisons are being made are fake.' When public payers accept confidential discounts and rebates from the industry instead of imposing statutory price cuts, they achieve the same results for their own country, but they prevent a transfer to the reference countries of possible savings of price cuts in one country [30].

Further, this non-consideration of discounts and similar arrangements provides a false sense of security to payers: price control is limited since the whole system may be gamed. EPR tends to lead to a distortion of transparency which might be seen as a value of its own. Implicitly, it also has financial implications (loss of savings), thus possibly limiting the sustainability of the health care system. Furthermore, price confidentiality eliminates, or at least reduces, accountability since 'decision-makers involved in activities such as procurement and medicine regulation are less able to exercise institutional and democratic control, thus increasing opportunities for discrimination and corruption' [28].

Administrative efforts

EPR has been described as 'a relatively simple and easy-to-apply system compared to economic evaluation, for example' [28]. This is true insofar that EPR does not require authorities to provide for great investments in HTA and pharmaco-economics as they have to do for value-based pricing.

However, it would be wrong to conclude that EPR is a simple exercise, and some authors have acknowledged the complexity of EPR systems [45, 52]. Expertise is required to establish an appropriate EPR system, taking into account the implications of different

methodology parameters, and to monitor and regularly align the policy. Since price information is not always available, the search for and identification of easily accessible data that is comparable might be cost-intensive [28, 31, 45]. The capacity of staff needs to be built in order to perform the price surveys and comparisons correctly. In addition, in order to factor in price changes in the reference countries and possibly benefit from savings, regular price reviews are required which makes EPR both time and resource-intensive [30, 52].

Non-consideration of value and 'path-dependence'

EPR neither reflects the willingness-to-pay nor the ability-to-pay of a country, which is the case for other concepts as for instance value-based pricing [35]. By applying EPR, a country would only end up with a medicine price that offers both value for money and a reward for innovation if all referenced prices would be value-based [30]. Obviously not all countries can rely on EPR: at least one country should apply a different pricing policy, otherwise no new medicines would be priced and launched [28].

In general, EPR is said to be rather 'path-dependent' [52]. Prices obtained in EPR appear to be rather influenced by the rules of the systems itself (e.g. country basket, price methodology, frequency of updates), without necessarily paying attention to factors intrinsic to the health care system in which it operates.

Exchange rate volatility

Furthermore, EPR is exposed to exchange rate volatility when referenced prices are denominated in local currencies [45, 52, 89].

Predicted tendency for convergence

It has been argued that, if all (European) countries apply EPR and they all refer to each other, eventually the price levels across Europe will converge. Nonetheless, medicine price variations across Europe continue to exist, as confirmed by several price studies [17, 19-21, 45, 52, 89, 90].

Price convergence would mean that national (market) conditions are less reflected. A few studies that were performed a few years ago indicated price convergence within the European Union for newly launched medicines [64, 91-93]. A study looking at the effects of parallel trade identified a convergence but could not predict a 'race to the bottom' but a 'convergence to the top' [94].

However, recent studies suggested no substantial reduction in price dispersion within the EU countries [19, 22, 95]. The non-convergence in recent times was particularly attributable to the price developments in Germany (up-ward) and in Greece (down-ward trend); furthermore, these studies could not include any discounts due to their confidential nature [22]. If there were price convergence movements, it was found that these may be rather associated with cross-country coordination issues that impede on the accessibility for patients between Member States and also in a given Member State over time [45]. Price convergence can be a consequence of the spill-over effect of EPR related to new medicines in the reimbursement segment (comment by a peer reviewer). We are to see whether this development related to divergence will continue, e.g. after the global financial crisis.

4.1.2.2 Impact factors and proposals for change

Toumi M, Rémuzat C, Vataire A-L and Urbinati D [45] analysed possible impact factors of price reductions in EPR systems and identified the following one:

- regular price reviews and revisions;
- genericisation (might lead to major reductions in originator prices; furthermore, the mandatory price reductions of the originator medicines following patent expiry in some countries might also have an important impact in countries using this price cut for EPR and where the medicine is not yet generic);
- differences in the distribution remuneration, i.e. mark-ups/margin or fees to reward wholesalers, pharmacies or other retailers (due to referencing to different price levels);
- whether, or not, list prices or discounted prices are used; and
- the compilation of the country basket.

Their analysis adds to the findings in the previous chapter. The identified limitations of EPR could serve a basis for the development of improvements. Some suggestions have been made.

With regard to country baskets, Stargardt T and Schreyögg J [76] suggested including as many countries as possible, to reduce the direct and indirect impact of individual countries, and to exclude those countries that also use EPR. In European reality, it would, in fact, abolish the use of EPR. No other author has made these proposals.

The WHO Guideline on Country Pharmaceutical Pricing Policies also stressed that the selection of the country basket is a key methodological decision to be taken [31]. Having discussed benefits and downsides of EPR, the WHO took the following recommendation on EPR:

- 'Countries should consider using EPR as a method for negotiating or benchmarking the price of a medicine.
- Countries should consider using EPR as part of an overall strategy, in combination with other methods, for setting the price of a medicine.
- In developing an EPR system, countries should define transparent methods and processes to be used.
- Countries/payers should select comparator countries to use for EPR based on economic status, pharmaceutical pricing systems in place, published actual versus negotiated or concealed prices, exact comparator products supplied, and similar burden of disease.' [31]

The WHO Guideline as well as other literature [1, 19, 28, 30, 45, 52, 76] suggested proposals for change, and improvements of EPR, that included[16]:

- Legal framework as a fundamental requirement;
- Technical capacity (e.g. data management, data analysis);
- Clear procedures / methodology, including the country basket, calculation of reference prices;
- Consideration of the actual discounted prices instead of list prices (or at least adjustments required to account for confidential discounts or rebates in list prices);
- Regular monitoring and price revisions;

[16] The WHO Guideline on Country Pharmaceutical Pricing Policies [31] addresses all WHO Member States, thereof many low- and middle-income countries that have no price regulation in place and lack expertise in pricing policies such as EPR. Thus, basic implementation issues that are in place in EU Member States are mentioned.

- Procedures on how EPR feeds into the decision-making process;
- Adjustments for the economic situation/development of a country;

In addition, suggestions to ease the administrative burden include the following: A well-defined methodology, with clear rules, is supportive for staff doing the price surveys and comparisons. A lower number of countries could reduce the work load, in particular if no cooperation and supportive tools such as a central medicine price database exist; and it has yet to be seen whether the results differ between a small, well-defined basket of countries and a large basket of reference countries (test of this hypothesis cf. Chapter 4.1.4). Improved access to price data is a major issue in this field; thus initiatives such the European medicine price database Euripid (cf. Chapter 5.1.1) are supportive for authorities doing EPR.

There is a debate of the appropriateness to combine EPR with other pricing policies. While Kanavos P, Nicod E and Espin J [52] highlighted the ability of EPR to be combined with additional policy measures for reimbursement purposes and the WHO Guideline [31] recommends using EPR as part of an overall strategy, there is reluctance by some authors to combine EPR and VBP [35, 45]: It is argued that value definitions differ across countries as well as the willingness-to-pay to pay a defined value, and it would be considered inconsistent to set a price in a country based on value and then adjust the prices based on decisions in the reference countries which use other grounds to assess the value. But it is acknowledged that value assessment is associated to uncertainty, and as such, it might be reasonable to inform the price decision using assessments performed by other countries [45]. However, several authors strongly called for EPR being a supportive criterion in pricing policies that should be flanked by pharmaco-evaluations [96-100]. This reflects reality in EU Member States: EPR is a supportive criterion for pricing in some countries (cf. Chapter 4.1.1), and/or HTA and pharmaco-evaluations are a standard in the pricing and reimbursement process for new (high-cost) medicines [3].

Several institutions and authors ([36, 37, 62, 79, 81, 101-105] proposed considering the economic situation of a country, arguing for 'differential pricing' or 'price discrimination', depending on their perspective (for the definition and different perspectives cf. Chapter 4.2). However, EPR and differential pricing (DP) are frequently considered as mutually exclusive policy options. However, the proposal for considering indicators of economic wealth (e.g. GDP, power purchasing parities) as increasingly been tabled [19, 31] would constitute such a combination.

4.1.3 Proposal for further information included in EPR

The authors were asked to propose possible further information that might be included in an EPR system, with the aim to improving the policy. Based on the reported experiences with EPR in literature, we would suggest considering possible inclusion of the following information that covers two types of information:

- Information linked to the medicine (so-called 'direct price information'; this is information to be included in a price database), such as
  - Medicine price type (i.e. whether it is ex-factory price, or wholesale price),
  - Date of price data,
  - Exchange rate information,
  - Information on discounts,
  - Information on the underlying pricing procedure and arrangements (e.g. managed-entry agreements);

- Information related to more 'general elements' at country level (so-called 'indirect price information', this information might be included with a view to developing a formula for optimizing the EPR system), such as
  - Gross domestic product (GDP), purchasing power parities (PPP) or similar economic indicator,
  - Pharmaceutical expenditure data,
  - Information about the applied methodology related to EPR,
  - Statutory discounts,
  - Market size.

Annex 5 provides the full list of proposed information for consideration of inclusion, supplemented by some explanatory notes. The proposed information is both of quantitative and qualitative character. Some information is basic and essential for EPR, whereas others would require changes to the EPR system. The presentation of the information in Annex 5 also includes an assessment on whether the authors consider this information as basic, relevant or supplementary information.

It is not suggested that countries include all listed elements into their formal EPR mechanisms. This is merely a list of important information that countries may consider for improving their EPR system. For instance in the case of PPP or GDP per capita could formally include into their EPR calculation mechanism if they wanted to account for different countries' economic situation. As building price databases and conducting EPR evaluations is administratively time-consuming (cf. Chapter 4.1.2.1) and costly (for an indication of cost see the information requested and received from the central medicine database Euripid in Chapter 5.1.1), the benefit of any extension of the EPR mechanism by including further information should be weighted with the costs of increased administrative burden.

4.1.4 Simulations exploring the impact of different EPR scenarios

As outlined in Chapter 3.3.1, a basic simulation model was built with the aim of illustrating the general workings of EPR in Europe and the impact of changes in EPR mechanisms. Further detail on model approach and characteristics included in the model can be found in Chapter 3.3.2.

4.1.4.1 Base scenario

A simple base scenario was constructed to show-cast the model and highlight general features of the EPR system within Europe.

The base scenario uses the following additional simplifying assumptions:

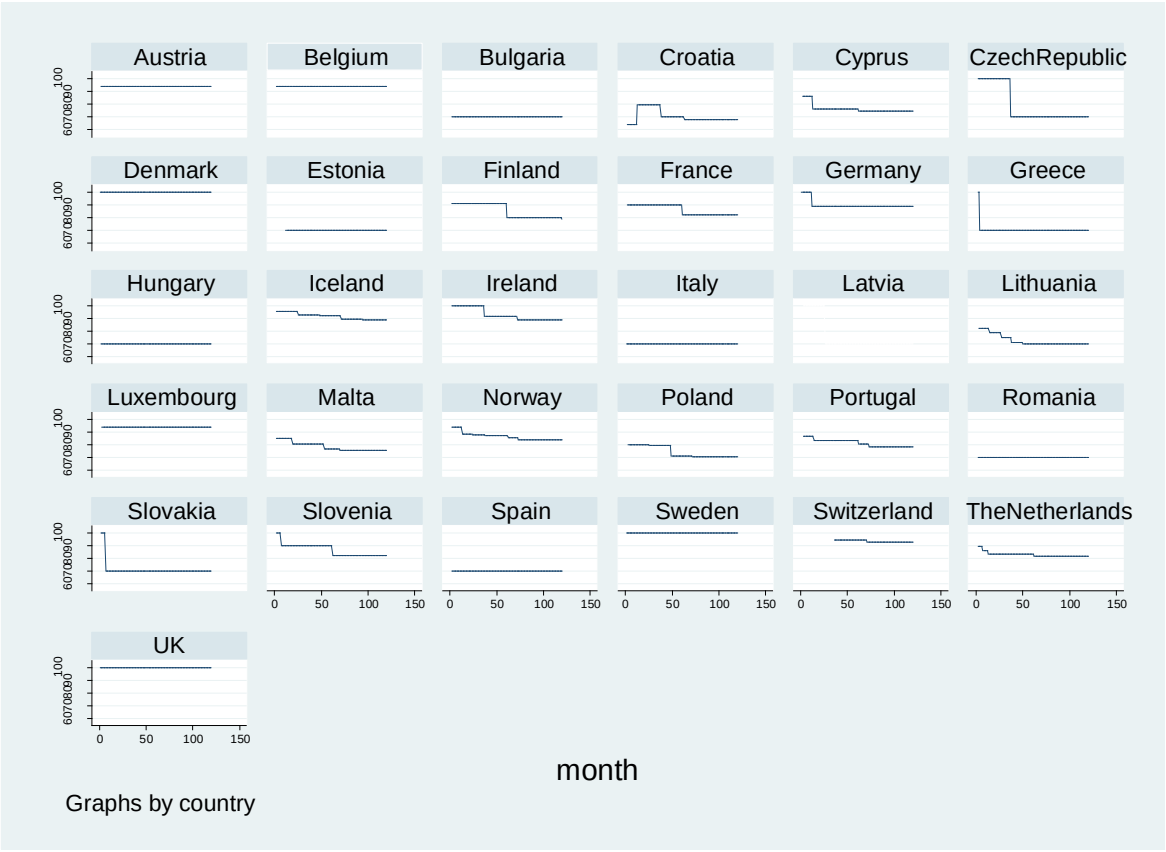
- The prices in countries that do not use EPR are fixed;
- In this case, prices in non-EPR countries have been fixed to 100 Euros equal to the launch price of the pharmaceutical in Germany.
- The time period of interest is 120 month/10 years;
- Prices are constant unless the country is at a re-evaluation point, i.e. no 'exogenous' price deflation or inflation mark-ups are taken into account;
- Exchange rates are constant across time;
- There is no (EPR) price available until the minimum number of reference prices is available in the basket;

- Where EPR is applied, it is assumed to be the only price-setting criterion; As was done in Toumi et al. Germany is assumed to be an EPR-applying country despite more complex official regulations;[17]
- Specific national assumption for Luxembourg (Belgium is used as the reference country[18]) and Germany (re-evaluation of its price after one year[19]);
- Countries reference to official prices and do not take into account discounts/rebates;

To kick-off the scenario, a launch price of 100 Euros is set in Germany and 70 Euros in Italy, in time-period 1.

As can be seen in Figure 12, for countries that state not to be re-evaluating their EPR prices, medicine prices stay constant over the years since EPR is the only factor influencing prices within this model. In other countries, prices drop at consecutive re-evaluation rounds.

Figure 12: Medicine price progression



Source: Authors' calculations

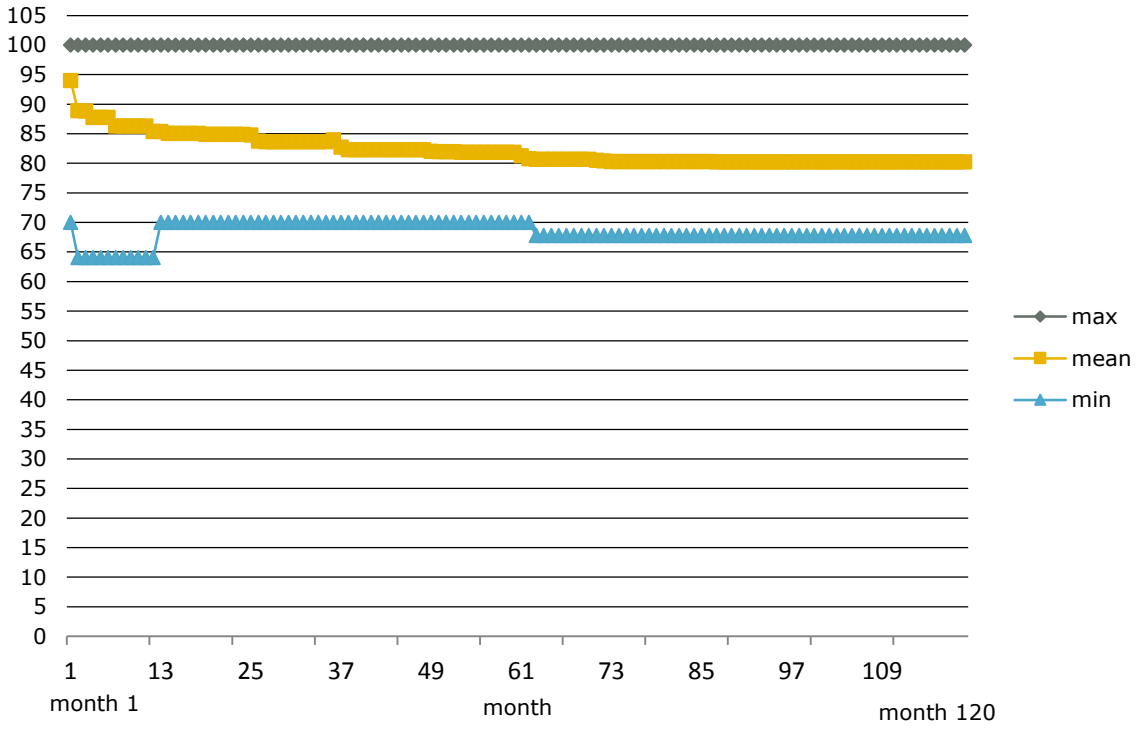
[17] In the case of Greece, due to very late receipt of the survey questionnaire, the model considers the old basket with 12 instead of 27 reference countries.

[18] Luxembourg refers to the country of origin, which is in the predominant majority of cases Belgium.

[19] Similar to Toumi M, Rémuzat C, Vataire A-L and Urbinati D [45] the medicine in the base case is launched in Germany and it is assumed, that prices there are re-evaluated after one year. After that, since Germany states not to have any mandatory, regular re-evaluations, the price stays constant.

Figure 13 shows erosion of the average price over the years, which is low at about 15%.[20] As was explained in the model assumptions, prices are assumed to start at EUR 100 and EUR 70 in the launch countries Germany and Italy, and a set price of EUR 100 in the non-EPR countries, i.e. with a mean price of 94. The average price then falls consecutively as more and more countries receive and re-evaluate a price based on the average, minimum or other arithmetic measure of existing prices.

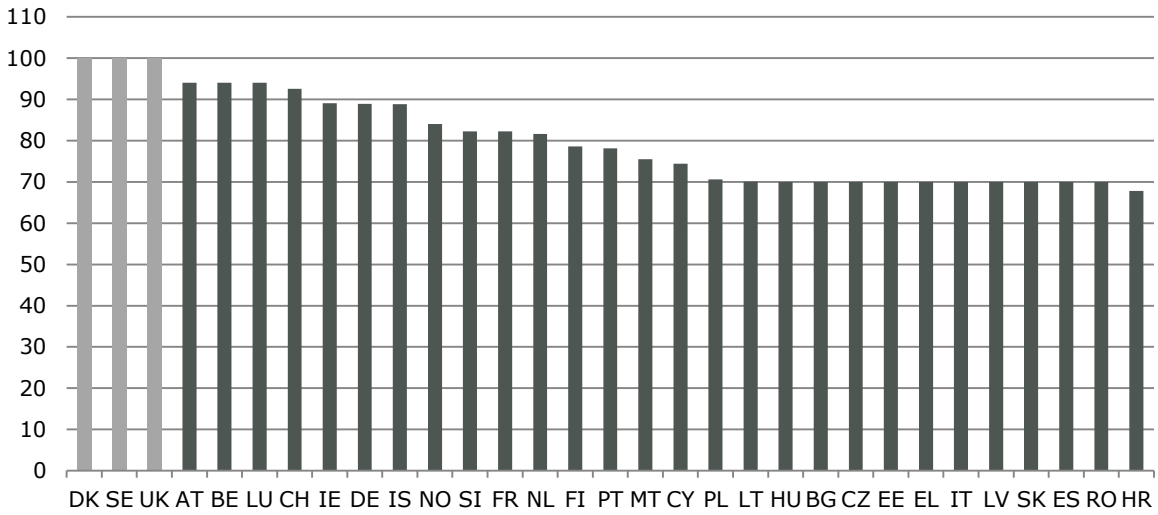
Figure 13: Base case evolution of minimum, maximum and average ex-factory price



Source: Authors' calculations

[20] An average price erosion over ten years of 15% equals the results of the base case in Toumi M. et al.'s model. The initial increase of prices presented in Toumi M, Rémuzat C, Vataire A-L and Urbinati D [45] is due to the fact that countries have different wholesale and pharmacy margins. Prices here are reported at ex-factory level for all countries and thus this effect is not visible. Given that countries have different wholesale and pharmacy systems under their own responsibility, the ex-factory price was taken to be the most appropriate illustration when analysing international fairness issues and impacts of DP methodologies.

Figure 14: Ex-factory medicine prices after ten years



Source: Authors' calculations

After ten years, the average price over the 31 countries is EUR 80.2 and EUR 78.1 for those 28 countries applying EPR, i.e. between the two starting prices. Under the conditions specified above, the highest price countries (excluding countries for which prices are assumed fixed within the model because they do not apply EPR) are Austria, Belgium, Luxembourg and Switzerland.[21]

4.1.4.2 Scenario I: Application of discounts

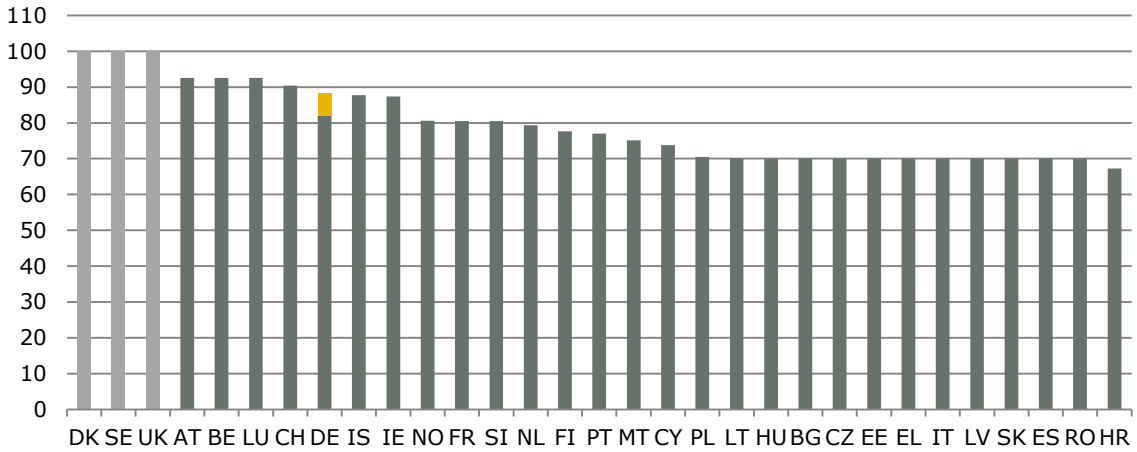
Under the base case, as in real-life EPR, the reference prices taking into account are the officially published medicine prices. This means, for instance, that countries referring to the German official ex-factory price might be referring to a price substantially higher than the one that is actually being paid by the German health system, since a statutory discount of 7% for sickness funds is in place[22]. Discounts and claw-backs are often confidential and non-transparent and difficult to take into account in international referencing. This scenario illustrates how prices can change when discounts are taking into account by deducting the official, legally mandated discount from the German ex-factory prices.[23]

[21] Prices in Luxembourg here equal Belgian prices, which are assumed to be the country of origin and thus the only country in Luxembourg's country basket.

[22] The statutory discount of 7% is only one part of the discounts, but additional contract-based rebates are confidential and cannot be taken into account in this report.

[23] Mandatory discounts are currently 7% of the ex-factory price (http://www.kbv.de/html/2948.php , accessed May 2015) and 6% for off-patent generics outside the reference price system. For generics and parallel imports an additional discount of 10% is applied in case where the price is not at least 30% below the reference price. For the sake of simplicity the calculations above use a discount of 7 percent.

Figure 15: Medicine prices taking into account German statutory discounts



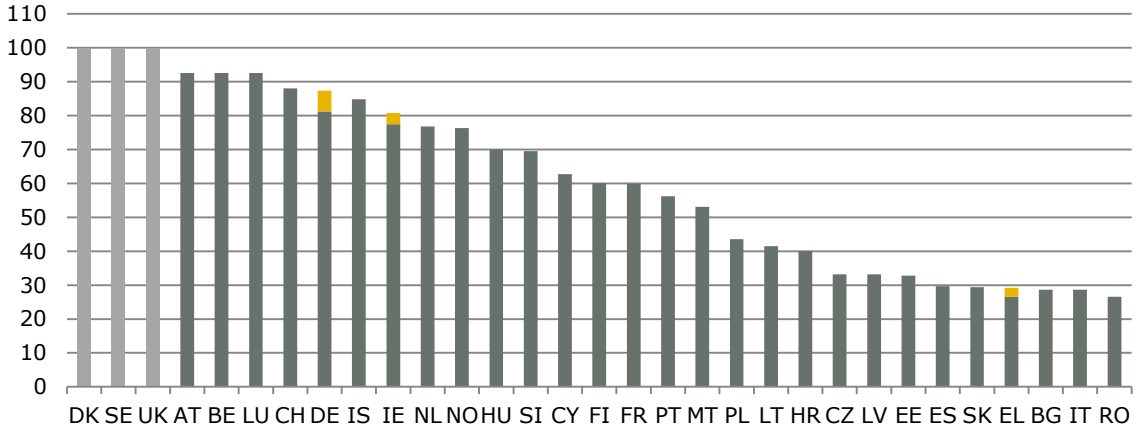
Source: Authors' calculations

When a 7 percent discount on German prices is taken into account, the average price after ten years in all other countries using EPR[24] drops from EUR 78.1 to EUR 77.3, i.e. about 1 percent. The reduction in the price of other countries is smaller than 7 percent since a) not all countries include Germany in their country basket and b) the price is averaged/combined with that of other countries; however a significant overall price change can be observed.

Germany is not the only country applying mandatory, statutory discounts. The graph below shows price levels when in addition to German official discounts, statutory 9% discounts on ex-factory prices (for social health insurance) are taking into account when referencing to Greece and 4% when referencing to Ireland (information provided from the PPI service of the Austrian Public Health Institute).

[24] I.e. countries for which prices are not assumed to be fixed within the model such as the UK, Sweden and Denmark.

Figure 16: Medicine prices taking into account German, Greek and Irish statutory discounts



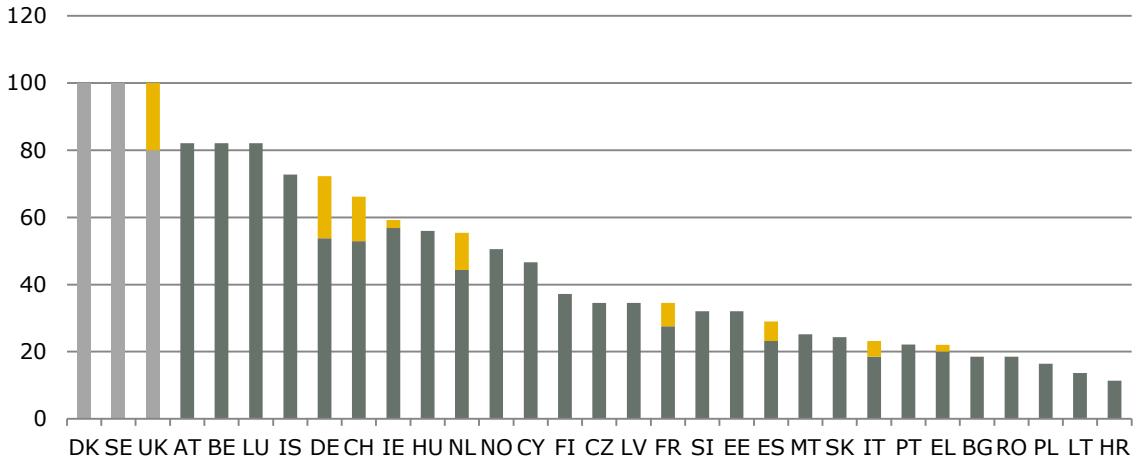
Source: Authors' calculations

Average medicine prices fall drastically in this scenario, from EUR 78.1 for all countries applying EPR to EUR 57.15[25], i.e. **by 27 percent**. This is possibly because referencing to discounted Greek prices changes the minimum price in many countries' baskets and thus directly affects the prices of all countries choosing the minimum price within their baskets as their methodology.

In addition to these well-defined and publicly known statutory discounts, most countries further receive confidential discounts for reimbursable products as part of their negotiation process with providers. No information on the magnitude of such discounts is available, and estimations vary widely, thus only a wild estimate can be made. The below table presents an example of what prices would be if confidential discounts were made public and countries decided to reference to the actual prices paid. In this example, it is assumed that large markets (based on GDP) such as Germany, France, the UK, Italy, Spain, the Netherlands and Switzerland receive an additional discount or rebate of 20%. This example is purely figurative and this analysis does not aim to suggest that this is an actual estimate of the magnitude of current discounts and rebates in Europe.

[25] This figure is the average of official medicine prices. When using the discounted prices here for Germany, Ireland and Greece the average drops to EUR 56.7.

Figure 17: Medicine prices taking into account an additional 20% discount / rebate / clawback for large economies



Source: Authors' calculations

The average price in this scenario falls even further to EUR 41.2.[26]

4.1.4.3 Scenario II: Regular price revisions

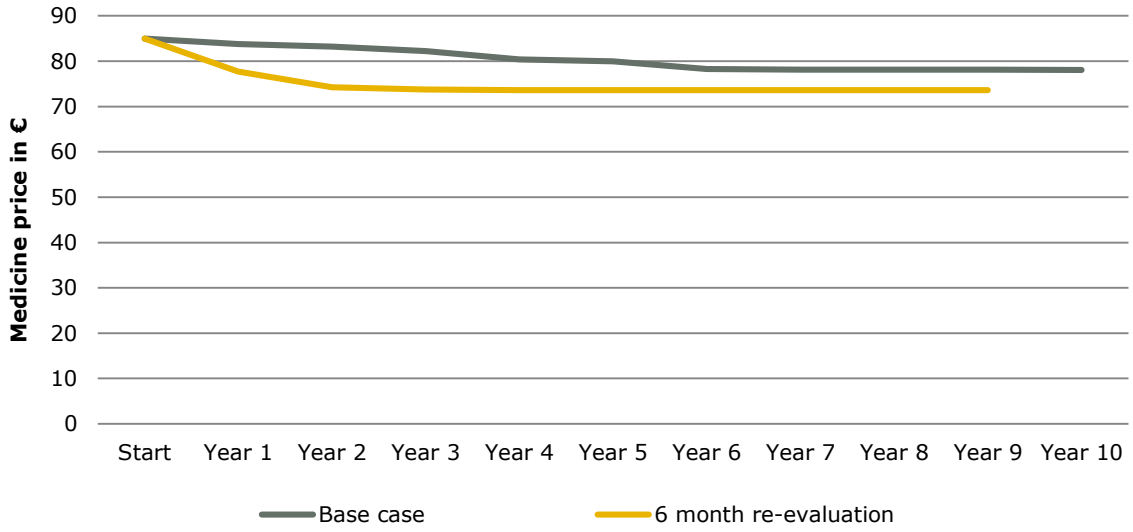
Under the base case, countries re-evaluate at different time intervals depending on their current national policies. Some countries, such as Austria or Belgium, do not re-evaluate their EPR-prices at set, regular intervals. Also in Ireland there are no regular intervals, but prices have to be reviewed as part of the national framework agreements. The legal framework allows HSE to conduct price revisions at any time. While the Czech Republic re-evaluates prices according to their EPR mechanism every 36 months, Greece usually do so every 3 months. On average, countries state that they are re-evaluating approximately every 22 months.

The four countries that use EPR but do not re-evaluate have an average price of EUR 86.7 after 10 years compared to an average price of EUR 78.1 of other countries using EPR.

In this scenario, the base case is modified, so that **all countries re-evaluate their prices every 6 months** after an initial price is available in the specified country. This results in a drop of the average price of all 28 EPR countries after 10 years from 78.1 to 73.6 Euros, i.e. a reduction of about 6 percent. The largest drop occurs for countries which did not re-evaluate at all in the base case. For these countries the average price drops from EUR 86.7 to 75.6, i.e. about 13 percent.

[26] The average price of EUR 41.2 refers to the official prices in all countries applying EPR (i.e. excluding Denmark, Sweden and the UK) after a ten year period. The average of prices 'actually paid', i.e. including statutory and assumed confidential discounts in the average, gives an average price of EUR 38.9.

Figure 18: Evolution of average medicine prices under different re-evaluation rules



Source: Authors' calculations

Figure 18 shows the progression of medicine prices in EPR countries under the base case and the scenario with periodic re-evaluations every 6 months. One can note that **not only does the final average drop under period re-evaluations, but a low price is also achieved quicker** given that most countries evaluate at less frequent intervals under the base case.

4.1.4.4 Scenario III: Changes in country baskets

When performing EPR, countries choose to refer to different selections of countries, i.e. use different country baskets. Some countries, such as Cyprus, use a small number of countries spanning high as well as low-priced countries. Others try to strategically over-include low-cost countries. Some, such as Austria, refer to all 28 EU Member States.

This section illustrates some example results when country baskets are modified. First, the impact of different basket sizes is illustrated, to inform the discussion on optimal basket size. Secondly, highest-income and lowest-income countries are excluded from the basket to show whether prices would reduce in lowest-income countries through such methodological changes.

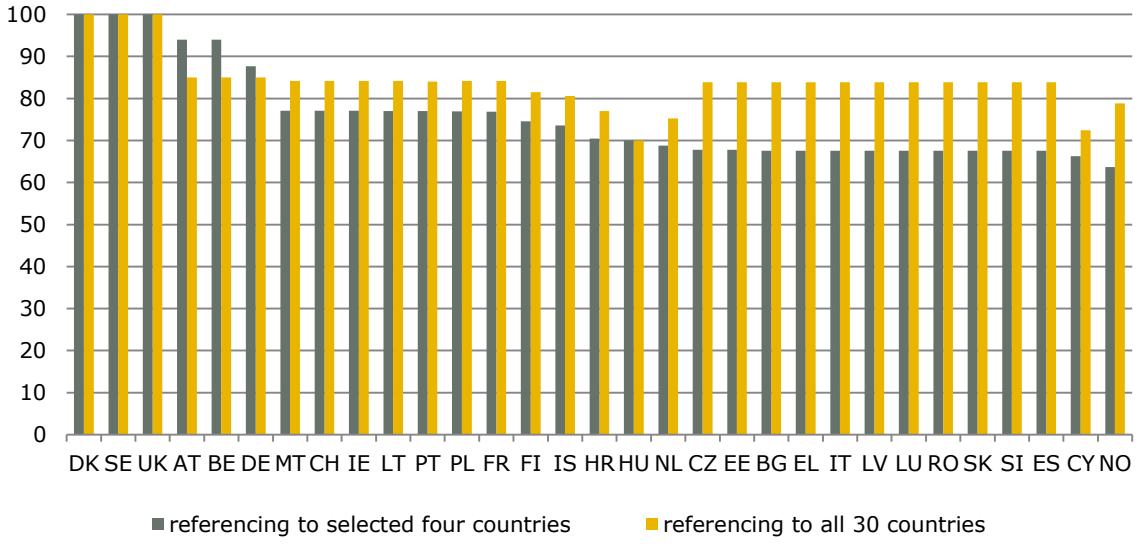
a) Changing basket size

A large basket size reduces the influence of price levels and price level data from single basket countries on national prices. It thus reduces the risk, for instance, of national prices being influenced by price outliers, i.e. countries that have a particularly high or low price for a certain medicine. This benefit has to be balanced by the administrative burden of implementing a large reference basket. On average, European countries reference to 13 countries. Some countries, such as Greece, have attempted to implement a smaller country basket aiming to select a well-balanced sample of high and low-priced countries.

Figure 19 below shows the difference in prices between a scenario in which all countries include all 30 other countries within their basket, to an alternative scenario in which all

baskets only include 4 selected countries.[27] The countries referred to here is one high-priced country (Germany), one low price-level country (Italy), i.e. the two launch countries, as well as two middle price-level countries according to baseline results (Finland, Portugal).[28] Prices do change drastically for some countries depending on their methodologies, average EPR prices rise from EUR 73.0 to EUR 82.2 within this comparison. Having said that, a selection of few countries might lead to similar price effects than referencing to a large basket and might be preferable depending on administrative burden and country preference; however the selection clearly needs to be well thought-through and country-specific depending on EPR methodologies used. The choice of basket countries is a similarly important strategic tool as the calculation method and countries might, for instance, choose to take the average of a basket of low-priced countries rather than the minimum of a basket including very high and low priced examples.

Figure 19: Referencing to all countries, compared to referencing to selected four



Source: Authors' calculations

b) Excluding the lowest income countries

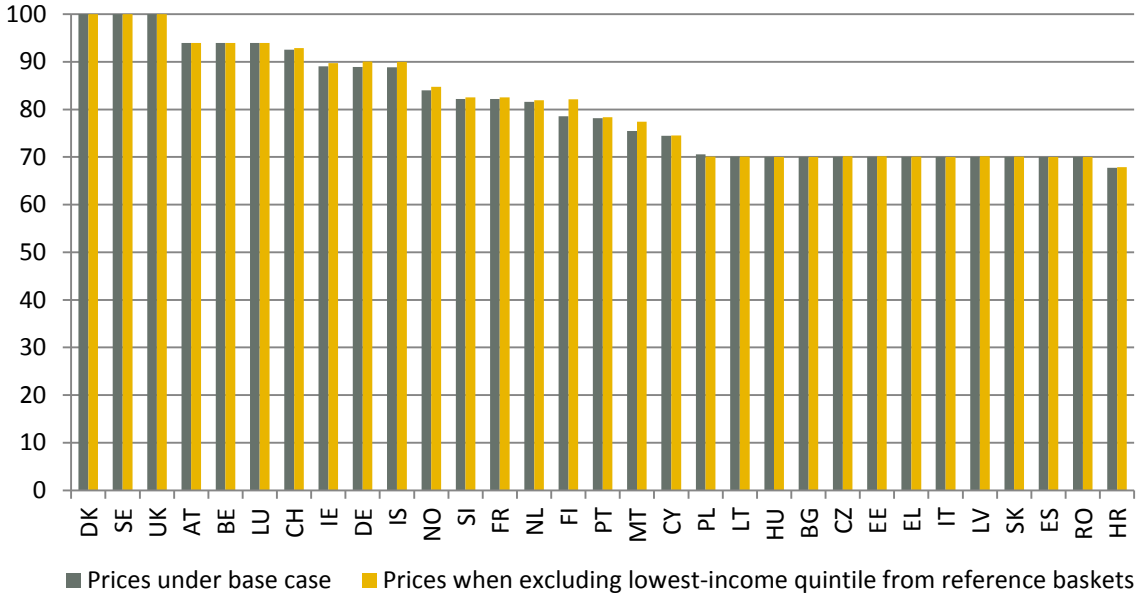
This example illustrates the result when the least wealthy quintile of countries (defined according to GDP per capita) is not referenced to. Arguably this might enable a higher degree of pricing to market, i.e. negotiating lower prices in these countries since firms will not have to worry about external effects on prices of other, potentially much larger, markets. In this sample this amounts to Bulgaria, Croatia, Hungary, Latvia, Lithuania and Poland. Removing these countries from all the country baskets leads to a slight increase in the average EPR price from EUR 78.1 to 78.5. The countries with the highest

[27] To make this comparison, the methodology of countries which refer to the third lowest price or average of three lowest prices was changed to referring to the minimum in the small basket example. Otherwise, selecting a smaller sample of countries balanced between high and low-priced countries would drastically increase prices in such countries. Further, the usual rule regarding the minimum number of prices available within the basket was not applied.

[28] In this example, Italy refers to Spain instead of itself, Germany to Sweden and Portugal and Finland to the Netherlands.

price increases are Finland and Malta, whereas prices decrease in Poland. Thus, the effect depends on the methodologies and country baskets used by different countries. Prices of lower-income countries might increase if they were more likely to reference to other lower-income countries which tend to have slightly lower prices. This scenario ignores any dynamic effects as well as any effects on prices not coming directly from formal EPR mechanisms. If low-income countries are in a different position to negotiate for lower prices or negotiate for higher discounts or rebates if their prices are not referenced to, this would not be included in such a scenario.

Figure 20: Medicine prices, excluding quintile with the lowest GDP per capita from reference baskets



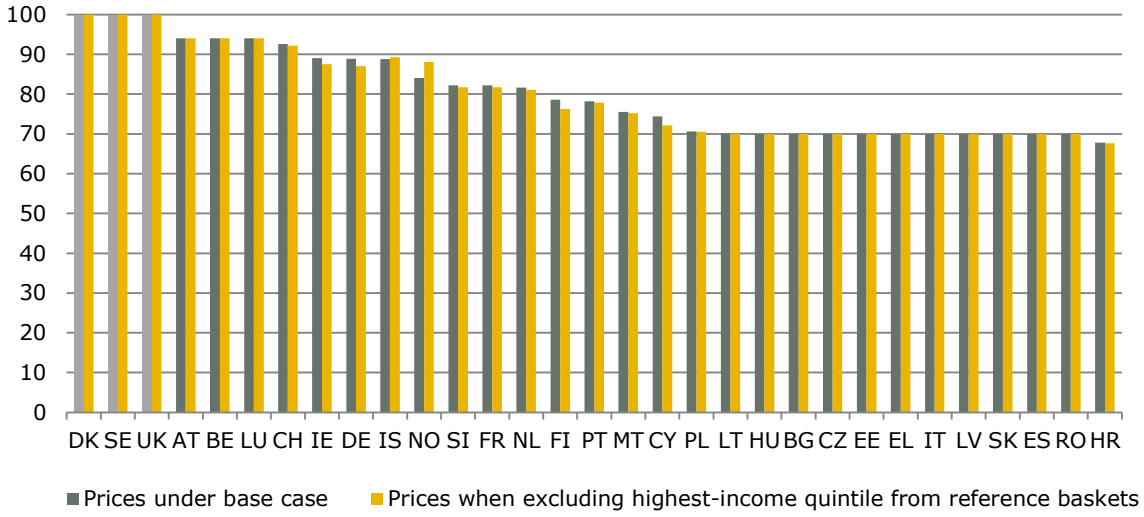
Source: Authors' calculations

c) Excluding the highest-income countries from reference baskets

This example illustrates the resulting prices when the highest-income quintiles of countries, i.e. the countries with the highest GDP per capita, is not used as reference.[29] In this case average prices barely change (EUR 77.9). As can be seen in Figure 7, prices fall for instance in Ireland, Finland and Cyprus. Prices, however, rise in Norway which, for instance, usually references to the Netherlands, a rich but not very high-price country within this framework.

[29] Out of the 31 country sample the highest-income quintile according to GDP per capita amounts to Austria, Ireland, Luxembourg, Norway, Switzerland and the Netherlands.

Figure 21: Medicine prices, excluding quintile with the highest GDP per capita from reference baskets

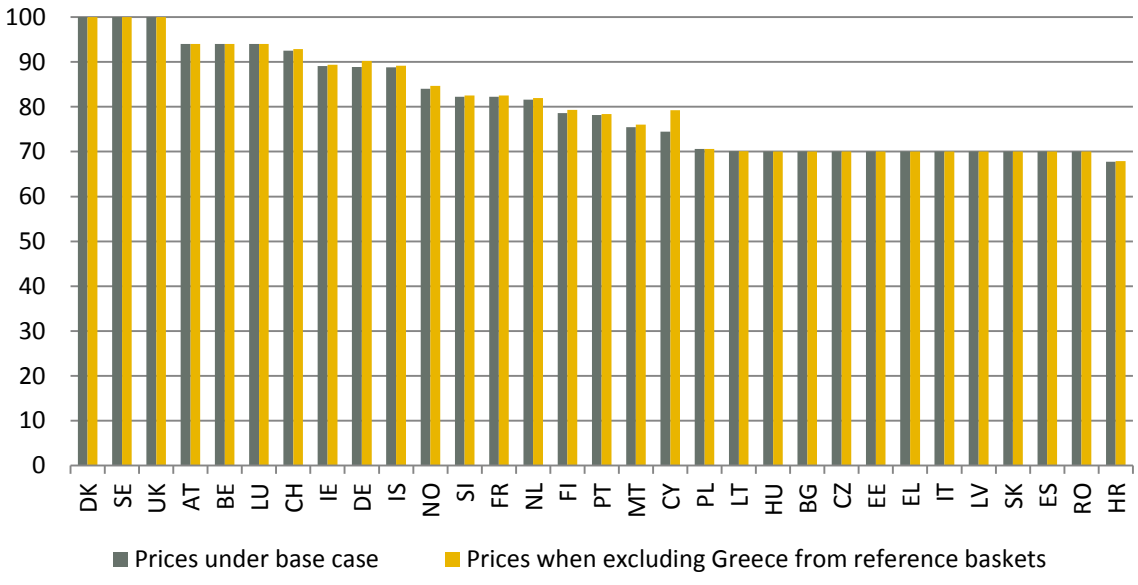


Source: Authors' calculations

d) Excluding Greece from country baskets

Interestingly, in this simplified framework, prices do not change as much as expected when Greece is removed from country baskets. This is due to the fact that many countries such as Austria, Belgium and Germany who have Greece within their country baskets do no re-evaluate their EPR-price and thus do not incorporate Greece's lowering prices. Further, under the outlined conditions, Greece does not constitute the lowest-priced country within the EU and thus eliminating it from country baskets does not affect prices in countries such as Bulgaria, Romania and Hungary who take the minimum price out of their basket.

Figure 22: Medicine prices, excluding Greece from country baskets



Source: Authors' calculations

Average prices across all 28 EPR countries only rise from EUR 78.1 to EUR 78.5 when Greek prices are not referred to. As can be seen in Figure 22, the only country whose prices rise substantially within this example is Cyprus which uses an average over the prices of four reference countries including Greece.

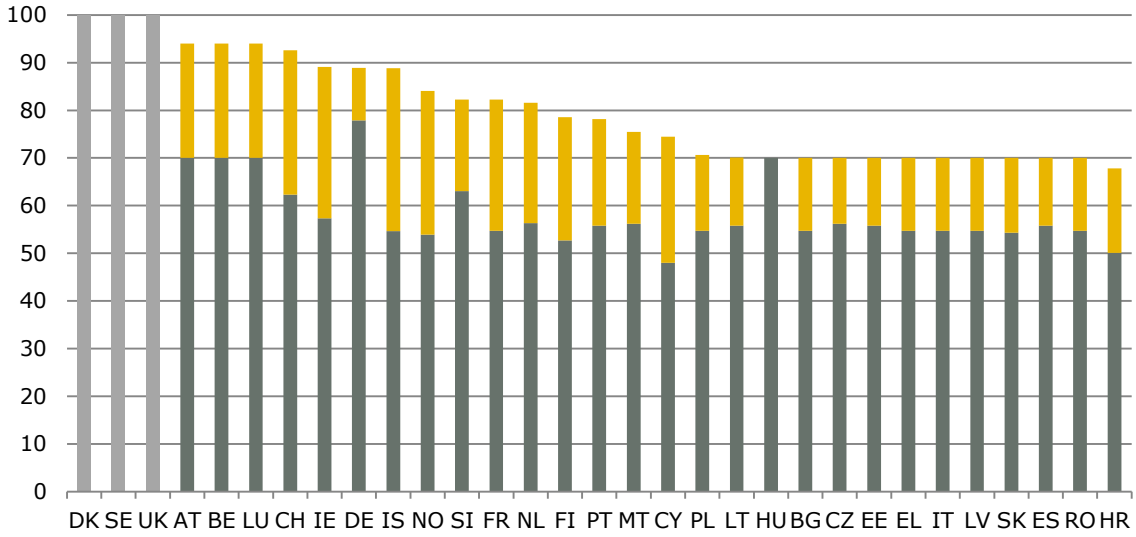
4.1.4.5 Scenario IV: Changes in calculation mechanism

Countries use different calculation mechanisms when combining the international reference prices they are referring to. Most countries use an average over the reference prices, however many also use the minimum and some the average of the three lowest, or third lowest price.

Under the base scenario the average price in those countries using an average to calculate EPR prices is EUR 81.8 whereas it is 74.5 for those countries using the minimum reference price.[30]

This example illustrates the outcome if all countries used the minimum price of their basket country rather than their current policies.

Figure 23: Changes in medicine prices when the minimum price is used in calculations



Source: Authors' calculations

If all countries apply the minimum price as their calculation strategy the average price drops sharply from EUR 78.1 to EUR 58.2. As can be seen in Figure 23 for some countries the change is quite drastic constituting a drop in original prices of more than 30 percent for countries such as Norway, France, Ireland, Switzerland and the Netherlands.

It has to be noted that such an example ignores any possible dynamic effects such as the effect of such pricing policies on the price-building and negotiating processes in lowest-price countries.

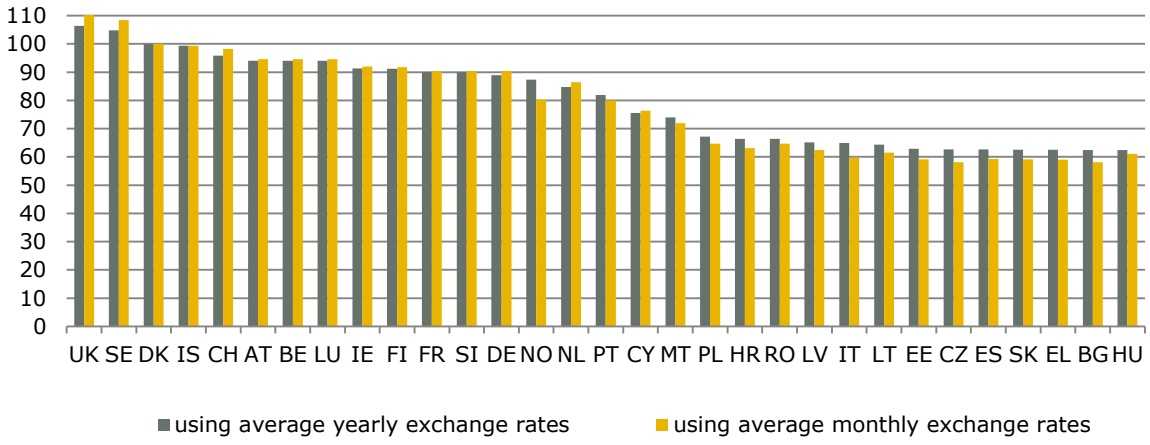
[30] The positive price difference between countries using an average compared to the other calculation mechanisms mentions is statistically significant at the 1% level.

4.1.4.6 Scenario V: Changes in choice of exchange rate

This scenario loosens the assumption that exchange rates are constant over time. Figure 13 shows the resulting prices when average yearly exchange rates are used by all countries, compared to average monthly exchange rates. For some countries not having the Euro as its currency such as Norway, Bulgaria and the Czech Republic, this choice matters, however, prices are also affected to an equal extent for countries within the Euro zone such as Italy, Greece, Slovakia and Estonia. For Bulgaria, Czech Republic, Italy and Norway the price changes by more than 7 percent in this policy comparison. In the case of Italy, for instance, the minimum reference price is chosen during external price referencing. This means that the Italian EPR price depends directly on the exchange rate to the lowest-priced country within its basket, in this case Hungary.

This illustrates, that the type of exchange rate used within the EPR mechanism matters and should be given careful consideration. There are obvious trade-offs between using annual averages which even out short-term outliers and more precise, monthly averages or forward currency estimates.

Figure 24: Price comparison when countries use yearly average compared to monthly average exchange rates[31]



Source: Authors' calculations

4.1.4.7 Scenario VI: Affordability to pay

EPR has often been argued to lead to price convergence and criticised for making it more difficult for lower income countries to achieve lower medicine prices. It has been suggested that these mechanisms could possibly be modified by taking into account the economic situation of countries within EPR methodologies, i.e. including an adjustment parameter related to purchasing power. This scenario explores some possible examples of how this could be achieved.

Under the base scenario, in year 10, prices vary between EUR 67.8 and EUR 100. One can observe a positive correlation between prices and a country's GDP per capita[32], with

[31] In this case, the time period chosen is 60 months, i.e. the prices illustrated here are after five years of reference pricing.

[32] correlation: 0.69 (for EPR countries it is as high as 0.77)

richer countries tending to have significantly higher medicine prices under the specified country policies. The highest-income tercile of countries, according to GDP per capita, has an average price of EUR 91.3 compared to EUR 70.6 in the least wealthy tercile.

Thus, the base scenario presented here already has quite a large positive correlation between medicine prices and a country's economic situation, for instance measured by GDP per capita (for a list of per capita GDP data in US dollar as well as in PPS in the analysed countries see Table A8 in Annex 10). This implies that prices tend to be higher in higher-income countries, however does not necessarily indicate that prices are more or less affordable on an absolute level. This correlation within the model might be different than real life data for several possible reasons. Firstly, the model only captures EPR effects on country medicine prices, ignoring any other effects such as bargaining power or cases where EPR is only used as a supportive criterion. Secondly, where possible, the model uses EPR methodology as reported by the relevant country, and it is possible that especially lower GDP per capita countries have problems with enforcing these mechanisms, for instance performing periodic re-evaluations as planned. Since real price levels are not always lower in countries with relatively lower GDP per capita, it remains of interest how EPR methodologies can increase such an effect, despite the high price-GDP correlation within the base case.

- One possibility that has been mentioned would be, if countries weighted the different reference prices in their basket by some general economic index, for instance an index based on GDP (PPS) per capita.[33] In this example, countries weight all used reference prices by the inverse of a GDP (PPS) index.[34] An index above 1 means that the country has a higher GDP (PPS) per capita than the average of the 31 countries included in the sample and its price when referenced to will be deflated. By definition this means that if a country references to a higher-than-average income country it should receive a lower price than the higher-than-average income country.
- This method leads to a spread of prices between EUR 48 and EUR 100. However, it is interesting to note that the correlation between prices and countries' GDP per capita reduces when adjusting prices in this simplistic manner.[35] This is due to the selection of countries in different countries' baskets. Lower-income countries tend to include a higher proportion of lower-income countries in their baskets thus receiving a higher price through this type of adjustment. Thus, weighting countries' prices within reference baskets in this manner does not help to receive a more 'fair' distribution in prices across countries.[36]

[33] Gross domestic product (GDP) is a measure for economic activity and expressed in per capita Purchasing Power Standards (PPS) is a good indicator of a country's standard of living. The values used in this report are taken from Eurostat [106] which expresses GDP per capita in PPS in relation to the European Union (EU28) average with is set equal to 100. (PPS is the term used by Eurostat when expressing national accounts aggregates adjusted for price level differences using PPPs, i.e. PPS are derived by dividing economic aggregates in national currency by PPP.)

[34] The index is based on the GDP (PPS) per capita Eurostat figures, normalised to a mean of 1 and normalising standard deviation by a factor 5. Normalising the index to a standard deviation of 1 (i.e. dividing by the original standard deviation) provides a too large, unrealistic, spread in prices (with some countries even having negative medicine prices). Thus, the presented example normalises the variance by dividing through the standard deviation*5. Different factors may be chosen to give a different weight on economic situation in the EPR methodology and to achieve a different spread in medicine prices.

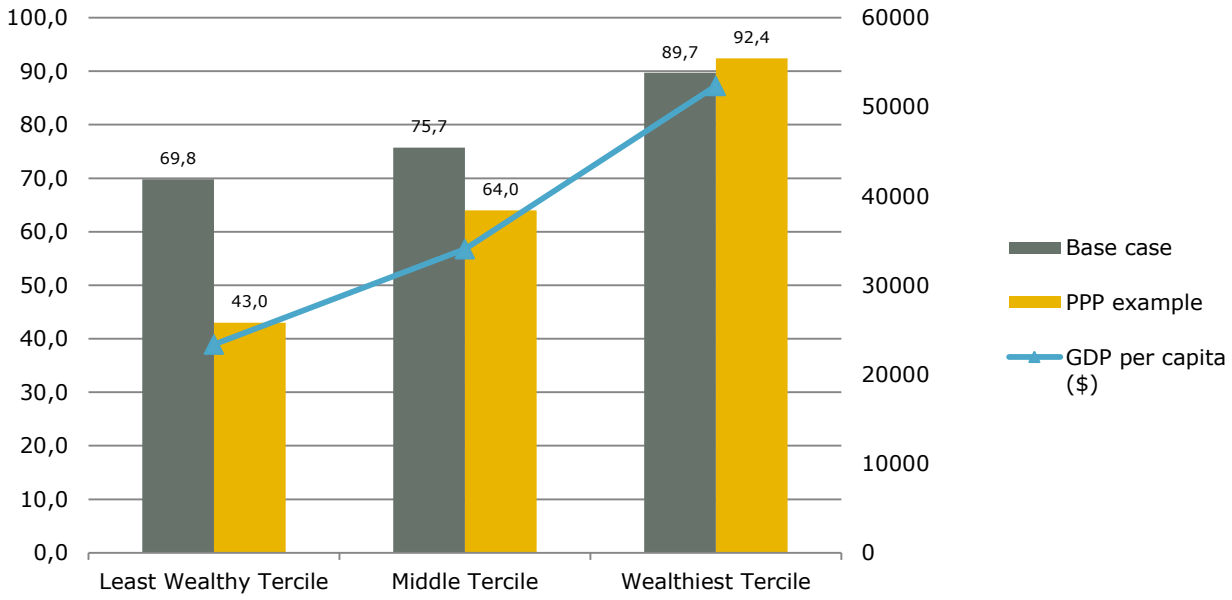
[35] The correlation between price and GDP per capita of EPR countries falls to 0.54.

[36] Further, there are issues around whether GDP (PPS) is the most adequate adjustment parameter to be used, versus for instance GNI measures which would make a large difference for countries such as Luxembourg, Ireland and the Czech Republic.

- One possible way to account for different economic situations is to use purchasing power parity rather than nominal exchange rate conversions when constructing the reference price basket. I.e. in this example countries adapt their EPR methodologies to take into account the purchasing power of different countries when converting their medicine price into their own exchange rate and price level.[37]

Including PPP comparisons in EPR mechanisms strongly increases the correlation between medicine prices and countries' economic situations.[38] As can be seen in Figure 25, the average price (after ten years) in the least wealthy tercile of countries reduces from EUR 69.8 to EUR 43.0, whereas the average price in the highest-income tercile of countries increases slightly from EUR 89.7 to EUR 92.4.

Figure 25: Medicine prices by GDP per capita tercile when including PPP adjustments in EPR mechanisms



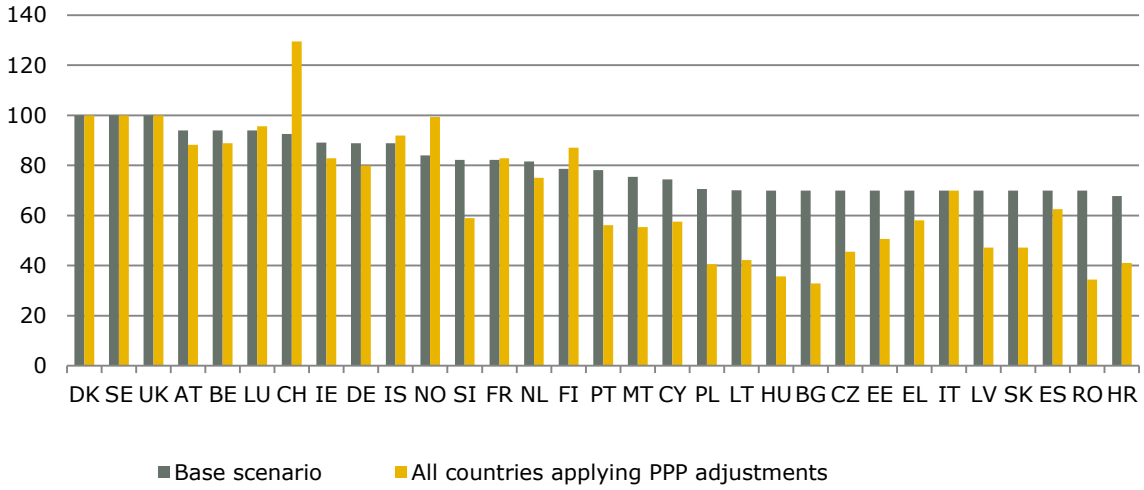
Source: Authors' calculations

Figure 26 shows medicine prices when PPP adjustments are made during EPR evaluations. Again it can be seen that prices in some wealthy countries such as Switzerland increase (from EUR 93 to EUR 129 in this example) whereas prices in some less rich countries fall drastically, for instance by more than 40 percent in Bulgaria, Hungary, Poland and Romania.

[37] PPP values used here are for 2013 sourced from Eurostat [106], with the EU 28 as the reference. As in the baseline scenario it is assumed that PPP values and exchange rates are constant over the time horizon of the model.

[38] The correlation between price and GDP per capita increases to 0.82.

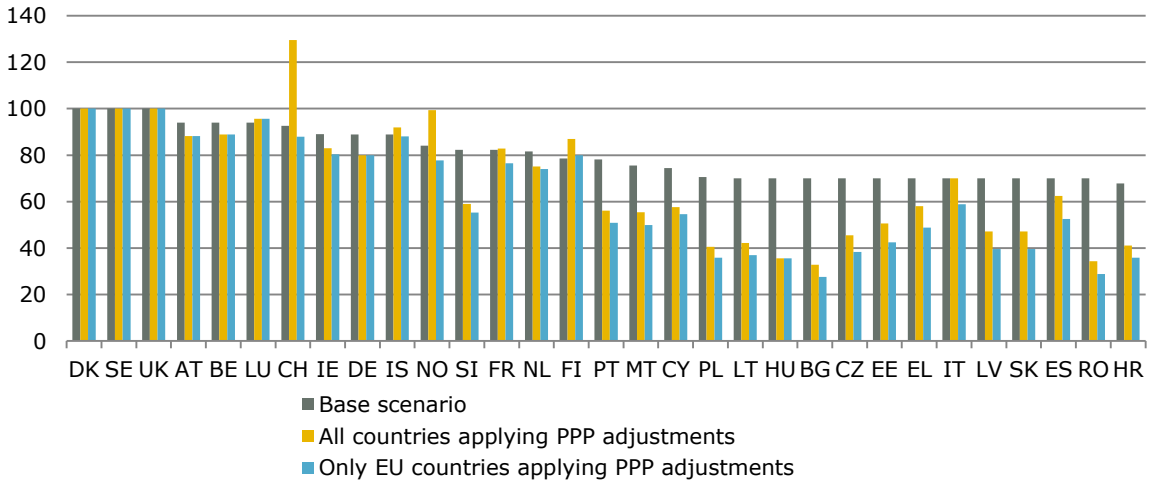
Figure 26: Medicine prices when including PPP adjustments in EPR mechanisms



Source: Authors' calculations

While the above scenario clearly constitutes an improvement for the less wealthy countries in Europe, it would be politically difficult to implement in the highest-income countries. Making such adjustments would probably require a strong cooperation mechanism and a strong wish to have a solidarity-based element in pharmaceutical price setting.[39] The below figure shows medicine prices after 10 years when only EU Member States adjust their reference prices according to PPP whereas Iceland, Norway and Switzerland do not. The association between medicine price and GDP per capita still increases compared to the base case and prices of the less wealthy countries decline. It can be noted that the prices in Norway, Iceland and Switzerland increase by far less than under the previous example.

Figure 27: Medicine prices when only EU Member States apply PPP adjustments



Source: Authors' calculations

[39] The above calculations do not include volumes data and thus make no judgements on how companies' profits would develop within such an example scenario.

4.1.5 Possible EPR formulae

The presented EPR model incorporates the fact that European countries apply a wide range of different EPR methodologies and formulae. Countries make different strategic decisions, for instance, regarding country baskets, re-evaluation periods, which type of prices to refer to as well as whether to calculate an average, minimum or other statistic. Countries also vary on how much weight is given to price comparisons, and thus whether EPR is the main criterion in price setting or merely supporting information, a difference which is not taken into account by the presented framework. The model illustrates that such choices in the design of EPR mechanisms matter and impact national price levels. In most cases, **which methodology is preferable depends on the country-specific situation and national interests**. For instance, a country could use EPR purely out of a public savings objective, whereas other countries might be more balanced regarding interests in incentivizing R&D and supporting national pharmaceutical industries. Further, optimal choices also depend on national capacity, with larger baskets, more frequent re-evaluations and more complex formulae requiring a higher level of administrative resources.

The model shows that whether discounts are considered in EPR matters. This is of particular interest since all countries applying EPR choose to refer to official prices, rather than actual prices paid, even though some discounts, e.g. statutory discounts in Germany, are transparent and thus publicly known. **Referring to actual prices paid, wherever possible, might enable countries with low negotiation power and thus which tend to receive less discounts themselves, to benefit from the negotiated discounts of other countries.** However, an obvious limitation of such an approach is the confidentiality of almost all discounts, rebates, clawbacks, managed-entry agreements or other negotiated deals. This means that it would only be possible to include a small fraction of discounts in EPR mechanisms (i.e. those mandatory discounts published in laws) and might increase pressure for discounts and other arrangements to stay confidential, thus impeding any movements to make such arrangements more transparent.

The illustrated scenarios also show, that **regular EPR re-evaluations tend to lead to faster price drops and a lower average price level overall**. Thus, it might be in countries' interest to introduce regular re-evaluations if they are not already doing so. This, of course, needs to be balanced with the administrative burden of conducting such re-evaluations. Some countries are reporting to have large challenges in implementing the period re-evaluations theoretically foreseen within their EPR systems. One might think of ways to increase periodic re-evaluations while keeping administrative burden as small as possible. For example, re-evaluations could be targeted at medicines with particularly high budget impact. Otherwise, regular re-evaluations could be based on a very small country basket, only triggering a 'full' re-evaluation if a large percentage change in the resulting EPR price is observed during the small-scale evaluation.

As outlined in Chapter 4.1.2.1, many criticise EPR systems for leading to price conversion and most importantly limiting accessibility of medicines in lower-income countries. DP policies are often discussed as a response to such perceived limitations of EPR systems. However, **coordinating to adapt EPR formulae might also help to reduce some of these limitations and reduce medicine prices in lower-income countries in relation to wealthier countries**. For instance, as illustrated in Chapter 4.1.4.7, countries could agree to adjust reference prices by countries' purchasing power parities, rather than merely by nominal exchange rates, when making price comparisons for EPR. For instance, if a country now uses the average price within their country basket converted to euro prices, it would then use the average price within its basket converted to euro prices and the same price level. This would increase the correlation between

medicine prices and countries' economic situation, such as GDP per capita, and thus arguably potentially lead to a more 'equitable' dispersion of prices. Under this approach, compared to any DP systems, countries would continue to independently decide upon their EPR methodologies and thus continue to use different country baskets, calculation strategies and price types. However, they would adjust their relevant reference prices used by a measure of PPP.

Alternatively, countries could potentially collaborate by strategically adapting their EPR methodologies in other ways, for instance by cooperating on the timing of revisions or through the choice of country baskets. High-income countries could agree to leave out certain low-income countries from their reference baskets, thus potentially enabling such countries to negotiate lower prices. The simulations show that this might lead to small price increases in wealthier countries, depending on the mechanisms used. Further, countries could choose to collaborate via increasing transparency on discounts and thus potentially allowing smaller countries with less negotiation power to benefit. Additionally, there are numerous ways in which countries could collaborate to reduce the administrative burden of conducting EPR, as discussed in later chapter for instance regarding the central price database.

4.2 Differential pricing

A standard definition of differential pricing is 'the strategy of selling the same product to different customers at different prices' [25] even though costs are the same. Differential pricing in this report means that 'in the case of (reimbursable) medicines prices would vary among the countries according to their ability to pay' [25]. In literature and debate, several synonyms are found for applying different prices to different customers, the most common ones being 'tiered pricing' [4, 107, 108], 'Ramsey pricing' (to acknowledge the founder of the concept of market discrimination [109]), 'price differentiation' and 'market differentiation' [79, 81]. Further terms used include 'equity pricing' [36, 110], and 'minimum-level pricing' [111, 112].

The two latter imply that pricing is done in a way that ensures fairness and equity for the purchasers whereas the terms 'Ramsey pricing' and 'pricing discrimination' come from the business sector. Ramsey's concept of optimal pricing states that prices should differ across markets according to demand elasticity: more price-sensitive users are charged a lower price than users that are less sensitive [109]. It is thus a commercial strategy for companies to 'differentiate' (or 'segment' the market) in accordance with the observed price elasticity of the consumers, thus the ability-to-pay and willingness-to-pay. Charging different prices to different groups of buyers is a strategy commonly seen in many business areas such as airline tickets, telecommunication or electric devices [113]. Specific groups with high demand and groups with lower income (e.g. students, pensioners) are given lower prices (comment by peer reviewer). It is argued by some authors that price discrimination can increase efficiency and supplier surplus as well as consumer welfare. Depending on market conditions, differential pricing and price discrimination might constitute the same concept. If lower-income countries are more responsive to price changes, then companies that are allowed to price discriminate might yield them lower prices and thus optimise profits by increasing volumes as well as increasing the country's benefit through improved access and lower prices per patient. In this case, differential pricing and price discrimination are similar, and to achieve such an outcome it would be sufficient to allow companies to segregate markets and differentiate prices. However, lower-income countries do not necessarily have a higher elasticity of demand, especially in the health sector. Such markets might be less responsive to price, perhaps due to different organization of the health sector and purchaser groups, and high inequality might mean that it is profit maximizing for companies to cater a high price to a small elite, rather than increasing volumes through

reducing prices. In this case, price discrimination as a profit-maximising business strategy of companies would not yield the same result as differential pricing according to ability-to-pay and would perhaps not increase overall welfare in such countries.

The fact that such profit-maximising strategies might not yield an optimum outcome is due to the fact that public health, including access and provision of medicines, is a public good. It is characterised by a triangle of providers/sellers (in the case of medicines: pharmaceutical companies, as well distribution actors), consumers (particularly patients) and payers (more affluent patients in the private sector, but predominantly third party payers in the public sector in countries with health insurance coverage, or global purchasers such as the Global Fund and international donor organisations at international level), information asymmetry, and limited application of price elasticity of the consumers. Willingness-to-pay can be high for the good 'health' but neither low-income countries nor patients in the private sector in many countries have the ability-to-pay. Thus, concerns of public welfare as well as fairness, in this case requires thinking beyond profit-maximising price-discrimination on the lines of publicly implemented differential pricing according to ability-to-pay.

In order to ensure equitable access to medicines, governments have the responsibility to implement appropriate pricing policies. Thus, we consider DP (or tiered pricing) as a policy of governments, or supranational institutions (but not business) which decide on prices of the same product for countries according to their ability-to-pay, and/or to the economic situation. While the authors are aware of the different designs of DP [114], it is this definition of a governments-led DP scheme that it will be used for this report.

This could be an area meriting further research. In designing a regulatory approach to a possible DP system, we cannot avoid the question of the criteria by which relative prices should reflect differences in income levels and in affordability by the public budget. Economic analysis of the extent to which such prices would be likely to result from commercial negotiations in a legal and policy framework facilitating DP could contribute to providing a comprehensive picture.

4.2.1 Use and experiences with DP

The information in this chapter is based on the findings of a literature review (for further information see Chapter 3.1), supplemented by interviews with DP experts (Annexes 6 and 7).

4.2.1.1 Existing DP schemes

Differential pricing in accordance with the definition applied in this study is not wide-spread across the world: It is particularly used in low- and middle-income countries (LMIC), and it is focused on a few therapeutic groups, particularly on vaccines, contraceptives and anti-retrovirals.

DP has predominantly been used for low-income countries, particularly least-developed countries (LDC); in addition, there are some experiences for middle-income countries. The purchasers were frequently international organisations (UN agencies) such as UNICEF, PAHO and UNFPA; programmes and initiatives such as Global Alliance for Vaccines and Immunisation (GAVI) or UNITAID and international NGOs. In a few cases, particularly related to middle-income countries, national governments are involved in DP.

Differential pricing does not only imply a tiered pricing structure between countries, but it may also lead to intra-country price differentials between the public sector, supplied at lower cost by programmes, and the private sector with higher prices.

In terms of products, DP is focused on a few therapeutic groups:

- HIV/AIDS: There are multiple examples of differential pricing with regard to HIV/AIDS medicines. Their implementation followed political pressure from low- and middle-income countries (LMIC). HIV/AIDS is considered as a therapeutic group with high risk of information arbitrage to erode margins in high-income markets.
- Vaccines: The buy-side market structure for vaccines is dominated by UNICEF and PAHO, with the latter procuring for most of the countries in the Latin America and Caribbean region. UNICEF procures the majority of the vaccines for the low-income and least-developed countries at the lowest possible price for low-income economies, whereas for any middle-income country that buys vaccines through UNICEF, it negotiates the prices with the manufacturer on a case-by-case basis. Vaccines is an area considered with higher opportunities for differentiation due to multivalency, little risk of leakage and good supply chain traceability. The prices of vaccines are much lower in LMIC.
- Malaria: For malaria medicines donations have been observed as well as intra-country price differentials.
- Contraceptives: The prices of contraceptives have been observed to be lower by a factor of 10-100 under the DP schemes. Careful product versioning and 'differential branding' were observed in this area.

With regard to essential medicines in general, a review concluded that there were few positive examples of differential pricing on a large scale, and no significant volume or income effects on prices were found in empirical studies [38].

Table A6 in Annex 8 provides an overview of the practice of DP across the world.

4.2.1.2 Benefits and limitations of DP

The literature review and interviews with experts concluded that the assessment of DP as a tool to ensure access to medicines and achieve lower prices is variable. DP might lead to the envisaged results, however under specific conditions.

Access to medicines

Overall, it was found that 'differential pricing is not a panacea' for ensuring access [38]. In some cases, for medicines such as ARV, vaccines and others, when differential pricing was applied, it apparently resulted in improving access to medicines for low-income countries, particularly LDC, where access to new products would otherwise have been unaffordable (expert interviews; [4, 108, 115, 116]). However, it was stressed that DP was not always effective in improving access: For instance, the number of patients receiving medicines through the Accelerated Access Initiative (AAI) was less than 1% of the patients needing treatment [112]. Examples of several DP schemes and their possible impact on granting access to medicines are listed in Table A6 in Annex 8. Furthermore, experience showed that DP proved not to be successful to achieve patient access in middle-income countries.

Differential pricing appears to be useful in those cases when markets are small and highly uncertain, production capacity is limited, rapid access is required and/or a time delay to overcoming barriers to competition, and small quantities of medicines are

required [107, 116]. It was suggested that DP works best when there is no market prior to the implementation of a DP scheme (personal communication in expert interviews). This might explain why DP has not worked for middle-income countries.

Concerns have been expressed regarding the sustainability of access, as to whether medicines will be available on a predictable long-term basis [110].

Lower prices and savings for public budgets

Overall, DP, as a government policy, is understood as a mechanism that *may* lead to equitable prices, but there is no guarantee that differential prices are affordable and more equitable than would otherwise be found [107]. There was evidence that in some cases DP helped reduce prices and thus made medicines affordable (cf. Table A6 in Annex 8; [4, 110, 111, 116, 117]).

However, expectations were not always fully met since price reductions have been limited for voluntary differential pricing agreements (AAI in particular): substantial price differences continued to exist between originator and generic medicines, with differential prices for originators still higher than generic prices (indicating that originator medicines might not be priced at marginal cost) so these medicines were still unaffordable. In addition, the DP scheme under AAI was considered to be connected with high transaction costs for all parties involved: the recipient countries, the international organisations managing the scheme and the private suppliers [112].

DP has apparently not led to savings but to increased efficiency in terms of addressing treatment of specific diseases and saving lives (expert interviews).

Another problem identified was that though due to DP prices were made affordable in public sector of LMIC, they continued to be high in the private sector. In general, public sector prices tend to be lower than in the private sector in LMIC, and availability usually higher [118]. In response, it has been proposed to extend differential prices from the public sector to non-for-profit suppliers in the private sector [117].

As shown by the example of AAI, differential prices are not immune to market forces since prices fall when generic competitors enter the market [119]. A study by Waning B, Kaplan W, King AC*, et al.* [120] that assessed ARV purchase transactions showed that for 15 out of 18 products, purchases made under DP schemes were significantly more expensive than generic purchases, with price differences ranging from 23-498% [120]. Again for ARV, a Médecins sans frontières (MSF) price analysis showed that WHO pre-qualified generic prices were lower than differentially priced originator medicines in the case of 27 out of 30 surveyed products [104]. Overall, the evidence from ARV strongly suggests that generic prices are generally lower than tiered prices, and that competition among multiple producers systematically results in dynamic price reductions. The same appears to be true for malaria, whereas the differential price has consistently remained below the generic prices of tuberculosis medicines [107]. From the evidence of several indications, Moon S, Jambert E, Childs M and von Schoen-Angerer T [107] found that differential pricing performed poorly compared to competitive production in generating reliable and sustained price reductions when markets were sizeable and multiple sources of production were available. Overall, it has been suggested that DP is weak compared to true competition [107, 121].

Frequently, DP contracts are signed on a long-term basis which limits the countries' ability to access less expensive medicines in the future, when the circumstances have changed (personal communication from expert interviews).

Concerns have been raised about a lack of guarantee that medicines are priced at the lowest possible level and will be available on a predictable long-term basis [107, 110].

Benefits for manufacturers

Through DP, manufacturers are likely to increase their (total) revenue by increasing sales in an additional market, while retaining high prices in the high-income market [108, 122]. It has been argued that, if a uniform price regime is in place, as is arguably the case under current EPR systems, manufacturers would have to reduce the price in the originally served (high-income) market in order to extend their total market into the low-price market [108].

In this context Plahte J [108] argued against understanding DP as a subsidy because the term 'subsidy' would suggest that prices under DP in high-income countries were higher than they would have been in the absence of low-price sales to LMIC. However, pharmaceutical pricing, in addition to ensuring access to medicines, also seeks to provide adequate incentives for R&D to thus also ensure access to future pharmaceutical developments. Such incentives, i.e. the level of profits needed to ensure adequate investments in R&D, are at the crux of the pricing policy challenge, particularly since there is lack of knowledge about R&D costs. Differential pricing should improve affordability and access to medicines in lower-income countries; however this cannot come at the expense of incentives to invest in R&D. The provision of pharmaceutical R&D is a global public good, one to which different countries currently contribute to at different extents. A differential pricing regime might mean that certain countries pay a larger share of this global public good, whereas lower-income of countries pay less above marginal cost and thus contribute less to R&D costs. In this sense a DP scheme might be seen as a subsidy.

Examples of DP schemes have been presented in which major pharmaceutical companies reduced their prices for specific markets to as little as 1% of their original level. There was no evidence that in doing so they would have sold these products at a loss [111].

It is generally known and acknowledged that the costs of manufacturing of most medicines are not prohibitive but high prices mainly result from the need to provide an adequate return on investment, to fund R&D and to pay high promotion costs in the highly competitive markets [111]. Manufacturers should be rewarded for innovation, so prices are seen as a financial incentive to fund R&D. However, costs of R&D are difficult to assess, and some authors demythologised the high cost of research [123-125]. The 'secondary costs' of rewarding industry for research and compensating management and marketing costs are mainly borne by high-income countries, typically with universal coverage, since considering these price elements in LMIC would make most medicines unaffordable in these countries. According to WHO estimates at the beginning of the new millennium, most originator medicines were sold at 20 to 100 times their marginal costs [111]. The idea of DP as it has been applied internationally is that, while manufacturers continue to receive high prices in high-income countries to cover all cost elements, medicines are provided to poorer countries at and slightly above their marginal costs. Since this would grant manufacturers additional markets where low profit margins might be outweighed by high unit sales, this would not be a loss for them [111, 126]. As a case from the vaccines markets in the early 1990s has shown, even though the procurer (UNICEF) did not pay the full costs (e.g. including reward for R&D), the marginal costs were covered (the price was slightly higher than the marginal costs) [127].

In a commentary Plahte J [108], who expressed regret for 'hostility' in the US towards differential vaccine prices, stated: 'Somewhat paradoxically, the pharmaceutical industry, in my opinion, would be better off admitting that they are making a profit from UNICEF/PAHO sales, not just because it is the truth but also because it might lessen the political pressure that for decades had kept US vaccine manufacturers out of a highly beneficial win-win-win situation' [108].

Thus, it has been argued that a condition for DP to be feasible is that the manufacturer's fixed costs (e.g. R&D costs, marketing and administration costs, fixed production costs) have to be substantial in relation to marginal production costs, and the manufacturer has the necessary degree of market power to be able to allocate those fixed costs differentially among different customers [117]. Thus, it was argued that marginal costs must be able to decrease with the increasing scale of production [108].

Impact on high-income countries

Plahte J [108] considered DP schemes in the vaccine market as rare examples of a win-win-win situation. He argued that DP benefitted not only to the low-priced countries (access to otherwise unaffordable medicines) and the manufacturers (additional markets), but also to consumers and patients in high-priced countries since the price in the high-priced markets would be slightly lower that what would have been the case under single-market conditions, and sales in the high-priced countries would be slightly higher than what would have been the case under single-market conditions. This view is not generally shared[40]. A study on differential pricing in the vaccines market in the 1990s did not confirm the hypothesis that consumers in the high-income countries subsidised the LMIC: it was argued that the high volume of medicines – in that case, vaccines – produced for LMIC would also moderate the prices in the high-income markets [108].

Reliance on the industry and limited potential for sustainability

One of the weaknesses of DP is that it heavily relies on the willingness of the pharmaceutical industry, and it does not encourage sustainability or autonomy in LMIC [110]. Some authors and NGOs, including MSF, have thus been calling for a strong uniform DP scheme. Danzon PM and Towse A [81], however, argued against such a system that 'does not leave discretion with companies', for the following reasons:

- Difficulty to translate the two main criteria (GDP per capita and disease burden) into a banded discount table applicable across many diseases and countries;
- Unlikeliness to reach an agreement on a specific band discount table by an international body;
- Published prices could 'freeze prices and undermine competition' in the sense that no large discounts would be granted;

[40] Reactions to Plahte included: '*However, evidence and experience suggest that, in practice, tiered pricing has a number of significant drawbacks. Examining specific drug-pricing case studies, […] critique of tiered pricing (is) organised around three key questions: (1) How can medicines be made affordable in LMICs? (2) Who should pay for research and development (R&D) and how much? (3) Who decides pricing and how?*' [107] '*… bigger problems lie elsewhere, with most R&D not being directed at discovering clinically superior medicines, even for affluent customers, because companies are so generously rewarded for developing hundreds of new products little better than the ones they replace. Policy needs to move away from de-contextualised magic bullets and towards context-sensitive, socio-economic programmes of health in which medicines can play a critical role*.' [123]

- Difficulty to define a benchmark price (particularly given the fact that EU regulation does not include a definition of price);
- Refusal of companies to offer discounts to some or all of the listed countries.

According to Danzon PM and Towse A [81], the approach to address these challenges would be a system in which companies offer confidential discounts and rebates to public payers. While the authors of the study at hand acknowledge some of the difficulties mentioned above, we are not convinced that an industry-led system would be able to successfully deal with these complexities. Furthermore, such a system is not in line with the definition for DP applied for this study that aims to develop a government policy whereas industry strategies to optimize their market segmentation are not scope of this study.

Mossialos E and Dukes G [111] called for a system led by governments and/or international institutions, and expressed scepticism about industry approaches: 'It is striking that over a period of more than a century, standards originally imposed by public authorities have not only been tolerated and assimilated by the industry, but have actually become regarded as an ideal and even as a minimum which a company should attempt to exceed. It is as if public initiatives are needed, not to fight industry, but to firmly encourage industry to overcome a degree of inertia with regard to developments that are in favour of the public interest. Moreover, the world community has begun to discover that in this field public intervention designed to provide a community benefit can also catalyse commercial success.' [111].

Summarizing, the assessment of DP is rather mixed. Table A7 in Annex 8 lists arguments against DP and responses from DP supporting authors as reported in a piece of literature [111].

Acknowledging its limitations, several authors [100, 107, 111, 112] and experts (personal communication in experts interviews) have been arguing in favour of DP schemes, however merely as second-best option to ensure patient access in lower-income countries under specific conditions. Originally, the concept of DP for creating a segmented market and a tiered price structure for LMIC has been met with high scepticism, both from countries as well as industry [108].

4.2.1.3 Prerequisites for differential pricing

From the experience with DP in the LMIC, literature and experts interviews identified the following prerequisites for DP to be successful.

Avoidance of leakage

A major prerequisite for DP to work is to ensure that the different categories of purchasers are prevented from trading with one another. Otherwise, lower-priced medicines from lower-income countries would 'leak' to higher-income countries [4, 30, 38, 108, 117, 122] and prompt pharmaceutical manufacturers to change their behaviour. Kyle M [128] has shown how manufacturers respond to changes in the legalisation of pharmaceutical parallel imports within the EU and assessed what negative effects on welfare and access to medicines these responses had.

There is, however, experience from DP for contraceptives and vaccines in LMIC that did not result in products flooding back into wealthier markets [110, 111]. To prevent re-importation, special regulations, contractual arrangements and provisions would be required if legally possible. The Council Regulation (EC) No 953/2003 of 26 May 2003

[129] in the area of trade is one example for such a legal safeguard (see below Chapters 4.2.1.4 and 3.4).

Transparency

There is a debate whether or not DP schemes should be connected with confidentiality related to the achieved prices. This is particularly of interest with regard to a possible application of DP in Europe where confidential discounts and rebates granted by industry to public payers were proposed by some authors as a way to implement DP [81, 102]. It should be reminded that confidential discounts and rebates granted by manufacturers to public payers are common (cf. also Chapter 4.1.1.9).

It has been argued in favour of confidentiality that confidential discounts and rebates (defined by the purchasers) are a way to achieving lower prices and encouraging competition whereas publishing bid prices would promote collusion between suppliers [81].

This viewpoint has been opposed by other experts (expert interviews; [110, 111, 117, 121, 126]) who argue that DP has to be based on transparency for equity reasons. Confidentiality would only mean that the best negotiated gets the best price and often leads to other countries closing worse deals. The way that DP is currently being performed (e.g. through international organisations, cf. Chapter 4.2.1.1) is, in fact, based on the principle of transparency. Purchasers have to be accountable to the public who has the right of disclosure of procedures and prices. Furthermore, it has been argued that confidentiality can lead to inefficiencies in the pharmaceutical system. It was questioned how priorities in treatment alternatives could be set (e.g. through HTA) if reliable information about the costs were missing. Confidentiality was said to possibly lead to unfair conditionalities due to an unequal bargaining power and access to information between the authority of a (low-income) country and the pharmaceutical company (personal communication from expert interviews; [117]).

Authors that argue in favour of confidentiality still acknowledge that transparency increases public accountability, enabling the public to see if buyers are doing a good job, and reduces the chance of collusion between a procurement body and a bidding company. It has been proposed that the disclosure of objectives could also be achieved through an audit by an approved third party [81]. In general, the discussion about transparency also highlights the need for more discussion and debate about the goals and trade-offs of a pricing system internationally.

Appropriate price setting

Lopert R, Lang DL, Hill SR and Henry DA [130] stressed that an agreement on the *principles* of DP is easy to reach, but an agreement on a *mechanism* to establish prices that represent good value in different settings is a much harder task. In particular, it would be required to define the highest and lowest price within a scheme with the aim of determining appropriate prices related to the economic and social value of a medicine as well as appropriate profits to incentivise R&D. The nature of the question on how to allocate R&D payments across countries is fundamentally political as well as technical, and no international norm has been established for setting price differentials that could be referred to [107, 130].

In addition, even if the principle of DP is agreed upon, the question on the actual price that should be applied remains. Some authors have argued for an increased use of pharmaco-economics [63, 130].

Avoidance of distortion through high mark-ups and taxes

DP can only be successful if the low prices achieved under the scheme are not made unaffordable again due to the high duties, tariffs, taxes and distribution margins [4, 38, 101, 112, 116, 117]. Evidence from WHO/HAI price studies has shown a high level of distribution margins, taxes and similar add-ons on the prices in many countries [118, 131, 132].

Combination with other policies

It has been repeatedly argued that DP as a single strategy is not sufficient, and that it needs to be combined with other strategies, or, in the long run, even be replaced by other strategies: Several authors stressed encouragement of generic competition as an option that may help bringing down prices to an affordable level. In the stakeholder review (see Annex 15), it was also stressed that other tools, in particular generic competition, are more effective in ensuring long-term access to medicines, compared to DP. Further strategies proposed in combination with DP are joint (regional/global) procurement, compulsory and voluntary licensing ([4, 107, 110, 117, 122], personal communication from expert interviews).

Voluntary licensing for LMIC has been recommended by the European Community's Development Council in its advice to the Council of Ministers of the EU. However, the granting of voluntary licenses is only feasible if there is adequate local production capacity in the country or region [111, 133].

Compulsory licensing is another measure discussed as a way forward to ensure access (personal communication in expert interviews; [112]). The World Trade Organization (WTO) members may grant compulsory licensing under specific conditions (e.g. public interest, national emergency, public non-commercial use) [134].

On top of the existing models, there was a call to find alternate solutions for financing R&D since the current system relies on the ability of industry to recoup R&D investments by charging a significant market premium above production costs. Proposals for alternative models that 'de-link medicine prices from R&D costs include prices (as alternative to patents), patent pools and patent buy-outs [110].

Addressing unbalanced negotiating power

DP was criticised for giving most of the decision-making power to private companies and leaving little decision-making power to governments that are accountable to their populations [107]. It was argued that 'because a country is small, prices should not be less favourable than for large countries' [117]. In order to address the perceived imbalance of the negotiating power, intergovernmental agencies were considered to play a useful mediating role in negotiations. Furthermore, the pharmaco-economic approach to price determination was proposed as another way in which to respond to the imbalance of negotiating power, by identifying 'value for money' prices [100, 117]. However, this would again require transparency about underlying costs.

Sufficient capacity

Limited capacity of countries to deal with DP offers of companies, including lack in logistics, might result in failure of DP. There is the example of the Novo Nordisk DP initiative on insulin. In some LDC Novo Nordisk was not selling insulin at all. In several cases, the government has not responded to the offer, either because there are no private wholesalers or other partners with which to work, or because wars or political

unrest have made it impossible to do business. Unfortunately, there was no way to guarantee that the price at which Novo Nordisk sells the insulin will be reflected in the final price on the pharmacist's shelf [135].

Political will and possible establishment of an international framework

It has been iterated by several experts that political commitment, supplemented by contractual arrangements, is required to make DP work. This concerns finding solutions with regard to avoiding leakage (parallel trade) as well as a common understanding of how to set prices (personal communication from expert interviews, [4, 116, 117]).

Some authors argued that DP should be a truly global system, not an initiative limited in time and place [111, 126]. The focus on a few therapeutic groups in existing DP schemes was also seen with concern [110]. In 2001, Mossialos E and Dukes G [111] proposed a framework for an international DP scheme in order to achieve access to essential medicines to medicines for low-income countries.

With regard to introducing such a 'global tiered priced' system for essential medicines, the European Commission suggested measures such as 'labelling products as preferentially priced for specific markets', 'special enforcement procedures' and 'contractual arrangements between importers and exporters' (Kaul I [136] cited in [4]).

4.2.1.4 Implications for Europe

In the background paper on valuation and pricing of medicines of the WHO Priority Medicines Report 2004, it has been argued that DP should not only be seen as a mechanism to be used for essential medicines in the lowest income countries, but as a mechanism with a wider application across LMIC and perhaps even high-income countries which vary substantially in their national measures of wealth [63]. Within the EU market differential pricing in accordance with the above-mentioned definition is not applied as a pricing policy.

As re-iterated in literature [79, 81, 102] and expert interviews, two major limitations hinder the implementation of a functioning DP scheme within the EU that would be able to achieve the objectives set (which would imply the avoidance of leakage). The first limitation is that medicines as such are no exception to the free mobility of goods in the internal market of the EU, and that parallel trade had gained a major dimension in the EU Member States [137]. It has been found that under certain conditions parallel trade of pharmaceuticals may reduce economic welfare and lead to price convergence [102]. There is variable evidence about possible savings for public payers arising from parallel trade with some studies showing savings for public payers [138, 139]. Research-oriented manufacturers that have strongly been opposing parallel trade have responded, and community and national case law has confirmed that pharmaceutical companies are entitled to adopt measures responding to –but not prohibiting or eliminating– parallel trade, and such measures are not contrary to the EC competition rules ([140], cf. legal analysis in Chapter 4.2.2 and in Annex 13).

A second limitation to differential pricing in Europe is the widespread use of external price referencing since there is limited incentive for companies to offer lower prices to lower-income countries when this would subsequently decrease prices through EPR [19, 30, 81].

One author [81, 102] argues in favour of introducing what she calls 'differential pricing' for Europe. However, the underlying concept is based on 'market segmentation', 'price segmentation' and 'Ramsey pricing', i.e. differential pricing is here defined equally to

price discrimination, or it is assumed that lower-income countries are more price-elastic and thus price discrimination will also lead to a more 'equitable' variation in prices. In these pieces of literature, it is argued that differential pricing would lead to an improved and more equitable access to medicines across Europe, more appropriate use of medicines and allow higher research and development [37, 81, 102]. The mechanisms proposed for such DP schemes would be the introduction of confidential discounts and rebates granted by the industry to different EU Member States, to exempt specified medicines (e.g. originator medicines) from parallel trade or to ban parallel trade, and to ask countries to commit themselves to not referencing to low-income countries (the example of the UK government which committed in 2002 not to benchmark or reference to developing countries has been brought in this context) [81, 102]. The mechanisms of how to set the prices and the arrangements between purchasers and sellers were not addressed by these authors.

It has been stressed that political will is a major prerequisite for introducing a DP scheme, and thus major political commitment would be required for introducing a DP in Europe (expert interview; [103]). 'Differential pricing policies hinge critically on the political acceptability of lower prices in poor countries.' [117]. Though this sentence was stated in a publication about DP from the global perspective, focusing on LMIC, it also has its relevance with regard to the discussion about DP in the European context.

While discussions about DP as a policy within the EU have started only recently, the European Commission passed legislation in the area of external trade that was intended to create a voluntary global differential pricing system for essential medicines in the areas of HIV/AIDS, TB, malaria and related diseases for the LDC and, at the same time, to prevent product diversion of these products to other markets by ensuring that effective safeguards are in place. The Council Regulation (EC) No 953/2003 of 26 May 2003 [141] invited exporters to put their products (both originator and generic medicines) on a tiered-price list managed by the EC. To qualify for this list, medicines had to be made available either with a price cut of 75% off the average ex-factory price in OECD countries, or at the cost of production plus 15%. In order to avoid leakage and to ensure that the tiered priced medicines stay in low-income countries they are meant for and are not diverted into high-price markets, re-importation into the EU was prohibited from 76 countries with those several countries which were not able to locally produce the medicines they need. The system was considered as 'simple and transparent' [142]. The mechanisms under this provision have, however, only been used by one company (GSK) [143].

4.2.2 Legal analysis

The legal analysis aims at investigating whether legal constraints exist in EU law that would prevent the introduction of an EU-wide coordinated Differential Pricing (DP) scheme and whether or which legal changes would be necessary in order to allow such an EU-wide policy (for more in-depth analysis see Annex 13).

A more comprehensive legal analysis with references can be found in Annex 13. Based on the findings in this analysis, the following legal conclusions can be drawn.

Legal constraints in EU law for an EU-wide DP scheme – current legal framework for pricing and reimbursement and Member States' interpretation:

Principle of subsidiarity

According to the **principle of conferred powers** (Art. 3a 1. TFEU), the EU can only perform legislative power within the limits of the competences explicitly conferred to the EU. The TFEU basically defines three different categories and areas of EU competence: exclusive, shared and the competence to carry out actions to support, coordinate or supplement the actions of MS.

The pharmaceutical market is a **cross-sectional field of competence** since medicines are products in the sense of Art. 28 of the TFEU. Thus, the EU basically has the power to set binding law in order to achieve **functioning and effective competition**. Among the main areas of shared competence, the most relevant one in the context of pharmaceutical policy is the **internal market** and its principle of free movement of goods (Art. 28 to 37 TFEU). According to Art. 34 and 35 TFEU, quantitative restrictions between MS are prohibited (i.e. restrictions on imports or exports and all measures having equivalent effects). In the field of **social policy and consumer protection** as well as **common safety concerns in the field of public health**, the MS are still allowed to set binding laws, if the EU did not regulate a specific field. Besides, in the field of **protection and improvement of public health** as well as the coordination of social policies, the EU shall support, coordinate and supplement actions of Member States (MS).

However, according to **Art. 168 (7) TFEU**, the '*Union action shall respect the responsibilities of the Member States for the definition of their health policy and for the organisation and delivery of health services and medical care and the allocation of the resources assigned to them*.'

Different MS policies

So far, in accordance with Art. 168 (7) TFEU MS are responsible for regulating pricing and reimbursement of medicines, given the **specific nature and tradition of their health systems**. However, they need to comply with the Transparency Directive[41] which defines procedural rules. As a result, pricing and reimbursement policies across EU MS differ, as evidenced in the differences in the design of the surveyed EPR schemes (cf. Chapter 4.1.1).

Parallel trade and possible responses

One of the major restraints to a functioning DP scheme is the leaking of medicines from lower-priced to higher-priced markets (cf. Chapter 4.2.1.2). This happens in the EU due to the existence of parallel trade.

Parallel trade arises when (parallel) traders, e.g. wholesalers, purchase a specific medicine in one MS in order to sell it at a higher price in another MS with a typically higher price level. Thus, parallel trade occurs, if a genuine product originally sold under

[41] Council Directive of 21 December 1989 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, OJ L 40/8, 11.2.89

the patent (copyright/trademark) protection is traded (in another country) without control or permission of the original patent holder. Related to specific patented products, this possibility creates some form of market separation, i.e. key parallel exporting countries (usually low-price level countries) and key parallel importing countries (usually high-price level countries). In parallel importing countries, the same products originally sold by the patent holder are then in competition with the same (imported) products. It has been argued that in a market with patented products, parallel trade is the sole possibility to create some form of intra-brand (price) competition. On the basis of the Treaty provisions, the European Institutions traditionally support parallel trade.

Parallel trade is thereby restricted to the European market, since the EU practices, so called '**regional exhaustion doctrine**', allowing only parallel trade of goods authorised in the EU. This practice is in line with international trade and patent agreements (i.e. **TRIPS**), since WTO members could not agree on the implementation of an 'international exhaustion doctrine' within the TRIPS framework. The implementation of the 'international exhaustion doctrine' would have made legal parallel imports of patented products, no matter where the product had been distributed first (world-wide).

Due to different price levels and resulting parallel trade, the **European pharmaceutical market is divided in parallel importing and parallel exporting states**. This leads – at least in the short-term – to reduced prices for consumers and third party payers in parallel importing MS with higher price levels (though the extent of savings for payers due to parallel trade has been challenged, cf. Chapter 4.2.1.4), but potentially threatens the supply in MS with low price levels for pharmaceuticals. In addition, pharmaceutical companies' revenues in high-price countries allegedly decrease, possibly leading to higher prices and reduced investments in R&D.[42] For this reason, pharmaceutical companies have developed several strategies in order to diminish the effects of parallel trade, i.e. **dual pricing strategies**, **supply quota restrictions**. These strategies have been scrutinised by the European Commission and the ECJ and have in some cases been classified as anti-competitive. The ECJ ruled that agreements of pharmaceutical companies with wholesalers in low-price countries providing for different prices – depending on whether wholesalers would export products to high-price countries – in order to limit parallel trade violate EU competition law and are a restriction by object. However, the ECJ upheld the General Court's finding that dual pricing strategies might benefit from an exemption under Art. 101 (3)**, if its efficiencies outweigh its anti-competitive effects**. Besides, the ECJ ruled that a company in a dominant position may refuse to supply out of ordinary orders of exporters in lower price countries, if these measures are **proportionate and reasonable**, thereby acknowledging existing legitimate commercial interests of pharmaceutical companies. If a company does not abuse a dominant position, a manufacturer may adopt a supply policy, which he considers necessary, even if by the very nature of its aim, the implementation may restrict competition. However, the Commission and the ECJ criticised the strategy of pharmaceutical companies to delay market entry of generic products by using different life cycle management strategies. These rulings show that the ECJ, on the one hand, still stresses positive effects of parallel imports, but on the other hand acknowledges legitimate commercial interests of pharmaceutical companies, if reasonable and proportionate strategies are applied or if consumer and/or patients

[42] See e.g. Kanavos P, Kowal St, Does pharmaceutical parallel trade serve the objective of cost control?, *Eurohealth* Vol 14 No 2, pp 22-26, available at http://www.lse.ac.uk/LSEHealthAndSocialCare/pdf/eurohealth/VOL14N2/Kanavos%20and%20Kowal.pdf at p 24: '*For the pharmaceutical industry, the growing presence of parallel trade presents a challenge as it reduces potential profits and mitigates the ability of manufacturers to recoup research and development costs'.*

interests outweigh its anti-competitive effects. But even though the ECJ provides some guidelines on possibilities for pharmaceutical companies to diminish negative effects of parallel trade, these rulings leave many open questions, e.g. how to apply the reasonability and proportionality test, leading to legal uncertainty, e.g. what is specifically meant by a pharmaceutical company's 'legitimate commercial interest', which concrete market conditions in terms of concrete quantifiable criteria have to be fulfilled in order to justify limits in supply and how shall they be determined or how to determine best consumer interests?

Companies are not the only ones to have reacted to parallel trade as MS also did, in particular if targeted by medicines shortages, which has become a major problem in several European countries.

Recently some MS, specifically parallel exporting states, adopted laws introducing (temporary) **export bans** (e.g. Romania, Greece, potentially Estonia) and **notification / authorisation procedures for specific exports of** scarce medicines (e.g. Spain, Portugal, Slovakia, Bulgaria, Poland). These laws typically provide for a mandatory notification of medicine agencies, if reimbursed medicines are exported or if there is a disruption of supply. The competent agency then usually has the right to (temporarily) object to exports within a certain time limit, if quantities of the medicines are insufficient to meet demand, could lead to a (temporary) shortage or if the shortage could pose a serious threat to the health and life of patients. These laws, which could be seen as interference with internal market, potentially violate Art. 34-36 TFEU. However, if they are **suitable, proportionate** and **necessary** to attain the goal of **health and life protection,** such a violation of internal market rules might be **justified**. Up to now, no official Commission opinion or ECJ ruling on recently introduced State restrictions on exports of medicinal products on the basis of Art. 34-36 TFEU has been issued. Merely the Bulgarian constitutional court scrutinised the Bulgarian export ban law under Bulgarian constitutional law, stating that this **law violates the principles of equal treatment of market players and the principle of proportionality, since no specific quantifiable criteria have been established**. Regarding Greece, the Commission reported in 2014 that problems have been resolved and that in case problems with MS' export bans would '*remain unresolved, it could refer a case to the Court of Justice*.'

So far, (temporary) export bans or notification / authorisation procedures seem to be the sole policy that MS have undertaken to react to shortages of medicines. Another option to fight shortages might be a compulsory licensing measure by MS authorities. With a compulsory licensing decision, the competent authority breaks the patent holder's right to exclude others. In line with international law (TRIPS agreement), the right of the patent holder can be broken without prior negotiations, if there is a national emergency and the patent holder receives adequate remuneration and does have the right to legal review. Since the EU usually prioritises competition rules privilege over intellectual property protection, this possibility should be further assessed by MS. As Tudor (2012) states: 'One of the dominant beliefs across the globe, and what furthers the movement toward a reduction of intellectual property rights in favour of the public interest, is a belief that all people should have access to scarce resources, including medicine.' In fact, there were some examples of compulsory licensing in Europe (e.g. the abortion pill RU 486 in France, and cases in Italy [144].

Thus, through its market and competition policy, European Institutions guard Treaty provisions also dealing with accessibility issues related to medicines.

Necessary legal framework for an EU-wide DP scheme

According to **Art. 168 (2) TFEU** the Union shall **encourage cooperation** between Member States in the field of public health and – more specifically – the Union shall improve cooperation on building mechanisms for increased transparency and better coordination 'to minimise any unintended effects that current national pricing systems may have in terms of accessibility throughout the EU' (European Commission 2014). **Unintended effects** of MS' pricing policies include unequal access to **medicines** across Member States and **availability concerns**, e.g. shortages of medicines, forcing MS to implement (temporary) export bans or other authorisation / notification procedures. In order to protect consumers and patients, and to achieve equal access and affordable prices, shared competence might be justified according to the principles of subsidiarity and proportionality. However, since a definition of common principles through secondary legislation is a major challenge, **other mechanisms might be more successful**.

Open Method of Coordination (OMC)

Besides secondary legislation, it should be taken into consideration that initiatives through the so called '**Open Method of Coordination (OMC)**' sometimes prove to be more successful than legislative initiatives; specifically in fields traditionally not assigned to the European level by MS. The Lisbon Summit introduced this policy of 'spreading best practice and achieving greater convergence towards the main EU goals'. According to the Conclusions, this involves: fixing guidelines (with specific timetables); establishing quantitative and qualitative indicators and benchmarks (against the best in the World); national and regional targets; and periodic monitoring, evaluation and peer review organised as mutual learning processes.

Processes such as the G 10 Medicines, the High Level Pharmaceutical Forum and the platform 'Access to medicines in Europe' under the Process on Corporate Responsibility in the field of pharmaceuticals (cf. Chapter 2.3.1) have been important initiatives in the area of pharmaceutical pricing and reimbursement policies that reflects this area of cooperation.

In addition, there are some points of reference for the Commission to provide sound guidance for improved coordination for MS in order to **promote equal and affordable access** to medicines, **transparency of pricing and reimbursement measures** and to further **promote patients' rights.**

An extremely close cooperation and challenging mechanism is the implementation of an **EU-wide coordinated DP scheme**. Any approximation and coordination of MS' laws in this context will be easier, if **positive effects** of such a scheme on existing common points of reference can be shown, e.g. on **combating cross-border health threats** and **maintaining patients' rights** (equal, affordable and fair access to medicines through joint procurement of key medicines).

Point of Reference: cross-border health threats (joint procurement agreement (JPA))

There is one recent, concrete point of reference for the possible establishment of a common DP scheme. On a voluntary basis, 21 MS signed and internally approved, another 6 MS are in the stages of finalizing the national approval processes prior to signing, a Joint Procurement agreement (**JPA**). Thus all MS (except Poland) have agreed on a voluntary basis on closer cooperation for the procurement of medical countermeasures for serious cross-border threats to health. Patients and consumers in MS as well as the pharmaceutical industry shall benefit from this joint initiative. MS shall

gain better and more equitable access to existing and new treatments and the prices should be more balanced. For the **pharmaceutical industry** the administrative burden, together with access costs, could be reduced and turn-over could become more predictable. The capacity planning might be improved and financial revenues more predictable and constant (Pharmaceutical Committee – Human, 74th meeting, Brussels 17 March 2015).

Experiences in the context of the 2009 H1N1 pandemic highlighted the necessity for **joint action in the procurement of vaccines**. The European Parliament and Council Decision 1082/2013/EU on serious cross-border threats to health provides for this **joint procurement of medical countermeasures** (i.e. organisation of the evaluation of the tenders, decision process for the award of the contract) in case of a **serious cross-border threat to health.** Article 3 (g) of the Decision defines a serious cross-border threat to health as a '*life threatening or otherwise serious hazard to health of biological, chemical, environmental or unknown origin, which spreads or entails a significant risk of spreading across the national borders of MS, and which may necessitate coordination at Union level in order to ensure a high level of human health protection*.' According to Art. 5 (3), '*the institutions of the Union and any Member States which so desire may engage in a joint procurement procedure*.'

So far, joint procurements have started for **pandemic vaccines** and **personal protective equipment** for healthcare workers having to treat patients contaminated with a serious infectious disease of the type of Ebola in an EU hospital setting.

The whole process is managed by:

- The Joint Procurement Agreement Steering Committee (**JPASC**) that is in charge of all the matters relating to the JPA as such and decides on the specific procedures to be launched and on the timetable. The JPASC is the Committee where MS will decide on the organisation of different joint procurement procedures for different medical countermeasures and identify if there is a critical mass to launch a call for tender that could have an added value.
- The Specific Procurement Procedure Steering Committee(s) (**SPPSC**) that will be in charge of the matters relating to specific procurement procedures organised under the JPA. Thus, the role of the SPPSC is to agree on the final decision on the successful and unsuccessful tenderers or candidates. A separate SPPSC will be established for each specific procurement procedure; it will be composed of one representative of each Contracting Party (MS and the Commission) participating in a specific procurement. A MS that would not recognise itself in the final version of the specifications approved by the SPPSC will always have the possibility to retreat from the procedure before publication of the call. Decisions to award the market by the SPPSC will have to be approved on the basis of the opinions received from the evaluation committee. (for more detail see EC, Explanatory Note at http://ec.europa.eu/health/preparedness_response/docs/jpa_explanatory_en.pdf).

Secretariat and **Chair of each Steering Committee** are provided by the Commission. Regarding the decision-making process the **estimated financial volume of the participation** of each contracting party to the call for tender was considered as the most appropriate and objective criterion to determine a qualified majority.

According to a recent presentation at the Workshop on the joint procurement of medical countermeasures in Luxembourg on 29 April 2015, it is **not clear how to address the issue of 'price'** under the JPA ('*Can there be several JPAs for a given product, clustering MS by purchasing capacity*?', Which clusters/groups of MS are appropriate for specific procurements according to which criteria?, How to organise tenders for low-price countries? etc.).

Alternatively, minimum / maximum entry prices could be defined for all MS in addition to specific, value and GDP-based / per capita income calculation procedures. According to the authors of this report, the JPA procedure then might be a point of reference to allocate a possible DP scheme in the EU.

The success of the first JPAs will determine whether further common approaches under the lead of the European Commission, possibly moving into the direction of DP schemes, will be established in the EU. Alternatively, MS might turn to other possibilities for pooled procurement, i.e. through bilateral agreements. Given latest developments, the latter appears more realistic since it was confirmed during the meeting of JPA Steering Committee [145] held in July 2015 that the JPA allows jointly procuring of medical countermeasures against communicable diseases that can be considered as serious cross-border threats to health as expressed in the explanatory note on the scope of the JPA [146]. It was made clear that hence it could not be employed for the joint procurement of innovative medicines against cancer, multiple sclerosis, orphan medicines, as it has been discussed in the month before.

Point of Reference: specific mechanisms of Council Regulation (EC) No 953/2003 of 26 May 2003 (currently under revision: 2014/0165 (COD))

Even though Council Regulation (EC) No 953/2003 (currently under revision: 2014/0165 (COD)) is based on Art. 207 TFEU and relates to external trade, some specific mechanisms might be interesting in providing guidance for internal coordination mechanisms. This Regulation has been introduced to support the principle of tiered pricing between EU MS and low- and middle income countries. This regulation provides for safeguards to prevent the leaking of tiered products from LMIC outside Europe into the EU: Authorised tiered priced products are marked with a logo. As explained in Chapter 4.2.1.4, the manufacturer basically has two options to achieve the differential price: a certain percentage of the average ex-factory price charged in high-priced countries (e.g.: 25%) or the direct production costs plus a certain percentage (e.g.: 15%). These tiered priced products with logo are then subject to specific trade. For reasons of public health and access to medicines within the EU, such mechanisms might be considered for specific, essential medicines.

The impact of this Regulation was evaluated. According to the draft report as published in July 2015, little impact of the Regulation was found in terms of direct impact on reducing the risk of product diversion, or the ultimate objective of lowering prices and raising access in the poorest developing countries. However, in terms of the wider benefits, many interviewees addressed during the evaluation highlighted that the Regulation did provide less tangible but wider benefits 'signalling' the Commission's commitment to differential pricing and in broad terms its opposition to exploiting the price differences through international arbitrage. The signal was described in a number of different ways:

- It was a signal that companies should be adopting tiered pricing
- It was a signal that lower prices in low income countries should not be used as a reference for the price to be paid for the same products in developed country markets.
- The need for a wider discussion on the factors affecting access to medicines in developing markets [143].

Principles for a DP scheme

Since no official legal framework for a DP has been established, constitutional principles of **equal and affordable access** have to be considered in case of an introduction of a

DP scheme. General principles as, for instance, provided for the Transparency Directive could be the basis for considering in setting up a DP scheme:

- **transparent and comprehensive criteria** for pricing strategies using best scientific evidence for assessing additional value of new technologies (e.g.: prices according to per capita income of participating MS);
- **fixed time-limits and procedural steps**;
- **adequate legal remedies** for companies that did not succeed in order to challenge procurement decisions.

In order to strengthen MS' confidence in common price building mechanisms, **results for MS achieved through JPAs (and possibly DP) should be critically and independently assessed** on a regular basis and made publically available in order to support future decisions for MS and to establish best practice. For this reason, a **common communication platform and a central price database for MS together with transparent monitoring mechanisms** would be a supportive option.

Successful implementation of DP requires the guarantees to avoid leakage. However, parallel imports from lower-priced countries to higher-priced countries are likely to benefit from this re-importation. While medicines as such are no exception to the free mobility of good in the internal market and parallel trade is considered as part of free market rules, some legal tools **to protect public health and access to essential medicines**, such as **temporary export bans, authorisation / notification procedures** or **compulsory licensing,** for lower-priced countries could be considered in order to achieve DP as government policy. Such measures would mean restrictions to free movement of goods and thus would have to be assessed under the principles of proportionality and necessity, referring to essential medicines and specific quantifiable criteria. For each product an analysis would be necessary to what extent such measures would be necessary to protect health as a justifiable objective.

4.2.3 Simulations exploring possible DP scenarios

Applying a similar framework and basic assumptions as under EPR, this section highlights some simple differential pricing scenarios. Under differential pricing, as defined in this study, pricing decisions are taken centrally based on countries' economic (and possibly social) indicators, rather than being set by each country through an individual EPR mechanism. The aim of these examples is to clearly illustrate what is meant under this concept of differential pricing.

Two main scenarios are presented, one in which an entry price is defined and 'mark-ups' are applied to account for different national ability-to-pay, and one in which a highest price is defined using 'mark-downs'. **One of the most difficult tasks when introducing a differential pricing methodology is how to define said highest and lowest price**. In this sense a differential pricing mechanism does not avoid the difficult questions usually faced by individual countries trying to set appropriate prices related to the economic and social value of a medicine as well as appropriate profits given the need for research and development incentives [63].

The definition of the lowest or **'minimum' price** within a differential pricing system is an ideological, political as well as statistical challenge. The minimum price could be defined depending on the break-even point of companies, however, in a truly solidarity-based system with low-income, low ability-to-pay countries the chosen minimum price might even be lower than a company's break-even point with the profits in richer

countries compensating for such losses.[43] Indeed, on a global scale differential pricing has sometimes meant giving away medicines below marginal cost of production, for instance through donations [111, 117]. Even if it was decided that the lowest price within the system should equal marginal cost of production, this would be difficult to implement given the asymmetric information on companies' cost structure and further development costs also need to be taken into account.

Defining and deciding on a **'maximum' price** within the system is equally challenging. Conceptionally the highest price could be the maximum that is financially sustainable, or affordable by the relevant country. However, financial sustainability and affordability are difficult to define and assess. Otherwise, the highest price could be based on a medicine's value, similar to value-based pricing. This would mean that no country pays more than the value it places on the medicine, which is conceptionally desirable. However, this would also mean that most countries pay a lower price than the economic and social value of the medicine which might be difficult to justify towards the pharmaceutical industry and might lead to a lowering in medicine prices.

Creating a differential pricing system does not just require the definition of either a minimum or a maximum price. If a system is chosen in which a 'minimum' entry price is defined applying subsequent 'mark-ups' based on some economic indicator such as GDP per capita, one also needs to decide on the size or weight of such mark-ups. I.e. one needs to decide how much relative importance one puts on the economic situation of a country and thus **how large a variance one wants to create between prices in high-income and low-income country**. This requires a decision on the range or standard deviation of prices, or the fixing of a maximum price as well with all prices spread between minimum and maximum points according to their situation. The same challenges apply when a maximum price is used as the starting point.

Thus, centralised differential pricing requires decisions on a 'fair' and equitable spread in prices, as well as agreement of what an appropriate medicine price is to start from, given considerations of affordability, access and incentives for innovation. The significant challenge of defining such an appropriate price has led to the use of second-best policies such as EPR to begin with. Solutions such as profit caps or cost-plus pricing are other second-best options, however more difficult to implement given information asymmetry particularly on development costs, Value-based pricing might be more adequate, however remains a challenge and more efforts should be put in analysing whether and how it could be used more extensively.

The following simple scenarios are intended to illustrate how differential pricing might technically work and provide examples of what prices might be achieved. The scenarios cannot and do not attempt to solve the challenges of deciding on an optimal minimum or maximum price and will take these starting values as given.

The report illustrates some simple examples based on GDP per capita and PPP data, which were the most discussed in the DP literature. Other adjustments that have been suggested, such as based on population size, market volume, public pharmaceutical expenditure or pharmaceutical sales, do not make conceptual sense in the authors' view.[44] Adjusting pharmaceutical prices according to public expenditure per capita, for

[43] This highlights the difference between the economic concept of price discrimination and differential pricing as defined here. Under price discrimination the lowest possible price offered by companies would equal marginal cost. Under a differential pricing system which is based on ability-to-pay and which is decided through international coordination taking into account some concept of citizens' welfare, the optimal minimum price might lie below marginal cost.

[44] These calculations illustrate the basic relationship of prices under a DP mechanism. An analysis of volume data and demand elasticity would be necessary to estimate the effects of such schemes on companies' profits and to evaluate

instance, would favour rich countries if prices are adjusted upwards with higher public expenditure per capita. If prices are adjusted downwards with higher public expenditure per capita it punishes countries of equal economic strength that invest more in their public health systems compared to out-of-pocket expenditure. An adjustment based on market size is equally difficult to justify on fairness grounds.

In addition, we looked at different price studies (based on price data of European countries) in order to explore possible price impacting factors (see Chapter 4.2.3.3, with the long versions in Annex 11 and Annex 12).

4.2.3.1 Applying mark-ups to a set entry price

In this scenario, an entry price (i.e. the lowest price for the medicine in one of the included countries) is set as a starting point, and then mark-ups are applied to account for different ability-to pay.

a) Pricing according to GDP per capita

Example 1: Starting price EUR 30, uncapped proportional mark-ups

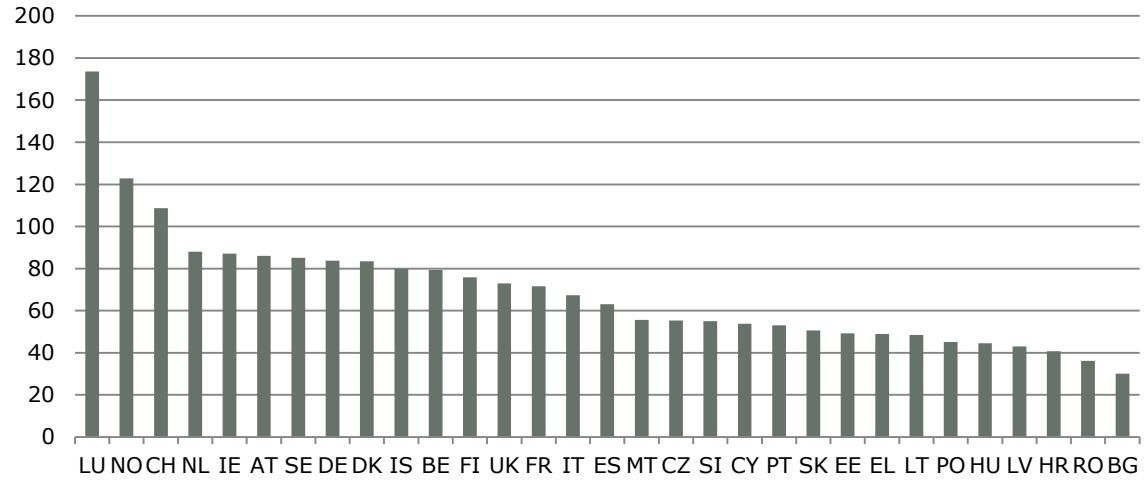
In this scenario, mark-ups according to GDP per capita are applied to capture local purchasing power. Within the 31 countries, Bulgaria has the lowest GDP per capita[45] and thus a starting price is set there. In this first example the starting price is fixed to EUR 30 and mark-ups are applied simply proportionally to GDP per capita. I.e. Luxembourg which has 5.8 times the GDP per capita of Bulgaria here has a medicine price that is 5.8 times as high.[46] Thus the medicine price ranges from EUR 30 in Bulgaria to EUR 174 in Luxembourg.

whether such schemes could indeed perhaps constitute a win-win situation. Thus, thorough research on volume data and demand-elasticity information would be necessary to decide upon a specific DP mechanism and indicator to use in order to quantify the effects on all stakeholders. However, while volume data is necessary to decide upon the indictor and mechanism, the indicator itself on which mark-ups and mark-downs are based does arguably not need to be based on volume information as discussed above.

[45] GDP per capita figures here are sourced from the World Bank which provides GDP per capita for 2013 in PPP in current US dollars.

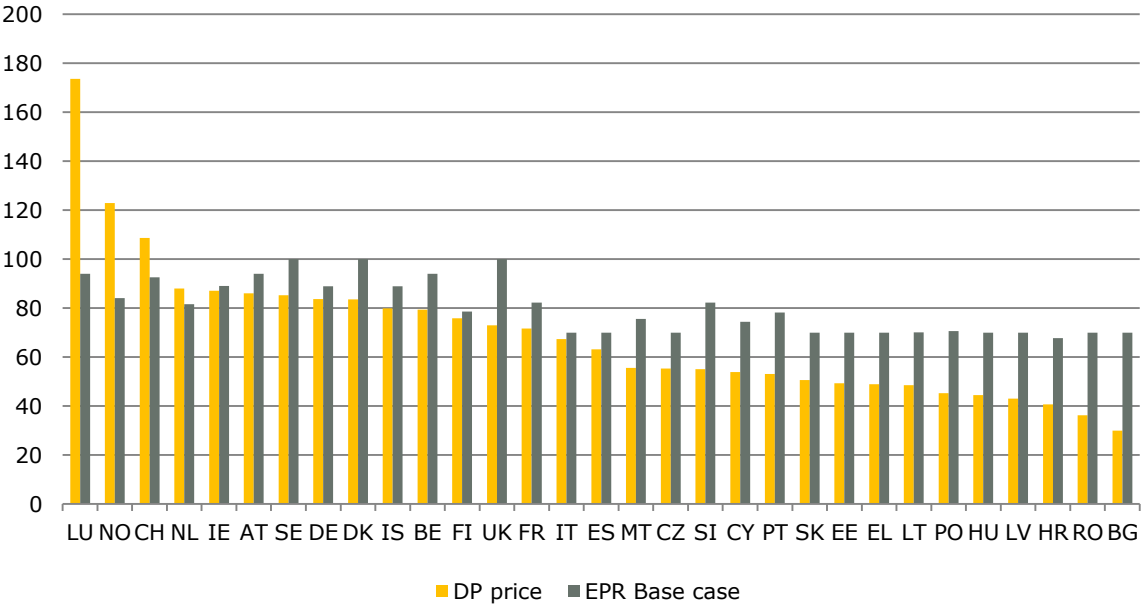
[46] In this example the correlation between medicine prices and a country's GDP per capita is 1.

Figure 28: Medicine prices when pricing proportional to GDP per capita (starting price EUR 30)



Source: Authors' calculations

Figure 29: Medicine prices compared to EPR base scenario



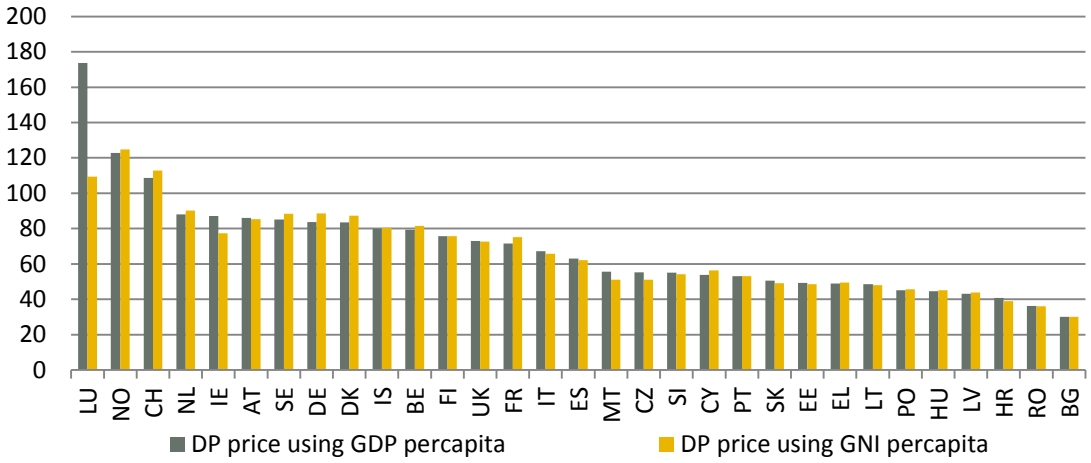
Source: Authors' calculations

As can be seen in Figure 29, medicine prices in this example increase compared to the EPR base scenario for well-off countries like Luxembourg, Norway and Switzerland, but decrease for countries with relatively lower GDP per capita such as Bulgaria, Romania and Croatia.

It should be noted that GDP is a measure of national income/national output and does not take into account net income receipts from abroad. Thus it might arguably be preferable to use GNI (Gross National Income) figures instead. Figure 27 shows results for the same scenario (i.e. applying linear, proportional mark-ups to a starting price of

30) when GNI per capita is used instead of GDP per capita.[47] It can be noted that especially in the case of Luxembourg the resulting price difference is extreme; however the choice also matters for other countries such as Ireland, Germany and others.

Figure 30: GDP versus GNI per capita



Source: Authors' calculations

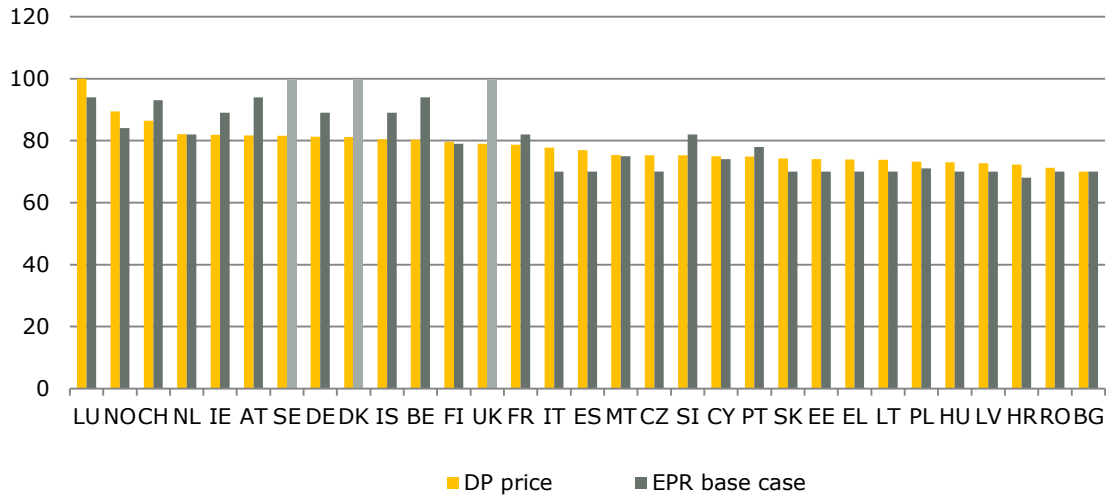
Example 2: Entry price EUR 70, maximum price EUR 100

In this example the entry price is assumed to be EUR 70, which is approximately consistent with the lowest price within the presented EPR base scenario. It is possible to adjust prices according to GDP per capita in numerous ways, constructing different indices and thus giving different weight to a country's economic situation, arriving at different price dispersions. Very simply put, it could be decided that a country with twice the GDP per capita has a price twice as high, or four times as high, or only 30% higher based on different indices and mark-ups based on GDP per capita. Similarly the relationship between GDP per capita and prices do not need to be linear, it could be decided that adjustments should be increasing or decreasing for extremely high-income or extremely low-income countries.

The decision on how highly mark-ups should vary with a country's economic situation would be a political and ideological question. In this scenario, linear mark-ups based on GDP per capita are applied so that the highest price is EUR 100 as in the EPR base scenario. Thus, whereas in scenario a) Luxembourg has a price 5.8 times that of Bulgaria, its price is only 1.43 times that of Bulgaria under this regime.

[47] GNI per capita figures are sourced from the World Bank and provided in PPP current international $ for 2014, or the latest available year.

Figure 31: Medicine prices when varying prices between EUR 70 and EUR 100 according to GDP per capita[48]



Source: Authors' calculations

Luxembourg, which has by far the highest GDP per capita in PPP values in this data, here has a price of EUR 100 followed by a medicine price of EUR 89 in Norway. All other prices range between EUR 86 and EUR 70.

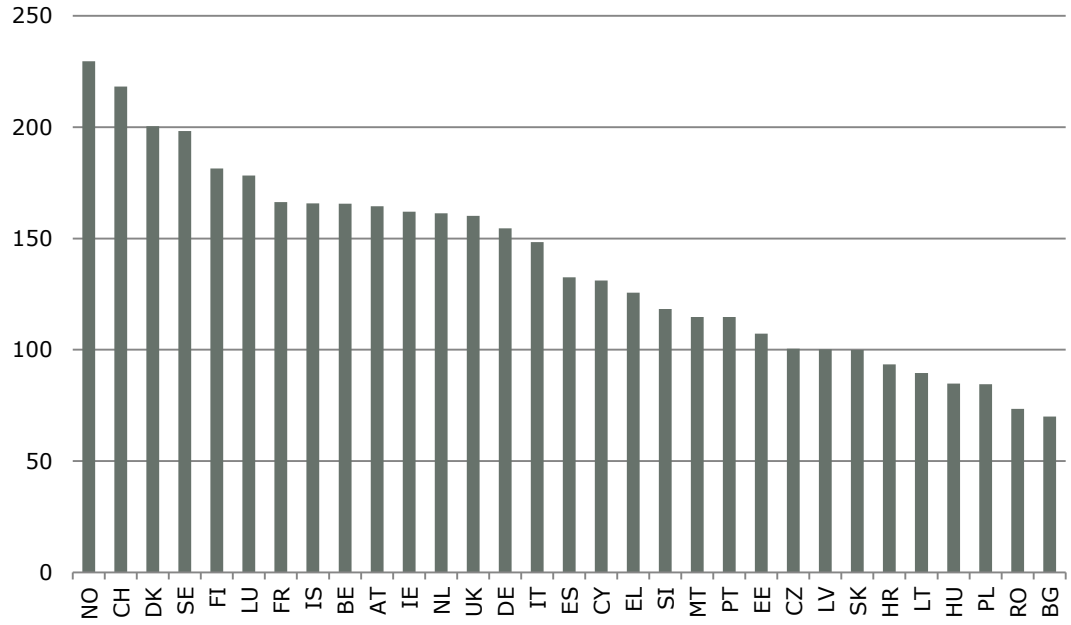
b) Pricing adjusted according to purchasing power parity

Again an entry price of EUR 70, similar to the lowest price within the EPR case scenario, is assumed and mark-ups are applied according to a Eurostat price level index derived through purchasing power parity adjustments.[49]

[48] Since SE, DK and UK apply different pricing methods it has been assumed that their price remains unchanged after launch (see also figure 12 medicine price progression)

[49] Price level indices are sourced from Eurostat and provided for 2013 with EU28=1.

Figure 32: Medicine prices using purchasing power parity/price level index adjustments



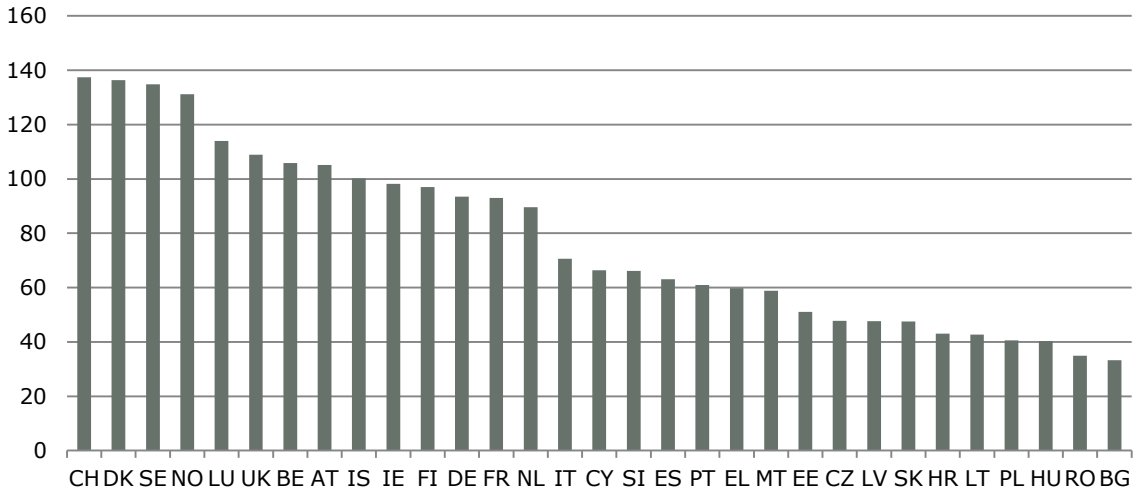
Source: Authors' calculations

In this example Norway, rather than Luxembourg, has the highest pharmaceutical price which ranges from EUR 70 to EUR 230.

The previous DP scenarios assume that prices are set entirely through a centralised or coordinated DP mechanism, irrespective of current price levels. This would be the case if a new medicine comes to market, or if a DP system has been functioning for a period of time. In this case an entry price is chosen based on considerations such as breakeven point of firms. The below figure provides an example when not one entry price is chosen, but when EPR base case prices (or 'current' prices) are taken as starting values and adjusted for each country according to price levels.[50] As is evident, prices remain closer to the EPR base case than with a pure DP scenario of a 'new' drug with an arbitrary or new starting price.

[50] Note that this gives different results than the EPR scenario in which countries adjust the reference prices within their country baskets with the relevant PPPs. Here 'current' prices, taken to be EPR base case prices, are adjusted centrally, or through some cooperation mechanism, by price level indices of the relevant countries. In the EPR affordability-to-pay scenario EPR mechanisms are modified to include PPP adjustments of reference prices. Thus, the impact on each country depends on which countries are selected in the relevant country basket and there are dynamic effects through countries referring to each others' modified prices.

Figure 33: Medicine prices applying purchasing power parity/price level index adjustments to EPR base case prices



Source: Authors' calculations

4.2.3.2 Applying mark-downs to a set maximum price

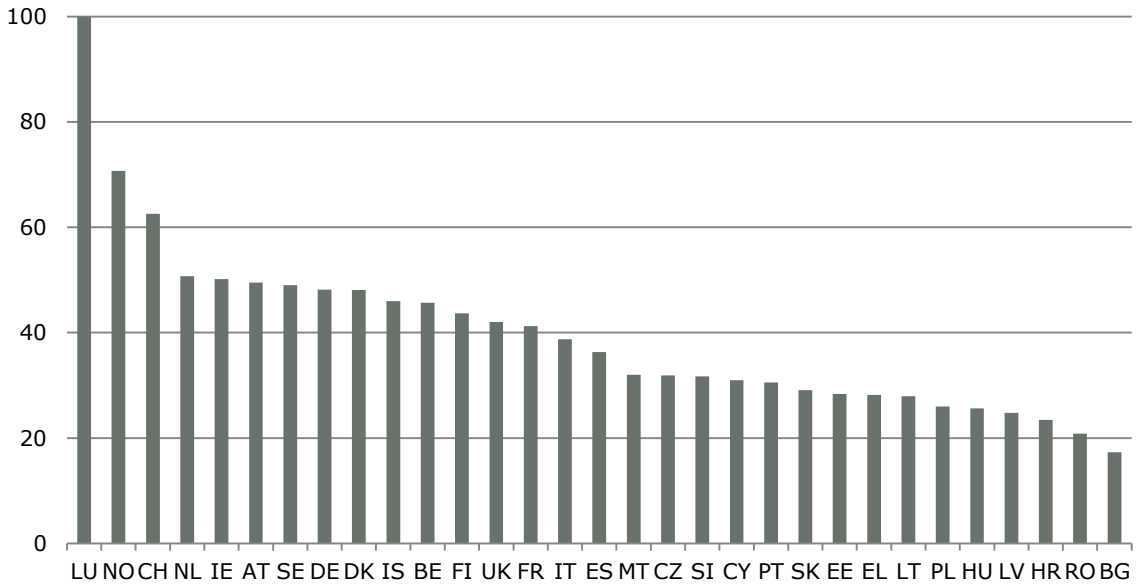
In this scenario, a highest price is defined (i.e. the price in the country with the highest ability and willingness to pay) and then 'mark-downs' are applied for other countries.

a) Pricing according to GDP per capita

Example 1: Starting price EUR 100, GDP proportional mark-downs

In this example a starting, or maximum, price of 100 EUR is set for the wealthiest country. Consecutively mark-downs are applied according to GDP per capita, similar to the very first example given. In this simple GDP-weighting the lowest income country in the sample, Bulgaria, which has a GDP per capita 5.8 times lower than Luxembourg, also has a medicine price 5.8 times lower, i.e. EUR 17.3. Different indexes or weights based on GDP per capita can be constructed to apply larger or smaller mark-downs.

Figure 34: Medicine prices when pricing according to GDP per capita (starting price EUR=100)



Source: Authors' calculations

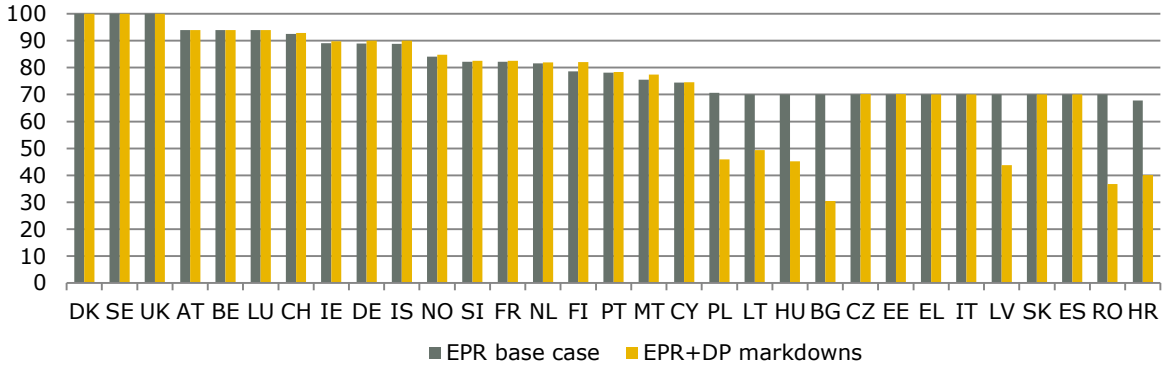
Example 2: Maximum price EUR 100, minimum price EUR 70

Prices here are started off at EUR 100 and again mark-downs according to GDP per capita are defined so that the lowest price is EUR 70, i.e. so that the spread is the same as observed under the EPR base case. Since prices are adjusted linearly and similarly as before, the resulting prices are identical to the scenario when a minimum entry price is defined and 'mark-ups' are applied. Since minimum and maximum prices are very difficult to define, this decision might boil down to political questions of which can potentially be more easily agreed upon.

b) GDP per capita based mark-downs mixed with EPR methodologies

The following example constitutes a **mixture between EPR and DP mechanisms**. In this scenario countries continue to set prices through EPR mechanisms, however the quintile of countries with **the lowest GDP per capita** (Bulgaria, Croatia, Hungary, Latvia, Lithuania, Poland and Romania) receive large, **transparent mark-downs according to their GDP per capita**. In this example, if the GDP per capita of a country among the least wealthy quintile is 40% below the average GDP per capita among the 31 European countries, a 40% markdown is granted. This is combined with countries continuing to use EPR, however, countries no longer refer to these lowest income countries.

Figure 35: DP mark-downs for least wealthy quintile under EPR framework



Source: Authors' calculations

As can be seen in Figure 23, pharmaceutical prices among the least wealthy quintile reduce drastically, for instance by 57 percent in Bulgaria, while prices in other countries barely change. They merely increase very slightly in countries like Finland, Malta and Germany who lose low-price reference prices within their basket.

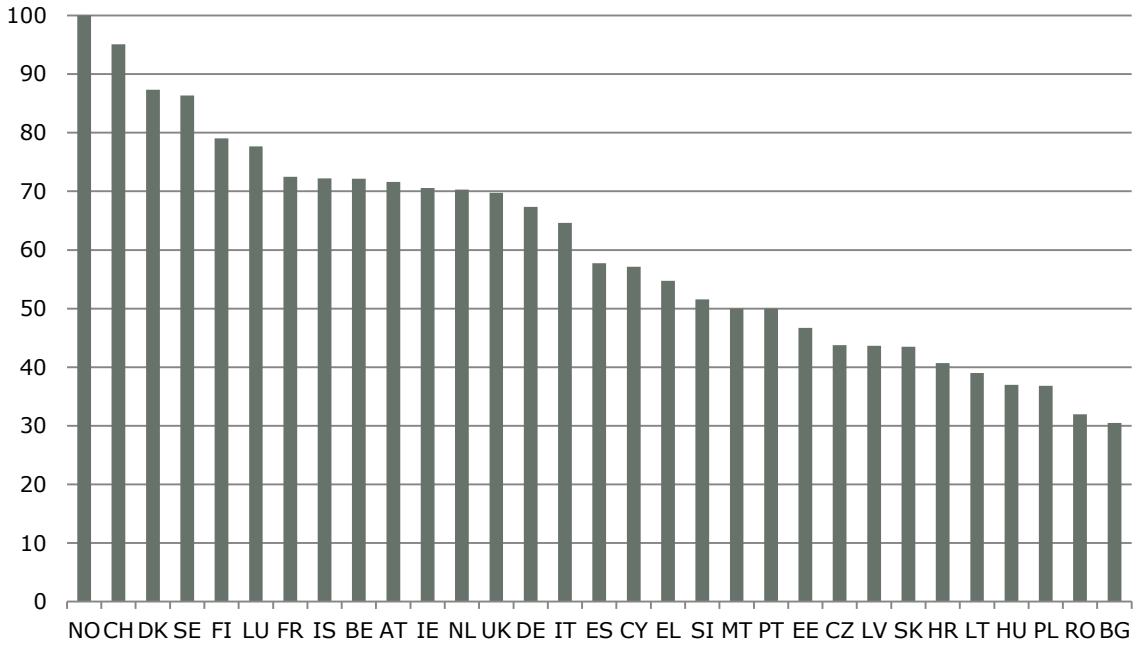
Within this example, compared to other DP scenarios, the prices in high ability-to-pay countries stay almost constant, whereas they still fall in low-ability-to-pay countries. Such a situation, depending on the magnitude of mark-downs, might still be profit neutral for industry, if it allows companies to reach a larger market, or enter certain countries with less delay. In this example, since these countries are no longer referenced to in other countries' reference basket, a company no longer needs to delay entry or base their pricing decisions on worries of dampening prices elsewhere through EPR mechanisms. Needless to say any such scenarios require guarantees of no leakage, such as possibly the imposing and enforcement of export trade bans (cf. Chapter 3.4).

c) Pricing adjusted according to purchasing power parity

Again an entry price of EUR 100, equal to the launch price in the EPR scenario, is chosen and mark-downs are applied according to price level indices.[51] Prices here vary between EUR 100 in Norway and EUR 30.5 in Bulgaria, with the ranking of countries being the same as under the mark-ups example.

[51] Price level indices are sourced from Eurostat and provided for 2013 with EU28=1.

Figure 36: Pricing adjusting according to price levels (starting price EUR=100)



Source: Authors' calculations

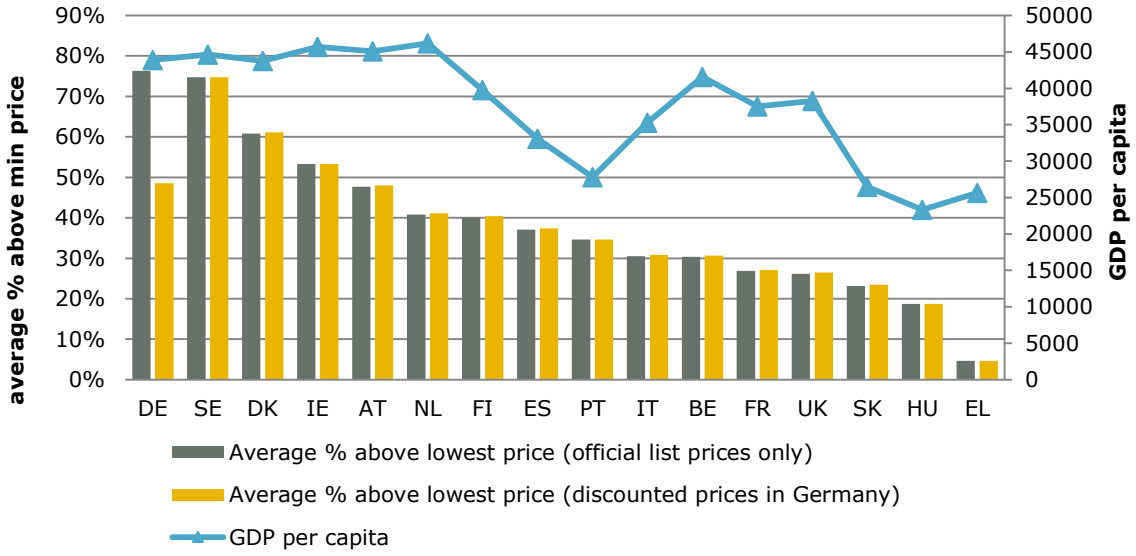
4.2.3.3 Observed price levels and price impacting factors

This section aims to provide an overview of real price data, i.e. how price levels compare between countries and relate to countries' economic situation, to complement the different scenarios under EPR and DP methodologies. The analysis is based on pricing data of 30 high-cost medicines, half from the in-patient and half from the out-patient sector for 16 European countries. The full version of this Chapter is in the Annex 11.

Figure 37 and Figure 38 compare the observed differences in price levels with GDP per capita. The countries with lowest GDP per capita among this sample are Hungary, Greece and Slovakia and a positive correlation between prices and GDP per capita can be observed, i.e. wealthier countries tend to have higher prices. Indeed, the correlation between average percentage from mean or minimum price and GDP per capita is as high as 0.74, almost identical to the correlation between pharmaceutical price and GDP per capita within the EPR model.[52]

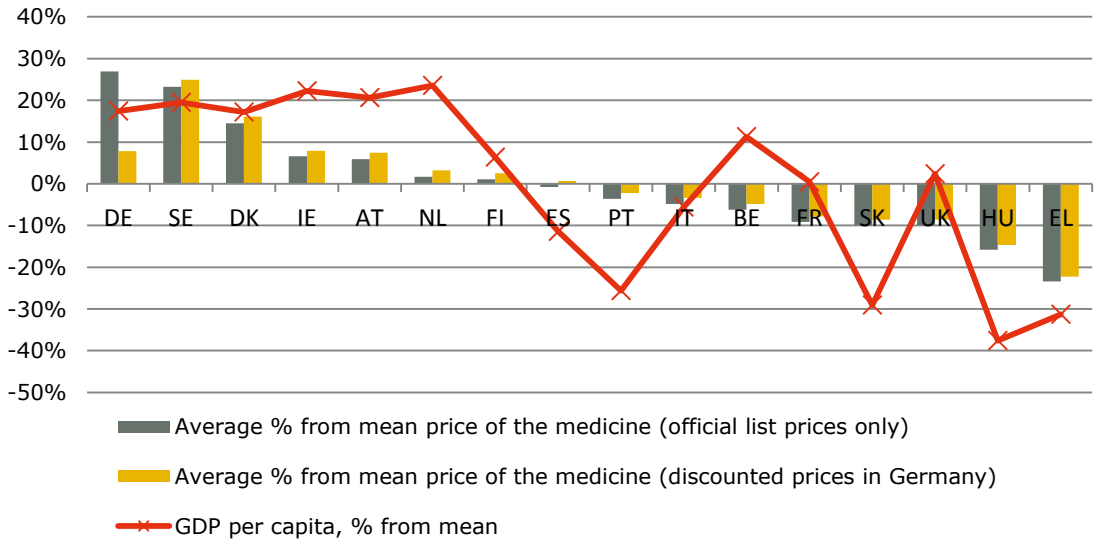
[52] No regression analysis is presented here, since it is difficult to identify any causal relationships within such a small sample, available for one time period.

Figure 37: Percentage above minimum pharmaceutical price and GDP per capita



Source: Data provided by Pharma Price Information (PPI) of Austrian Public Health Institute, Authors' calculations

Figure 38: Percentage from mean medicine price and GDP per capita



Source: Data provided by Pharma Price Information (PPI) of Austrian Public Health Institute, Authors' calculations

In addition, an analysis of further price studies also helped to understand the possible factors able to impact medicine prices (for the detailed extraction tables see Annex 12).

Table 4: Studies about impacting factors for medicine prices

Study	Results
Konijn (2005)	The prices expressed in purchasing power parities varied between different groups of countries, in accordance to their economic situation. Prices for original medicines (those that are or have been covered by a patent) are less dispersed than those of generics
Brekke et al. (2008)	UK, Norway and Sweden consistently have the lowest pharmacy retail prices of prescription medicines whereas Ireland, Belgium and Germany have the highest prices. Comparing price indices from 2007 to 2009 revealed that there are large changes in the price indices from 2008 to 2009. All countries become more expensive than Norway, but this is mainly driven by exchange rate fluctuation
Leopold et al. (2012)	On average EPR as a pricing policy leads to lower prices. Prices for patented products were generally lower in the countries which applied external reference pricing. However, the large variation in price levels among countries using EPR confirmed that the price level is not only driven by EPR.
Leopold et al. (2013)	Short-term and long-term economic conditions play a crucial in the level of medicine prices. From 2007 to 2008 price divergence decreased, but increased from 2008 to 2012. Another contributing factor is Currency fluctuations.
Kanavos/Vandoros (2011)	Newer classes of prescription medicines are more expensive. Product age has a significant effect on originator brand prices in all settings. Price convergence is observed across countries for newer originator brands and could be partly attributed to the extensive use of external price referencing
Vogler et al. (2015)	Medicine prices varied considerably between European countries and New Zealand. These difference are likely attributable to underlying national pricing and reimbursement policies, which are affected by public health and industry-related policy goals as well as by the economic situation of the country.
Danzon/Furukawa (2003)	The relatively unregulated, more competitive market structure of the US market seems to result in relatively high prices for on-patent originator products and relatively high use of new products, but also strong generic competition, high generic shares and low generic prices. Extensive use EPR may prompt strategic behaviour of pharmaceutical manufacturers
Danzon/Furukawa (2008)	Price differentials remain roughly in line with differences in per capita income. This suggest that prices depend strongly on economic conditions in the countries. Further factors are national regulatory structures which can lead to strategic behaviour of originator manufacturers.

Source: Brekke KR, Holmås TH and Straume OR [90], Konijn P [20], Leopold C, Mantel-Teeuwisse AK, Seyfang L, et al. [21], Leopold C, Mantel-Teeuwisse AK, Vogler S, et al. [22], Kanavos PG and Vandoros S [93], Vogler S, Kilpatrick K and Babar ZUD [17], Danzon PM and Furukawa MF [147], Danzon PM and Furukawa MF [148]

Konijn P [20] calculated purchasing power parities by using prices for medicines. For 33 countries (all European Union Member States, Bulgaria, Croatia, Romania, Switzerland, Iceland, Turkey, Macedonia and Norway) lists of best-selling medicines were analysed and price data for 181 different medicines were collected in November 2005 and studied. The prices expressed in purchasing power parities varied between different groups of countries, in accordance to their economic situation: The top group (Iceland, Switzerland) had significantly higher price levels, being 60 to 87% higher than the EU-25 average. In the second group of most expensive countries price levels were between 15% and 30% higher than the EU-25 average (Denmark, Germany, Ireland, Italy, Norway). The third group had price levels between 0% and 15% higher than the EU average (Belgium, Cyprus, Luxembourg, Malta, the Netherland, Austria, Finland). The fourth group had price levels between 0% and 15% lower than the EU-25 average (France, Portugal, Slovenia, Sweden, and UK). A large group (mainly new EU Member States) had price levels between 68 and 80% of the EU-25 average (Bulgaria, Czech

Republic, Estonia Greece, Spain, Latvia, Lithuania, Hungary, Poland, Romania, Slovakia, Croatia, Turkey). The lowest price levels were found in the Former Yugoslav Republic of Macedonia at 58% of the EU-25 average.

Brekke KR, Holmås TH and Straume OR [90] compared prices of pharmaceuticals in Norway and nine Western European countries (Austria, Belgium, Denmark, Finland, Germany, Ireland, the Netherlands, Sweden, and UK) which constitute the basket of countries that form the basis for setting maximum prices for prescription-only medicines in Norway. Using sales data of 300 top-selling (prescription bound) active substances in Norway, volume weighted average prices were computed. UK, Norway and Sweden consistently had the lowest pharmacy retail prices of prescription-only medicines whereas Ireland, Belgium and Germany had the highest prices. Comparing price indices from 2007 to 2009 showed large changes in the price indices from 2008 to 2009. Over this period all countries had become more expensive than Norway, but this is mainly driven by exchange rate fluctuation.

Leopold C, Mantel-Teeuwisse AK, Seyfang L, et al. [21] examined the impact of external price referencing (EPR) on 14 on-patent medicine prices at ex-factory level in 14 European countries (Austria, Belgium, Denmark, Germany, Greece, Finland, France, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, Slovakia). The authors adjusted for other factors that may affect price levels such as sales volume, exchange rates, gross domestic product (GDP) per capita, total pharmaceutical expenditure, and size of the pharmaceutical industry. For the linear regression analysis, the unit ex-factory prices in Euro of all selected medicines, all countries and of both years 2007 and 2008, were adjusted to a fixed exchange rate (if necessary). Prices for patented medicines 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 ranks. However, it needs to be acknowledged that huge price differences could be found between countries which apply external price referencing

Leopold C, Mantel-Teeuwisse AK, Vogler S, et al. [22] explored whether ex-factory prices of ten on-patent medicines in 15 Western European countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland) converged over time. To analyse the price variance between countries for each product the range as well as the average of the unit ex-factory price in Euro per DDD indexed to 2007 was calculated 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. Differences in medicine prices across countries and over time were confirmed. The expected price convergence was not confirmed since a price divergence was observed driven by price developments in only two of the 15 countries. Prices in the other European countries were stable around the country average.

Kanavos PG and Vandoros S [93] investigated the determinants of the prices of branded prescription-only medicines across different regulatory settings and health care systems, taking into account their launch date, patent status, market dynamics and the regulatory context by which they diffuse. Ex-factory prices for 50 leading originator branded prescription-only medicines in 15 OECD countries (United States, Japan, France, Germany, Italy, Spain, UK, Australia, Mexico, Austria, Portugal, Sweden, Greece, Slovakia and Belgium) where collected, and an econometric model was build. Explaining variables were (1) the number of years since the product's launch in a local market plus its square (2) if generics are available (3) country dummies for UK, US and Mexico (4) exchange rate movements (5) dummy variables for the application of HTA, internal price referencing and EPR and (6) therapeutic class. Ex-factory prices for

branded originator prescription-only medicines between US and other countries, particularly key European markets, are significant, but these are not the prices that health insurers pay. By contrast, public retail price differences have been exaggerated and are not as high as originally thought. Differences between the US and the examined European countries are greatest for off-patent originator brands and significantly lower for in-patent originator brands. Product age has a significant effect on originator brand prices in all settings. Price convergence was observed across countries for newer originators. The longer an originator had been on the market, the greater were the price differences between highest and lowest price. This could be partly attributed to the extensive use of external price referencing for new medicines.

Vogler S, Kilpatrick K and Babar ZUD [17] compared prices of 14 medicines of December 2012, both originators and generics, in New Zealand and 16 European countries (Austria, Belgium, Denmark, Germany, Greece, Finland, France, Italy, Ireland, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and the UK). Official list prices at ex-factory prices per unit in Euro were analysed. Medicine prices varied considerably between European countries and New Zealand. Within the European countries, Greece, Portugal, the United Kingdom and Spain had prices at the lower end, whereas prices in Switzerland, Germany, Denmark, and Sweden were at the upper end. These difference are likely attributable to underlying national pricing and reimbursement policies, which are affected by public health and industry-related policy goals as well as by the economic situation of the country. The study confirmed that countries that were strongly hit by the global financial crisis took several cost-containment measures related to medicine prices such as price cuts.

Danzon PM and Furukawa MF [147] examined how relative medicine prices on ex-factory level for 249 molecules in nine countries (USA, Canada, Chile, France, Germany, Italy, Japan, Mexico, UK) have changed. For each active ingredient a price is calculated through a volume-weighted average price per case over all presentations in that molecule-indication in that country. Adjusted for US manufacturer discounts, show Japan's prices to be higher than US prices. The decline of the Canadian dollar and rise of the UK pound contributes to the finding of lower Canadian prices and higher UK prices in 1999 than in 1992. The findings suggest that US-foreign price differentials are roughly in line with income and smaller for medicines than for other medical services. The tendency for US policymakers to compare US prices to Mexican prices and the threat of importation plausibly makes manufacturers reluctant to offer prices in Mexico that are more in line with that country's average per capita income. The relatively unregulated, more competitive market structure of the US market seems to result in relatively high prices for on-patent originator products and relatively high use of new products, but also strong generic competition, high generic shares and low generic prices.

Danzon PM and Furukawa MF [148] compared pharmaceutical spending, availability, use and prices of pharmaceuticals in 12 countries (US, Canada, France, Germany, Italy, Spain, UK, Japan, Australia, Brazil, Chile, and Mexico). Two price indexes were constructed: (1) an index that compared prices for all medicines that match on active ingredient and indication, regardless of formulation, strength, brand or prescription status (2) an index that compared prices only for products that match on molecule, indication, strength and formulation. All price indexes are weighted by US volume weights and converted into US dollars. Price comparisons with US are biased upward, because it ignores the US tendency to use more new, expensive products. The higher overall per capita volume in other countries compared to the US is solely attributable to the use of older products. Differences between US medicine prices and the prices in other countries are smaller at pharmacy retail prices, than at manufacturer prices, because distribution margins are generally higher abroad. Price differentials remain roughly in line with differences in per capita income. This suggests that greater

affordability of medicines in these countries will require a review of their regulatory structure and a strengthening of generic competition. Furthermore, policy makers need to consider strategic behaviour of pharmaceutical manufacturers which arise as a response to pharmaceutical regulations and may contribute to higher prices.

From the studies it is possible to extract factors that seemed to have an impact on medicine prices: (1) pricing policies: For on-patent medicine countries with EPR or VBP have lower prices, whereas for off-patent medicines countries with free pricing have lower prices, (2) Economic situation of a country: prices of medicines are strongly influenced by short or long-term economic conditions. Wealthier countries tend to have higher prices, but prices are adjusted to situations of economic hardship (3) age of the medicine: Newer therapeutic classes of prescription medicines have on average higher prices (4) HTA; Countries that use HTAs in the pricing and reimbursement procedure have on average lower prices; (5) distribution margins: In the context of an pharmacy retail prices the design of the distribution margin has an impact on prices.

5 Proposals for cooperation mechanisms

In this chapter, we develop proposals for cooperation mechanisms aimed to help improve EPR and develop a possible outline for DP. The analysis draws upon the findings presented in the various sections of the previous Results Chapter and is thus based on the literature review, expert interviews, legal analysis and simulations, as well as inputs received during the stakeholder review and peer review.

5.1 External price referencing

One defined objective of this study is to present options for optimizing the effectiveness of existing EPR schemes through EU-level cooperation. However, as shown in the previous chapters, though EPR uses medicine prices in other countries, it is not a cooperation tool per se. Some improvements (e.g. methodologies) can be done unilaterally by EPR applying countries which may benefit from an exchange of information and sharing of best practices. Other improvements (e.g. joint medicine price database) benefit from the joint efforts and contributions of countries.

In the following chapters, we explore four avenues for the improvement of EPR which, apart from the database (cf. Chapter 5.1.1), do not always necessarily require cooperation but could also be done unilaterally. Two options (central database, EPR formulae) had been defined in the Terms of Reference of this project for further analysis. Given the relevance to discounts and evaluations, as shown in the previous analyses, we decided to also discuss these policy options.

5.1.1 Use of an extended central database

The first option to explore is a medicine price database that may also take an extended form (e.g. including market volume data, or further supporting data, cf. Chapter 4.1.3).

In Europe, the work on building a medicine price database dates back to the late 1990s. The initial project, Ecphin, with institutional support from the Commission's Joint Research Centre, was set out to create a database on the basis of voluntary contributions from Member States and built the technical basis. Within the framework of the next project, EudraNet, it was then fed with price data from Member States, however it was stopped after some time. The European Commission explained that it was difficult to undertake comparisons due to the different times and means of data delivery [149].

Based on a decision in the EU Transparency Committee, EU Member States agreed in 2005 on sharing medicine prices for a selected range of medicines. The exercise called INFOPRICE was done on a bi-annual level (i.e. every six months). It was stopped at the end of 2012 to avoid redundancy since a European medicine price database (Euripid) had meanwhile been set up [30].

With the support of an EC grant (2020-2013) [150], the Euripid database was established, with data provided by the participating countries. Euripid built on a pilot project by the Hungarian National Health Insurance Fund Administration (OEP). From 2014 on, with the end of the EC grant, the Euripid Collaboration was set up with the participating countries represented in the Board of Participants. Euripid is a database of competent authorities for pharmaceutical pricing and reimbursement, but only authorities that provide data to Euripid are granted access. Supranational organisations such as the European Commission or WHO may have access if the Board of Participants approves and an agreement regarding a contribution is concluded. The prices provided by authorities are validated by Gesundheit Österreich GmbH as outlined in the data

validation plan. By the end of 2015, the Euripid database contained data from 27 European countries, thereof 25 EU Member States ([151], updated personal information from the Euripid secretariat). From mid-2015 on, the Euripid Collaboration with its 25 participating countries was funded with another EC grant which could also include the coverage of new data input ('extended database') [152].

Financial implications

The financial implication of building a medicine database can partially be derived from the Euripid experience.

Euripid reported the following cost information: 'The cost of building up and running the database in 2010-2013 including the development of the IT platform and the standardisation of more than 200,000 medicinal products cost EUR 640,000. The reproduction of the database might not be done with the same amount as the success of the project depended on the good relation between the national competent authorities that cannot be expressed in monetary terms, and the voluntarily participating authorities invested from their side as well which is not reflected in the figure. Approximately 80% of the costs were personnel costs. The cost factor of the addition of a new country is the cost of the initial data standardisation. This cost depends on the extent and quality of the list of reimbursed medicinal products. The estimation of fixed costs is EUR 40,000 per year while the variable cost per country is approximately EUR 5,500 per year. The participation of at least 10 countries is required.' (written information of the Euripid secretariat, 15 June 2015).

SWOT analysis

Table 5 presents a SWOT analysis for a central database.

Assessment

As the example of the existing Euripid database has shown, a European price database is extremely supportive for policy-makers when doing price comparisons. Even if most competent authorities do not solely rely on Euripid, but have their own price information systems (cf. Chapter 4.1.1.7), a coordinated price database is a big help since price search, validation and comparison for EPR is highly time-intensive and involves a lot of administrative efforts.

A small non-representative survey done with four competent authorities showed that, the search and/or price of one medicine in one country was estimated to amount to three, ten and thirty minutes respectively (depending on the complexity), whereas a Euripid user estimated 40 seconds as working time for doing the same task (authors survey).

It is not possible to assess the contribution of a centralised price data to savings for public payers, since the cost of such an exercise is not fully known. While some data about the cost of building Euripid are available, this can only be considered as the very minimum amount, since neither the contributions of the participating countries nor the long-term expertise of the Euripid consortium that allowed building the database could be monetarily assessed. Furthermore, any estimation of the costs for an extension of a price database is difficult without the specification of the scope and technical requirements of the extensions.

Table 5: SWOT analysis of an extended price database

	Positive aspects	*Negative aspects*
	Strengths	**Weaknesses**
Internal factors	▪ Comparability of price information: a price database provides standardised data and facilitates the comparisons of medicine prices in different countries ▪ Reduction of search costs / higher efficiency: Although prices can mostly also be found in official national sites, a central price database can considerably lower transaction costs (search costs of information) and the administrative burden ▪ Easy-to-use tool: compared to other methodologies, a central price database facilitates the acquisition of price information ▪ Flexibility: The operational model of a database allows some flexibility in joining and opting out ▪ Platform for competent authorities: A medicine price database fed by participating countries (as in the case of Euripid) may serve as a platform for competent authorities and facilitates the exchange of information	▪ Ownership of data: If the ownership of data has been delegated to commercial providers, participation in the database might not be possible for competent authorities ▪ Focus on list prices: If a price database only contains list prices, the discrepancy between real prices and list prices may undermine the relevance of the database ▪ Voluntary exercise: If not all EU Member States contribute by providing data to a database, the relevance of the database might be limited ▪ Misuse: Public access would not only encourage 'free-riding' but might encourage commercial providers to use these data for business
	Opportunities	**Threats**
External factors	▪ Basis for further possible extension: If properly designed, a price database can be used to incorporate further information (sales volume, market availability, reimbursement conditions, types of medicines, discounts, etc., cf. also the proposal in Chapter 4.1.3) ▪ Give-and-take situation: A medicine price database based on fairness principles (allowing only access to those authorities that provide data, as in the case of Euripid) helps preventing 'free-riding' ▪ Acceptance through use: An increasing number of countries participating is likely to contribute to acceptance and use of a price database ▪ Policy support: The information that an extended price database offers can support policy initiatives in other areas beyond pricing, e.g. pharmaceutical consumption monitoring ▪ Capacity-building: Working with databases (sole price databases or extended ones) helps building capacity, e.g. by strengthening the qualification for doing price comparisons and EPR (capacity-building measures such as manuals or training sessions for users are supportive)	▪ Pressure of stakeholders to disclose: Stakeholders not contributing might exercise pressure on participating Member States to disclose the database which would lead to 'free-riding' ▪ Misuse of information: Although the access to the database can be password protected, it does not necessarily prevent the misuse of information by making price information public ▪ Financing: An extension of a database may increase costs. Limited financial resources can put a limit on the maintenance and particularly the extension of a price database ▪ Losing 'critical mass': If a high number of countries decides to opt out, the database may lose its relevance for cross-country comparisons and – in case of self-financing – a higher cost burden has to be shared between the participants left ▪ Missing validation: The quality of the provided information needs to be regularly revised by thorough controls (data validity checks). If this is not done, the database may lose its relevance for pricing authorities

Source: Based on authors' analysis performed as part of this study, such as literature review, interviews with Euripid representatives and further information provided [153]

Following up on the avenue of a centralised price database that builds on existing work (such as Euripid) is clearly a promising route for the future that will continue supporting competent authorities doing technical work connected to EPR. It will likely reduce the administrative burden and improve capacity.

With regard to an extension, the authors consider the full coverage of EU Member States in a price database as a higher priority rather than an extension in content. However, there are legal constraints in some countries that limit the participation in Euripid. Possible elements for consideration of extending a price database were proposed in Chapter 4.1.3, but we would like to stress again that the administrative cost of an extension, including maintenance of an extended database, should be balanced against possible benefits. If an extension of a price database was considered, it is suggested focusing on price-connected elements (e.g. information on the discounted price, or, if that was not feasible, marking whether or not, discounts and similar arrangements are applied, see also the option below) instead of including further elements such as volume data.

The database with price data from Member States is one option that can be combined with any of the following three other policies discussed below.

5.1.2 Consideration of discounts and similar price reducing arrangements

As stated in Chapter 4.1.1.9, discounts and rebates granted by industry to public payers are common. These include both statutory discounts and rebates, such as in Germany, Greece, Ireland and Spain, as well as commercial discounts or similar arrangements, including managed-entry agreements (cf. Chapter 4.1.1.9).

Financial implications

Considering real prices paid in EPR, rather than official prices, would lead to price reductions in countries referring to countries receiving such discounts. This might particularly impact countries with low negotiation power that are currently not receiving large discounts, rebates or other financial benefits themselves. However, one needs to consider dynamic effects of whether considering real prices in EPR would limit the willingness of companies to grant such discounts.

While the simulations undertaken in this study (cf. Chapter 4.1.4.2) showed a high financial potential even based on modest assumptions, financial implication of the consideration of publicly available mandatory discounts in Germany, Greece and Ireland, cf. Figure 16) were estimated to lead to the price fall of 27 percent in average medicine prices for the EPR applying countries.

SWOT analysis

The strengths, weaknesses, opportunities and threats of the consideration of discounted prices are displayed in Table 6.

Table 6: SWOT analysis of the consideration of discounts and similar arrangements

	Positive aspects	*Negative aspects*
	Strengths	**Weaknesses**
Internal factors	▪ Price reductions: Considering discounts in EPR would allow countries to refer to the actual price paid, or at least, some discounted price, and lead to lower prices ▪ Fairness of countries with lower negotiation power: This might lower prices in countries that have low negotiating power and do not manage to negotiate high discounts themselves ▪ Financial sustainability: Savings ensure sustainability of the health care systems under pressure ▪ Real data: Consideration of discounts would shed light on the real price, or, at least, give an indication of it (in case on consideration of some, but not all discounts) ▪ Prioritization: Knowledge of actual price would help policy-makers to better inform their decision	▪ Limited political feasibility: Disclosing or even incorporating statutory discounts in EPR might be politically difficult as it is neither in the interest of the pharmaceutical industry, nor necessarily of the country receiving the discount ▪ Monitoring costs: Administrative efforts and resource required to follow up and capture the actual discounts ▪ No full transparency: Only parts of the discounts (statutory ones) and maybe some confidential ones might be accessible
	Opportunities	**Threats**
External factors	▪ Transparency: Disclosure of discounts would lead to more transparency ▪ Bargaining power: Availability of real prices is the basis for joint negotiations and procurement ▪ Evidence base: Increase in quality of available data for evaluations ▪ Trust building: Transparency fosters trust building between the actors in the pharmaceutical system ▪ Solidarity: Transparency fosters trust building and fairness between MS ▪ Technical tool: A price database could be easily used to be extended by discounted / actually paid prices	▪ Opposition of stakeholders: Stakeholders, particularly pharmaceutical industry, would oppose a disclosure of confidential discounts ▪ Upward price development: Disclosure or incorporation of discounts in EPR might be perceived to limit the ability of countries to receive discounts and thus raise prices for some ▪ Out-dated information: Quick changes in legislation in some countries due to emergency situations and unclear legal situation might make it difficult and resource-intensive to follow up and capture the actual discounts (this threat is embedded in EPR in general)

Source: Based on authors' analysis performed as part of this study, such as literature review, interviews, country survey and price simulations

Assessment

On the one hand, referencing to too high 'artificial' prices is the well-known major limitation of EPR, and this limits the effectiveness of this policy, in particular as a cost-containment tool able to contribute to financial sustainability. On the other hand, the consideration of discounts, in particular disclosure of confidential discounts, is a highly sensitive proposal that is likely to be opposed both by pharmaceutical companies that would thus reduce their negotiation power as well as by some MS that fear being granted no or fewer discounts. Eventually, there might also be the concern of some countries (e.g. small markets) not to be offered medicines at all, which will create an access issue.

The challenge of disclosing discounts may perhaps best be described using a game theoretical approach as a collaboration or prisoner's dilemma, depending on assumptions made. If all countries disclosed discounts, this would not only increase transparency but arguably reduce the overall price level. However, from a single country's perspective that receives discounts, it might not appear optimal to disclose

such agreements for the worry of losing the ability to negotiate such deals and thus experiencing an increase in prices.

The authors are not sure whether a disclosure of discounts is at the moment politically feasible. However, it should be taken into consideration that an increasing number of institutions among Member States call for a disclosure of discounts, for instance the International Association of Mutual Benefit Societies AIM and European Social Insurance Platform ESIP in their joint position paper related to the review of the Transparency Directive: 'pharmaceutical companies should act in a transparent manner regarding 'real' prices, including price strategies of marketing authorisation holders and rebates negotiated by Member States' [154]. A shift in attitude towards more transparency might be observed in future.

Apart from political feasibility, there are also some technical limitations to consider price reductions of financial arrangements. For instance, some arrangements (e.g. price volume agreements) link price reduction to sales, and rebates are granted ex-post. Thus, EPR applying countries would require additional information from the reference countries (often only available ex-post) to build in their EPR mechanism.

Since it does neither require major administrative efforts nor addresses confidentiality issues, a first approach that appears feasible in this context is the consideration of reduced prices due to statutory discounts (i.e. published in law) in the reference countries, as, for instance, the statutory manufacturer discounts in Germany. Though the extent of these comparably small discounts is likely to be considerably underestimated compared to confidential discounts (up to 100% [155]), this would be a starting point.

If at a later stage Member States could agree on a disclosure of discounts, this would not only have positive impacts on financial sustainability but would be a milestone in trust-building between countries which could eventually strengthen the EPR policy. Disclosure of discounts would be definitely a cooperative approach between Member States since it is done via a communication between countries (e.g. providing discounted prices to a price database), or, if discounted prices of other countries are to be supplied by pharmaceutical industry, authorities and payers would have a role as validation body.

We are aware that it has been suggested that disclosure of discounts could mean that fewer discounts were offered, and affordable access was significantly reduced.

5.1.3 Regular price monitoring and price revisions

Another option to explore concerns the performance of regular price reviews with subsequent price revision. According to the findings of the survey (cf. Chapter 4.1.1.8), some European countries do not perform regular (i.e. bi-annual or annual) price re-evaluations even if price reviews are provided for in the legislation.

Financial implications

The brief simulations presented in Chapter 4.1.4.3 clearly show that prices are higher among countries that choose not to re-evaluate at all, or only after a long time-interval.

Based on literature, there is evidence that price reductions were not automatically translated into price decreases in referencing countries as expected, which was, among others, explained by the fact that countries do not regularly monitor the medicines prices in the other countries [156].

SWOT analysis

The SWOT analysis of this policy option is displayed in Table 7.

Table 7: SWOT analysis of regular price reviews and revisions

	Positive aspects	*Negative aspects*
	Strengths	**Weaknesses**
Internal factors	▪ Savings: More frequent, regular price revisions can lead to price-drops and large savings ▪ Equity: Fair system, also price increases are taken into account (e.g. due to exchange rate changes) ▪ Capacity building: Helps strengthening the knowledge of EPR applying institutions about EPR ▪ Flexibility: Transforms EPR from a rigid system for setting the price into a flexible price policy over time	▪ Administrative burden: Regular price revisions are administratively costly, however these costs might be limited by choosing a well-balanced smaller sized country basket, or through a mechanism triggering targeted re-evaluations for instance when price changes are observed in certain countries
	Opportunities	**Threats**
External factors	▪ Legal framework: An already existing legal framework asking for regular price review facilitates the implementation and political feasibility ▪ Mechanisms to reduce the work load are existent or can be implemented: e.g. methodological approaches such as focus on fewer countries or specific, high-cost, medicines; include provisions in law to oblige manufacturers to inform about price changes ▪ Supportive technical tool: a price database would be very supportive – a European price database (Euripid) has already been established ▪ Trust-building: The flexibility in the EPR system (leading to both price reductions and increases) might lead to improved cooperation between Member States and pharmaceutical companies ▪ Addressing exchange rate volatility: Is likely to address the changes in exchange rates due to regular updates	▪ Alternatives: Decision to refrain from regular price review in return for being granted confidential discounts / price cuts which would be effective only short-term ▪ Capacity limitation: Insufficient capacity / knowledge, particular in difficult economic situations

Source: based on authors' analysis performed as part of this study, such as literature review, interviews, country survey and price simulations

Assessment

Price revisions are a very effective tool in terms of savings, as shown in the simulations (cf. Chapter 4.1.4.3), and at the same time, they are not necessarily a cost-containment measure but could also be designed in a way that they also take price increases into account, which could benefit manufacturers.

The major argument against regular price revisions, however, is their administrative cost. These efforts might be limited by choosing a well-balanced smaller sized country basket, or perhaps through using a mechanism triggering targeted re-evaluations for instance when price changes are observed in certain countries. In addition, a centralised price database (particularly an extended one, with an alert system, or notification in the system about price changes) would be very supportive for this option.

It is a policy option that can be combined to all other options discussed here. Political feasibility is rather high since Member States can take this measure unilaterally. Still, it was discussed here as a coordination mechanism that outcomes are clearly impacted by the developments in the other countries. In addition, a cooperative approach between countries to exchange experience and best practices might be supportive.

5.1.4 Coordination of EPR formulae

The last option to explore is the coordinated use of EPR, for instance by extending the current formulae to include some measures of countries' economic situations.

Financial implications

The simulations in Chapter 4.1.4.5 provide some examples; for instance when PPP or GDP per capita of different countries is included in order to derive reference prices.

Financial implications of applying such extended or coordinated EPR formulae starkly depend on the type of modifications agreed upon. Adapting the EPR formulae, for instance to include PPP adjustments, might raise prices in certain high price level countries, while lowering medicine prices in others. The magnitude of price changes depends on the weight given to such reference price adjustments.

SWOT analysis

Table 8 provides the SWOT analysis for the policy option of coordinating of the EPR formulae.

Table 8: SWOT analysis of the coordinated EPR formulae

	Positive aspects	*Negative aspects*
Internal factors	**Strengths**	**Weaknesses**
	▪ Increasing fairness: Extending the EPR formulae to adjust for PPP or take into account the GDP per capita of different countries can potentially arrive at a fairer distribution of prices with lower-income countries having lower prices ▪ Accessibility: Lower prices in lower-income countries might lead to higher patient access to medicines in these countries, or, at least, fewer delays in accessibility	▪ Administrative efforts: Any extension of the EPR formulae increases the administrative burden ▪ Coordination efforts: Efforts between MS to agree on the coordination ▪ Delays: Time needed to agree between MS could delay market access ▪ Agreement of MS required: In order to achieve the best effect, as many MS as possible would be required to participate in agreeing about the formulae
External factors	**Opportunities**	**Threats**
	▪ 'DP light' scheme: Adapting an EPR formulae provides an opportunity to keep with the current EPR system, however responding to current criticisms and limitations regarding price convergence and the difficulty of enabling lower-income countries to have lower prices, without fully implementing a DP scheme ▪ Combinations possible: the EPR formulae could co-exist with other pricing and reimbursement policies, and might be connected to joint procurement ▪ Unilateral or bilateral application: In contrast to a real DP scheme, it does not require the involvement of all MS, but could be done in a coordinated way between a few MS, or even unilaterally	▪ Disadvantages for some MS: Such adaptation of the EPR formulae will be difficult to agree upon politically, especially if they are not in the best interest of some actors, such as high-income countries ▪ Limited political feasibility: High-income countries that would be worse off after the application of the formulae are likely to opt out. This would weaken the effectiveness of the system ▪ Limited stakeholder support: Stakeholders, in particularly pharmaceutical industry, might not support such a system that is less strong than a 'real DP scheme' ▪ Leakage and shortages: Parallel trade would continue to undermine the coordinated pricing mechanism by allowing the leakage of medicines from lower-income to higher-income countries (problem of shortage would continue to exist)

Source: Based on authors' analysis performed as part of this study, such as literature review, interviews, country survey and price simulations

Assessment

Whereas the previously presented options were focused on the improvement of the efficiency of EPR and cost-containment, this approach is one which might possibly be able to reduce some negative impact on access attributable to EPR. However, the exact impact on improving access is not known.

Adjusting prices by countries' purchasing power parities or by the GDP of the reference countries would represent possible ways of implementation. This method can be applied unilaterally by countries but a cooperative approach in which information and best practices on criteria and methods for adjustment are shared is likely to be supportive for policy-makers.

One might argue that this is a 'DP light'. Given the restraints and prerequisites described for introducing a real 'DP system', an adjusted EPR system could be a more feasible option.

5.2 Differential pricing

5.2.1 Outline of a differential pricing scheme

The authors were asked by DG SANTÉ / Chafea to develop a possible outline for a DP scheme in the EU to be able to analyse its feasibility, as well as systematically analyse advantages and drawbacks of such policy mechanisms.

By developing a possible outline for a DP scheme in Europe in accordance with the specifications of this study, the authors do not take any position on whether or not a DP scheme should be implemented in the EU. In the following sections, we present possible options of what a DP scheme through EU coordination could look like and will assess its feasibility based on evidence and experience from literature and expert opinions.

The outline of the DP scheme below is in line with the definition applied for DP in this study: a government policy to set medicine prices across countries, taking into account the ability-to-pay of the Member States. An assessment of a market-based approach was not within the scope of this study and would require an extension of the present research.

5.2.1.1 Starting off: Implementation and adaption

For the implementation of a DP scheme, a **two-step approach** appears appropriate:

- Agreement on principles and mechanisms of the DP,
- Inclusion of medicines into the DP scheme on a case-per-case basis

The first step would be fundamental, and would include achieving an agreement between the EC and the participating, ideally 28 EU Member States about major organisational (incl. funding for organisation), political (e.g. decision-making procedures), legal and technical rules discussed in the sections below. Part of the first step would be an agreement on the mechanism to set a starting price and on the mark-ups/mark-downs applied. These agreements would be decided to be valid for a specific time.

These agreements would be stipulated in a contractual arrangement (or law) possibly to be ratified by the national Parliaments in the MS. These fundamental arrangements would involve and inform policy-makers beyond the members of the DP.

Having set the general principles, a DP working group would then decide, in accordance with the decision processes defined, on the medicines to be included in the DP scheme. In general, the **scope of the medicines** to be included could be limited. The scope of medicines might be defined to address only new high-cost, on-patent medicines that are not likely to be clustered into internal price referencing.

Given the complexity of the DP scheme, also in terms of political feasibility, it is suggested to consider operating the DP scheme on a case-per-case basis for each product. It would be part of the decision framework to specify who would be eligible to propose a medicine to be covered under a DP. This could be any country (through the representative in the General Assembly), the DP secretariat, but also a marketing authorisation holder.

It is suggested to start with a **pilot project** of the first medicine to be put under DP and to monitor its processes and outcomes closely. The lessons learned from this pilot are recommended to flow into a revised, improved system.

With regard to the **geographic scope**, the outlined DP is described with the European Union in mind. One could develop a DP system for EU Member States only, or for EU Member States and the European Economic Area (EEA) states Iceland, Liechtenstein and Norway or European Free Trade Association (EFTA) countries (i.e. EEA states and Switzerland) respectively. For simplicity, we will refer to the EU within this chapter.

5.2.1.2 Decision process

Decision-making would lie with the national competent authorities for pricing and reimbursement, possibly in consultation with or coordinated by the EC (see below).

For practicality, a defined structure and process is recommended to be implemented. Besides a kind of secretariat for organisational issues (see below), a working group (WG) needs to be established. Competent authorities for pricing and reimbursement could nominate representatives to the WG (e.g., one representative and one substitute), who would have the mandate to decide.

The WG would include all Member States and the EC; important decisions should be tabled to this **working group** and voted upon. The **principle 'one Member State – one vote'** could be applied; however, this could give a disproportionate importance to smaller MS compared to the number of inhabitants and to lower-income Member States compared to the economic wealth. Such voting rights would give higher weight to smaller and less affluent markets that are disproportionately affected by the non-affordability of medicine.

The Member States would constitute a **General Assembly** (GA) of the DP WG. To facilitate the decision-making process, an **Executive Board** (EB) consisting of a defined number of a few Member States could be set up. The EB could, supported by a Secretariat, prepare meetings and decisions, by collecting and providing relevant information and evidence to support the decision-making process. An uneven number of members within the EB (e.g. three or five) could facilitate internal discussion and decision-making. The members of the EB could represent the different geographic regions, the size and the economic situation of Member States, etc. Most probably, they would be elected by the GA. While a rotation of the EB would be favourable for equity reasons, some stability of the EB would facilitate the working mechanism. It might be considered to vote members of the EB for a period of 2 years, for instance, with the possibility to be re-elected for a second term. Ideally, the EB should also reflect the appropriate representativeness of the Member States.

Voting rights would be defined at the beginning of the implementation of the DP scheme. It might be considered to have simple, or weighted majority on which medicines are to be included in the DP scheme. However, basic principles on the mechanisms of the DP scheme (before starting off) could be decided with a stronger majority, even unanimity which would be able to ensure sustainability and commitment of the MS.

A key decision would be the **role of the EC** as a strong one in a coordination mechanism, with full respect for the subsidiarity principle. One option would be to establish a secretariat (see below) attached to the EC, and to agree on the work plan that provides for close coordination and cooperation between the DP Secretariat and the EB. It would be a major decision in the beginning of the DP process whether or not, the EC would be granted a voting right.

The DP scheme will impact further **stakeholders**, particularly the MAH. Therefore, a good communication, consultation and dissemination strategy is necessary. While the

decision-making power will lie with the Member States who decide on pricing and funding, dialogue with stakeholders should be considered (cf. also Chapter 5.2.1.6).

5.2.1.3 Legal aspects

The implementation and management of a DP scheme through an EU cooperation mechanism requires a **legal framework**, e.g. based on regulations or contractual arrangements. All authors and experts who called for a DP, as defined by government policy, consistently stressed this need for legal arrangements and some of them [110-112] opted for an international convention or a global contractual framework that would help to create equity word-wide. Though the rationale of these arguments is well understood, the outline of a DP scheme to be developed within this study will be limited to the **EU**. However, any expansion or bridging to world-wide existing legal instruments could be considered to be addressed at a later stage.

The statutory, or contractual, framework should cover all the legal, technical, organisational-administrative and financial aspects discussed here, as appropriate.

A safeguard would be particularly required to be included in the legal framework to **avoid marketing or selling of medicines in other Member States** from lower-priced countries to higher-priced ones. This might be a commitment of Member States involved in the DP scheme to impose, and monitor, an export ban for medicines and notification / authorisation law covered under the DP. As explained in Chapter 3.4, export bans of Member States can be justified for public health reasons. Another option that could also be introduced as a supplementary measure could be a contractual arrangement with the MAH as well as further traders not to engage in exporting defined differentially priced medicines from lower-priced to higher-priced countries. Supplementary tools could be a registry for these medicines and tracing of the medicines, as well as specific package labels.

In case the DP scheme was defined as the solely pricing policy (i.e. excluding EPR) for the specified medicine, the agreement would then require a commitment of the Member States to keep to the agreed differential price for the defined DP medicines, and not to apply EPR on top of DP. In this context, the authors suggest considering elements of the proposed **Regulation of the European Parliament and of the Council to avoid trade diversion into the European Union of certain key medicines** (codification), 2014/0165 (COD) [157] which codifies Council Regulation (EC) No 953/2003 of 26 May 2003 (cf. Chapter 4.2.2). Though this regulation is from another policy area (external trade), it contains some technical specifications related to how to deal with leakages and mark-ups/mark-downs, that might be taken into consideration. It has been argued that this Regulation is not a good practice example since it has only been used by one company since its implementation (cf. 4.2.1.4). It should be considered that other companies even if they did chose not to register their products under the Regulation they adopted differential pricing approaches [143].

Finally, in the area of legal aspects, it could be explored whether a possible DP, or, some DP mechanisms, could be built in the **EU Joint Procurement Agreement** for vaccines and medical counter-measures as of 2014 (cf. Chapter 4.2.2). However, as it was stated in Chapter 4.2.2, it was clarified in July 2015 that the scope of JPA should not be extended beyond vaccines and antivirals against pandemic influenza.

5.2.1.4 Organisational aspects

For DP to be introduced as a scheme, moving beyond a single pilot, the authors consider the establishment of a coordination structure as necessary (thereafter called 'DP

secretariat'). Experience with any networking and cooperative activity, even on a voluntary basis, have highlighted the need for such a structure since several tasks (see below) need to be done at a central level for all those included in such a structure.

The **tasks of the DP secretariat** could include:

- Administrative and organisational tasks to support the Executive Board and General Assembly (e.g. organisation and documentation of meetings);
- Information, consultation and dissemination (e.g. in charge of organising the internal information and decision-making processes; liaison point to (other) Commission services, contact point for industry and external parties such as the public and media, capacity-building measures in the field);
- Monitoring the application of the agreed DP schemes according to defined indicators and reporting to the EB or other parties designated to deal with compliance;
- On top of the monitoring, an assessment and evaluation of DP after the pilot and/or after the first cases.

5.2.1.5 Policy and technical aspects to implement a DP

Policy and technical issues include the following aspects:

- Design of DP scheme in terms of the number of participants and the approach on how to get to a differential price;
- Predictability and reliability for industry;
- Question of transparency versus confidentiality.

What should be the **minimum number of countries** of a DP in technical terms? A joint negotiation and/or joint procurement might be organised by a lower number of countries (see also the provision of a minimum of four MS to any specific procurement procedure in the EU Joint Procurement Agreement [146]), even though a higher number of participating countries is likely to increase the bargaining power. However, from the authors' understanding, DP requires the inclusion of all countries of the addressed region, thus in the EU in this respect.

If a mechanism of adjusting for a country's economic situation, for instance, proxied by GDP or PPP was applied, DP would help make medicines affordable for lower-income countries but high-income countries could be worse off compared to the current situation, since the consideration of economic criteria would require them to pay a higher price. Why should a more affluent, typically high-priced country accept an even higher price? It could be argued that high-income countries were willing to do so in terms of solidarity and equity across the EU, and the difference of the higher price would be perceived as a kind of subsidy, similar to the concept of 'net payers' and 'net recipients' related to the EU budget. Similar to the EU budget, or any solidarity based system, the structure would not work if all well-off countries that are 'net payers' opted out of the system.

Another approach could be to mark down current medicines prices in accordance with the economic situation of a country in order to achieve the same price for the high-priced countries as it would have been without DP. The DP formula would still be applied, but the overall medicine prices would be lower.

With such an approach, the industry might risk to be negatively impacted in the case that this approach would actually reduce their profits. In literature, it has been argued that DP should not be perceived as a subsidy but as a win-win (or even 'win-win-win') situation [108], since the manufacturers get access to markets that would otherwise

not have been supplied. Though manufacturers would have to accept a lower price in lower-income countries, they might still benefit due to higher sales. In addition, some originator medicines under DP might be considered as 'loss leaders', strategically used to access a market and gain market shares. In Europe, achieving lower prices in certain defined markets, in combination with no longer referencing to these marked-down prices, might be potentially done without negatively impacting profits as sales might be increased as well as strategic delays in launch would no longer be necessary. Further analysis on the demand of relevant pharmaceutical markets is required to gain further insight into how DP schemes would need to be designed to still allow for adequate profits and thus adequate R&D incentives for pharmaceutical firms.

Manufacturers could be granted some 'safeguards' to support their forecasts and ensure a reliable, predictable system. One safeguard would be, as mentioned (cf. Chapter 5.2.1.3 above), a functioning mechanism to avoid the leakage from lower-priced to higher-priced countries. In addition, a DP scheme would ideally include **purchase guarantees** from the countries; these could be combined with **supply guarantees** by manufacturers to deliver the markets included in the DP scheme.

Summing up, technically, a **mechanism** to set differential prices could work in different ways. For instance, a maximum price could be defined and then mark-downs based on ability-to-pay, such as an indicator based on GDP per capita, could be applied. Similarly, a minimum price could be defined and mark-ups based on an indicator of the ability-to-pay applied. The main difficulty lies in defining the maximum or minimum price which might be related to break-even points of firms, financial sustainability or related to the value of a medicine. Otherwise, some mixed system could be used in which rich countries continue to have the same level of prices as under current EPR schemes, whereas lower-income countries receive transparent mark-downs based on GDP per capita or other measures of ability-to-pay. Depending on the magnitude of such mark-downs and design (e.g. whether other countries still refer to such discounts, whether costly delays in market access can be reduced, whether sales can be increased) such a mixed DP system might potentially still be profit-neutral for companies.

A major issue of debate is whether or not a DP scheme should be public, or confidential. As shown in Chapter 4.2.1.3 authors ([110, 111], personal communication from expert interviews) who called for a global DP scheme led by government or supranational institutions stressed that DP has to be based on transparent prices and procedures for equity reasons. This approach has also been reflected in DP schemes coordinated by international institutions that disclose price information. Other authors [81] have a different viewpoint and consider confidential discounts and rebates granted by the industry to public payers as a way of implementing DP. These authors, however, also acknowledge that sharing information on prices may increase the bargaining power by increasing the information available to buyers about the companies' willingness to supply, and that transparency also assures public accountability. It was argued that, though confidentiality should be kept, this could be achieved through audits by an approved third party, and also by putting an asterisk to mark the discounted prices [81, 102].

Granting confidential discounts and rebates to public payers is not a new strategy, and it is commonly practiced across Europe. There is no evidence that it has brought any improved access to medicines. If DP understood as a government and supranational policy was to be implemented, the authors strongly argue in favour of **transparency** in all respects: clear, transparent procedures and disclosure of actual paid prices since otherwise equitable pricing could not be guaranteed. This also has to be seen in the light of the fact that, in this case, these are not unilateral discounts between a pharmaceutical

company and a country, but agreements with the company and the whole EU whose authorities are accountable to its citizens.

5.2.1.6 Information, consultation and dissemination

As stated in Chapter 5.2.1.2, the decision-making power would remain with the decision-making bodies, the competent authorities for pharmaceutical pricing and reimbursement in the EU Member States, in coordination with the EC. Appropriate mechanisms for the sharing of information and on-time consultation of the Member States before decision-making are required.

The stakeholders, such as the pharmaceutical industry, are targeted by the policies; thus their involvement as dialogue partners and information providers could be sought. In the setting up of a DP scheme, its Terms of Reference could define the dialogue with the MAH of the medicines to be differentially priced as fixtures, at a rather early stage. These contacts and meetings could also be accompanied by a list of information that is potentially required from the marketing authorisation holders. Apart from a structured procedure of request for information from marketing authorisation holders, an invitation of defined stakeholder representatives to an open part of the general assembly could be considered.

It is suggested considering that the EU Member States, when starting with DP, perform a DP pilot project, and launch a call to invite interested pharmaceutical companies to cooperate and to market their product under a DP.

In addition, attention should be paid on how to inform further stakeholders and the public about the application of a DP scheme. This is also relevant in the light of the fact that DP (for LMIC) has been met with reluctance in former times ([108], cf. Chapter 4.2.1).

5.2.1.7 Financial aspects

Based on the elements proposed for consideration in the development of a DP scheme, its implementation would include, among others, the following costs in the light of an EU coordination mechanism[53]:

- Staff costs of the national competent authorities and the EC (secretariat) for agreeing on the scheme (meetings, internal negotiations);
- Possible costs for external consultants to support technically designing the DP scheme;
- Possible costs for legal experts to support developing appropriate statutory provisions or contractual arrangements;
- Costs for establishing a DP secretariat at EU level;
- Costs for communication and dissemination to the public (if considered necessary and appropriate).

As soon as the DP scheme has been set up, the costs for running the system are likely to be lower; they would include:

- Costs for running a DP secretariat at EU level;

[53] There might be cost for the business actors (industry) as well when they might be involved in the negotiations with the EC.

- Costs for monitoring the existing DP scheme and development of proposals for adjustment (part of DP secretariat and commissioned externally);
- Staff costs of the national competent authorities for communication, consultation and negotiation in case of a need for adjustment and the introduction of new medicines to be included in the DP scheme.

The following Chapter 5.2.2 will present high-level estimations of the costs of other EU coordination mechanisms which might provide an indication.

5.2.2 Assessment of a possible DP scheme

5.2.2.1 Examples of EU cooperation mechanisms

The authors of this report were asked in the Tender Specification to explore European cooperation mechanisms related to differentiated prices in use in other policy areas such as for (Carbon) Emission Trade Schemes, price setting schemes in the field of agriculture, with a particular focus on cost extrapolations derived from coordination mechanisms in use. Three examples of the EU cooperation mechanisms from other policy fields (EU Emission Trade System, the Common Agricultural Policy (CAP) and air transport regulations were identified. For a detailed description see Annex 14. Overall, however, we felt that there was limited transferability to pharmaceutical policies. A few lessons that could be drawn were that the duration of decision findings in political sensitive areas can take time and the size of the group increases the extent of the efforts required. Designing a DP mechanism for all 28 European Member States may take longer than for a lower number. On the other hand, experiences have shown, that a working mechanism for a few number of Member States might have its limitation when further Member States join in.

Furthermore a cooperation mechanism influences the relative signal function of prices. The prices and reimbursement lists reflect the priorities that governments set in their health policy, when it comes to spending limited financial resources. The implementation of a cooperation mechanism will have signals in both directions: It may put pressure on national authorities to include some medicines in the reimbursement list, although the focus of their national health policies be similar as in other areas. Pharmaceutical manufacturers might be incentivised (or disincentivised) to strengthen R&D in certain areas. Even if countries initially agree on cooperation mechanisms, they require regular adjustments. Any coordination mechanism needs to be adjusted for transformations which occur with the system and is at best a snapshot of ongoing adjustment processes.

Within the field of pharmaceutical policies, there is one initiative, though not directly related to the pricing, worthwhile mentioning: the Transparent Value Framework (TVF). The TVF was initiated by the Belgian EU Presidency and developed as part of the 'Mechanism of Coordinated Access to Orphan Medicinal Products' working group in the EU Process on Corporate Social Responsibility in the field of pharmaceuticals, with the aim to help European countries in their value assessment of orphan medicinal medicines. The purpose was to develop a proposal on how to create a future voluntary European collaboration as well as a pilot project on voluntary basis to improve access to orphan medicinal products in Europe. The use of the TVF enables to compare therapeutic alternatives with similar scores to provide future guidance in pricing and reimbursement negotiations (cf. Table 9). Thus, it helps to define the added value, and support to start priced-value negotiations from an agreed basis which should lead to more predictable market conditions and more equitable access for patients.

Table 9: The Transparent Value Framework (TVF)

Criterion	Lower Degree	Medium Degree	High Degree
Available Alternatives / unmet need, including pharmaceutical treatment options	Yes, new medicine does not address unmet need	Yes, but major unmet need still remains	No alternatives except best supportive care – new medicine addresses major unmet need
(Relative) Effectiveness, degree of net benefit (clinical improvement, quality of life, etc. vs. side effects, societal impact, etc.) relative to alternatives, including no treatment	Incremental	Major	Curative
Response rate (based on best available clinically relevant criteria)	< 30%	30-60%	>60%
Degree of certainty (documentation)	Promising but not well-documented	Plausible	Unequivocal

While seen as a start, there is ongoing debate about the feasibility of implementing the TVF in national reimbursement authorities [3]. Other frameworks of evaluation for medicines that do not fit standard methodologies of HTA have been proposed. Hughes-Wilson and colleagues proposals included ten criteria by which orphan medicinal products could be evaluated, indicating potential price differentials based on baseline measures for each individual criterion [158].

5.2.2.2 Financial implications

In Chapter 5.2.1.7 we provided an overview of possible cost elements for the establishment and maintenance of a possible DP scheme in European countries.

In Annex 14, high-level estimates were surveyed for other EU cooperation mechanisms. For the EU Emission Trading System, the costs of the extension system in 2008 were estimated at EUR 3.05 million for operational expenditure, EUR 6.727 million for human resources and associated costs, and EUR 1.881 million for administrative expenditures other than human resources, summing up to EUR 11.658 million. For the Common Agricultural Policy (CAP), a total of EUR 480.37 million of administrative costs was estimated at the producer level in Germany (cf. Annex 14).

The cost for running a DP scheme for medicines also depends of whether the DP Secretariat will be set up as a large Agency, or rather as a small coordination structure (cf. Chapter 5.2.1.4), and which synergies (e.g. affiliated to the Joint Procurement Agreement, or secondments by Member States) are possible.

However, it should be considered that the primary aim of a DP is to improve the patients' access to medicines, and not savings. It is expected that the overall expenditure across Europe for a medicine under the DP scheme in Europe will be higher than without DP. This is even likely to be the case if a DP formula that does not increase the price for higher-income countries and only reduces the prices for lower-income countries will be chosen.

5.2.2.3 SWOT analysis

Table 10 provides an overview of identified strengths, weaknesses, opportunities and threats of a DP system. DP has been identified as a policy option able to improve patients' accessibility (under certain conditions) whereas the evidence on its capacity to generate savings is rather mixed.

Table 10: SWOT analysis of a DP scheme in Europe

	Positive aspects	*Negative aspects*
	Strengths	**Weaknesses**
Internal factors	▪ Accessibility: Could be a solution which offers, if implemented properly, equitable access to medicines ▪ Transparency: Could be a transparent tool if implemented with disclosed prices ▪ Equity: Could ensure that opportunity cost of purchasing medicines and investing in R&D would be roughly equivalent across countries of variable wealth	▪ Political will: ideally requires the commitment of all 28 EU Member States if implemented properly ▪ Common understanding: Requires a good understanding of the concept of all involved participants ▪ Coordination: High coordination efforts, particularly at the beginning, leading to costs ▪ Leaking: Risk of failing to avoid leakage ▪ Disregard of further price impacting factors: A DP scheme if feasible for implementation in the EU would be limited to consider the ability-to-pay, but still ignore further factors such as country-specific epidemiologic characteristics ▪ Resources: Time- and resource-intensive implementation (even for a pilot)
	Opportunities	**Threats**
External factors	▪ Access in under-supplied markets: Could contribute to improved access, in particular access to medicines in countries otherwise not supplied ▪ Quicker access: Could contribute to improved access in terms of fewer delays for lower-priced countries (no strategic launch but simultaneous launch) ▪ Savings for some countries: Could contribute to lower prices for some countries, thus generate savings ▪ Increased revenues for industry: Could generate higher revenues for the industry due to sales in markets not supplied previously ▪ Dialogue among stakeholders: Might contribute to an improved dialogue with the industry and a common understanding about the needs ▪ Cooperation mechanism: Might contribute to new ways of cooperation between MS	▪ Delays: Could also contribute to delayed access for higher-priced countries due to time for coordination ▪ Need for agreement: Non-agreement between MS could lead to delays and to an possible failure of the system ▪ No savings: Might lead to price increases in wealthy countries to compensate for lower prices and potentially lower profits in lower-income countries. ▪ Risk of higher prices: Might potentially lead to higher prices overall if joint negotiations are not performed well whereas current prices are curtailed through EPR and thus consecutively refer to each other's price reductions as well as being pressures on prices through the possibility of parallel trade and arbitrage ▪ Alternative: Focus on DP might lead to exclude further policy alternatives and coordination mechanisms

Based on the authors' analysis performed as part of this study, such as literature review, interviews and price simulations

5.2.2.4 Concluding summary

If a DP scheme was introduced in Europe, it would need to meet the following prerequisites:

- A mechanism to **avoid the leakage** of products from lower-priced to higher-priced countries;
- A strong **political will** and **commitment**;
- A **common understanding** of the scope and mechanisms of the DP of all involved and targeted parties;
- An **administrative structure (secretariat)** and clear, transparent mechanisms for sharing information and decision-making
- The **involvement** of the MS and a **dialogue** with the stakeholders.

Some of the issues are of technical and methodological nature, whereas others are political and even ideological. The authors believe that the key prerequisite would be the political will and commitment of the MS to opt for a DP scheme, for specific medicines. While some policy options with traits of a DP (e.g. weighing prices based on the economic situation) might be taken unilaterally and through cooperation of a few Member States, a real DP scheme, with an agreement on the starting price and central formulae (mark-ups/mark-downs) would require the commitment of all 28 EU Member States. The authors are not fully convinced whether or not, given these key prerequisites, a DP scheme would be politically feasible in the EU.

If political commitment of all EU Member States to a DP scheme as outlined above existed, further technical and even legal requirements would need to be solved. Export bans or notification or authorisation law of Member States imposed on medicines put under the DP scheme could be an option to avoid leakage, however might be problematic in the legal context. But a more centralised policy could also be implemented such as a registry for DP medicines, by possibly drawing from some mechanisms applied by the Regulation of the European Parliament and of the Council to avoid trade diversion into the European Union of certain key medicines (codification), 2014/0165 (COD). Options to deal with technical challenges were outlined above in Chapter 5.2.1. Further analysis would be needed, for instance on volumes and demand structures, to better predict which impacts different methodological choices would have on industry turnover.

Impact on countries outside the EU

It is well-known that policies in EU Member States have an impact on countries beyond Europe. For instance, several countries, including some of the emerging markets, reference to European countries in addition or instead of their neighbouring countries when doing EPR [28].

If a DP scheme was introduced in Europe, external price referencing to single European countries would likely continue and countries cannot be prevented from using prices data from Europe in their price setting strategies. Within a DP scheme some lower-income countries which are currently prevented from access, might receive access to further medicines and generally tend to have a lower price level than the average on these medicines. Thus, depending on what countries a non-European country refers to, DP in Europe might put negative pressure on prices outside Europe and thus be a concern for pharmaceutical companies. Further, differential pricing, in the most extreme sense where the least well-off countries only pay marginal production costs, has also been argued to implicitly provide information on costs and break-even points of firms and thus can put further pressure on prices. These concerns need to be discussed with relevant stakeholders before any DP like mechanisms can be designed.

One possible solution that the EU could propose is to define a 'European list price', or some 'European prices' (e.g. a price for highest-income Member States, a price for less high-income MS, and a price for lower-income Member States) for the medicines under the DP scheme, and to publish these prices. In this case, countries would for example receive transparent mark-ups or mark-downs on such an official listing price, however, as currently done, the list price would be used for external price referencing purposes.

Alternative policy options

The implementation of a full-fledged 'real DP' scheme might not be politically feasible in the short run within the EU. Moreover, further analysis, for instance on market structure and demand, is necessary to comprehend the impact and benefits of such potential mechanisms on different stakeholders and thus clearly outline whether such a

mechanisms would be desirable. However, despite such limitations, some lessons can still be learned.

- Although the evidence on DP is still at an early stage and it might not be politically feasible at this stage, current challenges in new high-cost medicines and access issues highlight that solutions should and can only be sought through some form of collaboration.
- EPR and DP have usually been considered as two mutually exclusive policy options. However, if they are not considered in a pure form, there is the possibility to take some DP traits. This could, for instance, include a consideration of PPP or GDP to be built into EPR formulae, the application of EPR with referencing to the average price for all 28 Member States and then setting the prices for each country at a fixed percentage rate above or below the average, or cooperation through agreeing on a smaller number of Member States in the basket (cf. also Chapter 4.1.5).
- The study discussed the importance of cooperation between Member States, and the sharing of evidence. Chapter 5.1.1 has highlighted the importance of a European central medicine database, and has outlined some, possibly combined, EPR related coordination mechanisms. The discussion on DP has highlighted the promising route of the EU Joint Procurement Agreement, as a supplement to DP. In any case, with or without DP, procurement of medicines would be another way forward to improve cooperation between Member States, in order to improve access to medicines as well as to ensure financial sustainability, and, given a lower number of involved MS and the early experiences, this actually appears politically feasible.

6 Conclusions and policy recommendations

European countries have been struggling to achieve the partially conflicting goals of granting patient access to medicines, while containing costs in order to ensure financial sustainability as well as providing a reward for industry to incentivise R&D. The challenges have been aggravated by the emergence of new, high-cost medicines and the financial crisis which significantly impacted some EU Member States.

Pharmaceutical pricing is a **competence of the EU Member States** though overall provisions at EU level such as the Transparency Directive have to be respected.

The study investigated two pricing policy options: external price referencing (EPR), and differential pricing (DP) which are different policies with regards to their aims, their current implementation in Europe, and their potential to achieve the policy objectives they are intended to pursue. EPR is predominantly a tool for medicine price control, whereas DP has been applied as a strategy to improve access to (otherwise unaffordable) medicines.

6.1 External price referencing

Key findings and conclusions

External price referencing is the **key pricing policy** applied in European countries: Apart from Germany (though provided for in legislation), Sweden and the UK, EU Member States as well as Iceland, Norway, Switzerland and Turkey make use of external price referencing to set medicine prices, usually at least for a subset of medicines.

However, **variations** in the setting, the scope of medicines covered and the relevance of the policy exist between the European countries. For instance, 20 of the 32 surveyed European countries use EPR as sole or key pricing policies, whereas the other countries perform price comparisons as an additional tool to inform their pricing decisions; for new, high-cost medicines pharmaco-economic evaluation and HTA have been increasingly used. When applying EPR, EU Member States opted for different methodological approaches with regard to the reference countries' basket, the price type compared, the calculation method of the reference price, the exchange rate fluctuations and the non-availability and/or non-comparability of data.

With regard to the objective of ensuring **patient accessibility of medicines**, EPR has some limitations. It incentivises the marketing authorisation holders to first launch their products in high-priced countries and to delay, or not to market, in lower-priced countries, in order not to negatively impact their reference price. Medicine shortages that have increasingly been observed in European countries in recent years might be attributable to strategic launches of the pharmaceutical industry in response to the commonly applied EPR policy. Moreover, manufacturers are likely inhibited from offering lower prices to lower-income countries, and thus reduce affordable access.

EPR has been shown to be a pricing policy able to generate **savings for public payers** in some countries, at least in the short-term. However, as simulations also confirmed, savings might be higher if actual paid prices (discounted prices) instead of list prices were considered and regular price revisions were undertaken. 22 out of the 32 surveyed European countries reported that discounts, rebates or similar arrangements (e.g. managed-entry agreements) were in place. While this helps generating savings for the public budgets of a country, the other countries that reference to the latter do not benefit from the actual lower prices.

In practical terms, EPR is a **cost- and time-intensive exercise** and would benefit from tools and mechanisms to ease the work load.

Policy recommendations

- In designing EPR, policy-makers should carefully decide on the **methodology** in line with the underlying policy objectives and principles since methodological specifications can have a major impact on the effectiveness of EPR, in particular with regard to the potential of savings to be generated.
- In this context, policy-makers are advised to ensure the performance of price monitoring at regular intervals, with subsequent **price revisions**. This would have a major impact on the prices since medicines in lower-priced countries, though reference countries, were not considered in the initial price setting due to the non-availability of the medicines in these markets. If the administrative burden for price revisions is too high, supportive collaborative approaches and tools (see below) should be sought, and the price revisions could be limited to selected medicines considered as the most relevant (e.g. the 100 medicines that account for highest public pharmaceutical expenditure). Policy-makers should ensure that price revisions are not only foreseen in legislation, but are actually performed.
- Policy-makers should consider referencing to **discounted prices** instead of list prices. Since the disclosure of confidential prices is highly politically sensitive and might not be feasible in the short-term, Member States might consider in a first step to reference to officially published discounted prices (statutory discounts), and to elaborate strategies, together with other countries, about a possible consideration of confidential discounts. Policy-makers may also consider marking those medicines in the database that was supplied with a discount while not disclosing the extent of the discount.
- Policy-makers should carefully consider the selection of the **reference countries**. In technical terms, a smaller number of countries means less administrative work. The selection of the countries also has major policy implications on savings and access. Thus, policy-makers could consider choosing reference countries of a similar economic situation.
- In addition, in order to factor in the economic situation of the reference countries, policy-makers could consider **weighting medicine prices** by GDP or purchasing power parities (PPP). This could help addressing the EPR limitation of limited, delayed access to medicines and unaffordable prices in lower-priced countries. An exchange of information and of best practices between Member States would be highly supportive.
- In order to ease the work load, policy-makers should consider strengthening their cooperation, in particular through the contribution and benefits of existing tools such as a **European medicine price database** (Euripid).
- In addition to the above-mentioned methodological specifications, policy-makers should also, and in particular, consider defining specifications in their EPR methodology on how to deal with **missing price information** of a defined medicine, and with **exchange rate fluctuations**. Lessons can be learned from other countries.

6.2 Differential pricing

Key findings and conclusions

Given the identified limitations of EPR, in particular possibly the setting of high, unaffordable prices in less wealthy countries as well as limited access in these countries, there has been a call for alternative pricing mechanisms. One of them is DP which was explored within this study. In the context of this study, DP is understood as a **policy of governments (or international institutions)** that set medicine prices according to the ability-to-pay, and/or to the economic situation of countries.

DP related to medicines, as defined above, has not been applied in European countries, and literature suggests the global implementation of this policy at a comparably low scale: DP has typically been used for **low- and middle-income countries** (LMIC) related to specific **groups of medicines** (vaccines and medicines against HIV/AIDS, tuberculosis and malaria). A comprehensive literature review, including interviews with experts on the field (procurement officers performing DP-based tenders) has, however, shown very few examples of collaborative approaches of governments (e.g. in Central America) to jointly decide on tiered pricing among their countries, whereas DP was usually designed in a way that the differential prices for the included countries were decided at a central level (e.g. by international agencies or programmes such as UNICEF, PAHO or UNITAID in charge of procuring and funding the medicines).

DP was introduced in these countries with the aim to ensure access to medicines that would otherwise not have been supplied to these markets. Thus, the major rationale behind DP is the expected ability to grant or increase **patient access** to medicines. However, literature and expert opinions suggest mixed experiences with DP related to its ability to actually improve accessibility. Certain prerequisites were identified to ensure the effectiveness of DP, such as the feasibility of competitive production, the need for rapid access to small quantities of medicines and lack of market prior to the implementation of the DP scheme. According to experts, the latter prerequisite is also the most likely reason why DP would not be successful in improving patient access in middle-income countries where markets already exist.

In those situations where DP was applied, it was used as a policy to improve access, but it has **never** been intended as a tool for **cost-containment**. For those medicines procured under a DP scheme, pharmaceutical expenditure has obviously increased since no money had been spent on medication in these indications before. Case studies on some countries showed that DP contributed to **lower medicine prices**, but competition (particularly the entry of generic medicines) has proven to be more effective to bring prices down.

Some authors argued that under certain conditions DP might also be **beneficial for manufacturers** since sales in the new markets, though at low prices, would increase overall revenue.

These conclusions refer to the experiences with DP, as defined above as a government policy, for which some evidence based on the implementation in LMIC is available. No experiences for DP in high-income countries are available due to the lack of its implementation, and it might be questioned whether the fact that EU Member States are **high-income countries** might be a limitation per se. At the same time, there are major discrepancies in the economic situation between EU Member States with the GDP per capita in 2013 of EUR 83,400 in Luxembourg and EUR 5,500 in Bulgaria. Furthermore, international experience with DP is limited with regard to those situations when governments (and not a central body) decide, which would also be the case in a

collaborative approach between EU Member States, in full respect of the subsidiarity principle.

The two limitations of DP most frequently quoted in peer-reviewed literature, policy papers and discussions in the European Union are the existence of **parallel trade** that favours the 'leakage' of medicines from lower-priced countries into countries with a higher price level, and the widespread use of **EPR** that does not incentivise pharmaceutical companies to offer lower prices to lower-income countries when this would subsequently decrease medicine prices in the EPR applying, higher-priced countries. These are serious limitations to an effective and functioning EPR system; however they only come into play after the implementation of a DP scheme. Still, they need to be addressed at the stage of the preparation of a DP scheme.

The major prerequisite for the introduction a DP scheme for – selected – medicines would be the agreement of the EU Member States on principles and mechanisms of this new collaborative approach. Technical solutions would have to be sought to ensure that no MS is disadvantaged under a DP scheme, and political commitment of all EU Member States would be required. It has yet to be explored whether, or not, the implementation of a DP would be **feasible** in the European Union. The implementation of a DP scheme would require the acceptance of, and the commitment to, the provision of premium-priced medicines to the lower-income countries at considerably lower prices. Thus, higher-income countries would contribute with a higher share to research and development which is a global public good.

This study did **not deal with 'price discrimination'** ('market discrimination', 'Ramsey pricing') that describes a business strategy of economic actors to segment the market according to the observed demand-elasticity of the consumers since this is neither a government policy nor a cooperation mechanism between countries. Furthermore, this strategy is not a new approach either since it is already done in European countries, through discounts and rebates granted by manufacturers to public payers.

Policy recommendations

- If EU Member States opt for the implementation of the collaborative approach of a DP scheme, **all 28 EU Member States** need to **agree on principles and mechanisms** of such a scheme. These principles and mechanisms should be fully transparent.
- A major point of agreement would concern the mechanism on how to decide the **maximum or minimum entry price** from which mark-ups or mark-downs are based. A mere consideration of macro-economic indicators such as the gross domestic product (or the gross national income) or purchasing power parities in the sense that prices in lower-priced countries will be reduced compared to a situation without DP but higher in the higher-priced countries is unlikely to be accepted by high-income countries. Thus, in case of moving forward with a DP scheme, policy-makers should consider agreeing on a design in which prices in higher-priced countries will not be higher than without DP, but it still incentivises industry to join such a DP scheme by offering overall increased sales.
- Since there is no experience with DP in high-income countries, and limited experience on DP as a collaborative approach between countries, EU Member States should consider performing a **DP pilot** to gain experience in this field. If required, EU Member States could consider launching further pilots.
- Possible candidates for a DP pilot could be **high-cost medicines**, such as orphan medicinal products or medicines with expected high therapeutic benefits. It is recommended defining the criteria for possible 'candidate medicines' in advance. A

candidate medicine could be identified in a joint early dialogue and scanning exercise involving regulators, HTA bodies, and payers.

- Member States should consider launching a **call for inviting industry** to cooperate under a DP pilot. In doing so, they should take into account the experience of cooperation with industry in other pilot projects such as the 'adaptive pathways' and MoCA (Mechanism of Coordinated Access to orphan medicinal products).
- Member States are advised to provide an **evaluation** mechanism accompanying all DP pilot projects as well as a possible 'standard' DP scheme to allow for lessons to be learned, and, in response to the experiences, to adjust the scheme.
- In full respect of the subsidiarity principle, EU Member States could consider installing a **central coordinating structure** in charge of operational issues based on the principles and mechanisms agreed upon.
- In case of implementing a DP scheme, EU Member States should consider building in mechanisms that **avoid the leakage of differentially priced medicines** from lower-priced to higher-priced countries. They could consider exploring whether mechanisms of export bans and notification/authorisation procedures already unilaterally applied in case of preventing medicine shortages due to parallel exports might be used, which is however currently legally problematic.
- Furthermore, EU Member States could consider learning lessons from **specific mechanisms of the Council Regulation (EC) No. 953/2003** of 26 May 2003 to avoid trade diversion into the European Union of certain key medicines (currently under revision: 2014/0165 (COD)) and its evaluation published in summer 2015, even if this regulation is from the area of external trade, focused on specific indications and has not be broadly used. However, certain specifications, such a logo for differentially priced medicines, could be investigated as to whether to be also applied for a possible DP in Europe.

6.3 Possible avenues for the future

The authors were asked to assess the pricing policy options of EPR and DP, respectively in terms of increased cost-containment and increased accessibility of medicinal care. Depending on whether the policy objectives of cost-containment (financial sustainability) or access to medicines should be more stressed, policy-makers in EU Member States would need to decide whether they opt for technical improvements in EPR which they can implement unilaterally (may help ensuring financial sustainability), or to consider socio-economic features in pricing (either unilaterally or in a collaborative approach such as a DP scheme; as a measure to improve access). If the industry perspective (reward for innovation) were to be taken further into consideration (not the scope of this study), the mix of selected policies and their design would require to be adjusted appropriately.

The introduction of a fully-fledged DP scheme in Europe, as a government policy or EC supported policy in full respect of the subsidiarity principle, though not completely impossible, would however require addressing major obstacles in legal, technical, organisational and political terms and might not be the most preferred policy to address challenges in equitable access to medicines.

The report recommends focusing on improvements to existing EPR schemes as a concrete first step, and aiming to achieve improvements in access to medicines across Europe via exploring options of collaboration within the current EPR structure. The report recommends, as technical improvement to EPR, performing regular, at least annual,

price **re-evaluations** (in order to decrease work load, a focus on a limited number of medicines, e.g. those with high budget impact, could be laid) and referencing to actual prices paid, thus considering possible **discounts**, rebates and similar financial arrangements (as a minimum considering published statutory manufacturer discounts granted to public payers).

The study investigated the policy options of EPR and DP. Further pricing policies, and also reimbursement mechanisms closely linked to pricing (such as value-based pricing, HTA, economic evaluations, managed-entry agreements) were not the scope of this study. While this study argues for a non-mutually exclusive approach of EPR and DP, EU Member States might consider introducing **combinations of further policies** and mechanisms beyond the scope of this report. For instance, the Priority Medicines Report 2004 proposed a methodology to combine cost-effectiveness analysis with a measure of national wealth. It is recommended to initiate further research whose scope is not limited to the two pricing policies of EPR and DP, but allows for consideration of further pricing mechanisms and alternative collaborative approaches, as called for by the Council conclusions on innovation for the benefit of patients as of December 2014. This would involve aiming to provide an answer that will be accepted by Member States and stakeholders of what constitutes a 'fair' price. Both EPR and DP have the limitation of defining the starting price. This highlights the importance of HTA and pharmaco-economic evaluations, and more cooperation in this field among Member States is highly appreciated. However, debates about a 'fair' price for all parties would move beyond (pricing) policies but would also require exploring new ways of financing medicines. Further research on these issues would be required, likely followed up by pilots (similar to the work around the Transparent Value Framework). In this context, debates might no longer be restricted to the issue of pricing (and reimbursement) of single medicines, but finding solutions for funding (and thus ensuring access to) treatments. More evidence base for these discussions will be needed, including knowledge about the components of the costs for research.

Such discussions should be based on evidence (technical work done by researchers) supplemented by inputs of stakeholders. These debates should involve further stake-holders in addition to pricing / reimbursement authorities and industry. In particular, citizens and patients should not be forgotten. The stakeholder review meeting related to this report with representatives from the EC, Member States and associations / interest groups offered a platform for dialogue among the participants. It is re-commended considering similar fora for the future in which stakeholders can openly discuss without being bound to an institutional mandate. Such dialogue could allow 'thinking out of the box', beyond pricing policies and beyond the European Union.

Note: Current challenges, in particular the emergence of high-priced medicines, have shown the urgent need for improving existing pricing mechanisms and developing alternative, possibly cooperative, approaches, as expressed in policy papers quoted earlier in this report. In this context, the authors were asked 1) to work out proposals for improving EPR and 2) to develop a possible outline for a DP scheme in Europe. In doing so, in accordance with the specifications of this study, the authors suggested policy recommendations based on existing (though in some fields somewhat limited) evidence and on their own simulations. However, they do not take a relative preference for either EPR or DP schemes at EU-level, but rather present a juxtaposition of technical, economic and legal considerations for both broad policy avenues.

7 References

[1] Carone G, Schwierz C, Xavier A. Cost-containment policies in public pharmaceutical spending in the EU. Brussels: European Commission, Directorate-General for Economics and Financial Affairs, 2012.

[2] Kaplan W, Wirtz VJ, Mantel-Teeuwisse A, Stolk P, Duthey B, Laing R. Priority Medicines for Europe and the World 2013 Update; Geneva: World Health Organization (WHO); 2013.

[3] World Health Organization (WHO). Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research. Geneva: World Health Organization (WHO), 2015.

[4] Babar ZUD, Atif M. Differential pricing of pharmaceuticals: a bibliometric review of the literature. Journal of Pharmaceutical Health Services Research. 2014;5(3): 149-56.

[5] Lorenzoni L, Belloni A, Sassi F. Health-care expenditure and health policy in the USA versus other high-spending OECD countries. The Lancet. 2014;384(9937): 83-92.

[6] Karanikolos M, Mladovsky P, Cylus J, Thomson S, Basu S, Stuckler D, et al. Financial crisis, austerity, and health in Europe. The Lancet. 2013;381(9874): 1323-31.

[7] Kentikelenis A, Karanikolos M, Papanicolas I, Basu S, McKee M, Stuckler D. Health effects of financial crisis: omens of a Greek tragedy. The Lancet. 2011;378(9801): 1457-8.

[8] Leopold C, Mantel-Teeuwisse AK, Vogler S, Valkova S, de Joncheere K, Leufkens HG, et al. Effect of the economic recession on pharmaceutical policy and medicine sales in eight European countries. Bulletin of the World Health Organization. 2014;92(9): 630-40D.

[9] Leopold C, Zhang F, Mantel-Teeuwisse AK, Vogler S, Valkova S, Ross-Degnan D, et al. Impact of pharmaceutical policy interventions on utilization of antipsychotic medicines in Finland and Portugal in times of economic recession: interrupted time series analyses. International Journal for Equity in Health (JEH). 2014;13(1): 53.

[10] Simou E, Koutsogeorgou E. Effects of the economic crisis on health and healthcare in Greece in the literature from 2009 to 2013: a systematic review. Health policy. 2014;115(2): 111-9.

[11] Stuckler D, Basu S, Suhrcke M, Coutts A, McKee M. Effects of the 2008 recession on health: a first look at European data. The Lancet. 2011;378(9786): 124-5.

[12] OECD. Health Data. Paris: OECD, 2015.

[13] Karikios D, Schofield D, Salkeld G, Mann K, Trotman J, Stockler M. Rising cost of anticancer drugs in Australia. Internal medicine journal. 2014;44(5): 458-63.

[14] Kelly R, Smith T. Delivering maximum clinical benefit at an affordable price: engaging stakeholders in cancer care. The lancet oncology. 2014;15(3): e112-e8.

[15] European Health Forum Gastein. Key Outcomoes of the EHFG 2015: Securing Health in Europe - Balancing Priorities, sharing responsibilities (available under

http://www.ehfg.org/fileadmin/ehfg/Programm/2015/EHFG_Gastein_Health_Outcomes_2015.pdf). 2015.

[16] Vogler S, Zimmermann N, Babar ZUD. Abstracts from the 3rd International PPRI Conference 2015: Pharmaceutical Pricing and Reimbursement Policies: Challenges Beyond the Financial Crisis. Journal of Pharmaceutical Policy and Practice. 2015;8.

[17] Vogler S, Kilpatrick K, Babar ZUD. Analysis of Medicine Prices in New Zealand and 16 European Countries. Value in Health. 2015;18(4): 484-492.

[18] Vogler S, Vitry A, Babar Z-U-D. Cancer drugs in 16 European countries, Australia, and New Zealand: a cross-country price comparison study. The lancet oncology. 2015 (published online first: 3 December 2015).

[19] Europe Economics. External Reference Pricing. London: Europe Economics, 2013.

[20] Konijn P. Pharmaceutical products-comparative price levels in 33 European countries in 2005. Statistics in focus: Economy and finance. 2007;45: 1977-0316.

[21] Leopold C, Mantel-Teeuwisse AK, Seyfang L, Vogler S, de Joncheere K, Laing RO, et al. Impact of External Price Referencing on Medicine Prices-A Price Comparison Among 14 European Countries. Southern Med Review. 2012;5(1).

[22] Leopold C, Mantel-Teeuwisse AK, Vogler S, de Joncheere K, Laing RO, Leufkens HGM. 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: 209-16.

[23] Vogler S. How large are the differences between originator and generic prices? Analysis of five molecules in 16 European countries. Farmeconomia Health economics and therapeutic pathways. 2012;13 (Suppl 3): 29-41.

[24] European Communities. High Level Pharmaceutical Forum 2005-2008. Conclusions and Recommendations. European Commission, Directorate-General Health & Consumers and Entreprise and Industry. 2008.

[25] WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies. Glossary of pharmaceutical terms. Update 2013. Vienna 2013.

[26] Council Directive 89/105/EEC 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.

[27] Vogler S, Martikainen JE. Pharmaceutical Pricing in Europe. Pharmaceutical Prices in the 21st Century: Springer; 2015. p. 343-70.

[28] Espin J, Rovira J, de Labry AO. Working paper 1: External price referencing - review series on pharmaceutical pricing policies and interventions. Geneva: World Health Organization and Health Action International, 2011.

[29] 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.

[30] Bouvy J, Vogler S. Background Paper 8.3 Pricing and Reimbursement Policies: Impacts on Innovation. In: Organization WH, Ed. Priority Medicines for Europe and the World "A Public Health Approach to Innovation" Update on 2004 Background Paper. 2013.

[31] World Health Organization. WHO Guideline on Country Pharmaceutical Pricing Policies. Geneva, 2013.

[32] Brekke KR, Dalen DM, Strøm S. Should pharmaceutical costs be curbed?; 2012.

[33] Håkonsen H, Horn AM, Toverud E-L. Price control as a strategy for pharmaceutical cost containment—What has been achieved in Norway in the period 1994–2004? Health policy. 2009;90(2): 277–85.

[34] Merkur S, Mossialos E. A pricing policy towards the sourcing of cheaper drugs in Cyprus. Health policy. 2007;81(2): 368–75.

[35] Paris V, Belloni A. Value in Pharmaceutical Pricing. OECD Health Working Papers, No. 63. Paris: OECD Publishing, 2013.

[36] Rovira J. Can EU citizens afford their medicines? The financial crisis and access to medicines in Europe. Presentation. High Level Meeting. 2013.

[37] EFPIA. Improving Patient Access to Innovative Medicines. The Framework in which Differentiated Pricing May Offer a Solution. European Federation of Pharmaceutical Industries and Associations (EFPIA). Brussels, 2014.

[38] Yadav P. Differential pricing of pharmaceuticals: Review of current knowledge, new findings and ideas for action. A study conducted for the UK Department for International Development (DFID). Zaragoza: MIT Zaragoza International Logistics Program, 2010.

[39] Simoens S. Sustainable Provision of Generic Medicines in Europe. Leuven, Netherlands: KU Leuven 2013.

[40] Vogler S. The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries—an overview. Generics and Biosimilars Initiative (GaBI) Journal. 2012;1(2): 93–100.

[41] European Commission. Communication from the Commission: On effective, accessible and resilient health systems. Brussels: European Commission; 2014.

[42] European Commission. Council conclusions on the "Reflection process on modern, responsive and sustainable health systems". Employment, Social Policy, Health and Consumers Affairs. Council meeting. Brussels, 10 December 2013.

[43] European Commission. Council conclusions on the economic crisis and healthcare. Brussels; 2014.

[44] European Commission. Council conclusions on innovation for the benefit of patients. Brussels, 2014.

[45] Toumi M, Rémuzat C, Vataire A-L, Urbinati D. External reference pricing of medicinal products: simulation-based considerations for cross-country coordination. Final Report. European Commission, 2014.

[46] Vogler S, Zimmermann N, Habimana K. Study of the policy mix for the reimbursement of medicinal products. Proposal for a best practice-based approach based on stakeholder assessment. Gesundheit Österreich Forschungs- und Planungs GmbH and Sogeti (commissioned by the European Commission). 2014.

[47] Gambardella A, Orsenigo L, Pammolli F, Lacetera N, Magazzini L, Mariani M, et al. Global competitiveness in pharmaceuticals, a European perspective. Report prepared for the Directorate General Enterprise of the European Commission. 2000.

[48] European Commission. High Level Group on innovation and provision of medicines-recommendations for action. Brussels, 2002.

[49] European Commission. Communication from the Commission to the Council, the European Parliament, the Economic and Social Committee and the Committee of the Regions - A Stronger European-based Pharmaceutical Industry for the Benefit of the Patient - A Call for Action Brussels; 2003.

[50] European Commission. Better access to medicines for patients in Europe. Brussels; 18 April 2013.

[51] European Commission DG Entreprise. Call for Proposals - DG ENTR NO ENT GWP 2008 1.2.7.4. Pricing and Reimbursement of medicinal products in EU. Available from: http://www.ueonline.it/networking/uploadorig/27133_orig.pdf. 2008.

[52] Kanavos P, Nicod E, Espin J. Short-and Long-Term Effects of Value-Based Pricing versus External Price Referencing. 2010.

[53] European Commission Enterprise and Industry Directorate-General. Development of a database on pricing of medicinal products in the EU. Call for proposal. ACTION ENT/IMA/1.1.10.3.8. Brussels 2009.

[54] European Parliament. European Parliament legislative resolution of 6 February 2013 on the 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. Brussels; 2013.

[55] Sion J-L, Kolowca M. Joint Procurement of medical countermeasures: Workshop Joint Procurement for pandemic vaccines. Luxembourg; 2015.

[56] European Commission. Pharmaceutical Industry: A strategic sector for the European Economy. Brussels: European Commission; 2014.

[57] Eichler HG, Baird LG, Barker R, Bloechl-Daum B, Børlum-Kristensen F, Brown J, et al. From adaptive licensing to adaptive pathways: Delivering a flexible life-span approach to bring new drugs to patients. Clinical Pharmacology & Therapeutics. 2015;97(3): 234-46.

[58] European Medicines Agency. Adaptive pathways: a future approach to bring new medicines to patients?: European Medicines Agency (EMA); 2014.

[59] European Commission. Safe and Timely Access to Medicines for Patients (STAMP); Presentation for the EC Expert group; Available under (http://ec.europa.eu/health/technology_assessment/docs/ev_20150323_co08_en.pdf). 2015.

[60] Record from the 1st STAMP Commission Expert Group meeting, (2015).

[61] Pan American Health Organization (PAHO). Access to High-Cost medicines in the Americas: Situation, Challenges and Perspective. Technical Series No. 1. Essential Medicines, Access and Innovation. Washington, D.C.: Pan American Health Organization, 2010.

[62] Kaplan W, Laing R. Priority Medicines for Europe and the World; Geneve: World Health Organization, Essential Drugs and Medicines Policy.; 2004.

[63] Henry D, Lang D, Hill S. Background Paper 8.2 Approach to the Valuation and Pricing of Future Medicines. In: Priority Medicines for Europe and the World "A Public Health Approach to Innovation", Ed. World Health Organization (WHO), 2004.

[64] OECD. Pharmaceutical Pricing Policies in a Global Market. Paris: OECD, 2008.

[65] Kaplan W, Laing R. Priority Medicines for Europe and the World. Geneva: World Health Organization (WHO); 2004. p. 134.

[66] European Commission. Joint Report on Health Systems. European Economy, Occassional Papers 74. Brussels: European Commission; 2010.

[67] Toumi M, Rémuzat C. EU Pharmaceutical expenditure forecast. Paris: Creativ_Ceutical, 2012.

[68] Vogler S, Schneider P. Vergütung der Arzneimitteldistribution in den europäischen Ländern. Vienna: Gesundheit Österreich Forschung und Planung GmbH (GÖ FP), 2015 (unpublished).

[69] Riesenhuber K. Europäische Methodenlehre: Handbuch für Ausbildung und Praxis: Walter de Gruyter GmbH & Co KG; 2014.

[70] Gestel R, Micklitz HW. Why Methods Matter in European Legal Scholarship. European Law Journal. 2014;20(3): 292-316.

[71] Hervey T, Cryer R, Sokhi-Bulley B, Bohm A. Research methodologies in EU and international law: Bloomsbury Publishing; 2011.

[72] Ognyanova D, Zentner A, Busse R. Pharmaceutical reform 2010 in Germany. Eurohealth. 2011;17(1): 11-3.

[73] GKV Spitzenverband. Rahmenvereinbarung nach §130b Abs. 9 SGB V zwischen dem GKV Spitzenverband und der Verbänden der pharmazeutischen Unternehmer. 2012.

[74] Filko M, Szilagyiova P. The Slovak experience in the international price benchmarking for prescription drugs. Value in Health. 2009;12 (7): A229-A30.

[75] Windmeijer F, De Laat E, Douven R, Mot E. Pharmaceutical promotion and GP prescription behaviour. Health economics. 2006;15(1): 5-18.

[76] Stargardt T, Schreyögg J. Impact of Cross-Reference Pricing on Pharmaceutical Prices. Applied Health Economics and Health Policy. 2006;5(4): 235-47.

[77] Rosian I, Habl C, Vogler S. Pharmaceuticals Market Control in Nine European Countries. Vienna: Österreichisches Bundesinstitut für Gesundheitswesen (ÖBIG), 1998.

[78] Gandjour A. Reference pricing and price negotiations for innovative new drugs : viable policies in the long term? Pharmacoeconomics. 2013;31(1): 11-4.

[79] Danzon PM. Price Discrimination for Pharmaceuticals: Welfare Effects in the US and the EU. International Journal of the Economics of Business. 1997;4(3): 301-21.

[80] Danzon PM, Epstein AJ. Effects of regulation on drug launch and pricing in interdependent markets. Advances in Health Economics & Health Services Research. 2012;23: 35-71.

[81] Danzon PM, Towse A. Differential pricing for pharmaceuticals: reconciling access, R&D and patents. International Journal of Health Care Finance & Economics. 2003;3(3): 183-205.

[82] Kyle MK. Pharmaceutical price controls and entry strategies. The Review of Economics and Statistics. 2007;89(1): 88-99.

[83] De Weerdt E, Simoens S, Hombroeckx L, Casteels M, Huys I. Causes of drug shortages in the legal pharmaceutical framework. Regulatory Toxicology and Pharmacology. 2015;71(2): 251-8.

[84] PGEU. PGEU Statement on Medicine Shortages in European Community Pharmacies. 2013.

[85] Italian Antitrust Authority. Decision of the case between Aspen Pharma Trading Limited vs Altroconsumo. Rome: Italian Antitrust Authoritiy; 2014.

[86] Gray A, Manasse Jr HR. Shortages of medicines: a complex global challenge. Bulletin of the World Health Organization. 2012;90(3).

[87] Vogler S, Zimmermann N, Habl C, Piessnegger J, Bucsics A. Discounts and rebates granted to public payers for medicines in European countries. Southern Med Review. 2012;5(1): 38-46.

[88] Robertson J, Walkom EJ, Henry DA. Transparency in pricing arrangements for medicines listed on the Australian Pharmaceutical Benefits Scheme. Australian health review. 2009;33(2): 192-9.

[89] Kanavos P, Vandoros S, Irwin R, Nicod E, Casson M. Differences in costs of and access to pharmaceutical products in the EU. Brussels: European Parliament, 2011.

[90] 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. 2010.

[91] Cambridge Pharma Consultancy. Pricing & Reimbursement Review 2003. Cambridge, 2003.

[92] European Commission. European Competitiveness Report. Economic Reforms and Competitiveness. Brussels; 2006.

[93] Kanavos PG, Vandoros S. Determinants of branded prescription medicine prices in OECD countries. Health Economics Policy and Law. 2011;6(3): 337.

[94] Kanavos P, Costa-Font J. Pharmaceutical Parallel Trade in Europe: Stakeholder and Competition Effects. Economic Policy. 2005(44): 751.

[95] Kyle MK, Allsbrook JS, Schulman KA. Does Reimportation Reduce Price Differences for Prescription Drugs? Lessons from the European Union. Health Services Research. 2008;43(4): 1308-24.

[96] Cabiedes Miragaya L. Nuevas perspectivas sobre el precio de los medicamentos: El caso espanol. Estudios de Economia Aplicada. 2013;31(2): 397-415.

[97] Franken M, Nilsson F, Sandmann F, de Boer A, Koopmanschap M. Unravelling drug reimbursement outcomes: a comparative study of the role of pharmacoeconomic evidence in Dutch and Swedish reimbursement decision making. Pharmacoeconomics. 2013;31(9): 781-97.

[98] Iskrov G, Miteva-Katrandzhieva T, Stefanov R. Challenges to orphan drugs access in Eastern Europe: the case of Bulgaria. Health policy. 2012;108(1): 10-8.

[99] Iskrov GG, Raycheva RD, Stefanov RS. Insight into reimbursement decision-making criteria in Bulgaria: implications for orphan drugs. Folia Medica (Plovdiv). 2013;55(3-4): 80-6.

[100] Lopert R, Ruiz F, Chalkidou K. Applying rapid 'de-facto' HTA in resource-limited settings: experience from Romania. Health policy. 2013;112(3): 202-8.

[101] Danzon P, Towse A, Mestre-Ferrandiz J. Value-based differential pricing: efficient prices for drugs in a global context. Health economics. 2015;24(3): 294-301.

[102] Danzon PM. The economics of parallel trade. Pharmacoeconomics. 1998;13(3): 293-304.

[103] Kalo Z, Annemans L, Garrison LP. Differential pricing of new pharmaceuticals in lower income European countries. Expert Review of Pharmacoeconomics & Outcomes Research. 2013;13(6): 735-41.

[104] Perez-Casas C, Herranz E, Ford N. Pricing of drugs and donations: options for sustainable equity pricing. Tropical Medicine & International Health. 2001;6(11): 960-4.

[105] Kindermans JM, Matthys F. Introductory note: The access to essential medicines campaign. Tropical Medicine & International Health. 2001;6(11): 955-6.

[106] Eurostat. Eurostat Health Database http://ec.europa.eu/eurostat/web/health/health-care/data/database. 2015.

[107] Moon S, Jambert E, Childs M, von Schoen-Angerer T. A win-win solution?: A critical analysis of tiered pricing to improve access to medicines in developing countries. Online] Globalization and Health. 2011;7: 39.

[108] Plahte J. Tiered pricing of vaccines: a win-win-win situation, not a subsidy. The Lancet infectious diseases. 2005;5(1): 58-63.

[109] Ramsey FP. A Contribution to the Theory of Taxation. The Economic Journal. 1927: 47-61.

[110] T'Hoen E, Moon S. Pills and pocketbooks. Equity pricing of essential medicines. 2001: 4-5.

[111] Mossialos E, Dukes G. Affordably priced new drugs for poor populations: Approaches for a global solution. International Journal of Risk & Safety in Medicine. 2001;14(1): 1-29.

[112] Grace C. Equitable Pricing of Newer Essential Medicines for Developing Countries: Evidence of the Potential of Different Mechanisms. London: London Business School. 2003: 1-70.

[113] Shepherd WG. Ramsey pricing: Its uses and limits. Utilities Policy. 1992;2(4): 296-8.

[114] Towse A, Pistollato M, Mestre-Ferrandiz J, Khan Z, Kaura S, Garrison L. European Union Pharmaceutical Markets: A Case for Differential Pricing? International Journal of the Economics of Business. 2015;22(2): 263-75.

[115] Sun H, 孙赫. Differential pricing strategy in improving access to medicine in developing countries: The University of Hong Kong (Pokfulam, Hong Kong); 2012.

[116] Lang D, Hill S. Differential Pricing of Pharmaceuticals: What about the rest of the world. University of Newcastle, Australia; 2004.

[117] World Health Organization, World Trade Organization. Differential Pricing and the Financing of Essential Drugs. In: Granville B, Ed. The economics of essential medicines: London: Royal Institute of Economic Affairs, International Economics Programme; distributed by the Brookings Institution, Washington, D.C.; 2002. p. 209-31.

[118] 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. The Lancet. 2009;373(9659): 240-9.

[119] Mackay B. Summary Report of Industry Government Forum on Access to Medicines. Centre DHR. London, 2009.

[120] Waning B, Kaplan W, King AC, Lawrence DA, Leufkens HG, Fox MP. Global strategies to reduce the price of antiretroviral medicines: evidence from transactional databases. Bulletin of the World Health Organization. 2009;87(7): 520-8.

[121] Balasegaram M. Is tiered pricing the way for vaccines? Lancet. 2014;384(9946): 852.

[122] Hammer PJ. Differential Pricing of Essential AIDS Drugs: Markets, Politics and Public Health. Journal of International Economic Law. 2002;5(4): 883-912.

[123] Light DW, Warburton R. Demythologizing the high costs of pharmaceutical research. BioSocieties. 2011;6(1): 34-50.

[124] DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. Journal of health economics. 2003;22(2): 151-85.

[125] Kantarjian HM, Fojo T, Mathisen M, Zwelling LA. Cancer drugs in the United States: Justum Pretium—the just price. Journal of Clinical Oncology. 2013;31(28): 3600-4.

[126] Berkley S. Improving access to vaccines through tiered pricing. Lancet. 2014;383(9936): 2265-7.

[127] Children's Vaccine Initiative (CVI). Report of the Sixth Meeting of the Management Advisory Committee (MAC). London, 1994.

[128] Kyle M. Strategic responses to parallel trade. The BE Journal of Economic Analysis & Policy. 2011;11(2).

[129] European Commission. Report from the Commission Annual Report (2010-2011) on the application of Council Regulation (EC) No 953/2003 of 26 May 2003 to avoid trade diversion into the European Union of certain key medicines. 2012.

[130] Lopert R, Lang DL, Hill SR, Henry DA. Differential pricing of drugs: a role for cost-effectiveness analysis? Lancet. 2002;359(9323): 2105-7.

[131] Ball D. Working paper 3: Regulation of mark-ups in the pharmaceutical supply chain - review series on pharmaceutical pricing policies and interventions. Geneva: World Health Organization and Health Action International, 2011.

[132] Creese A. Sales Taxes on Medicines. Working Paper 5, WHO/HAI Project on Medicine Prices and Availablility, 2011.

[133] Otero Garcia-Castrillon C. El acceso a los medicamentos: Las patentes y el Acuerdo sobre los Derechos de Propiedad Intelectual Relacionados con el Comercio. Informacion Comercial Espanola Revista de Economia. 2003(804): 197-217.

[134] World Trade Organisation (WTO). Agreement on Trade-Related Aspects of Intellectual Property Rights. Signed in Marrakesh, Morocco on 15 April 1994; 1994.

[135] Global Health Progress. Novo Nordisk: Differential Pricing on Insulin. Available from: http://www.globalhealthprogress.org/programs/novo-nordisk-differential-pricing-insulin. 2015.

[136] Kaul I. New Ways of Financing the Millennium Development Goals. Prepared for a Seminar Co-Organized by Agence Française de Développement (AfD), Institut du Développement Durable et des Relations Internationals (Iddri) and UNDP, 22 January 2004. Paris; 2004.

[137] Kanavos P, Costa-i-Font J, Merkur S, Gemmill M. The economic impact of pharmaceutical parallel trade in European Union member states: A stakeholder analysis: London School of Economics and Political Science London; 2004.

[138] West P, Mahon J, Consortium YHE. Benefits to payers and patients from parallel trade: York Health Economics Consortium; 2003.

[139] Ganslandt M, Maskus KE. Parallel imports and the pricing of pharmaceutical products: evidence from the European Union. Journal of health economics. 2004;23(5): 1035-57.

[140] Forrester IS, Dawes A. Parallel Trade in Prescription Medicines in the European Union: The Age of Reason? Yearbook of Antitrust and Regulatory Studies. 2008;1(1): 9.

[141] European Commission. Council Regulation (EC) No 953/2003 of 26 May 2003 to avoid trade diversion into the European Union of certain key medicines. Official Journal of the European Union. 2003.

[142] European Commission. Access to medicines: EU clears plan to ensure delivery of cheap medicines to developing countries 2003.

[143] Charles River Association. Evaluation of council regulation (EC) 953/2003 to avoid trade diversion into the European Union of certain key medicines; A draft report prepared for a stakeholder workshop at 17th of July. 2015.

[144] Knowledge Ecology International (KEI). Recent examples of the use of compulsory licenses on patents. KEI Research Note 2; 2007.

[145] European Commission. Minutes of the meeting of the Joint Procurement Agreement Steering Committee held in Luxembourg on 9 and 10 July 2015 (unpublished). 2015.

[146] European Commission. Medical Countermeasures that could be procured in common under the joint procurement agreement. Luxembourg; 2014.

[147] Danzon PM, Furukawa MF. Prices and availability of pharmaceuticals: evidence from nine countries. Health Affairs. 2003: W3-521.

[148] Danzon PM, Furukawa MF. International prices and availability of pharmaceuticals in 2005. Health Affairs. 2008;27(1): 221-33.

[149] European Commission. Written Question E-2545/97 by Mihail Papayannakis (GUE/NGL) to the Commission. Official Journal of the European Communities. 1997.

[150] European Commission DG Entreprise. Call for Proposals - Development of a database on the pricing of medicinal products in the EU. Grant Programme 2009. Available from: http://ec.europa.eu/DocsRoom/documents/2790/attachments/1/translations/en/renditions/pdf.; 2009.

[151] EURIPID. An Introduction to the EURIPID Collaboration. A Presentation at the Workshop with EFPIA. Brussels; 2014.

[152] EURIPID. Presentation of the proposal of EURIPID Collaboration for DG SANCO call on Statistical data for medicinal product pricing. Presentation for the Workshop with EFPIA. Brussels; 2014.

[153] EURIPID. The EURIPID project: Added value to the European Commission, Member States and European citizens (not published). Budapest; 2013.

[154] ESIP, AIM. Review of Council Directive 89/105/EEC 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 (Transparency Directive). Joint Position Paper. Submitted 10 February 2011. 2011.

[155] 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.

[156] Vogler S, Zimmermann N, Leopold C, Schmickl B, Windisch F. Impact of medicines price reductions in Greece and Spain on other European countries applying external price

referencing. Poster. Drug Utilisation and Health Policy Meeting; 30.05.2012; Antwerp: EuroDURG 2011.

[157] European Commission. Proposal for a regulation of the European Parliament and of the Council to avoid trade diversion into the European Union of certain key medicines (codification). Brussels; 2014.

[158] Hughes-Wilson W, Palma A, Schuurman A, Simoens S. Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments. Orphanet J Rare Dis. 2012;7(1): 74.

Annex

Table of Contents

List of tables

List of figures

1 Annex 1: Literature review – Methodological specifications

1.1 Search strategy

1.1.1 Overview of the search strategy

A systematic structured literature review was conducted to identify and characterise the use of external price referencing (EPR), to describe its impacts on the prices of pharmaceuticals and to discuss the possible cross-country coordination issues in the EU Member states and in the other countries cited in the scope of the project.

A systematic structured literature search on EPR was conducted to evaluate the use of EPR and its impacts on the prices of pharmaceuticals. The search strategy followed Toumi M, Rémuzat C, Vataire A-L and Urbinati D [1] since the tender specifications required the literature review on EPR to be incremental to that study. The scope of the search was external price referencing (not internal price referencing) for medicines (except vaccines) in the 28 Member states of the European Union (EU), Norway, Switzerland, Turkey and Iceland. As an incremental literature search to EPR, the period was restricted to the period from December 2012 till January 2015. In contrast to, the systematic literature search on differential pricing (DP) was not restricted to any country, and it covered the period from January 1997 till January 2015. In both searches, studies in English, German, French Spanish and Italian language were considered.

In order to conduct an adequate incremental systematic literature review the same international databases were searched:

- Medline® (searched on the OVID website)
- EMBASE® (searched on the OVID website)
- EconLit

Additionally, a thorough hand search was conducted including a systematically search on the internet, the reference lists of the identified studies and on websites of the international organisations e.g. EU, World Health Organization (WHO), Organisation for economic co-operation and development (OECD), and networks for relevant literature. The literature review as completed by a search in Gesundheit Österreich Forschungs- und Planungs GmbH (GÖ FP) internal information and reports, when relevant.

Screening and selection of the abstracts and full texts was based on criteria defined ex-ante, which are depicted in Table A1 and Table A2. The selection of the studies was subdivided into the first selection of publications and the second selection of full texts, both of which are described below.

1.1.2 Results of the search strategy

The incremental literature search for EPR retrieved 867 records in Embase, 847 in Medline and 71 records in EconLit, adding up to a total of 1,785. 670 duplicates were removed, leaving a total of 1,115 titles and abstracts that were reviewed. Out of the 1,115 abstracts that were reviewed, 66 were included and 1,049 were excluded. Of the 66 papers ordered for full paper review, 2 papers were not available. 35 papers were included for the data extraction, and 29 papers were excluded. The hand search in Google Scholar and other databases retrieved 10 publications which were included, yielding 45 publications for EPR. Search strategy results are summarised in Figure A1.

The literature search for DP retrieved 449 records in Embase, 138 records in Medline and 214 records in EconLit, adding up to a total of 801. 149 duplicates were removed, leaving a total of 652 titles and abstracts that were reviewed. Out of the 652 abstracts that were reviewed, 59 were included and 593 were excluded. Of the 59 papers ordered for full paper review, 1 paper was not available. 49 papers were included for the data extraction, and 9 papers were excluded. The hand search in Google Scholar and other databases retrieved 7 publications which were included, yielding 56 publications for EPR. Search strategy results are summarised in Figure A2.

1.2 Selection criteria

Table A1 and Table A2 specify the selection criteria applied in the literature review for EPR and DP.

Table A1: Selection criteria (abstracts and full texts) for EPR

Exclusion criteria	
Formal criteria	
E1	Papers published before 01/12/2012
E2	Duplicates
E3	Study is not published in a language listed in the inclusion criteria
E4	Countries which are not listed in the inclusion criteria
Contextual criteria	
E5	Internal Reference Pricing
E6	Devices/Services
E7	Vaccines
E8	Studies related to Diagnostic/Epidemiology/Treatment
E9	Not related to pharmaceutical pricing/Study is not relevant for EPR
E10	Subject of the study is related to alcohol/drinking
E11	Subject of the study is related to tobacco/cigarettes/smoking
E12	Subject of the study is related to food/nutrition
E13	Subject of the study is related to environment/nature
E14	Theoretical/Formal modelling
E15	Subject of the study is related to illegal/illicit drugs
Inclusion criteria	
I1	All Pharmaceutical products
I2	External Reference Pricing
I3	28 Member states of the EU
I4	Switzerland, Turkey, Norway, Switzerland
I5	Papers in the following languages: English, Italian, French, Spanish, German
I6	Papers published from December 2012 to current

Source: Authors

Table A2: Selection criteria (abstracts and full texts) for DP

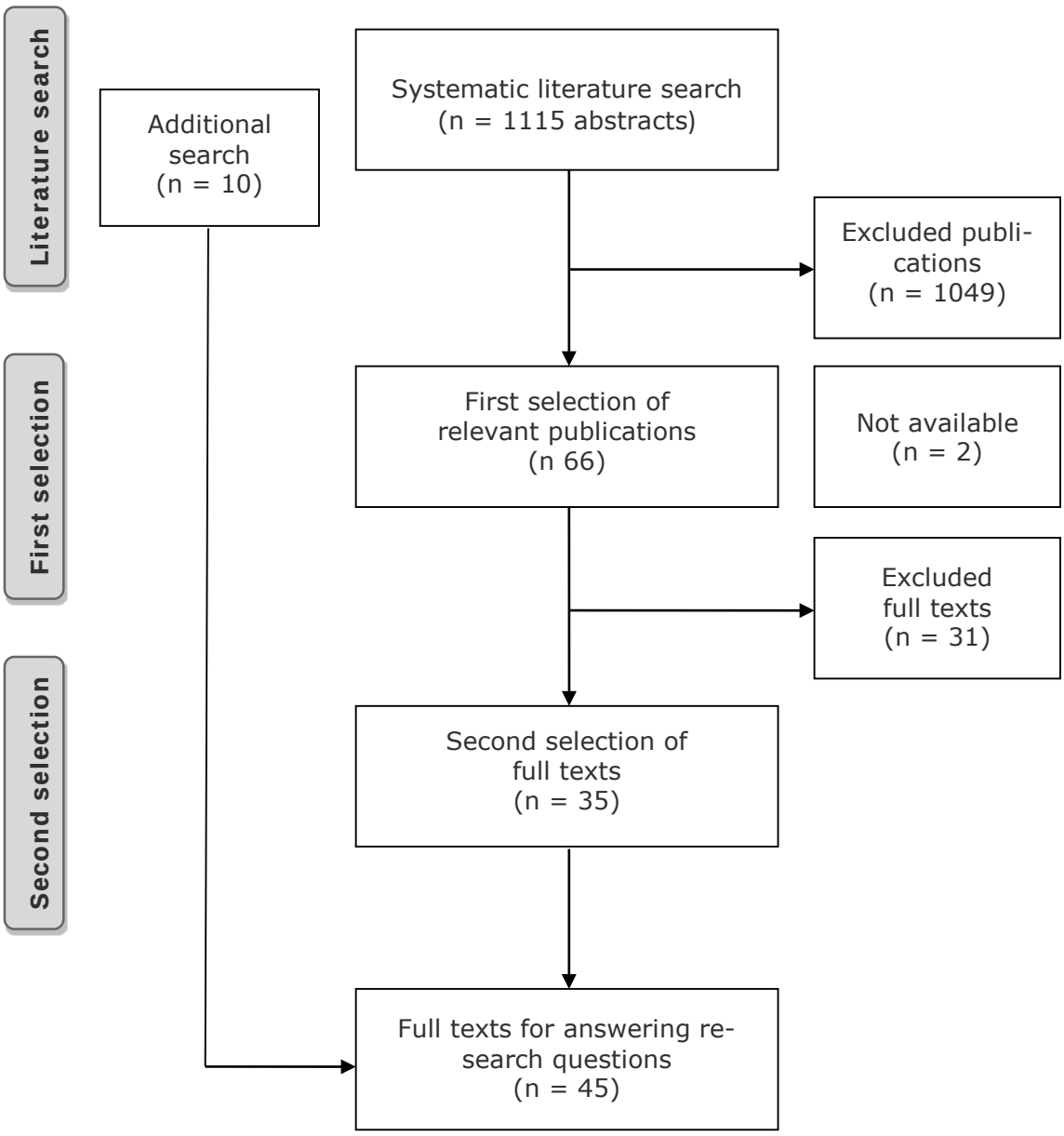
	Exclusion criteria
Formal criteria	
E1	Papers published before 01/01/1997
E2	Duplicates
E3	Study is not published in a language listed in the inclusion criteria
E4	Abstract is not based on a study / Newspaper article / Newsletter / Press release / Poster
Contextual criteria	
E5	Internal Reference Pricing
E6	External Reference Pricing
E7	Devices/Services
E8	Studies related to epidemiology/diagnostic/treatment of diseases
E9	Study is not relevant for DP
E10	Subject of the study is related to alcohol/drinking
E11	Subject of the study is related to cigarettes/tobacco/smoking
E12	Subject of the study is related to food/nutrition
E13	Subject of the study is related to Environment/Nature
E14	Subject of the study is related to illegal/illicit drugs
	Inclusion criteria
I1	All Pharmaceutical products
I2	All countries with relevant experience in DP
I3	Papers in the following languages: English, Italian, French, Spanish, German
I4	Papers published from January 1997 to current

Source: Authors

1.3 Selection process

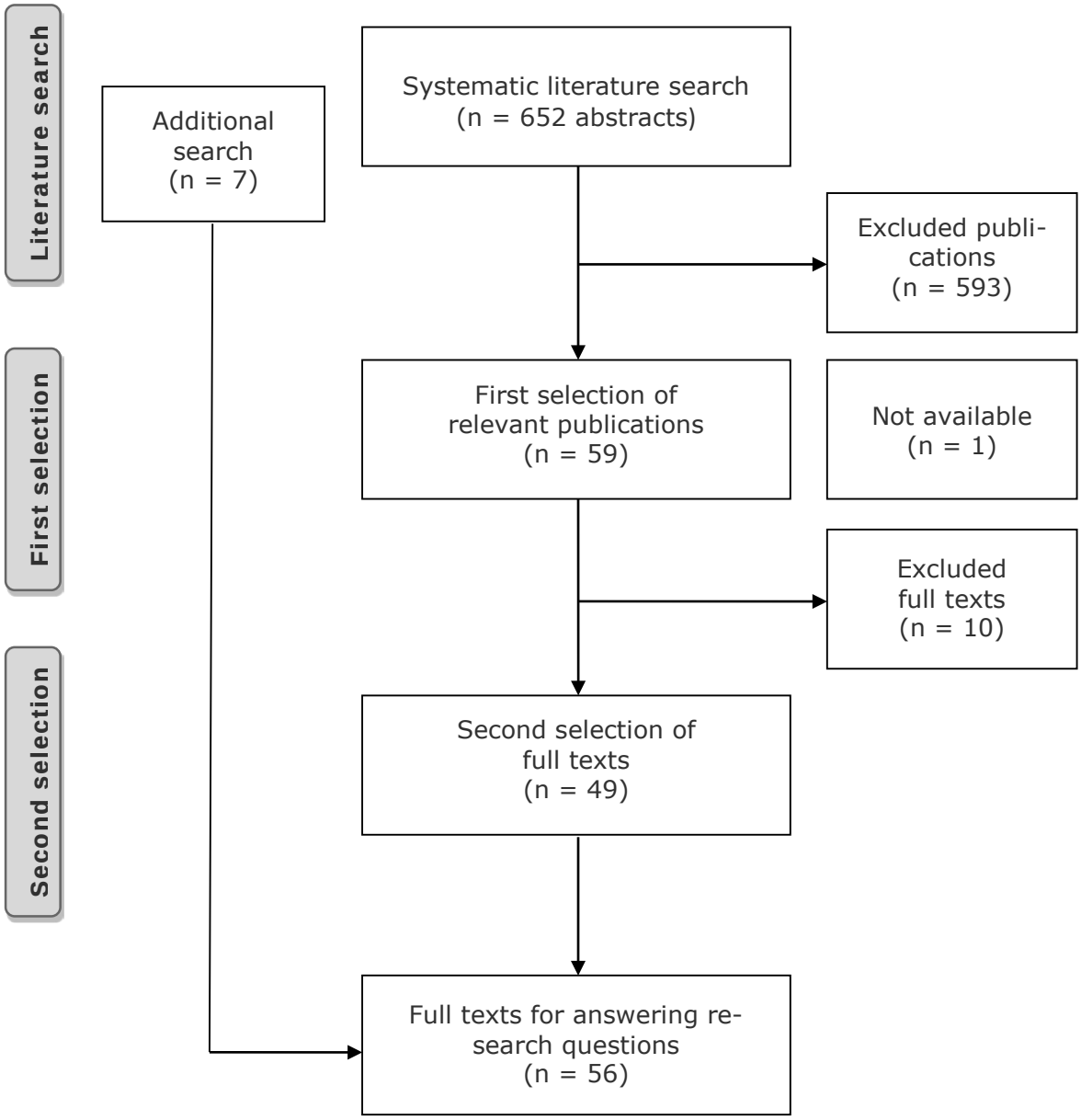
Figure A1 and Figure A2 illustrate the selection processes for literature related to EPR and DP.

Figure A1: Graphical illustration of the selection process for literature related to EPR



Source: Illustration by authors

Figure A2: Graphical illustration of the selection literature related to DP



Source: Illustration by authors

1.4 Analysis of literature

When reading the full texts, relevant information was collected and documented in a literature matrix.

For all references, it was reported:

- Reference (Authors, Title, Journal/source, date of publication)
- Language of the full article/report
- Abstract
- Countries to which the pricing policy was applied to
- Year of reference
- The policy mentioned in the article (EPR, DP, other policies)
- Study design

- Further/Background Information

For literature related to EPR, the following information was reported:

- whether an impact assessment and experiences on EPR were available in terms of savings to public budgets, patient access to medicines, reward for innovation or others
- country specific features of EPR (Number of countries in the basket, Countries in the basket, Medicines covered by EPR, price type which is taken into account for EPR, Calculation method, Evaluation, Changes in EPR
- Suggestion for best practice or improvements
- Further/Background Information

For literature related to DP, the following information was reported:

- whether an impact assessment and experiences on DP were available in terms of savings for public budgets, patient access to medicines, reward for innovation or others
- country specific features of DP (International or national legal framework, purchaser, medicines covered, specific examples of products or companies)
- Hurdles in implementation
- Suggestion for best practice or improvements
- Further/Background Information

2 Annex 2: Literature review – Included references

Anonymous (2001): Differential pricing of essential drugs. In: Pan American Journal of Public Health 9/4:275-279

Babar, Z. U. D.; Atif, M. (2014): Differential pricing of pharmaceuticals: A bibliometric review of the literature. In: Journal of Pharmaceutical Health Services Research 5/3:149-156

Balasegaram, M. (2014): Is tiered pricing the way for vaccines? In: Lancet 384/9946:852

Barros, P. P.; Martinez-Giralt, X. (2008): On international cost-sharing of pharmaceutical R&D. In: International Journal of Health Care Finance & Economics 8/4:301-312

Barton, J. H.; Emanuel, E. J. (2005): The patents-based pharmaceutical development process: rationale, problems, and potential reforms. In: JAMA 294/16:2075-2082

Berkley, S. (2014): Improving access to vaccines through tiered pricing. In: Lancet 383/9936:2265-2267

Bloom, D. E. (2000): Something to be done: treating HIV/AIDS. River Path Associates. In: Science 288/5474:2171-2173

Brick, A.; Gorecki, P. K.; Nolan, A. (2013): Usage of generics in Ireland: Recent trends and policy developments. In: Journal of Generic Medicines 10/2:72-85

Calmy, A.; Hirschel, B. (2003): Antiretroviral drugs in developing countries: Myth or reality?. [French]. In: Medecine et Hygiene 61/2431:725-730

Children's Vaccine Initiative (CVI) (1994): Report of the Sixth Meeting of the Management Advisory Committee (MAC), London

Class, J. N. (2012): Emerging markets and differential pricing policies: A question of global health? In: Journal of Commercial Biotechnology 18/4:40-43

Cockburn, I; Lanjouw, J. O.; Schankerman, M. (2014): Patents and the Global Diffusion of New Drugs. Centre for Economic Performance, LSE, CEP Discussion Papers

Costa-Font, J.; McGuire, A.; Varol, N. (2014): Price regulation and relative delays in generic drug adoption. In: Journal of Health Economics 38/1-9

Costa-i-Font, J.; Font Vilalta, M. (2005): Por un sistema de precios diferenciales de los medicamentos. (Medicines: Differential Prices and Globalization. With English summary.). In: Comercio Exterior 55/5:418-424

Daems, R.; Maes, E.; Glaetzer, C. (2013): Equity in pharmaceutical pricing and reimbursement: Crossing the income divide in Asia Pacific. In: Value in Health Regional Issues 2/1:160-166

Danzon, P.; Towse, A.; Mestre-Ferrandiz, J. (2015): Value-based differential pricing: efficient prices for drugs in a global context. In: Health Economics 24/3:294-301

Danzon, P. M. (1998): The economics of parallel trade. In: Pharmacoeconomics 13/3:293-304

Danzon, P. M.; Towse, A. (2003): Differential pricing for pharmaceuticals: reconciling access, R&D and patents. In: International Journal of Health Care Finance & Economics 3/3:183-205

Danzon, P. M.; Epstein, A. J. (2012): Effects of regulation on drug launch and pricing in interdependent markets. In: Advances in Health Economics & Health Services Research 23/35-71

Danzon, P. M. (1997): Price Discrimination for Pharmaceuticals: Welfare Effects in the US and the EU. In: International Journal of the Economics of Business 4/3:301-321

Darrow, J. J. (2011): Recent developments in health law. Essential medicines: why international price discrimination may increasingly be the wrong solution to a global drug problem. In: Journal of Law, Medicine & Ethics 39/2:291-296

Davies, J. E.; Neidle, S.; Taylor, D. G. (2012): Developing and paying for medicines for orphan indications in oncology: utilitarian regulation vs equitable care? In: British Journal of Cancer 106/1:14-17

Degrassat-Theas, A.; Paubel, P.; Parent de Curzon, O.; Le Pen, C.; Sinegre, M. (2013): Temporary authorization for use: does the French patient access programme for unlicensed medicines impact market access after formal licensing? In: Pharmacoeconomics 31/4:335-343

Ding, M.; Eliashberg, J.; Stremersch, S. eds (2014): Innovation and Marketing in the Pharmaceutical Industry: Emerging Practices, Research, and Policies. International Series in Quantitative Marketing. New York and Heidelberg: Springer,

Dranitsaris, G.; Truter, I.; Lubbe, M. (2011): The development of a value-based pricing index for new drugs in metastatic colorectal cancer. In: Journal of Clinical Oncology 1

Dubois, P.; Lasio, L. (2014): Identifying Industry Margins with Unobserved Price Constraints: Structural Estimation on Pharmaceuticals. C.E.P.R. Discussion Papers, CEPR Discussion Papers: 9881

Dunne, S.; Shannon, B.; Dunne, C.; Cullen, W. (2013): A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study. In: BMC Pharmacology & Toxicology 14/1

Espin, J.; Rovira, J.; de Labry, A. O. (2011): Working paper 1: External price referencing – review series on pharmaceutical pricing policies and interventions. World Health Organization and Health Action International, Geneva

Filko, M.; Szilagyiova, P. (2009): The Slovak experience in the international price benchmarking for prescription drugs. In: Value in Health 12 (7)/A229-A230

Formosa, T.; Adami, M. Z. (2012): Reference pricing for pharmaceuticals: A policy perspective. In: Journal of EuroMed Pharmacy2:4-6

Fraeyman, J.; Van Hal, G.; Godman, B.; Beutels, P. (2013): The potential influence of various initiatives to improve rational prescribing for proton pump inhibitors and statins in Belgium. In: Expert Review of Pharmacoeconomics & Outcomes Research 13/1:141-151

Franken, M.; Nilsson, F.; Sandmann, F.; de Boer, A.; Koopmanschap, M. (2013): Unravelling drug reimbursement outcomes: a comparative study of the role of pharmacoeconomic evidence in Dutch and Swedish reimbursement decision making. In: Pharmacoeconomics 31/9:781-797

Gandjour, A. (2013): Reference pricing and price negotiations for innovative new drugs : viable policies in the long term? In: Pharmacoeconomics 31/1:11-14

Gandjour, A.; Gafni, A.; Schlander, M. (2014): Determining the price for pharmaceuticals in Germany: comparing a shortcut for IQWiG's efficiency frontier method with the price set by the manufacturer for ticagrelor. In: Expert Review of Pharmacoeconomics & Outcomes Research 14/1:123-129

Glynn, D. (2000): Reimbursement for new health technologies. Breakthrough pharmaceuticals as a 20th century challenge. In: Pharmacoeconomics 18 Suppl 1/59-67

Grace, C. (2003): Equitable Pricing of Newer Essential Medicines for Developing Countries: Evidence of the Potential of Different Mechanisms. In: London: London Business School 1-70

Granville, B. ed (2002): The economics of essential medicines. London

Royal Institute of Economic Affairs, International Economics Programme; distributed by the Brookings Institution, Washington, D.C.,

Hammer, P. J. (2002): Differential Pricing of Essential AIDS Drugs: Markets, Politics and Public Health. In: Journal of International Economic Law 5/4:883-912

Hawkes, N. (2013): The government's drug pricing policy is falling apart messily. In: BMJ 346/f3634

Henry, D.; Lexchin, J. (2002): The pharmaceutical industry as a medicines provider. In: Lancet 360/9345:1590-1595

Henry, D.; Lang, D.; Hill, S. (2004): Background Paper 8.2 Approach to the Valuation and Pricing of Future Medicines. In: Priority Medicines for Europe and the World "A Public Health Approach to Innovation". Ed. by World Health Organization

Henschke, C.; Sundmacher, L.; Busse, R. (2013): Structural changes in the German pharmaceutical market: price setting mechanisms based on the early benefit evaluation. In: Health Policy 109/3:263-269

Horn, H.; Nink, K.; McGauran, N.; Wieseler, B. (2014): Early benefit assessment of new drugs in Germany - results from 2011 to 2012. In: Health Policy 116/2-3:147-153

Inotai, A.; Pekli, M.; Jona, G.; Nagy, O.; Remak, E.; Kalo, Z. (2012): Attempt to increase the transparency of fourth hurdle implementation in Central-Eastern European middle income countries: publication of the critical appraisal methodology. In: BMC Health Services Research 12/332

Iskrov, G.; Miteva-Katrandzhieva, T.; Stefanov, R. (2012): Challenges to orphan drugs access in Eastern Europe: the case of Bulgaria. In: Health Policy 108/1:10-18

Iskrov, G. G.; Raycheva, R. D.; Stefanov, R. S. (2013): Insight into reimbursement decision-making criteria in Bulgaria: implications for orphan drugs. In: Folia Medica (Plovdiv) 55/3-4:80-86

Jack, B.; Lanjouw, J. (2003): Financing Pharmaceutical Innovation: When Should Poor Countries Contribute? Georgetown University, Department of Economics, Working Papers

Jack, W.; Lanjouw, J. O. (2005): Financing Pharmaceutical Innovation: How Much Should Poor Countries Contribute? In: World Bank Economic Review 19/1:45-67

Kaier, K. (2013): The impact of pricing and patent expiration on demand for pharmaceuticals: an examination of the use of broad-spectrum antimicrobials. In: Health Economics, Policy, & Law 8/1:7-20

Kaiser, U.; Mendez, S. J.; Ronde, T.; Ullrich, H. (2014): Regulation of pharmaceutical prices: evidence from a reference price reform in Denmark. In: Journal of Health Economics 36/174-187

Kalo, Z.; Annemans, L.; Garrison, L. P. (2013): Differential pricing of new pharmaceuticals in lower income European countries. In: Expert Review of Pharmacoeconomics & Outcomes Research 13/6:735-741

Kanavos, P.; Costa-Font, J. (2005): Pharmaceutical Parallel Trade in Europe: Stakeholder and Competition Effects. In: Economic Policy44:751

Kanavos, P.; Nicod, E.; Espin, J. (2010): Short-and Long-Term Effects of Value-Based Pricing vs. External Price Referencing

Kolasa, K. (2014): Are pricing and reimbursement decision-making criteria aligned with public preferences regarding allocation principles in the Polish healthcare sector? In: Expert Review of Pharmacoeconomics & Outcomes Research 14/5:751-762

Kontoghiorghe, C. N.; Andreou, N.; Constantinou, K.; Kontoghiorghes, G. J. (2014): World health dilemmas: Orphan and rare diseases, orphan drugs and orphan patients. In: World Journal of Methodology 4/3:163-188

Kremer, M. (2002): Pharmaceuticals and the Developing World. In: Journal of Economic Perspectives 16/4:67-90

Lang, D.; Hill, S. (2004): Differential Pricing of Pharmaceuticals: What about the rest of the world.

Leopold, C.; Mantel-Teeuwisse, A. K.; Seyfang, L.; Vogler, S.; de Joncheere, K.; Laing, R. O.; Leufkens, H. (2012a): Impact of external price referencing on medicine prices - a price comparison among 14 European countries. In: Southern Med Review 5/2:34-41

Leopold, C.; Vogler, S.; Mantel-Teeuwisse, A. K.; de Joncheere, K.; Leufkens, H. G. M.; Laing, R. (2012b): Differences in external price referencing in Europe-A descriptive overview. In: Health Policy 104/1:50-60

Leopold, C.; Mantel-Teeuwisse, A. K.; Vogler, S.; de Joncheere, K.; Laing, R. O.; Leufkens, H. G. (2013): Is Europe still heading to a common price level for on-patent medicines? An exploratory study among 15 Western European countries. In: Health Policy 112/3:209-216

Leopold, C.; Mantel-Teeuwisse, A. K.; Vogler, S.; Valkova, S.; de Joncheere, K.; Leufkens, H. G. M.; Wagner, A. K.; Ross-Degnan, D.; Laing, R. (2014): Effect of the economic recession on pharmaceutical policy and medicine sales in eight European countries. In: Bulletin of the World Health Organization 92/9:630-640

Lichtenberg, F. R. (2010): Pharmaceutical Price Discrimination and Social Welfare. In: Capitalism and Society 5/1:

Lopert, R.; Lang, D. L.; Hill, S. R.; Henry, D. A. (2002): Differential pricing of drugs: a role for cost-effectiveness analysis? In: Lancet 359/9323:2105-2107

Lopert, R.; Ruiz, F.; Chalkidou, K. (2013): Applying rapid 'de-facto' HTA in resource-limited settings: experience from Romania. In: Health Policy 112/3:202-208

Lopez-Casasnovas, G.; Puig, J. (2000): Review of the Literature on Reference Pricing. Department of Economics and Business, Universitat Pompeu Fabra, Economics Working Papers

Madhi, S. A.; Levine, O. S.; Hajjeh, R.; Mansoor, O. D.; Cherian, T. (2008): Vaccines to prevent pneumonia and improve child survival. In: Bulletin of the World Health Organization 86/5:365-372

Mateev, N. D.; Manova, M. M.; Petrova, G. I. (2013): Analysis of the changes in pricing regulation on leading analgesics medicines prices and utilization in Bulgaria. In: International Journal of Pharmaceutical Sciences and Research 4/1:231-236

Milstien, J. B.; Batson, A. (1998): Accelerating availability of new vaccines: The role of the international community. In: Drug Information Journal 32/1:175-182

Miraldo, M. (2009): Reference Pricing and Firms' Pricing Strategies. In: Journal of Health Economics 28/1:176-197

Moatti, J. P.; Ventelou, B. (2009): Economie de la sante dans les pays en developpement des paradigmes en mutation. (Health Economics in Developing Countries: The Changing Paradigms. With English summary.). In: Revue Economique 60/2:241-256

Moon, S.; Jambert, E.; Childs, M.; von Schoen-Angerer, T. (2011): A win-win solution?: A critical analysis of tiered pricing to improve access to medicines in developing countries. In: Global Health 7/39

Mossialos, E.; Dukes, G. (2001): Affordably priced new drugs for poor populations: Approaches for a global solution. In: International Journal of Risk & Safety in Medicine 14/1:1-29

Mrazek, M. F. (2002): Pharmaceutical Pricing in the Developing Worlds: Issues of Access to Medicines. In: Expert Review of Pharmacoeconomics and Outcomes Research 2/1:43-50

Otero Garcia-Castrillon, C. (2003): El acceso a los medicamentos: Las patentes y el Acuerdo sobre los Derechos de Propiedad Intelectual Relacionados con el Comercio. (Access To Drugs: Patents and the Agreements on Trade-Related Aspects of Intellectual Property Rights. With English summary.). In: Informacion Comercial Espanola Revista de Economia804:197-217

Parker-Lue, S.; Santoro, M.; Koski, G. (2015): The ethics and economics of pharmaceutical pricing. In: Annual Review of Pharmacology & Toxicology 55/191-206

Pascual, F. (2014): Intellectual property rights, market competition and access to affordable antiretrovirals. In: Antiviral Therapy 19 Suppl 3/57-67

Perez-Casas, C.; Herranz, E.; Ford, N. (2001): Pricing of drugs and donations: options for sustainable equity pricing. In: Tropical Medicine & International Health 6/11:960-964

Plahte, J. (2005): Tiered pricing of vaccines: a win-win-win situation, not a subsidy. In: The Lancet Infectious Diseases 5/1:58-63

Ridley, D. B.; Schulman, K. A. (2004): Differential pricing of pharmaceuticals in the internet age. In: Journal of Ambulatory Care Management 27/3:210-214

Ridley, D. B. (2005): Price Differentiation and Transparency in the Global Pharmaceutical Marketplace. In: Pharmacoeconomics 23/7:651-658

Satyanarayana, K. (2008): Towards equitable health care: drug prices, and beyond. In: Indian Journal of Medical Research 127/4:301-304

Scherer, F. M.; Watal, Jayashree (2002): Post-TRIPS Options for Access to Patented Medicines in Developing Nations. In: Journal of International Economic Law 5/4:913-939

Scherer, F. M. (2007): Essential Drugs. Harvard University, John F. Kennedy School of Government, Working Paper Series

Scherer, F. M. (2013): Patents, Monopoly Power, and the Pricing of Pharmaceuticals in Low-Income Nations. Harvard University, John F. Kennedy School of Government, Working Paper Series

Schmidt, F.; Egler, M.; Geursen, R. G. (2002): Ramsey pricing as an explanation and justification for price differences in the European pharmaceutical market. [German]. In: Pharmazeutische Industrie 64/6:513-519

Schweitzer, S. O.; Comanor, W. S. (2011): Prices of pharmaceuticals in poor countries are much lower than in wealthy countries. In: Health Affairs 30/8:1553-1561

Siskou, O. R. N.; Kaitelidou, C. D.; Litsa, S. P.; Georgiadou, S. G.; Alexopoulou, A. H.; Paterakis, G. P.; Argyri, P. S.; Liaropoulos, L. L. (2014): Investigating the Economic Impacts of New Public Pharmaceutical Policies in Greece: Focusing on Price Reductions and Cost-Sharing Rates. In: Value in Health Regional Issues 4/107-114

Srivastava, D.; McGuire, A. (2014): Analysis of prices paid by low-income countries - how price sensitive is government demand for medicines? In: BMC Public Health 14/767

Stargardt, T.; Schreyogg, J. (2006): Impact of Cross-Reference Pricing on Pharmaceutical Prices: Manufacturers' Pricing Strategies and Price Regulation. In: Applied Health Economics and Health Policy 5/4:235-247

Stephenne, J. (2011): Vaccines as a global imperative-a business perspective. In: Health Affairs 30/6:1042-1048

T'Hoen, E; Moon, S (2001): Pills and pocketbooks. In: Equity pricing of essential medicines4-5

Tekiner, H. (2014): Pharmacy in Turkey: past, present, and future. In: Pharmazie 69/6:477-480

Tetteh, E. K. (2009): Implementing differential pricing for essential medicines via country-specific bilateral negotiated discounts. In: Applied Health Economics & Health Policy 7/2:71-89

Thomas, A. (2002): The WHO and Drug Pricing: A Proposal for Differentiated Drug Pricing for Developing Countries. In: New Economy 9/2:91-95

van de Ven, N.; Fortunak, J.; Simmons, B.; Ford, N.; Cooke, G.; Khoo, S.; Hill, A. (2014): Minimum target prices for production of direct acting antivirals and associated diagnostics to combat Hepatitis C Virus. In: Hepatology

Vitezic, D.; Madjarevic, T.; Gantumur, M.; Buble, T.; Vitezic, M.; Kovacevic, M.; Mrsic-Pelcic, J.; Sestan, B. (2012): Drug usage by outpatients in Croatia during an 8-year period: Influence of changes in pricing policy. In: International Journal of Clinical Pharmacology & Therapeutics 50/7:483-489

Vogler, S.; Habimana, K. (2014): Pharmaceutical pricing policies in European Countries. Commissioned by Change to Win, Vienna

Waning, B.; Kaplan, W.; King, A. C.; Lawrence, D. A.; Leufkens, H. G.; Fox, M. P. (2009): Global strategies to reduce the price of antiretroviral medicines: evidence from transactional databases. In: Bulletin of the World Health Organization 87/7:520-528

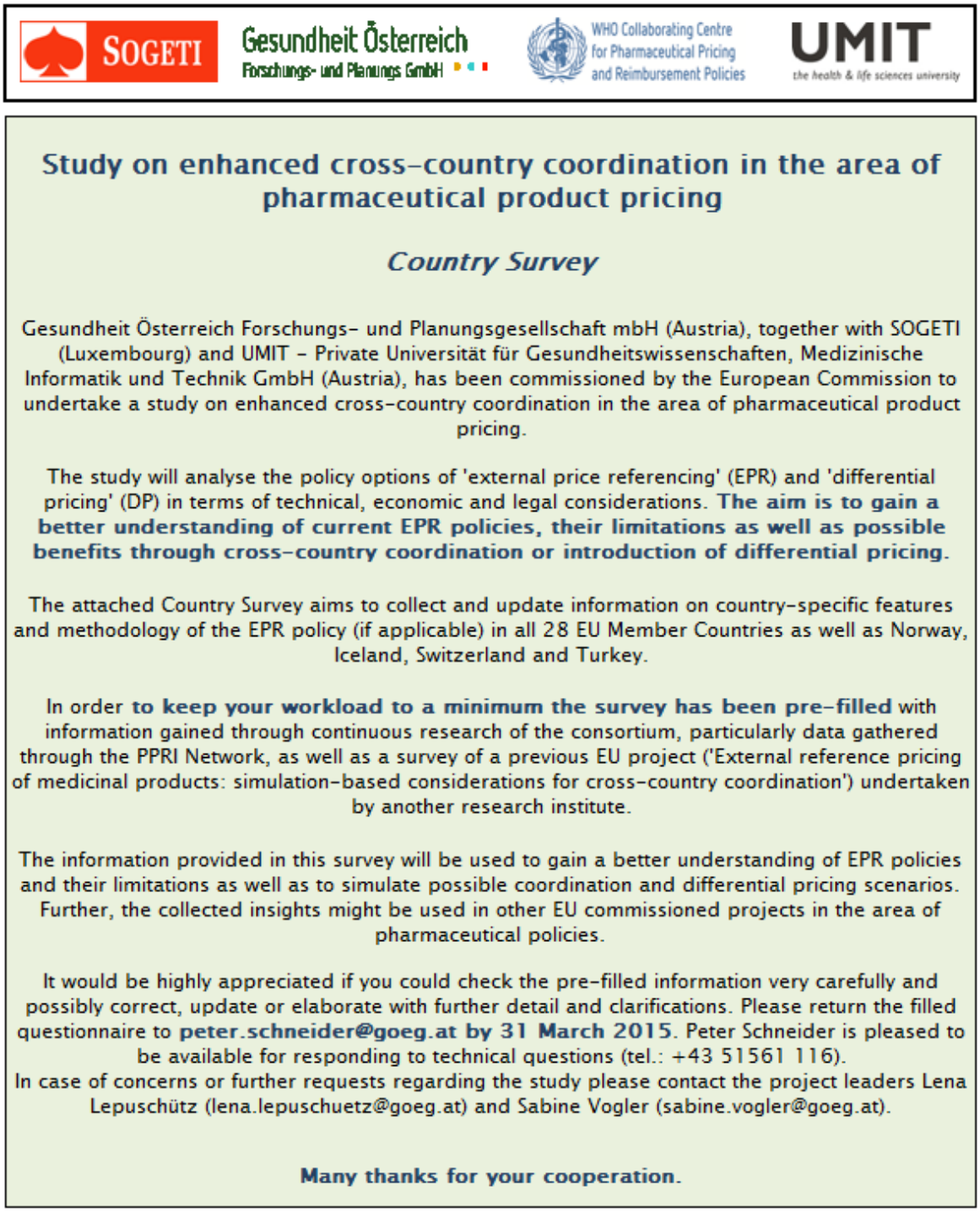
World Health Organization; World Trade, Organization (2002): Differential Pricing and the Financing of Essential Drugs. In: The economics of essential medicines. Ed. Granville, Brigitte. London: Royal Institute of Economic Affairs, International Economics Programme; distributed by the Brookings Institution, Washington, D.C.: 209-231

World Health Organization (2013): WHO Guideline on Country Pharmaceutical Pricing Policies, Geneva

Yadav, P. (2010): Differential pricing of pharmaceuticals: Review of current knowledge, new findings and ideas for action. Accident; analysis and prevention. Ed. DFID, A study conducted for the UK Department for International Development. MIT Zaragoza International Logistics Program, Zaragoza

3 Annex 3: EPR survey with competent authorities – Questionnaire

Figure A3: Coversheet of the survey



SOGETI | Gesundheit Österreich Forschungs- und Planungs GmbH | WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies | UMIT the health & life sciences university

Study on enhanced cross-country coordination in the area of pharmaceutical product pricing

Country Survey

Gesundheit Österreich Forschungs- und Planungsgesellschaft mbH (Austria), together with SOGETI (Luxembourg) and UMIT – Private Universität für Gesundheitswissenschaften, Medizinische Informatik und Technik GmbH (Austria), has been commissioned by the European Commission to undertake a study on enhanced cross-country coordination in the area of pharmaceutical product pricing.

The study will analyse the policy options of 'external price referencing' (EPR) and 'differential pricing' (DP) in terms of technical, economic and legal considerations. **The aim is to gain a better understanding of current EPR policies, their limitations as well as possible benefits through cross-country coordination or introduction of differential pricing.**

The attached Country Survey aims to collect and update information on country-specific features and methodology of the EPR policy (if applicable) in all 28 EU Member Countries as well as Norway, Iceland, Switzerland and Turkey.

In order **to keep your workload to a minimum the survey has been pre-filled** with information gained through continuous research of the consortium, particularly data gathered through the PPRI Network, as well as a survey of a previous EU project ('External reference pricing of medicinal products: simulation-based considerations for cross-country coordination') undertaken by another research institute.

The information provided in this survey will be used to gain a better understanding of EPR policies and their limitations as well as to simulate possible coordination and differential pricing scenarios. Further, the collected insights might be used in other EU commissioned projects in the area of pharmaceutical policies.

It would be highly appreciated if you could check the pre-filled information very carefully and possibly correct, update or elaborate with further detail and clarifications. Please return the filled questionnaire to **peter.schneider@goeg.at by 31 March 2015**. Peter Schneider is pleased to be available for responding to technical questions (tel.: +43 51561 116).
In case of concerns or further requests regarding the study please contact the project leaders Lena Lepuschütz (lena.lepuschuetz@goeg.at) and Sabine Vogler (sabine.vogler@goeg.at).

Many thanks for your cooperation.

Figure A4: Example of the questionnaire without pre-filled information

Question:	Data gathered from literature/previous surveys:	Data Validation/Is data acurate? (Yes/No)	Corrections/Updates/Further Comments
Does EPR apply in your country?			
Is EPR used as sole or main systematic criterion or as supportive information when setting the price of a new medicine in your country?			
How many reference countries do you have in the ERP basket used by your country?			
Which are the reference countries in the EPR basket used by your country? Please specify, if there are "first-line" or highly prioritised countries and alternative countries.			
What are the types of products regulated by EPR in your country?			
Which price level is taken into account for reference purposes in your country?			
How is the reference price calculated in your country?			
Is there any weighting applied? (e.g. GDP)			
Methodological Issues/Selection of reference Products:			
a) How do you deal with the fact when there is no price available in a reference country?			
b) If a generic form of a product is available in a reference country, which type of product is selected for reference purposes in your country?			
c) If a product is not reimbursed in a reference country, is the price of the non-reimbursed product used as reference?			
d) When different pack sizes are approved in the reference countries at different prices, which pack size is used as reference in your country?			
How are the exchange rates chosen and taken into account?			
Who provides the price information?			
Is the price provided by the manufacturer validated?			
Does your legal framework provide regular revisions of the EPR-based prices in your country? If so, at what frequency?			
How often do you undertake price monitoring and revisions related to EPR-based prices? When was your last revision? (What was the outcome?)			
Are there mandatory discounts, rebates, or similar financial arrangements granted by pharmaceutical industry to the public payer? If so, please describe			
What have been the most important changes in the EPR methodology/process since 2010? (e.g. change in the basket, change in the calculation?			

4 Annex 4: EPR survey – List of respondents

Table A3: Responding institutions to the country survey about EPR

Country	Institution
Austria (AT)	Austrian Federal Ministry of Health, Gesundheit Österreich GmbH (GÖG)
Belgium (BE)	National Institute for Health and Disability Insurance
Bulgaria (BG)	National Council on Prices and Reimbursement of Medical Products
Croatia (HR)	Croatian Health Insurance Fund
Cyprus (CY)	Ministry of Health, Department of Pharmaceutical Services
Czech Republic (CZ)	State Institute for Drug Control
Denmark (DK)	Ministry of Health
Estonia (EE)	Ministry of Social Affairs
Finland (FI)	Ministry of Social Affairs and Health
France (FR)	Ministry of Social Affairs, Health and Women's Rights
Germany (DE)	Ministry of Health, Department of Pharmaceutical Product Supply AOK Research Institute
Hungary (HU)	National Health Insurance Fund of Hungary
Greece (EL)	National Organisation for Medicines
Iceland (IS)	Icelandic Medicine Pricing and Reimbursement Committee
Ireland (IE)	Department of Health
Italy (IT)	Italian Medicines Agency
Latvia (LV)	National Health Service, Department of Pharmaceuticals and Medical Devices
Lithuania (LV)	National Health Insurance Fund
Luxembourg (LU)	Ministry of Social Affairs
Malta (MT)	Ministry of Health, Pharmaceutical Affairs
Netherlands (NL)	Ministry of Health, Welfare and Sport
Norway (NO)	Norwegian Medicines Agency
Poland (PL)	Ministry of Health, Department of Drug Policy and Pharmacy
Portugal (PT)	National Authority of Medicines and Health Products
Romania (RO)	Ministry of Health, Pharmaceuticals and Medical Devices Policy Department
Slovakia (SK)	Ministry of Health
Slovenia (SI)	Agency for Medicinal Products and Medical Devices
Spain (ES)	Ministry of Health, Social Services and Equality
Sweden (SE)	Dental and Pharmaceutical Benefits Agency
Switzerland (CH)	Federal Office of Public Health
United Kingdom (UK)	Department of Health
Turkey (TR)	Ministry of Health, Turkish Medicines and Medical Devices Agency

5 Annex 5: Proposal for further information to be included in EPR

Table A4: Proposal for further information to be included in EPR, by suggested order of importance

Information	Description	Relevance
Direct price information		
Information on discounts	An information whether the prices indicated are the official list prices, or discounted prices	Basic information
	Discounted prices are displayed in addition to the official list prices	Would considerably improve the EPR system
	An indication whether the discounts are statutory manufacturer discounts granted to public payers, and/or voluntary commercial discounts	In case that no disclosure of the discount were possible
Medicine price type and setting	Defines whether the price data is indicated as ex-factory price, pharmacy purchasing price, pharmacy retail price net or gross Indication of relevant setting (e.g. hospital price)	Basic information for any price comparison; since otherwise no correct price comparison / EPR would be possible
Data of price data	Indication of the latest price update	Basic information
	Information on historic prices, with information on the different uptake dates	Would be recommended for consideration of inclusion; would allow time series analysis
Exchange rate	Current exchange rate and indication of date/period of exchange rate (daily exchange rate, monthly / quarterly average)	Basic information
	Information on the exchange rates over time (in line with historic data)	Relevant and recommended for consideration of inclusion if information on price developments were included
Market volume data	Information on market volume data of the latest available year	Could be used to improve the EPR system by informing about the volume component, thus the relevance of the medicine in terms of consumption
	Developments of market volume data of the last years	Would allow improved interpretation of the data
Information on underlying pricing procedure and arrangements	Information on whether, or not, the price is based on a public tender, or whether it has been further negotiated Information on discount-like financial arrangements such as various managed-entry agreements Information whether EPR is applied as a main policy and price information is used as a supportive information (An asterisk or footnotes might indicate the existence of public tenders, and financial arrangement)	Information allows interpreting better the price data and indicates the validity of prices
Marketing authorization information	Information on whether, or not, the medicine has been centralised authorised, and if yes, the European Medicines Agency (EMA) number Date of marketing authorization Therapeutic indications	Information improves the interpretation of the price data by indicating whether, or not, these are newly launched medicines

Information	Description	Relevance
Pharmaco-economic data	Information on whether, or not, a pharmaco-economic study or Health Technology Assessment (HTA) report is available	Information improves the interpretation of the price data
Indirect price information		
Mandatory discounts	Information on whether, or not, statutory manufacturer discounts to public payers are in place If yes, information on the legal basis and its design/extent	Information could be used for change in the EPR system (consideration of published statutory discounts)
Economic situation	Indicator such as gross domestic product (GDP), purchasing power parities (PPP)	Would indicate on the ability-to-pay of a country Information required in case of the change of the design of EPR system (factoring in the economic situation)
Pharmaceutical expenditure	Information on total pharmaceutical expenditure, and public pharmaceutical expenditure per capita, in the latest available year	Supportive information allowing improved interpretation of price data
	Development total pharmaceutical expenditure, and public pharmaceutical expenditure per capita, of the last years	Supportive information
Methodology of EPR	Number and list of reference countries	Supportive information allowing improved interpretation of price data
	Methodology of reference price calculation	Supportive information allowing improved interpretation of price data
	Methodology of consideration of exchange rate	Supportive information allowing improved interpretation of price data
	Methodology related to non-availability of data	Supportive information allowing improved interpretation of price data
Price reviews	Information on whether regular price reviews are planned If yes, information on the legal/contractual basis, the frequency of reviews, the scope of medicines and planned further measures (revisions) If yes, information on actual implementation, including latest price review and price implementation	Supportive information allowing improved interpretation of price data
Market size	Information on total pharmaceutical sales per capita, supplemented by information on reimbursement and non-reimbursement market	Supportive information allowing improved interpretation of price data Information required in case of the change of the design of EPR system (factoring in market relevance)
Generic market share	Information on generic market share in volume	Supportive information allowing improved interpretation of price data Information required in case of the change of the design of EPR system (factoring in the relevance of off-patent product)
INN (International non-proprietary name) prescribing	Information, whether or not, INN prescribing is allowed, and whether it is mandatory	Supportive information allowing improved interpretation of price data

Source: The authors

It is not suggested that countries include all listed elements into their formal EPR mechanisms. This is merely a list of important information that countries may consider for improving their EPR system, and for instance in the case of PPP or GDP per capita could formally include into their EPR calculation mechanism if they wanted to account for different countries' economic situation. As building price databases and conducting EPR evaluations is administratively time-consuming, the benefit of any extension of the EPR mechanism by including further information should be weighted with the costs of increased administrative burden.

6 Annex 6: DP survey with experts – Questionnaire

Are you involved / have you been involved in differential pricing? If yes, could you please report (countries, purchaser, medicines, procedure)

DP is often considered as 'second-best' option to allow access to medicines otherwise non-accessible; others judge DP as a subsidy. Which is your position on this?

What do you see as benefits of DP?

Benefits in terms of accessibility, savings for public budget, reward for manufacturer?

What do you see as limitations of DP?

It is often agued in literature that DP must be connected with confidentiality? Do you agree?

It is sometimes argued in literature that DP is not a stand-alone policy. Do you agree? Which further policies (e.g. voluntary/compulsory licensing, tendering, competition) would you recommend?

DP practice has been limited to LMIC (unless confidential discounts in Europe are considered as DP, as many argue). Under the condition that restraints for the implementation of DP in Europe could be overcome, would you see DP as a policy option relevant for European countries? Explain why, whether its yes or no?

Which would you consider as the main prerequisites to be addressed in legal, organisational and technical terms to introduce a DP in Europe?

Any further information to be added?

Ideas for further interview partners?

Contact

For further information please contact:

Sabine Vogler, Peter Schneider
Gesundheit Österreich Forschungs- und Planungs GmbH (Austria)
E-Mail: sabine.vogler@goeg.at, peter.schneider@goeg.at
Phone: +43 1 51561/147 or 116

7 Annex 7: DP survey with experts – List of interviewees

Table A5: Interview partners related to practice and experience with DP[1]

Name	Institution	Function
AANES Torfinn	Legemiddelinnkjøpssamarbeidet (NO)	Administrative Head of Drug procurement
BAK PEDERSEN Hanne	WHO Regional Office for Europe	Programme Manager
BARTHELS Dorthe	AMGROS (DK)	Head of procurement and logistics
BLANCO Francisco	United Nations Children's Fund (UNICEF) Supply Division	Chief of Medicines & Nutrition
CAMERON Alexandra	UNITAID	Technical Manager, Strategy and Results
HILL Suzanne	WHO	Senior Advisor
NGUYEN Aurelia	Global Alliance for vaccines and immunisation (GAVI)	Director Policy and Market Shaping

[1] The interview partners made no official statement on behalf of their institutions, but reported on personal experiences with DP.

8 Annex 8: DP use and experience – Additional information

Table A6: Differential pricing practice across the world

Medicines	Country/ies	Purchaser	Description	Results/Assessment
Anti-retroviral (ARV)	Less Developed Countries (LDC) or a composite criterion based on the country's income level, geographic location and the prevalence of human immunodeficiency virus (HIV)	National governments	In 2000, the Accelerated Access Initiative (AAI) was founded as a public-private partnership under which several originator pharmaceutical companies announced a voluntary price reduction programme for patients in poor countries. In addition, originator companies also made price offers through bilateral negotiations with individual governments. A two-tiered pricing structure was specified and how countries are eligible to purchase discounted products.	▪ Pharmaceutical manufacturers started publicly disclosing their ARV price structure which brought more transparency on the price and eligibility ▪ The initiative addressed mainly LDC, but middle-income countries prices were still negotiated bilaterally; After the success of AAI a three-tiered pricing structure emerged, which included discounted prices for lower and middle-income countries ▪ Price decline for most ARV from 2000 to 2003 ▪ Generic competition from mostly Indian and Brazilian manufacturers ▪ High risk of informational arbitrage to erode margins in high income countries
ARV	Middle-income countries in Latin America	Pan American Health Association (PAHO)	Purchasing of ARV was pooled through the Pan American Health association	▪ Lower prices through higher bargaining power as a collective buyer
ARV	Africa, LDC and middle-income countries	National governments	Some pharmaceutical manufacturers have started to offer differential pricing schemes e.g. a three-tiered pricing structure, according to the average income of a country	▪ Taking averages to calculate income tiers does not reflect the true issues impeding access/affordability since it does not take into account income inequality ▪ The two lowest income quintiles in Brazil (considered as upper middle-income country) have an income level lower than the average income in Thailand (which is considered as lower middle income country ▪ The poorest income segments in India have an income level much lower than the average income of Uganda (which is considered as low income country)

Medicines	Country/ies	Purchaser	Description	Results/Assessment
Various	Developing countries	National governments	In recent years pharmaceutical manufacturers have extended differential pricing schemes to other types of medicine. In India, a type-2 diabetes medicine was launched based on Indian Prices in consultation with different stakeholders (doctors and patients). Similar cases are known for anti-convulsing medicines or antibiotics to treat tuberculosis	▪ The price of the pharmaceutical is comparatively low, and the pricing strategy has so far been a success
Malaria	Intra-country differentiation	National governments, Non-Governmental Organisations (NGOs) or public sector programmes	A notable example of intra-country differential pricing is Artemether/lumefantrine to treat acute uncomplicated malaria. The public sector and NGO distribution channels receive a much lower price compared to the profit private sector.	▪ Small controlled pilots show little leakage into the premium private sector. However, there are reports of leakage of public sector medicines in the private for profit sector, but differences in packaging have allowed better tracking and monitoring of such leakages.
HIV, malaria, tuberculosis (TB), river blindness, elephantitis	Africa and LDCs	National governments, NGOs or public sector programmes	Another form of differential pricing is medicine donation programmes; Pharmaceutical companies donated pharmaceuticals to low-income countries i.e. the price is set to zero. To provide incentives for companies to introduce such schemes, there need to be such tax benefits in place which allow companies to offset at least some portion of the marginal costs.	▪ Economic theories suggest that companies should not run the risk of revealing the marginal costs of pharmaceuticals and therefore avoid adverse effects of price differentials (e.g. political pressure in high income countries to reduce prices) ▪ In the absence of market signals, the demand for donated medicines is more difficult to estimate and this may lead to wastage and poor utilisation ▪ Donation programmes have worked well for neglected diseases such as river blindness and elephantitis but are not sustainable for large-scale provision
Vaccines	Low- and middle-income countries	National governments or public sector programmes (GAVI), UNICEF, PAHO	Vaccines may constitute an archetype for medicines eligible for differential pricing. Lower prices for developing countries would have been only available years after the launch of the vaccine when R&D costs have been recovered to a large extent. At this stage the vaccine was sold at a different price for high income countries as compared to the price for middle- and low income countries. However, vaccine manufacturing is subject to economies of scale and manufacturers had large underutilised capacity in the first years after the product launch.	▪ Most vaccines now have a three-tiered pricing structure ▪ Countries belonging to GAVI enjoy the lowest prices

Medicines	Country/ies	Purchaser	Description	Results/Assessment
Contraceptives	Africa and LDC	National governments, NGOs or public sector programmes (e.g. United Nations Population Fund (UNFPA)	The purchasing of reproductive health commodities is carried out on a global level through the different public sector programmes. Reproductive health products typically have relatively low volume and weight compared to value, can tolerate long distance transport, and have long shelf lives;	▪ The price of contraceptives in low income countries is lower by a factor of 10-100 ▪ Medicines subject to differential pricing need careful product versioning and differential branding ▪ Social marketing and social franchising is often used as the sales channel
Vaccines	Global	National governments or public sector programmes (Global Alliance for Vaccines and Immunisation, GAVI), UNICEF, PAHO	Most vaccines have a three-tiered pricing structure with market prices charged in rich countries, low prices in countries belonging to the GAVI and intermediate prices in MICs The buy-side market structure for vaccines is dominated by the UNICEF and Pan American Health Organisation (PAHO) UNICEF is the main procurement agent for GAVI and procures the majority of the vaccines for LMC and negotiates the prices with the manufacturer on a case-by-case basis for MICs. PAHO procures vaccines for most of the countries in Latin America and the Caribbean region. PAHO obtains a single low price for all of its member countries;	▪ Differential pricing of vaccines is sustained because of the strict control on the supply line of vaccines. The main reason for that is the requirement of a cold chain for vaccines. The cold chain process has been important in limiting leakage and facilitating market segmentation ▪ Due to tiered pricing for vaccines, millions have gained access to essential medicines and also pharmaceutical manufacturers have increased their sales. The cold chain has contributed to the prevention of parallel trade
ARV	Thailand, Brazil, India	National governments	In 2006 and 2007, the Thai government issued a compulsory license for an active ingredient which is a component of many first-line HIV/AIDS treatment regimens. In 2007, Brazil followed this example and issued additional compulsory licenses.	▪ The license permitted the import of a generic for that active ingredient from India, where the medicine is not patented. The MAH – still holding a patient on the active ingredient in Thailand – received a royalty payment ▪ Brazil, Thailand and India have a substantial pharmaceutical sector and the capacities to produce generic medicines, allowing them to issue compulsory licenses.

Medicines	Country/ies	Purchaser	Description	Results/Assessment
Vaccines	Low- and middle-income countries	National governments or public sector programmes	Driven by the Bill and Melinda Gates Foundation, in 2011 the decade of vaccines was launched, with the goal to extend – by 2020 and beyond – the full benefits of immunisation to all people. During this initiative pharmaceutical manufacturers updated their tiered pricing schemes. For instance, one producer of vaccines classified countries into seven tiers according to their GNI ranking. To take account for the willingness to invest, each income tier is divided into price ranges based on four criteria: 1. The committed duration of vaccination in the disease area 2. Coverage of the target population which rewards the health benefit of well implemented vaccination programmes 3. Vaccines with broad age recommendations 4. The number of doses to be purchases	▪ The update of the tier schemes aims to support the 17 countries which are anticipated to graduate from GAVI financing ▪ The revised approach to tiered pricing should provide access to and build sustainable supply of vaccines and result in lower prices ▪ It should be noted that the described pricing procedure is not a broad pricing approach across all vaccines. Each manufacturer has its own specific pricing policy.
Several	India	National governments or public sector programmes	Pharmaceutical manufacturers started to create for basic primary care products such as antibiotics, painkillers and antacids separate brands for low-income markets. The packaging of the products use local language and smaller packet sizes for acute therapy in order to keep out-of-pocket costs low	-
Malaria	Africa	National governments	To address unmet patient needs in the context of neglected diseases, pharmaceutical manufacturers entered a public-private partnership. The aim of the partnership was to jointly develop a safe, rapidly acting fixed-dose combination (FDC) to treat malaria	▪ The result was the creation of the ASAQ approach (Adapted Simple Accessible Quality) ▪ Each partner provided considerable expertise within its own domain: Medicines for neglected diseases (DNDi) initiative did much of the pre-clinical and clinical work with various academic institutions around the world whereas the pharmaceutical manufacturer developed the process required to enable the production on an industrial scale ▪ The financial burden for each partner was reduced

Medicines	Country/ies	Purchaser	Description	Results/Assessment
ARV	LDC	National governments or public sector programmes	In recent years, originator companies have started to grant voluntary licences to generic manufacturers under specific conditions. These may include the requirement that producers meet good manufacturing practices (GMP) as defined by the U.S. Food and Drug Administration or the World Health Organisation, or that products be distributed only in LDCs.	▪ Originator companies either provide these licenses royalty fee, depending on the company, the product and the country. In one case, the Licensee pays a 5% royalty fee on finished products, but is free to establish his own prices for these medicines. Through this license approach ARVs of the originator company reach 95 developing countries ▪ A major challenge for local manufacturers in developing countries is to meet the GMP standards in order to obtain licenses and participate in international tenders
Vaccines	LDC	Global Alliance for Vaccines and Immunisation, GAVI	The global alliance for Vaccines and Immunisation (GAVI) established in 2007 the Vaccine Presentation and Packaging Advisory Group (VPAAG)	▪ The efforts of VPAAG targets packaging to ensure that future vaccine products and delivery technologies are designed with characteristics consistent with developing country needs (e.g. fixed dose combinations) and also allow market segmentation. VPAAG has developed a generic preferred product profile as a reference document for vaccines in developments for use in low- and middle-income markets.
ARV	LDC	National governments or public sector programmes	The proportion of patients on triple combination therapy has increased from one-third to nearly two-thirds in Africa. However, the	▪ No single model of price discrimination will be effective for all diseases (HIV, malaria, TB), since the clinical needs, economic incentives and epidemiology of each illness are substantially different ▪ Differential pricing is not necessarily a panacea for all pricing issues. For 15 of 18 differentially priced medicines, prices were higher than for generics. ▪ An Indian pharmaceutical company has repeatedly offered 5% royalty to any brand name pharmaceutical company that would grant a voluntary license to sell patented ARVs in the developing world

Medicines	Country/ies	Purchaser	Description	Results/Assessment
Malaria	African, Western Pacific and South-East Asian countries	National Governments or public sector programmes	Pharmaceutical manufacturers offer the same antimalarial at two different prices. The brand name is available at a normal price, while the same medicine, under a different name, is available at a preferential price for the needy	▪ Under this scheme the access to medicines has increased and in one case a company was able to distribute more than 10 million artemisinin-based combinations therapies.
Leishmaniasis	Worldwide	National governments or public sector programmes	In 2006, a 5 year public-private-partnership was signed, in which the pharmaceutical manufacturer agreed to contribute to 25% of the complete donation for combating leishmaniasis	▪ The Pharmaceutical Manufacturer distributed medicines by using a tiered pricing policy among a large number of patients worldwide.
Diabetes	India	National governments or public sector programmes	A pharmaceutical manufacturer has agreed on launching medicines against Diabetes in India. All these medicines will be priced lower than the price of the medicine in the originator's country.	▪ Differential pricing is considered by pharmaceutical manufacturers as a measure to increase market sales in emerging markets.
Tuberculosis	LDC	National governments or public sector programmes	Several pharmaceutical companies have signed in 2001 an arrangement to supply six classes of second-line anti TB medicines (variously under-patent, in non-patent monopoly and having generic status)	▪ The products are sold at a price that is as low as 5% of what some countries are currently paying for individual medicine ▪ Provisions have been included to prevent backflow of these DP pharmaceuticals into high-price markets
Insulin	49 LDC	National governments	Since 2001, a pharmaceutical manufacturer has offered public health systems in 49 LDC human insulin at prices which do not exceed 20% of the average price in Europe, Japan, and North America	▪ In 2009, 36 countries used the pricing scheme to buy insulin at or below the threshold price. ▪ There are 13 LDC countries which did not used the scheme; the pharmaceutical manufacturer reported that some countries did not respond to the offer, either because there are no private wholesaler or partners, with which to work or because wars or political unrest have made it impossible to do business.

Source: Authors' compilation based on literature review [2-7]

Table A7: Arguments against and in favour of DP reported in literature

Objection against DP	Argument in favour
DP will impair the economic well-being of the innovative industry and its ability to attract capital.	Substantial price reductions through DP will lead to an increase unit sales. As a consequence, manufacturing facilities would run more efficiently and will be subject to economies of scale i.e. reducing costs of production. Vaccines are regularly quoted as a good example, since this market is mainly driven by the volume effect. For the vaccine industry DP has been a profitable pricing strategy and furthermore created the basis for future expansion.
Low-price medicines will 'leak' into high-price markets, undermining earnings there. This 'pharmaceutical leakage' is a non-neglectable phenomenon and often reported in public medicine programmes.	Experience with existing agreements suggest that it is possible to overcome the problem of backflow through a number of complementary mechanisms ▪ Obligations imposed in supply contracts ▪ Differential labelling, nomenclature or trademarking of DP products ▪ Legislation to prevent parallel imports from countries with DP ▪ Policies in importing countries to control the flow of DP products
Introducing 'affordable' prices in developing countries, industrialised countries will take these prices as a starting point for their own national reference price systems.	It would be unrealistic if countries where prices had been lowered to serve a poor population (e.g. low- and middle income countries in Africa and Southern America), were to add to the reference list in one or more high-income countries. In order to avoid this risk, a global agreement on DP is needed, subscribed to by all countries rather than relying on ad hoc arrangements.
Industry has already shown that it can handle this problem without public intervention.	Many pharmaceutical companies have not been involved in DP, and those initiatives which apply DP tackle only a fraction of the immense global health problems. The participation of major manufacturers has only happened when there was extreme pressure from external sources.
There is little point in supplying advanced medicines if the mechanisms to deliver them to patients, to prescribe them responsibly and to supervise treatment are lacking; affordable prices are only one part of the 'access to medicines'-puzzle.	The lack of therapeutic skills is indeed a problem with regard to the use of some medicines, but it is not an obstacle in the treatment of other diseases (e.g. tuberculosis, malaria) where simple and practical solutions can be found.
Developing countries do not mobilise resources efficiently; with due effort they could pay more for medicines.	Inefficiency problems with respect to tax collection or excessive spending in questionable fields exist in developing countries, but these issues need to be tackled separately. It is also a questionable argument to suggest that the existence of such problems obviates or even reduces the need to tackle problems related to the access to medicine.
Some medicines are just too expensive in production to be sold at prices affordable to poor people	Pharmaceutical Manufacturers do not disclose the costs of producing pharmaceuticals, but there is plenty of evidence that the mere costs of production are extremely low. In many cases – even for complex molecules – prices fall if the medicine is produced at a large scale. If there are exceptions that justify a public subsidy in order to render them affordable, this needs to be documented
If the industry cuts prices to a bare minimum, they will then be raised again by taxes, import duties and wholesale and retail profits.	This has been observed in practice for contraceptives and vaccines involved in DP. The main question which needs to be settled in this context is whether differentially priced medicines should be restricted to the public or non-profit sectors. On the one hand it ensures better control over the supply and excludes excessive margins, but on the other hand the public sector plays a limited role in the countries where DP is applied

Objection against DP	Argument in favour
Current prices are necessary in order to fund research and development.	Since firms are reluctant to disclose information about their cost structure, it is difficult to assess the size of the fraction of expenditures that pharmaceutical companies devote to research and development (R&D). Creative innovative research represent only one of the elements determining cost and it can be assumed, that it has been superseded by expenditure on marketing and promotion as the main cost driver.
Some important offers of discounted prices or donations made by companies to developing countries have not been taken up.	It has occasionally been the case, but the documentation suggests that the rejection is related to the supply of inappropriate pharmaceuticals. The donation of pharmaceuticals intended to secure tax relief in the exporting country and did not take into account the need of the recipient country.
Differential pricing is illegal.	No documented basis whatsoever can be identified for this objection. In the context of the United States (US) Anti-Trust Law, the law aims to protect the public by preventing collusion between manufacturers on price maintenance. Concerning this goal it coincides with DP which tries to achieve price reductions to the public benefit.
Differential pricing is impossible where a medicine is only likely to be used in a disease occurring exclusively in poor populations.	This objection against DP is justified, as it is a severe limitation of DP to deal with heterogeneous income groups within a country.
Differential pricing by multinationals will adversely affect the generic industry and discourage manufacturing in developing countries.	The bulk of the generic manufacturing industry has related to older but valuable medicines on which patents have expired. Many of these will continue to be essential medicines and DP policies such as voluntary or compulsory licensing will provide the industry with new fields of production.

Source: Mossialos E and Dukes G [8]

9 Annex 9: Euripid survey – Questionnaire

Which would you consider as the benefits and strengths of Euripid?

Which were prerequisites for building up Euripid? Which would you consider as prerequisites for building an effective medicine price database in Europe? What would you do differently if you would build a price database in Europe?

Which would you consider as limitations (weaknesses) of Euripid / of any central medicine price database?

Which further information or classification in Euripid would be helpful?

Which do you consider as opportunities of Euripid, and which as threats?

Any further information / comments that you would like to share with us?

10 Annex 10: Simulations – Model inputs

Table A8: Model inputs for EPR simulations

Country	Is EPR the main criterion?	Regular re-evaluations (in months)	Min. available reference prices required	Calculation methodology	Type of price used	Approx. WS mark-up[1]	Purchasing power parities[2]	GDP per capita (in PPS)[3]	GDP per capita, PPP (in US$)[4]
Austria	Yes	No reevaluation	14	Average	Ex-factory price	9.10%	1.11761	128	45.081
Belgium	No	No reevaluation	1	Average	Ex-factory price	8.50%	1.1259	119	41.573
Bulgaria	Yes	6	1	Minimum	Ex-factory price	9.09%	0.930239	45	15.732
Croatia	Yes	12	2	Average	Pharmacy purchasing price	8.50%	4.81181	61	21.351
Cyprus	Yes	12	1	Average	Pharmacy purchasing price	14.00%	0.892329	89	31.198
Czech Republic	Yes	36	3	Average of 3 lowest	Ex-factory price	4.10%	17.739	82	29.018
Denmark	No EPR	No reevaluation	NA	NA	NA	6.30%	10.1622	124	43.782
Estonia	Yes	12	1	Minimum	Ex-factory price	5.90%	0.72914	73	25.823
Finland	No	60	1	Average	Pharmacy purchasing price	3.00%	1.23362	113	39.869
France	No	60	1	Average	Ex-factory price	4.30%	1.13105	107	37.592

[1] Information taken from Vogler S and Schneider P [9]

[2] Source: Eurostat Databank; 2013, EU28=1

[3] Source: Eurostat Databank; 2013, EU28=100

[4] World Bank, in PPP (current international US$), 2013

Country	Is EPR the main criterion?	Regular re-evaluations (in months)	Min. available reference prices required	Calculation methodology	Type of price used	Approx. WS mark-up[1]	Purchasing power parities[2]	GDP per capita (in PPS)[3]	GDP per capita, PPP (in US$)[4]
Germany	No[5]	No reevaluation	1	Average	Ex-factory price	5.90%	1.05124	122	43.887
Greece[6]	Yes	3	3	Average of 3 lowest	Ex-factory price	4.20%	0.83617	73	25.667
Hungary	Yes	No reevaluation	3	Minimum	Ex-factory price	5.10%	171.,208	66	23.336
Iceland	Yes	24	3	Average	Pharmacy purchasing price	4.30%	183.028	119	42.035
Ireland	Yes	36	1	Average	Ex-factory price	8.00%	1.1021	130	45.677
Italy	No	24	1	Minimum	Ex-factory price	9.10%	1.00888	99	35.075
Latvia	No	24	1	Third lowest price	Ex-factory price	3.30%	0.679363	64	22.534
Lithuania	Yes	12	1	Average	Ex-factory price	8.50%	0.608666	73	25.715
Luxembourg	Yes	12	1	Minimum	Ex-factory price	8.50%	1.21234	257	91.048
Malta	Yes	18	3	Average	Pharmacy purchasing price	0.00%	0.779959	86	29.127
Norway	Yes	12	1	Average of 3 lowest	Pharmacy purchasing price	6.00%	12.1889	186	65.640
Poland	No	24	1	Average	Ex-factory price	6.80%	2.41243	67	23.994
Portugal	Yes	12	1	Average	Ex-factory price	9.30%	0.779828	79	27.509
Romania	Yes	60	1	Minimum	Ex-factory price	12.00%	2.20446	55	18.972
Slovakia	Yes	6	1	Average of 3 lowest	Ex-factory price	13.00%	0.679476	75	26.497

[5] EPR is not applied in practice. For the simulations, the legal situation related to EPR in Germany was considered.

[6] Please note that in the case of Greece, due to late receipt of the survey questionnaire, the presented model still presents the old basket including 22 instead of 27 reference countries.

Country	Is EPR the main criterion?	Regular re-evaluations (in months)	Min. available reference prices required	Calculation methodology	Type of price used	Approx. WS mark-up[1]	Purchasing power parities[2]	GDP per capita (in PPS)[3]	GDP per capita (in US$)[4]
Slovenia	Yes	6	1	Minimum	Ex-factory price	6.00%	0.805192	82	28.859
Spain	No	12	1	Minimum	Ex-factory price	5.26%	0.90063	94	33.092
Sweden	No EPR	No reevaluation	NA	NA	NA	3.60%	11.6638	127	44.646
Switzerland	Yes	36	1	Average	Ex-factory price	8.00%	1.82671	163	56.940
The Netherlands	Yes	6	2	Average	Pharmacy purchasing price	10.60%	1.09748	131	46.162
UK	No EPR	No reevaluation	NA	NA	NA	12.50%	0.925106	109	38.255

approx. = approximate, EPR = external price referencing, GDP = gross domestic product, NA = not available, PPP =purchasing power parities, PPS = purchasing power standards, WS = wholesale

Source: Authors' compilation based on country survey with competent authorities

11 Annex 11: Simulations – Additional results

This section aims to provide an overview of real price data, i.e. how price levels compare between countries and relate to countries' economic situation, to complement the different scenarios under EPR and DP methodologies. A short version of the results is available in the main body of this study (cf. chapter 4.2.3).

Previous comparisons among countries in Europe have shown, for instance, that prices in Germany, Switzerland, Denmark and Belgium tend to be at the higher side, whereas prices in Spain, Italy and France tended to be relatively lower (e.g. [10-12]). However, the literature on price comparisons is scarce, limited by data availability and reliability issues. One limitation faced by almost all such analyses is the reliance on official list prices, which might differ from actual prices paid by social insurances through confidential discount or rebate arrangements.

The analysis is based on 30 high-cost medicines, half from the inpatient, half from the outpatient sector.[7] Prices are collected for 2013 and available for 16 European countries: Austria (AT), Belgium (BE), Denmark (DK), Finland (FI), France (FR), Germany (DE), Greece (EL), Hungary (HU), Ireland (IE), Italy (IT), Netherlands (NL), Portugal (PT), Slovakia (SK), Spain (ES), Sweden (SE) and the UK (UK). The analysis is based on unit prices, i.e. per unit of intake such as tablet or vial, and the data is sourced from the Pharma Price Information service (PPI) run by Gesundheit Österreich Forschungs- und Planungs GmbH (GÖ FP) [13].

The medicines were chosen on the basis of which constituted particularly large costs for public payers. The sample thus includes some high priced medicines (for 20 percent of chosen pharmaceuticals the median price per unit was above EUR 1,000), as well as some medicines which had large budget impacts due to the quantity prescribed (27% of all median had a median price below EUR 10).[8]

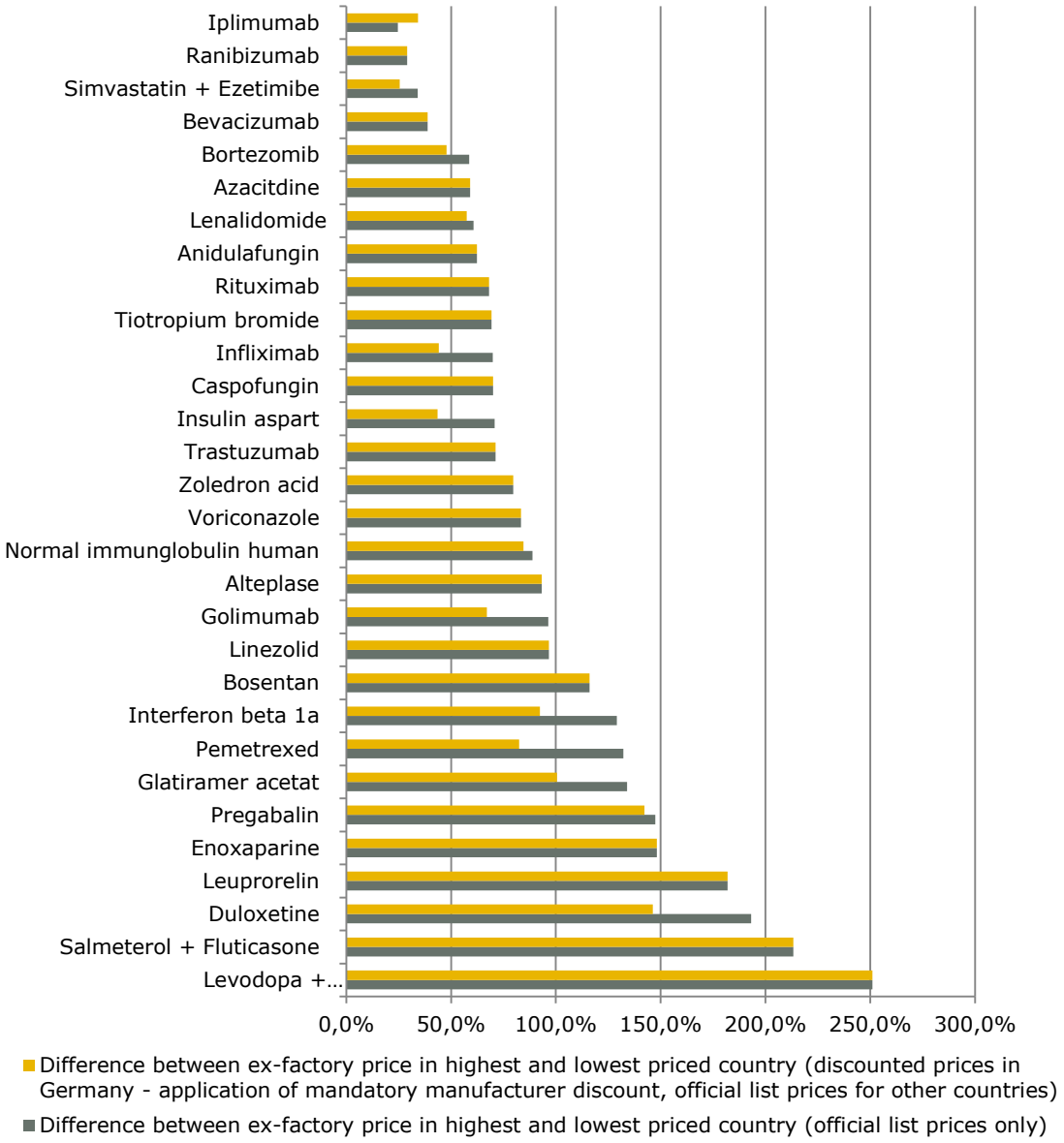
The data analysis uses official ex-factory prices (list prices) of the 16 European countries, and, additionally for Germany, the ex-factory price reduced by the mandatory statutory discount is used. For the other countries no discounted prices are considered, even though they may be reduced by law or rebates, discounts, clawbacks or Managed Entry Agreements which are agreed upon in confidential negotiations.

Prices vary widely between countries, with ex-factory prices in the highest-priced country being between 24.6 percent and 251.1 percent higher than in the lowest-priced country for the relevant medicine (see Figure A5).

[7] The 30 high-cost medicines were chosen based on information from the Main Association of Austrian Social Insurance Institutions (out-patient sector) and the Viennese hospital association (in-patient sector) about these medicines that accounted for highest expenditure in their budget in 2012.

[8] Price data of generics were excluded from this study. The exchange rates used to calculate Euro prices are the rates provided by the Austrian National Bank for March 2013.

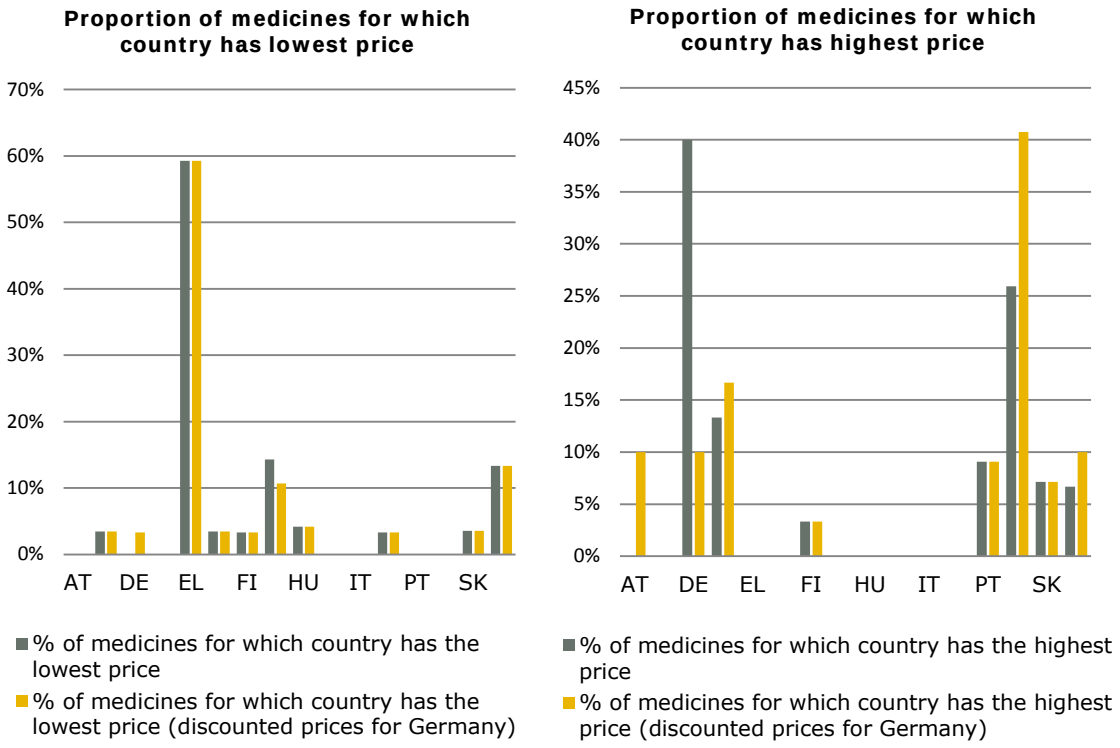
Figure A5: Differences (in percent) between ex-factory price in the highest and lowest price country, 2013



Source: Data provided by Pharma Price Information (PPI) of Austrian Public Health Institute [13]

Figure A6 shows the proportion of pharmaceuticals for which countries constitute the highest or lowest price level. It is striking that for this 2013 data, Greek prices constituted the lowest price for 16 out of 27 pharmaceuticals available in Greece.

Figure A6: Proportion (in percent) of medicines for which a country has the lowest/highest price among the sample

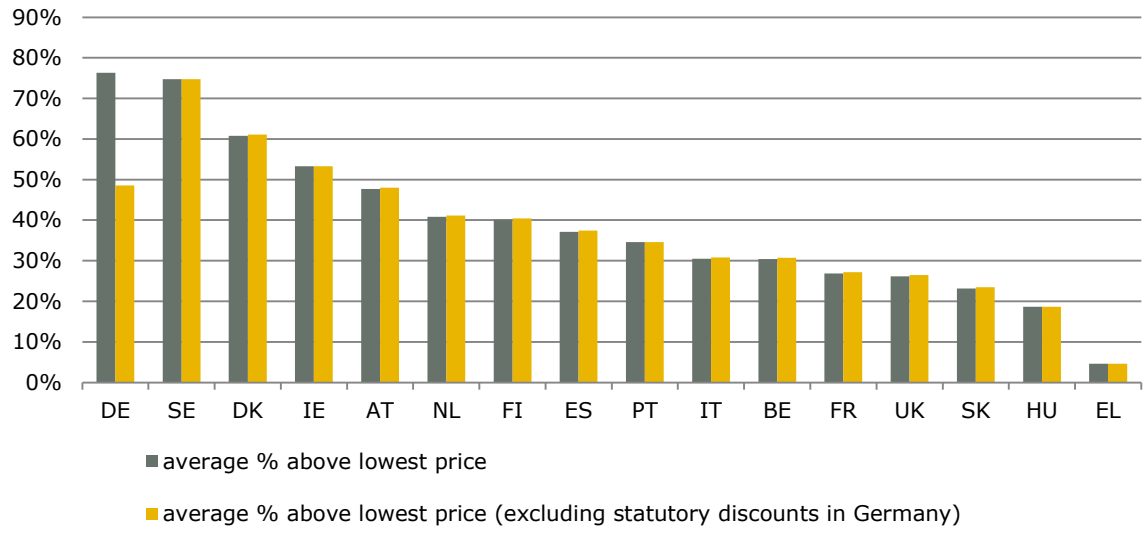


Source: Data provided by Pharma Price Information (PPI) of Austrian Public Health Institute [13], authors' calculations

Figure A7 compares price levels of the 30 chosen pharmaceuticals by showing the average percentage that prices are above the minimum price observed for a particular pharmaceutical.[9] Figure A8 shows the average percentage difference to the mean medicine price by country. This analysis confirms that Greece had the lowest medicine prices among the country sample, with, on average, prices being 4.6% above the minimum price and 23.4% below the mean price. This is in line with the results of other price studies [10, 14] which have found drastic reductions in Greek medicine prices, likely the result of numerous price cuts in recent years. By comparison, in Germany prices were on average 76.3% above the minimum and 26.9% above the mean price, which falls to 48.5% and 7.8% respectively when taking into account the statutory 7% discounts in place in Germany. According to this analysis, when considering mandatory discounts in Germany, the highest price countries within the sample were Sweden, Denmark and Ireland.

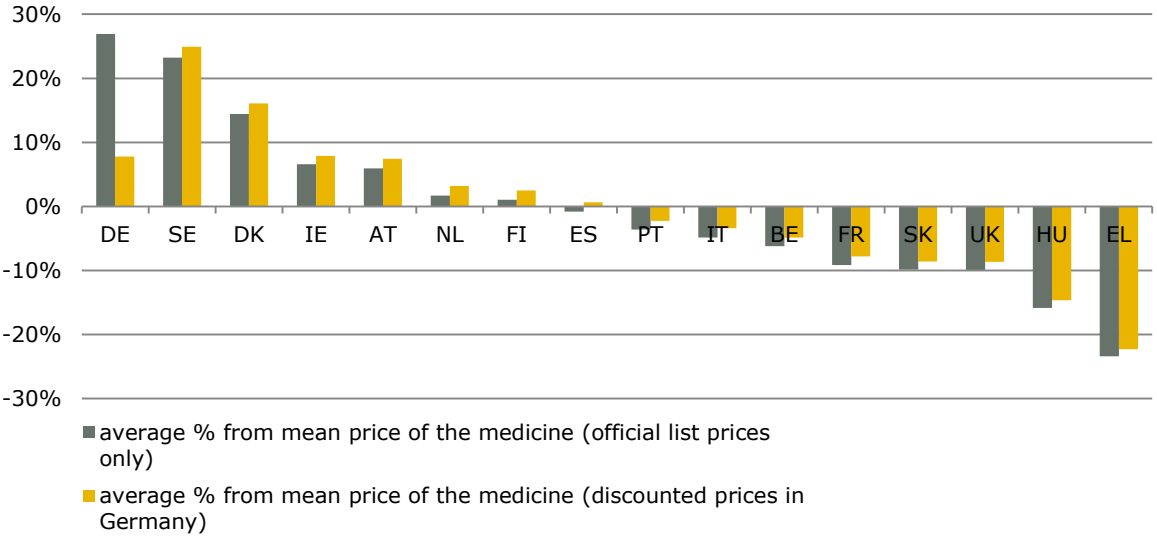
[9] Such representation is chosen for instance since not all pharmaceuticals have prices available for all countries. Using absolute averages would thus distort the comparison.

Figure A7: Average percentage above minimum price, by country



Source: Data provided by Pharma Price Information (PPI) of Austrian Public Health Institute [13], Authors' calculations

Figure A8: Average percentage difference to mean price, by country



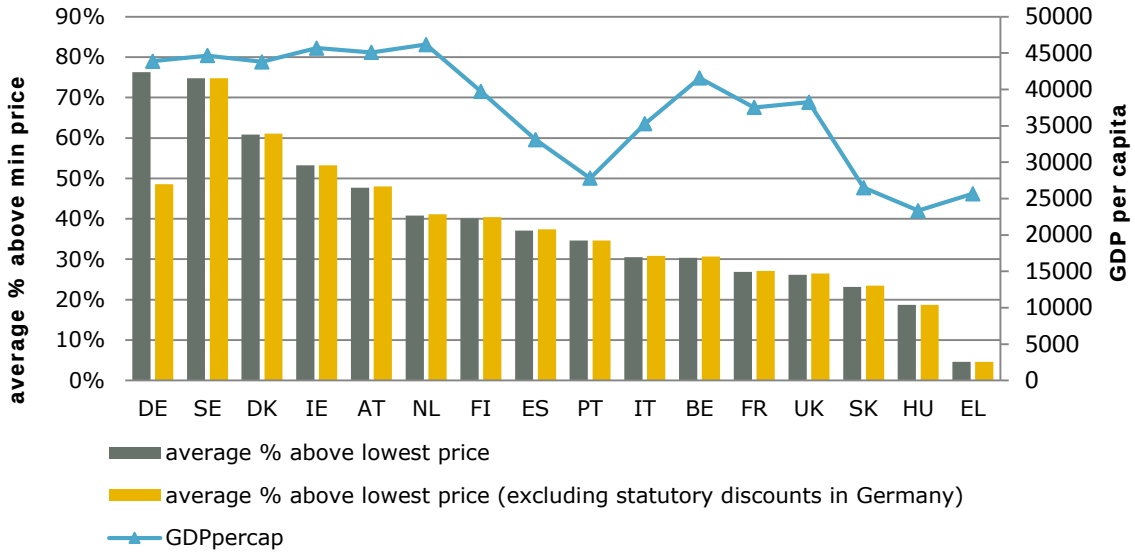
Source: Data provided by Pharma Price Information (PPI) of Austrian Public Health Institute [13], Authors' calculations

Price levels and GDP per capita

Figure A9 and Figure A10 compare the observed differences in price levels with GDP per capita. The countries with lowest GDP per capita among this sample are Hungary, Greece and Slovakia and a positive correlation between prices and GDP per capita can be observed, i.e. wealthier countries tend to have higher prices. Indeed, the correlation between average percentage from mean or minimum price and GDP per capita is as

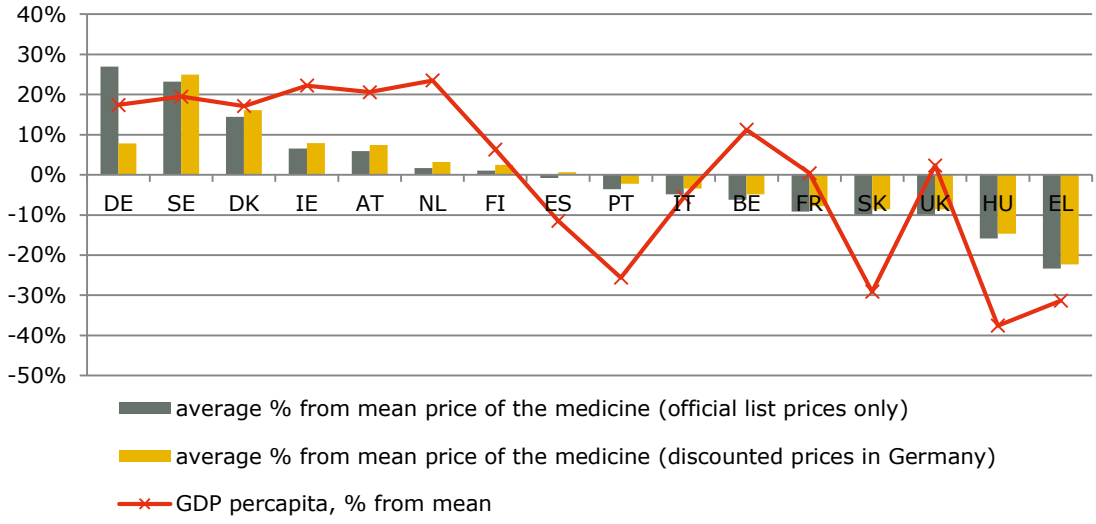
high as 0.74, almost identical to the correlation between pharmaceutical price and GDP per capita within the EPR model.[10]

Figure A9: Percentage above minimum pharmaceutical price and GDP per capita (in PPP)



Source: Data provided by Pharma Price Information (PPI) of Austrian Public Health Institute [13], Authors' calculations

Figure A10: Percentage from mean medicine price and GDP per capita (in PPP)



Source: Data provided by Pharma Price Information (PPI) of Austrian Public Health Institute [13], Authors' calculations

[10] No regression analysis is presented here, since it is difficult to identify any causal relationships within such a small sample, available for one time period.

Comparing Model Results to real 2015 List Prices

This section aims to **feed real-life list prices into the illustrative model** (Section 3.3) and compare results to observed pricing data. Model results are expected to differ to observed list prices for several reasons:

- First, the model makes several simplifying assumptions. Most importantly, the model assumes that all countries using EPR use it as their sole criterion when determining prices and thus only EPR leads to price changes within the model. Model results thus show prices that would result if countries used no other mechanisms (such as negotiation) in addition to their official EPR rules. It is also assumed that countries implement the official rules as stated (such as regular price revisions at the defined time intervals).
- Secondly, to make the comparison, the same exemplary situation as under the base scenario is used. That means that the observed prices in Germany and Italy are used as the starting prices for a newly launched medicine as is done under the base case. Consecutively prices in all other countries result from their EPR rules and price revisions over a time span of 10 years refereeing to these two initial launch prices. The comparison thus does not use the actual market entry prices when these medicines first came to the market but current prices of two countries as launch prices, and further uses the exchange rates over the past years, which would not be the same exchange rates used when EPR for these medicines was applied depending on when revisions actually took place.

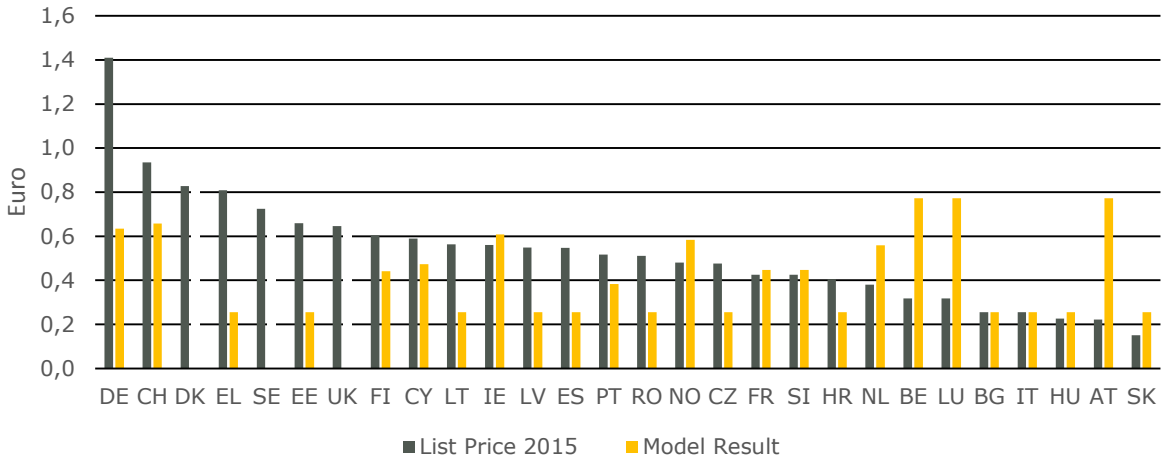
For the comparison **two originator medicines with high budget impact were selected**. First, the originator medicine of **Escitalopram**, an antidepressant with high budget-impact due to large sales quantity, and secondly the originator medicine **Imatinib,** an expensive cancer treatment. Prices are sourced from the Pharma Price Information service (PPI) located at the Austrian Public Health Institute and are list prices for July 2015 for medicines of the same dosage that have been normalised to unit size.[11] As was done in the base case, the model assumes that the medicine is launched in Germany and Italy. The simulation here uses the real German and Italian prices as starting prices and then allows all countries to perform EPR and re-evaluate according to their EPR rules over a time-span of 10 years.

Figure A11 shows real 2015 prices compared to model results for Escitalopram for all countries for which price data for Escitalopram is available.[12] For most countries, the model price is lower than the actual current price. This is unsurprising, since current prices are used as starting values and countries are able to re-evaluate regularly over a certain time-span. As can be seen, for instance for Greece, the model price is less than half of the current price. On the other hand, for Austria and Belgium the prices under the model are significantly higher than what is actually observed. Luxembourg in the model directly refers to Belgium and thus its price is dependent on the Belgian market. For Austria and Belgium, since the official rules do not require mandatory, regularly price-revisions, under the model there are no re-evaluations assumed and thus the price remains high.

[11] In the case of Imatinib, the Italian price refers to a different dosage but has been normalised to the same strength.

[12] Availability of a list price does not necessarily indicate that the product is on the market.

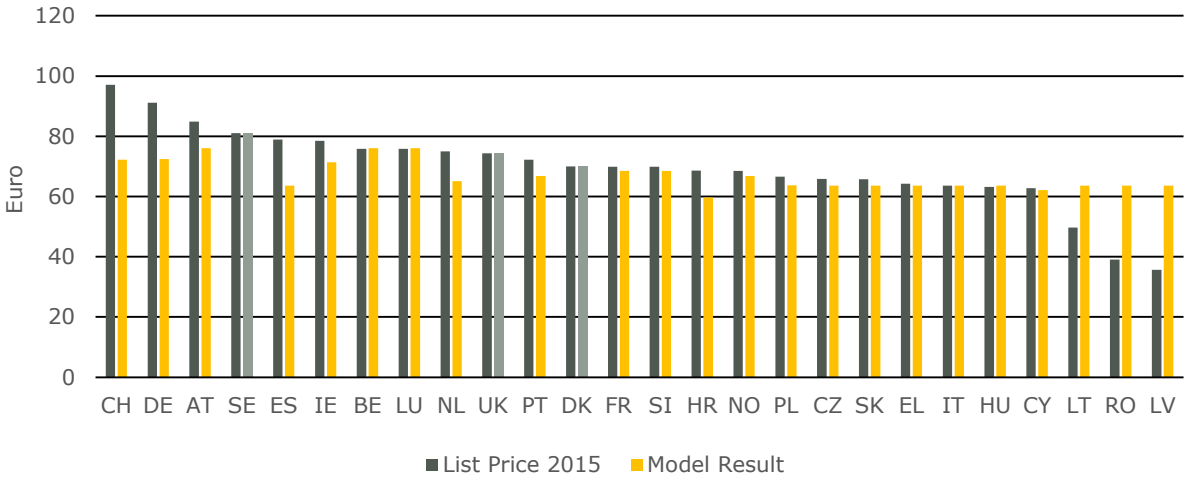
Figure A11: Escitalopram: 2015 List prices compared to Base Scenario Model Results



Source: Pharma Price Information (PPI) service of the Austrian Public Health Institute, authors' calculations

Figure A12 compares current prices of Imatinib with results from the model when actual prices for Germany and Italy are used as launch prices. Here, model prices differ less to the collected pricing data. They differ most for countries with very high or very low prices. Since the model only considers price changes due to EPR, and EPR signifies methodologies such as average or minimum of observed prices in other countries, the model prices never really go above the highest launch price, or below the lowest launch price, with some slight exceptions due to exchange rate fluctuations. Thus, the model results differ most for those countries with actual prices below Italy's where the model results in higher prices on the level of Italian prices.

Figure A12: Imatinib: 2015 List prices compared to Base Scenario Model Results



Source: Pharma Price Information (PPI) service of the Austrian Public Health Institute, authors' calculations

These comparisons illustrate the working of the model when using real rather than fictitious prices and show that model results differ from real prices, however in the directions expected due to the simplifying assumptions made by the model.

12 Annex 12: Price impacting factors

In the following, price studies are analysed with regard to their findings in general and in particular to possible factors.

Table A9: Price studies on possible price impacting factors

Author(s)	KONIJN, Paul
Title	Pharmaceutical products – comparative price levels in 33 European countries
Journal	Economy and Finance
Research question	To construct Purchasing Power Parities by using prices for pharmaceuticals
Country/Countries included	33 European countries (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Iceland, Italy, Latvia, Lithuania, Luxembourg, Macedonia, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom
Reference year(s)	November 2005
Products	181 different medicines; For each country a list of best-selling medicines has been compiled and products from the top of the list have been selected; the selected product contained on-patent (75%) and off-patent (25%) pharmaceuticals
At what price level	Not clearly specified; It is mentioned that the prices collected should represent the full market price of a product (independent of what is paid out-of-pocket or covered by social security schemes); The author mentions that prices were collected by visiting pharmacies, implying that the pharmacy retail price was used;
Methodology	With the obtained prices for the 181 medicines, purchasing power parities have been calculated
Results	Countries can be divided into six groups: The top groups (IS & CH) have significantly higher price levels, being 60 to 87% higher than the EU25 average. In the second group of most expensive countries price levels are between 15 and 30% higher than the EU 25 average (DK, DE, IE, IT, NO). The third group has price levels between 0% and 15% higher than the EU average (BE, CY, LU, MT, NL, AT, FI). The fourth group has price levels between 0% and 15% lower than the EU25 average (FR, PT, SI, SE, UK). A large group (mainly new EU member states) has price levels between 68 and 80% of the EU25 average (BG, CZ, EE, EL, ES, LV, LT, HU, PL, RO, SK, HR, TR). The lowest price levels are found in the Former Yugoslav Republic of Macedonia at 58% of the EU25 average.
Limitations	The level of uncertainty associated with the underlying price and other data, and the methods used for compiling PPPs and PLIs imply that strict ranking of countries is not advisable
Sponsors	None
Conclusions of the study	Prices for original medicines (those that are or have been covered by a patent) are less dispersed than those of generics
Comments (own)	The author does not adequately address the methodologically challenges when comparing pharmaceuticals. He simply states that pharmaceuticals are relatively easy to compare, since they can be identified among other things by active substance. He provides no description which prices are compared and how differences in packaging or strength are taken into account. If the author had used the pharmacy retail price he should explain how to deal with (1) different VAT rates, (2) the fact that in some countries it is not possible to calculate a pharmacy retail price (UK) and (3) some top-selling products are sometimes only administered in hospitals; No further description on the products and if availability in all countries was a requirement

Source: Konijn P [15]

Author(s)	LEOPOLD, Christine; MANTEL-TEEUWISSE, Aukje Katja; SEYFANG, Leonhard; VOGLER, Sabine; DE JONCHEERE, Kees; LAING, Richard Ogilvie; LEUFKENS, Hubert
Title	Impact of External Price Referencing on Medicine Prices – A price Comparison Among 14 European Countries
Journal	Southern Med Review
Research question	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
Country/Countries included	14 European countries (Austria, Belgium, Denmark, Germany, Greece, Finland, France, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, Slovakia)
Reference year(s)	2007 & 2008
Products	14 on-patent medicines in the out-patient sectors (hospital-exclusive products were excluded)
At what price level	Ex-factory prices in EUR (For price comparisons, the prices were analysed in prices per units)
Methodology	The unit ex-factory prices in Euro of all products, all countries and of both years were adjusted to a fixed exchange rates were converted to scaled ranks. For the regression analysis the scaled ranks per country and product where weighted. Each country had the same sum of weights. Within a country the weights were proportional to its sales volume in the year.
Results	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. This interaction persisted after inclusion of total pharmaceutical expenditure per capita and GDP per capita.
Limitations	The dummy variable EPR implies homogeneity which does not exist: EPR is very differently applied in the countries in terms of the country basket, frequency of price updated and the price calculation method; Another confounding factor is that EPR is only one of many pharmaceuticals price regulation policies
Sponsors	None
Conclusions of the study	Prices for patented products 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 ranks. However, it needs to be acknowledged that huge price difference could be found between countries which apply external price referencing
Comments (own)	▪ The authors state that the main criterion for choosing the products was the patent status of each medicine; Nothing is mentioned about the relevance of these medicines; ▪ No explanation for choosing the countries is provided ▪ Countries are ranked due to the prices of medicines; by using ordinary least squares (OLS) regression it is only possible to make statements about the qualitative effect of EPR (i.e. positive or negative) but not about the quantitative effect (i.e. size) → a logit regression would have been interesting to examine the probability of yielding a better rank when EPR is in place. ▪ The best predictor for TPE per capita is GDP per capita; the inclusion of both might not be necessary, since also the p-value for GDP per capita was low → a comparison of (adjusted) R^2, Schwarz-Bayesian Criterion (SBC) or Akaike information criterion (AIC) would have been interesting.

Source: Leopold C, Mantel-Teeuwisse AK, Seyfang L, *et al.* [16]

Author(s)	BREKKE, Kurt Richard; TOR, Helge Holmas; ODD, Rune Straume
Title	Are Pharmaceuticals Still Inexpensive in Norway
Journal	Report of the Institute for Research in Economics and Business Administration (SNF)
Research question	To compare prices of pharmaceuticals in Norway and nine Western European countries which constitute the basket of countries that form the basis for setting maximum prices for prescription medicines in Norway. To study the change in price levels and price indices over the three last three years To compare pharmacy margins across ten countries
Country/Countries included	10 European countries (Norway Austria, Belgium, Denmark, Finland, Germany, Ireland, the Netherlands, Sweden, UK)
Reference year(s)	2007 & 2008
Products	300 top-selling (prescription bound) active substances (include on-patent and off-patent)
At what price level	Pharmacy purchasing price & pharmacy retail price
Methodology	Using the sales data, the authors compute volume-weighted average prices for each active substance; When constructing price indices for other countries they have been assigned Norwegian consumption weights to reflect a representative pattern of consumption in the benchmark country; In this way, it can be ascertained what a typical Norwegian pharmaceutical basket would cost in the various reference countries;
Results	UK, Norway and Sweden are the three cheapest countries in the reference group of then Western European countries, whereas Ireland Belgium and (usually) Germany are the three most expensive countries. This ranking is also fairly consistent across submarkets as the patent and generic market segments;
Limitations	Disadvantages are essentially related to a lack of representativity: 1.) Picking only the best-selling pack for each substance, implies that we throw away information about all other packs for this substance 2.) Top-selling pack in Norway may not be among the top-selling ones in the reference countries
Sponsors	None
Conclusions of the study	UK, Norway and Sweden consistently have the lowest pharmacy retail prices of prescription medicines whereas Ireland, Belgium and Germany have the highest prices. Comparing price indices from 2007 to 2009 revealed that there are large changes in the price indices from 2008 to 2009. All countries become more expensive than Norway, but this is mainly driven by exchange rate fluctuation.
Comments (own)	▪ What does volume-weighted mean for an on-patent active ingredient? ▪ When constructing average prices for active ingredients, how are different strengths taken into account: e.g. Rosuvastatin 20 mg and 40 mg? Instead of IMS standard units DDD/ATC per package should have been used for regression ▪ The authors focused on pharmacy retail price without value added tax (VAT) but they did not discuss the comparability of this price level in other countries (e.g. UK). ▪ The authors did not explain if top-selling active ingredients are only administered in the out-patient sector. ▪ The two additional variables in the regression analysis should have been explained more in detail

Source: Brekke KR, Holmås TH and Straume OR [12]

Author(s)	LEOPOLD, Christine; MANTEL-TEEUWISSE, Aukje Katja; VOGLER, Sabine; DE JONCHEERE, Kees; LAING, Richard Ogilvie; LEUFKENS, Hubert
Title	Is Europe still heading to a common price level for on-patent medicines? An exploratory study among 15 Western European Countries
Journal	Health Policy
Research question	To explore whether ex-factory prices of on-patented medicines in Western European countries have converged over a recent period of time
Country / Countries included	15 Western European countries (Austria , Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland)
Reference year(s)	2007, 2008, 2010, 2011, 2012
Products	Ten on-patent products according to (1) Patent status (2) ATC groups (3) reimbursement (4) Marketing authorisation holder (MAH) and (5) price segment
At what price level	Ex-factory price in EURO For price comparisons, prices were analysed in prices per daily defined dosis (DDD)
Methodology	To analyse the price variance between countries for each product the range as well as the average of the unit ex-factory price in Euro per DDD indexed to 2007 was calculated 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:
Results	▪ The prices between countries and selected products varied to a great extent. Germany, Denmark and Finland were the countries with the highest prices. Greece was the country with the lowest prices followed by Italy, Spain and France. The price range was relatively small and constant over the years for some products whereas others experienced lager and increasing range. ▪ From 2007 to 2008 price divergence decreased, but from 2008 to 2012, the price divergence is only driven by two country: Germany (27 % higher prices) and Greece (32% lower prices) ▪ The prices of medicines decreases between 2007 and 2012 for all but one product
Limitations	▪ Disregard of discounts/rebates: the unit ex-factory price is 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. ▪ Unavailability of volume date: due to limited financial resource volume data could not be acquired. ▪ Sample size: Due to the small sample size it is a study with an explorative character, and conclusions should be considered tentatively. ▪ Currency fluctuations: Over the period exchange rates fluctuated extremely over time;
Sponsors	None
Conclusions of the study	Differences in medicine prices across countries and over time are confirmed. Instead of the expected price convergences a price divergence can be observed, driven by price changes in only two of the 15 countries. All other European countries remained stable around the country average.
Comments (own)	▪ Relevance of pharmaceutical industry is acknowledged and should be taken into account for further price analysis (e.g. employees in pharmaceutical industry per 100,000) ▪ Volume data are mainly used for the construction of price index

Source: Leopold C, Mantel-Teeuwisse AK, Vogler S, *et al.* [17]

Author(s)	KANAVOS, Panos; VANDOROS, Sotiris
Title	Determinants of branded prescription medicine prices in OECD countries
Journal	Health Economics, policy and law
Research question	To investigate the determinants of the prices of branded prescription medicines across different regulatory settings and health care systems, taking into account their launch date, patent status, market dynamics and the regulatory context by which they diffuse.
Country / Countries included	15 OECD countries (USA, Japan, France, Germany, Italy, Spain, UK, Australia, Mexico, Austria, Portugal, Sweden, Greece, Slovakia, Belgium)
Reference year(s)	2004 and 2007
Products	50 leading originator branded prescription-only products (off-patent/on-patent)
At what price level	Ex-factory prices in EUR (For price comparisons, prices were analysed in prices per DDD)
Methodology	With the collected prices the authors built an econometric model and applied panel data analysis; explaining variables were (1) the number of years since the product's launch in a local market plus it's square (2) if generics are available (3) country dummies for UK, USA and MEX (4) exchange rate movements (5) dummy variables for HTAs, IRP and ERP and (6) therapeutic class
Results	▪ Newer classes of prescription medicines are more expensive ▪ The influence of generics is not significant ▪ Country variables are all positive and significant
Limitations	▪ No available data on advertising, for example in the form of expenditure in detailing, to test its impact on prices, although a recent systematic review has shown that advertising influences prescribed volume The inclusion of the US dummy captures any unexplained heterogeneity surrounding direct to consumer advertising as this is the only country in the sample where it is allowed. ▪ Disregard of in-patient sector: it may be the case that outliers may exist in terms of products that are sold in in-patient settings, which are highly specialised. ▪ It is not possible to account for any hidden rebates given from manufacturer to health insurers
Sponsors	None
Conclusions of the study	Ex-factory prices for branded originator prescription medicines between United states and other countries, particularly key European markets, are significant, but these are not the prices that health insurers pay. By contrast, public price differences have been exaggerated and are not as high as originally thought. Differences between USA and Europe are greatest for off-patent originator brands and significantly lower for in-patent originator brands. Product age has a significant effect on originator brand prices in all settings. Price convergence is observed across countries for never compared with older originator brands and could be partly attributed to the extensive use of external price referencing.
Comments (own)	▪ Price comparisons have been conducted at ex-factory price level and pharmacy retail price level, but they did not discuss the comparability of pharmacy retail prices ▪ The inclusions of age square implies an U-shaped relationship probably related to the 'generic paradox' it could have been interesting to calculate at which age the vertex is; ▪ All country dummies for the other countries should have included and then tested if they could have been omitted

Source: Kanavos PG and Vandoros S [11]

Author(s)	VOGLER, Sabine; KILPATRICK, Kate; BABAR, Zaheer-Ud-Din
Title	Analysis of Medicine prices in New Zealand and 16 European Countries
Journal	Value in Health
Research question	To compare prices of medicines, both originators and generics, in New Zealand and 16 European countries
Country/Countries included	New Zealand, Austria, Belgium, Denmark, Germany, Greece, Finland, France, Italy, Ireland, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, UK
Reference year(s)	June 2012
Products	14 medicines according to (1) equal balance of medicines of different indications (2) different price segments (3) different patent expiry status and (4) different reimbursement status (On-Patent/Off-Patent medicines in In-patient/Out-patient sector)
At what price level	Ex-Factory prices in EUR (For price comparisons, prices were analysed in prices per Unit)
Methodology	After collecting price data on prices per Unit they were order and the range between highest and lowest price was divided into quartiles. Then the remaining prices of the other countries where assigned to each quintile
Results	▪ High variation in medicine prices; for most of the selected medicines, the price of the product in the highest price country was at least twice the price of the medicine in the country with the lowest price. For a few medicines, particularly generics, cross-country price differences amounted up to 1,000% ▪ Among European countries, Greece and Portugal, and also but to a lesser extent Spain United Kingdom, and The Netherlands frequently ranked in the lowest quartile, and have displayed the lowest price in some cases. Countries ranking at the higher end were Switzerland, Germany, Denmark and Sweden.
Limitations	▪ The study is based on single medicines, and therefore the findings can only provide an indication for the price level of medicines in a country ▪ The basket of medicines is not very large but includes a range of medicines addressing different indications. The rather small size of the basket resulted from limited data availability and comparability between European countries and New Zealand, ▪ The price survey is based on official list prices. Due to discounts and rebates in different forms granted by the industry to public payers, the actual prices are likely to be different (i.e. lower). Because these discounts and rebates are mostly confidential and not disclosed, they were not included in the price data
Sponsors	None
Conclusions of the report	Medicine prices varied considerably between European countries and New Zealand. Within the European countries, Greece, Portugal, the United Kingdom and Spain had prices at the lower end, whereas prices in Switzerland, Germany, Denmark, and Sweden were at the upper end. These difference are likely attributable to underlying national pricing and reimbursement policies, which are affected by public health and industry-related policy goals as well as by the economic situation of the country. The study confirmed that countries that were strongly hit by the global financial crisis took several cost-containment measures related to medicine prices such as price cuts.
Comments (own)	▪ Description how the quartiles are constructed is missing ▪ The article provides a good overview about differences in price levels in the examined countries, However, analysis of influences on these differentials is rather descriptive than quantitative (underpinned by an econometric analysis)

Source: Vogler S, Kilpatrick K and Babar ZUD [10]

Author(s)	DANZON, Patricia; FURUKAWA, Michael
Title	Prices and Availability of Pharmaceuticals: Evidence from Nine Countries
Journal	Health Affairs
Research question	To provide a more representative comparison of medicine prices and to examine how relative medicine prices have changed
Country/Countries included	USA, Canada, Chile, France, Germany, Italy, Japan, Mexico, UK
Reference year(s)	1999
Products	249 molecules; selected on leading active ingredients by US unit (dose) sales volume (On-Patent medicines, Off-Patent medicines/Generics, OTCs)
At what price level	(net) Ex-Factory prices in EUR (For price comparisons, prices were analysed in prices per IMS Standard Units)[13]
Methodology	For each active ingredient a price is calculated through a volume-weighted average price per dose over all presentations in that molecule-indication in that country.
Results	▪ Adjustment for off-invoice discounts reduces US prices by roughly 8 percent overall; the discount adjustment differs slightly across countries depending on the product mix ▪ Prices in Japan are highest followed by US Prices. in Canada prices are the lowest; ▪ When comparisons are restricted to identical presentations this yields upwards-biased estimates of US prices.
Limitations	▪ The data show use of the sample compounds only, not differences in total per capita medicine consumption ▪ The sample selection focused on leading US products and products recently launched in the US, and therefore could appear biased toward launches in the US ▪ The comparison of total units obscures differences in formulations, which are discussed elsewhere
Sponsors	None
Conclusions of the study	When Adjusting for US manufacturer discounts, Japan's prices are higher than US prices. Exchange rate fluctuations contribute to the finding of lower Canadian prices and higher UK prices in 1999 than in 1992. The findings suggest that US-foreign price differentials are roughly in line with income and smaller for medicines than for other medical services. The tendency for US policy-makers to compare US prices to Mexican prices and the threat of importation plausibly makes manufacturers reluctant to offer prices in Mexico that are more in line with that country's average per capita income; The relatively unregulated, more competitive market structure of the US market seems to result in relatively high prices for on-patent originator products and relatively high use of new products, but also strong generic competition, high generic shares and low generic prices.
Comments (own)	▪ The studies aims to make a price comparison between countries at discounted/net prices, but the size of the discounts base on an estimation; For all countries the same discount rate is assumed → sensitivity analysis would have been necessary. ▪ IMS Standard Units do not take into account if the same pharmaceutical form (i.e. tablet) has the same strength; Price per ATC/DDD would have been better

Source: Danzon PM and Furukawa MF [18]

[13] https://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/IMS_Therapy_Prognosis_Sample_Report.pdf

Author(s)	DANZON, Patricia; FURUKAWA, Michael
Title	International Prices and Availability of Pharmaceuticals in 2005
Journal	Health Affairs
Research question	To compare pharmaceutical spending, availability, use and prices of pharmaceuticals in 12 countries
Country/Countries included	USA, Canada, France, Germany, Italy, Spain, UK, Japan, Australia, Brazil, Chile, Mexico
Reference year(s)	2005
Products	All prescription medicines and Over-the-counter (OTC) of single-molecule products in the out-patient sector
At what price level	Ex-factory prices & Pharmacy (gross) retail prices
Methodology	Two price indexes where constructed: (1) an index that compared prices for all products that match on active ingredient and indication, regardless of formulation, strength, brand or prescription status (2) an index that compared prices only for products that match on molecule, indication, strength and formulation; All price indexes are weighted by US volume weights and converted into US dollars.
Results	▪ Index (1) showed that most countries' prices are 20-40 percent lower than US prices. Index (2) is similar, generally differing less than five percentage points; Mexican ▪ Foreign public prices are only 10-30 percent lower than the US prices, compared to 20-40 percent lower for foreign manufacturer prices. Distribution margins absorb a larger share of total pharmaceutical spending in several regulated markets. ▪ Comparisons using PPPs rather than exchange rates, because with exchange rates medicine prices are probably biased downwards poorer countries ▪ Manufacturer's prices should be normalised by average income (GDP per capita) as a rough measure for affordability
Limitations	Authors did not report explicitly limitations.
Sponsors	None
Conclusions of the study	Price comparisons with USA are biased upward, because it ignores the US tendency to use more new, expensive products. The higher overall per capita volume in other countries compared to the US is solely attributable to the use of older products The foreign U.S. medicine price differential is smaller at public prices, than at manufacturer prices, because distribution margins are generally higher abroad Price differentials remain roughly in line with differences in per capita income. This suggest that greater affordability of medicines in these countries will require review of their regulatory structure and lack of price competition among generics, in addition to strategies to prevent any concern of originator manufacturers over US price referencing of medicine importation that may contribute to higher prices.
Comments (own)	▪ Exclusion of combination medicines disregards medicines with a considerable proportion of sales (e.g. Eviplera, Altriplera, Harvoni, Symbicort, Truvada) ▪ The authors analysed ex-factory prices and pharmacy retail price with VAT but they did not discuss the comparability of the latter price level in other countries (e.g. UK).

Source: Danzon PM and Furukawa MF [19]

13 Annex 13: Legal analysis – Detailed results

The following legal analysis aims at investigating whether and which legal constraints exist in EU law that would prevent the introduction of a EU-wide coordinated Differential Pricing (DP) scheme and whether or which legal changes would be necessary in order to allow such a EU-wide policy.

Whereas there is usually free pricing for medicines not funded by public payer, pricing of medicines eligible for reimbursement are usually regulated by national competent authorities. In reality, different income levels of member states (MS), national policies for pricing and value assessment, varying national approaches to regulating wholesale and retail distribution as well as different taxation of pharmaceuticals influence a pharmaceutical companies' pricing strategies[14].

Pricing policies and **laws** for the marketing of medicines lie in the national **competence of the 28 EU Member States (MS)** and MS have implemented different pricing strategies and systems. The EU does not have the power to define common market pricing mechanisms, and so pricing is a national issue between national competent authorities.

In this whole process, the **bargaining powers which MS have towards industry differ to a high extent**, partially leading to different result that include, e.g. **volume controls**, **indirect price**, **profit controls** and recently Managed Entry Agreements (MEA).[15] As Hervey & McHale (2004) state, the reasons for one or the other approach depend more or less on the necessity of a MS to support its pharmaceutical industry.[16] Similar, the Advocate General argued in his opinion in *GlaxoSmithKline (GSK II)*[17]: '*the level at which the selling price or the amount of reimbursement of a given medicinal product is fixed reflects the relative strength of both, the public authorities of the rele-*

[14] For an overview see Directorate-General for Internal Policies (2011), Report requested by the European Parliament's Committee on Environment, Public Health and Food Safety, Executive Summary: Differences in Costs and Access to Pharmaceutical Products in the EU, available at europarl.europa.eu/document/activities/cont/201201/20120130ATT36575/20120130ATT36575EN.pdf (accessed: 3.4.2015): Table 1 at p. 37: Pharmaceutical regulation in Europe (overview) and Impact of MS regulation on differences in pharmaceutical prices and access to medicine, key findings at p. 32.

[15] In its 2008 Communication, the Commission stated in this context, that '[…]*stakeholders continue to raise concerns with regard to the market fragmentation linked to disparities in national pricing and reimbursement schemes, unnecessary regulatory burdens caused by divergences in the implementation of Community legislation, and a lack of commercial interest in national markets which are economically less attractive*.', Communication to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions regarding Safe, Innovative and Accessible Medicines, towards a Renewed Vision for the Pharmaceutical Sector, COM(2008) 666 final, 10.12.2008, p. 5.

[16] Hervey & McHale (2004), at 321: '*Where a state is concerned also to support its internal pharmaceutical industry, and to promote its research and development and export capacity, the former two methods* [remark: profit controls laid down by administrative action or as a result of negotiations between the national government and the pharmaceutical industry] *are favoured (for instance, Germany, UK). Where there is less of a concern for the home grown pharmaceutical sector, stricter profit or price controls are more likely to be used (for instance, Belgium, Spain, Portugal, Greece). This division goes some way to explaining the division between 'high price' Member States such as Germany, and 'lower price' Member States such as Belgium*.' For examples of price differences see Directorate-General for Internal Policies (2011), pp. 23 ff.

[17] Joined Cases C-468/06 to C-478/06, *Sot. Léos Kai Sia EE (and Others) v. GlaxoSmithKline AEVE* [2008] ECR I-7137, point 63.

vant Member State and the pharmaceutical companies at the time of the price negotiations for that product.' Recent studies show that **current pricing policies of MS do not lead to relatively lower prices for countries with lower GDP per capita**.[18]

When it comes to regulation of **competition and competition policy**, there would thus be many reasons for differentiating the pharmaceutical sector from other markets since health, including medicines, is public good. But even though pricing mechanisms depend to a high extent on MS' pricing and reimbursement policies and in fact there does not exist a regular market for pharmaceuticals[19], the pharmaceutical market has to respect EU rules resulting from the **four freedoms**, including free movement of goods and the pharmaceutical market is – to a certain extent – subject to subsequent **EU competition rules**. Especially in the field of generics and non-prescription medicines, the Commission relies on competition rules for a functioning market. But also the prescription pharmaceutical market, mostly under universal coverage of MS health systems, is subject to free market rules. One of the consequences of this fundamental Treaty principle of free movement of goods and Commission competition policy is the advancement of parallel trade. Albeit the European Court of Justice (ECJ) in the meantime slightly starts to demand a policy change in this context.[20]

This leads to a rather complicated system with **market influencing factors** resulting from market and competition rules **at EU level** and in the (legislative) power of the EU on the one hand and different **pricing policies in the power of Member States** on the other hand.

In this context it is also important to keep in mind that the EU's pharmaceutical sector policy is in line with its internal market policy and therefore the Commission strongly monitors its **policy impact on pharmaceutical investments and R&D developments**. The Commission already is highly alerted since pharmaceutical R&D activities declined in the EU in comparison to US activities, leading to the question of whether different pricing policies lead to budgetary shortfalls in the pharmaceutical industry and to reduced R&D investments in Europe.[21]

13.1 Division of powers (EU – MS) and the healthcare sector

From a legal perspective, limitations in EU law that can prevent the implementation of a DP scheme coordinated among EU Member States would have its origin in the impact of fundamental Treaty principles (i.e. free movement of goods and its impact: parallel

---

[18] Carone G, Schwierz C, Xavier A, Cost-containment policies in public pharmaceutical spending in the EU, Economic Papers 461, September 2012, Graph 1, p. 16, available at http://ec.europa.eu/economy_finance/publications/economic_paper/2012/pdf/ecp_461_en.pdf

[19] See e.g. Schulz-Weidner W, Felix F, Die Bedeutung des europäischen Wettbewerbsrechtes für die österreichische Sozialversicherung (Teil I), *SozSi* 2001, 435, at doc view print p. 20: '*Schließlich sprechen aus ökonomischer Sicht ernsthafte Erwägungen für die Annahme, dass durch ein koordiniertes Vorgehen die Voraussetzungen für einen effektiven Wettbewerb überhaupt erst geschaffen werden. Wettbewerb setzt auf der Nachfrageseite voraus, dass der Akteur äußerstenfalls auf das gewünschte Gut verzichten kann, wenn dieser Verzicht auch mit wirtschaftlichen Risiken verbunden sein mag. Mit anderen Worten: 'Risiko' bedingt wenigstens die rechtliche Freiheit, auf ein bestimmtes Produkt verzichten zu können. Im Bereich medizinischer Versorgung ist ein solcher Verzicht seitens der Kassen wegen des Sachleistungsprinzips und des gesetzlichen Sicherstellungsauftrags jedoch schon aus Rechtsgründen nicht möglich, ganz abgesehen davon, dass er im Interesse der Pflichtversicherten auch aus sozialpolitischen Gründen nicht akzeptabel wäre*.'

[20] See Legal Analysis, Chapter on Parallel Trade (intra-brand competition).

[21] See COM(2008) 666 final, supra note 14.

trade) and in areas or categories of missing or non-existing **EU competence**. The following legal analysis therefore first illustrates fundamental principles in this context before specifically analysing limitations on the one hand and areas of competence or possibilities of shaping pharmaceutical pricing policies at EU level on the other hand.

According to Art. 3a 1. Treaty on the European Union (**TEU**)[22], the EU can only perform legislative power within the limits of the competences explicitly conferred to the EU (**principle of conferred powers**): '[C]*ompetences not conferred upon the Union in the Treaties remain with the Member States*'. As stated for instance by the German constitutional court, this principle is not only implemented in EU law, but also in German constitutional law, since the European Union is a Union of 28 sovereign states.[23]

Further relevant principles defining EU's legislative powers are the principle of subsidiarity and proportionality. According to the **principle of subsidiarity**, '*the Union shall act only in so far as the objectives of the proposed action cannot be sufficiently achieved by the Member States, either at central level or at regional and local level, but can rather, by reason of the scale or effects of the proposed action, be better achieved at Union level*' **(Art. 5 3. TEU).** According to the **principle of proportionality**, '*the content and form of Union action shall not exceed what is necessary to achieve the objectives of the Treaties*'. **(Art. 5.4. TEU)**.

As stated by the Protocol (No. 2) on the Application of the principles of subsidiarity and proportionality[24] this means that each institution, respectively the **European Commission, is advised to find '*qualitative and, wherever possible, quantitative indicators*' to conclude that a specific objective can be better achieved at Union level**. *Draft legislative acts take account of the need for any burden, whether financial or administrative, falling upon the Union, national governments, regional or local authorities, economic operators and citizens, to be minimised and commensurate with the objective achieved*' (Art. 5). Besides and in order to implement a process to supervise compliance with these principles, the protocol defines that EU institutions shall forward draft legislative acts to national parliaments (Art. 4). The protocol further defines this process and states that '[w]*here reasoned opinions on a draft legislative act's non-compliance with the principle of subsidiarity represent at least one third of all the votes allocated to the national Parliaments* […] *the draft must be reviewed*.' After review, the respective EU institution may then '*decide to maintain, amend or withdraw the draft*, [whereby] [r]*easons must be given for this decision*.' (Art. 7.2).

[22] Consolidated Version of The Treaty on European Union (TEU), OJ C155/13, 9.5.2008.

[23] Lock T, Comments on the German Constitutional Court's Decision on the Lisbon Treaty, Why the European Union is Not a State, Some Critical Remarks, *European Constitutional Law Review*, 5: 407-420, 2009, referring to BVerfGE 89, 155, 12 October 1993 (187-188), at p. 410.

[24] Consolidated versions of the Treaty on European Union and the Treaty on the Functioning of the European Union - Consolidated version of the Treaty on the Functioning of the European Union - Protocols - Annexes - Declarations annexed to the Final Act of the Intergovernmental Conference which adopted the Treaty of Lisbon, signed on 13 December 2007, OJ C 326 , 26/10/2012 P. 0001 – 0390.

The Treaty on the Functioning of the European Union (**TFEU**)[25] defines three different categories and areas of EU competence (Art. 2-6):

- exclusive EU competence (Art. 3)
- EU competence shared with MS (Art. 4)
- EU competence to carry out actions to support, coordinate or supplement the actions of MS (Art. 6).

In the area of **exclusive EU competence**, the **EU can set binding law** and MS are only allowed to set binding law, if the EU explicitly empowers or obliges them to do so. Among other categories, the EU regulates and sets the **rules for competition** within the EU as well as rules ensuring the European customs union.

Pharmaceutical products (medicines) are products in the sense of Art. 28 ff TFEU. Thus, in the healthcare sector, respectively the pharmaceutical market, the EU has the power to influence and set binding law relating to rules for competition.

Shared EU competence means that MS are still allowed to set binding laws, if the EU declined to regulate, did not regulate at all or did only in part regulate a specific task. Among the main areas of shared competence, the most relevant one in the context of pharmaceutical policy is the **internal market** and its principle of free movement of goods (Art. 28 to 37 TFEU). According to Art. 34 and 35 TFEU, quantitative restrictions between MS are prohibited (i.e. restrictions on imports or exports and all measures having equivalent effects). Nevertheless, such restrictions or prohibitions can be justified on the ground of protecting health and life of humans (Art. 36 TFEU). Besides, **social policy**, **consumer protection** and **common safety concerns in the field of public health** are of relevance.

In the field of **supporting, coordinating or supplemental actions**, the EU is not allowed to take actions to harmonise the laws of the MS. Above other categories, the **protection and improvement of public health** as well as the coordination of social policies of MS falls within this area.

Besides, in Art. 9 TFEU, it is stated that the EU '[i]*n defining and implementing its policies and activities* […] *shall take into account* […] *a* ***high level of*** **[...]** ***protection of human health***.'

Even though the EU in some specific fields of public health related to common safety concerns may introduce a common standard by harmonising laws of MS (**Art. 168 (4) TFEU** in accordance with Art. 4 TFEU – shared competence), **Art. 168 (7) TFEU** explicitly states that '*Union action shall respect the responsibilities of the Member States for the definition of their health policy and for the organisation and delivery of health services and medical care. The responsibilities of the MS shall include the management of health services and medical care and the allocation of the resources assigned to them*.'

Anyhow, even besides internal market or competition rules, MS seem to more and more support increasing efforts at EU level for more coordination in the field of social and health policy, especially on the '**demand side**'[26], in the light of **consumer or patient**

[25] Consolidated Version of The Treaty on the Functioning of the European Union (TFEU), OJ C326/47, 26.10.2012.

[26] As supposed to the 'supply side' – see Sauter W, The impact of EU competition law on national healthcare systems, *TEILEC Discussion Paper*; Vol. 2012-032. TILEC, available at pure.uvt.nl/portal/files/1457810/2012_032.pdf (2.4.2015), at

rights. Even though experience shows that negotiations in these fields prove to be highly demanding[27] and Commission policy initiatives or even Council initiatives are sometimes (temporarily) rejected by MS, claiming their sovereign rights.

When it comes to health policy, access to healthcare services and consumer or patient rights it is important to understand and stress the **influence of the European Court of Justice (ECJ)** in this context: by increasingly strengthening **patient rights in cross border health care** in the past years (finally leading to Directive 2011/24/EU on the application of patients' rights in cross-border healthcare[28]), the Court gradually drove MS towards closer cooperation and coordination in this field. Most recently, the ECJ seems to adjust its opinion towards parallel trade by acknowledging its adverse impacts on patients.[29]

13.2 Primary EU law (internal market), including competition law, interfering with the pharmaceutical (pricing) market

In order to achieve a high level of human health and patient safety with regard to pharmaceuticals, the EU basically strives to promote a **safe** and **functioning pharmaceutical market** through an innovative and competitive industry.

To achieve a high level of patient **safety**, the EU introduced a **common system of market authorization, supervision and pharmacovigilance**. Through this system common principles for prior testing, supervision and assessing efficacy of new medicines have been implemented. Companies have two possibilities to obtain marked authorization for new medicines: either through (a) a **centralised application** to the European Medicines Agency (EMA)[30] or (b) a **decentralised application** covering only one MS with the option of recognition by other MS through the mutual recognition procedure[31]. Use of the centralised procedure is mandatory for '*biotechnology medicines, products containing [*new chemical entities*] (NCEs), for the treatment of certain disorders and diseases, and is optional for other NCEs and sufficiently innovative products.*'[32]

A **functioning pharmaceutical market** aims at providing sufficient supply and affordable prices of pharmaceuticals. To achieve this goal, the EU engages in market and

---

p.4: '*When interpreting these developments* [remark: meaning application of internal market freedoms to healthcare], *it is useful to distinguish between demand (services) and supply (establishment) factors*.'

[27] E.g. Van de Gronden J, Szyszczak E, Introducing Competition Principles into Health Care through EU Law and Policy: a Case Study of the Netherlands, *Medical Law Review*, 2014, Vol. 22, No. 2, pp. 238-254, at p. 240: '*The Member States' reluctance to allow EU regulation of health care services is seen in the removal of health care from the Services Directive and the tortuous negotiation of the Patients' Rights Directive in 2011*.'

[28] Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare, OJ L 88/45, 4.4.2011.

[29] See Legal Analysis, Chapter on Parallel Trade (intra-brand competition).

[30] Introduced through Regulation (EC) No 726/2004 of the European Parliament and the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136/1 30.4.2004 .

[31] Directive 2001/83/EC, as revised through Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 (amending Directive 2001/83/EC on the Community code relating to medicinal products for human use), OJ L 136/34, 30.4.2004.

[32] Hancher L, The EU pharmaceuticals market: parameters and pathways, in Mossialos E, Permanand G, Beaten R and Hervey T (Eds.), *Health Systems Governance in Europe, The Role of European Union Law and Policy*, European Observatory on Health Systems and Policy, Cambridge University Press, New York (2010), pp. 635-682, at p. 646.

competition policy. By pursuing and promoting an innovative and competitive pharmaceutical industry, consumers and patients shall have access to sufficient and high quality pharmaceuticals.

Normally, a functioning and effective competition is the result of free market price building mechanisms and policies. However, in the field of pharmaceuticals where prices are regulated by each MS, it seems that a functioning competition may only result from **better regulated and coordinated pricing policies**. The power to set binding laws in this field lies with the MS. However, through '**positive'** or **'negative' harmonisation efforts**[33] in this area, drawn from primary law in the field of free movement of goods, services and rules on approximation of MS laws as well as competition law, the **EU shapes pricing policies of MS**.

In this context it is important to understand, that EU integrated market and competition law – according to the **principle of primacy of EU law** – takes precedence over national laws of MS, even if these laws systematically have its origin in the social policy area.[34] Moreover, competition law has been 'decentralised', meaning that national competition authorities can apply EU antitrust rules to national competition cases with EU dimension.[35] Some recent steps taken by national governments after the financial crisis even indicate that '*the interface between competition policy and the healthcare sector is becoming more important*.'[36]

Internal market law (Art. 28 ff TFEU) generally applies to the pharmaceutical market and trade between MS, prohibiting MS '[q]*uantitative restrictions on imports and exports and all measures having equivalent effect*' (**Art. 34 and 35 TFEU**).[37] However, in line with **Art. 36 TFEU**, justifying such restrictions on grounds of health and life protection, the ECJ has given MS some discretion in its rulings, if harmonised law on EU level is missing and in so far as measures by MS are **proportional** and **necessary** to attain the **goal of health and life protection** (e.g.: Case C-400/96 *Harpegnies* [1998] ECR I-5121) or **social security policy** (e.g. the equilibrium of social security systems: Case C-120/95 *Decker* [1998] ECR I-1872 at margin. 39: '[…] *it cannot be excluded that the*

---

[33] 'Positive' harmonisation efforts mean regulations and directives, whereas 'negative' harmonisation efforts are efforts finally leading to an adoption of MS laws since laws of MS do not comply e.g. with the principle of free movement of goods or EU competition rules. See also Van de Gronden J, Szyszczak E (2014), supra note 26, at p. 239: '*In the absence of EU legislative competence and the political will on the part of the Member States to regulate health care at the EU level, EU competition law now 'forms a default regulatory framework for the sector''*.

[34] See Hervey T, EU law and national health policies: problem or opportunity, *Health Economics, Policy and Law* (2007), 2: 1-6: at p. 3: '*The free movement and competition rules take precedence over conflicting national rules, of any type, even over conflicting subsequent legislation adopted by national parliaments*. […] *This applies even if the aim of the national rules at issue is something other than trade or competition, for instance the protection of social welfare or public health*.' and ECJ case law: *Costa/ENEL* (Case C-6/64 [1964] ECJ 588), *Simmenthal II* (Case C-106/77 [1978] ECR 631), *Internationale Handelsgesellschaft* (Case C-11/70 [1970] ECR 1126).

[35] Prosser T, EU competition law and public services, in Mossialos E, Permanand G, Beaten R and Hervey T (Eds.), *Health Systems Governance in Europe, The Role of European Union Law and Policy*, European Observatory on Health Systems and Policy, Cambridge University Press, New York (2010), pp. 315-336 or Sauter W (2012), supra note 25, at p.6, referring to Council Regulation (EC) No 1/2003 of 16 December 2002 on the implementation of the rules of competition laid down in Articles 81 and 82 of the Treaty [now: Art. 101 and 102 TFEU], OJ 2003 L 1/1: '*At national level competition laws in all Member States have converged with EU competition law*.'

[36] See Sauter W (2012), supra note 25, referring to developments in Ireland, UK, Bulgaria and the Netherlands at p. 3.

[37] E.g.: *Merck & Co. Inc, Primecrown Ltd..*, ao, joined Cases C-267/95 and C-268/95, [1996], I-6371, at margin. 47: '*As to that, although the imposition of price controls is indeed a factor which may, in certain conditions, distort competition between Member States, that circumstance cannot justify a derogation from the principle of free movement of goods*.'

risk of seriously undermining financial balance of the social security system may constitute an overriding reason in the general interest capable of justifying a barrier of that kind [remark: a barrier to the fundamental principle of the free movement of goods] in line with Art. 36 TFEU. This so called '***Social Solidarity Exemption***' is based on the ECJ *Duhar* case, in which the Court stated: '*it must be recognised that Community law does not detract from the powers of Member States to organise their social security systems and to adopt, in particular, provisions intended to govern the consumption of pharmaceutical preparations in order to promote the financial stability of their health-care insurance schemes*'.[38]

The TFEU sets **rules for undertakings** on **competition in Art. 101 ff** and its subsequent secondary legislation. Competition rules **aim at equal rank** at providing **efficient competition and market structures** as well as **consumer welfare**.[39]

The rules are applicable for both, **public and private health care services**. Since *Höfner*, *Elser*[40] it is clear that EU competition rules are also applicable to the public sector and public sector agencies are **undertakings** in the sense of EU competition rules when engaging in economic activities.[41] However, for **bodies managing health care schemes**, a far more differentiated view has been taken by the ECJ in *AOK* [42], stating that '*sickness funds fulfil a function, which is exclusively social and entirely non-profit making*, […] [its] *operation is founded on a principle of solidarity* […] [and] *the state exercises control over the activity*.' Therefore, the court concludes that they '*do not act as undertakings engaging in economic activity*'. In *AG2R*[43] the ECJ then made clear that these requirements (**social, non-profit making function, operation founded on the principle of solidarity and state control**) **all** have to be satisfied in order **not to fall** under **EU competition rules** relevant for undertakings. In this field, as Leigh Hancher states, EU institutions have to '[…] *strike a balance between the objectives of stimulating innovation while securing affordable access through regulation ex ante* […].'[44]

---

[38] Case C-238/82 *Duphar* [1984] ECR 523, margin. 16; see also: Sauter W, supra note 25 summarises at p. 5: '*In sum although there is now a strong precedent for EU involvement in the internal market dimension of healthcare the actual effects of the four freedoms have so far been limited. This is the case especially on the supply side, although where constraints are involved they must be justified and rational, regardless of the absence of a common terms*.'

[39] Sauter W (2012), supra note 25, referring to *GSK II* (supra note 16), at p. 9: '*Here it overruled the General Court which had claimed that the consumer interest was indeed the highest value of competition law. The ECJ however clarified that market structure and the position of competitors were objectives of equal rank* […]'.

[40] Case C-41/90 *Höfner, Elser* [1991] ECR I-2010, see also *Pavlov*: joined Cases C-180/98 to C-184/98 [2000] ECR I-6497.

[41] See ECJ in *Höfner, Elser*, supra note 39, at point 21: '*It must be observed, in the context of competition law, first that the concept of an undertaking encompasses every entity engaged in an economic activity, regardless of the legal status of the entity and the way in which it is financed and, secondly, that employment procurement is an economic activity*.'

[42] *AOK Bundesverband* et al, joined Cases C-264/01, C-306/01, C-354/01 and C-355/01 [2004] ECR I-2524, points: 35-37 and 64. See also *Poucet and Pistre*, joined Cases C-159/91 and 160/91 [1993] ECR I-637, *FENIN*, Case C-205/03 [2006] ECR I-6295 and *José Garcia and Others*, Case C-238/94 [1996] ECR I-1679 at point 14: '*Finally, as the Court stressed in Joined Cases C-159/91 and C-160/91 Poucet and Pistre v Assurances Générales de France and Others [1993] ECR I-637, paragraph 13, social security schemes such as those in issue in the main proceedings, which are based on the principle of solidarity, require compulsory contributions in order to ensure that the principle of solidarity is applied and that their financial equilibrium is maintained. If Article 2(2) of Directive 92/49/EEC were to be interpreted in the manner contemplated by the national tribunal, the obligation to contribute would be removed and the schemes in question would thus be unable to survive. The Court has also pointed out that Member States retain their powers to organise their social security systems (see Poucet and Pistre, paragraph 6, and Case 238/82 Duphar v Netherlands [1984] ECR 523, paragraph 16).*'

[43] *AG2R Prévoyance v Beaudout Père et Fils SARL*., Case C-437/09 [2011] ECR I-1003.

[44] Hancher L (2010), supra note 31, at p. 655.

The rationale behind these judgments has been expressed by the Advocate General in the *FENIN* case[45]: '*The **power of the State**, which is exercised in the political sphere, is **subject to democratic control**. A **different control** is imposed on **economic operators** acting on a market: their conduct is governed by competition law. But there is no justification when the State is acting as an economic operator, for relieving its actions of all control*.'[46]

If the public or private player at hand is classified as undertaking, EU competition rules apply, irrespective of the fact that States might interfere through price setting or reimbursement policies.[47] According to these rules, relevant for undertakings, the following activities are **not allowed** since interference with the internal market results:

- agreements, which may affect trade between MS (Art. 101 TFEU – **prohibition of cartels**)
- any abuse of dominant position (Art. 102 TFEU – **abuse of dominant position** by a monopolist)
- mergers prohibiting free competition (**merger control**).

According to Art. 101 (3) TFEU agreements, which may affect trade between MS might basically be justified, if contributing to improving the production or distribution of goods or promoting technical or economic progress while allowing a **fair share for consumers**.[48]

In the field of competition law and **supply-side or price related practices**, **prohibition of cartels** and **abuse of dominant position** are the most relevant competition rules. Thus, the following competition law analysis will focus on these two practices and its application by the Commission and the Courts.

Before analysing relevant ECJ case law in the field of market freedom and competition law in the pharmaceutical sector, it is important to distinguish the following two **relevant product markets**. For **inter-brand competition** analysis (i.e. competition between different brands, .e.g. generics markets) the relevant market is defined by pharmaceuticals, whose prescription practice is based on '*fundamentally the same medical grounds* […], *for example, in terms of active principle, tolerance, toxicity, and side effects*.'[49] For **intra-brand competition** (i.e. competition in relation to the same pharmaceutical product or also called **parallel trade**), the relevant product market are '*all medicines which are capable of being subject to parallel trade in a given Member State*'.[50]

---

[45] Case C-205/03, *FENIN* [2006] ECR I-6295.

[46] Prosser T (2010), supra note 34, at p. 324.

[47] *Merck and Beacham*, joined cases C-267/95 and C-268/95 [1996] ECR I-6371, p. C-6389, point 47*: 'As to that, although the imposition of price controls is indeed a factor which may, in certain conditions, distort competition between Member States, that circumstance cannot justify a derogation from the principle of free movement of goods.'*

[48] See e.g. *GSK II*, supra note 16.

[49] Liberatore F, Resrictions on Parallel Trade of Pharmaceutical Products and EU Competition Law, Chapter 17 in Cortese B (Ed.), *EU Competition Law. Between Public and Private Enforcement*, Kluwer Law International BV, The Netherlands (2014), pp. 347-356, available at: www.jonesday.com/files/Publication/5a2fa4ac-8fcb-4fdd-ab38-02d252fcb01d/Presentation/PublicationAttachment/e89a2072-71df-4197-bfff-0254e30b42d8/Restrictrions%20on%20Parallel%20Trade%20-%20Francesco%20Liberatore.pdf (accessed: 3 April 2015), at p. 350-351, referring to 97/469/EC: Commission Decision of 17 July 1996 in a proceeding pursuant to Council Regulation (EEC) No. 4064/89 (Case No IV/M.737- Ciba-Geigy/Sandoz), 21.

[50] Liberatore F (2014), supra note 48, at p. 351, referring to Case T-168/01, *GSK*, 159.

There are a number of cases, both at EU and national level, declaring price fixing strategies or the coordination of market shares as being anti-competitive and thus prohibited.[51]

However, since on the one hand the above mentioned diversities in MS's pricing approaches exist, and on the other hand EU market rules (free movement of goods) demand for free movement of pharmaceuticals, the phenomenon of **intra-brand competition** (and **parallel trade**) is a highly relevant one for the European market. Thus, the following analysis will focus on this phenomenon and its handling under EU competition law.

13.3 Parallel trade (intra-brand competition)

Parallel trade arises when (parallel) traders, e.g. wholesalers, purchase a specific brand of a pharmaceutical product in one MS in order to sell this brand or product at a higher price in another MS. Thus, parallel trade occurs, if a genuine product originally sold under patent (copyright/trademark) protection is traded (in another country) without control or permission of the original patent holder. Under intellectual property law (IP law) a patent holder has an absolute right to dispose of the patented product. However, due to the so called '**exhaustion doctrine**' this right is restricted to first distribution. After first distribution, the right of the patent holder to control further distribution and trade is exhausted. With regard to the European market, parallel trade is restricted to the European market since the EU practices the so called '**regional exhaustion doctrine**', allowing only parallel trade of goods authorised and licenced within the EU. This practice is in line with international trade and patent agreements (**TRIPS**[52]) of World Trade Organisation (WTO) since members (especially the US and EU countries) could not agree on the implementation of an 'international exhaustion doctrine'[53] within the TRIPS framework.[54]

---

[51] For an enumeration and analysis of several recent cases see Lear J, Mossialos E and Karl B, EU competition law and health policy in Mossialos E, Permanand G, Beaten R and Hervey T (Eds.), Health Systems Governance in Europe, The Role of European Union Law and Policy, European Observatory on Health Systems and Policy, Cambridge University Press, New York (2010), pp. 337-378, at pp. 350 ff.

[52] WTO (1994, entering into force January 1995), Agreement on Trade-Related Aspects of Intellectual Property Rights, Annex 1 C to the Agreement Establishing the World Trade Organization. The EU (since 1995) and its MS are all members of the World Trade Organization (WTO).

[53] According to the 'international exhaustion doctrine' parallel imports would be legal no matter where the product has been distributed first and the IP holder loses the right to control further distribution after the product has been put on the market by the IP holder or with his consent at any place of the world.

[54] See Article 6 (Exhaustion) TRIPS: '*For the purposes of dispute settlement under this Agreement, subject to the provisions of Articles 3 and 4 nothing in this Agreement shall be used to address the issue of the exhaustion of intellectual property rights.*' According to analytic index LXXVIII. Relating to the Text of the Declaration of the TRIPS Agreement and Public Health, this legality of national or regional exhaustion has been explicitly confirmed in the public health context 5 d, '*The effect of the provisions in the TRIPS Agreement that are relevant to the exhaustion of intellectual property rights is to leave each Member free to establish its own regime for such exhaustion without challenge, subject to the MFN and national treatment provisions of Articles 3 and 4.*' See also Rai R K, Jagannathan S, Parallel imports and unparallel laws: an examination of the exhaustion doctrine through the lens of pharmaceutical products, *Information & Communications Technology Law*, Vol. 21, No. 1, March 2012, 53-89 and Sarah R. Wasserman Rajec, Free Trade in Patented Goods: International Exhaustion for Patents, 29 *Berkeley Tech. Law Journal* (2014), available at: http://scholarship.law.berkeley.edu/btlj/vol29/iss1/7.

In line with fundamental Treaty principles, the **EU Commission's as well as the ECJ's** attitude towards parallel trade and intra-brand competition traditionally was a supportive one[55]. According to the Commission, EU's market freedom and especially free movement of goods shall exactly enable this kind of competition.

For **pharmaceutical companies**, parallel trade and intra-brand competition means, that they possess intellectual property rights and patent protection for several years, but this does not mean exclusivity in resulting price benefits. Others (i.e. wholesalers) can also benefit from pricing advantages resulting from intellectual property right protection.

Pharmaceutical companies in reacting to the phenomenon of parallel trade (intra-brand competition) basically chose **four different strategies** to reduce parallel trade and its negative competitive effects[56]:

1. **dual pricing** (see below: GlaxoSmithKline I): 'Dual Pricing strategies seek to **reduce** the price differential between geographical markets and, as a result, the **incentive for arbitrage** in the form of parallel trade.'[57]
2. **supply quota restrictions** (see below: GlaxoSmithKline II and Adalat): 'Supply quota systems come in a variety of forms, but usually they involve a **restriction of supplies to wholesalers** commensurate with the latter's requirements in the domestic market, plus a limited margin.'[58]
3. **specific life cycle management** (see below: Astra Zeneca): Life cycle management practices by pharmaceutical companies are usually strategies aiming at delaying generic market entry (e.g. by using excessive procedures before national patent offices and regulatory authorities). If such strategies for instance are combined with a withdrawal of a marketing authorization, they might also be relevant in the context of parallel trade.[59]

---

[55] See e.g. European Commission, Communication on parallel imports of proprietary medicinal products for which marketing authorisations have already been granted, COM (2003) 837 final at p. 6: '*Parallel trade is based on the principle of the free movement of goods within the Internal Market (articles 28-30 of the EC Treaty). In the pharmaceutical sector, it benefits from price divergence as Member States set or, by other means, control the price of medicinal products sold within their respective markets. The European Court of Justice has repeatedly confirmed that medicinal products are not exempted from the rules of the Internal Market and has condemned State measures which restrict, without appropriate justification, parallel imports of medicines. The Court has ruled that certain Member State measures restricting parallel imports may be justified on the grounds of protection of industrial and commercial property and the protection of human health and life, according to article 30 of the EC Treaty*'.

[56] Liberatore F, supra note 48 and Gruber J, Wettbewerb in regulierten Märkten: Arzneimittel, *Österreichische Zeitschrift für Kartellrecht* (*ÖZK)*, 2010, 180.

[57] Hancher L (2010), supra note 31, at p. 663.

[58] Hancher L (2010), supra note 31, at p. 663.

[59] Hancher L (2010), supra note 31, at p. 655 and Liberatore F, supra note 48 at pp 355, 356: *„The Commission's Pharmaceutical Sector Inquiry Report identified a number of product life cycle management strategies that are at risk of violating EU competition law. The use of such strategies to limit parallel trade was assessed under EU competition law in the AstraZeneca case. In the AstraZeneca case, the Commission found that AstraZeneca had abused its dominant position in relation to its blockbuster medicine Losec by selectively deregistering the market authorizations for Lesoc capsules in three Member States; withdrawing Losec capsules from the market; and launching tablets in those same Member States. […]. It follows from the General Court's reasoning that, when there is no other documented explanation for the withdrawal of a marketing authorization, this may be assumed to have the sole purpose of restricting parallel trade and is therefore abusive."* .

4. **direct distribution systems**: distribution systems without wholesalers in between; this fourth strategy in most cases means a complete and often expansive restructuring of a company's distribution system and thus is the least relevant one.

Regarding the first three strategies, the ECJ issued rulings and further defined its position towards these practices. The first three strategies as well as the ECJ rulings in reaction to these practices shall be further assessed (the structure is inspired by Liberatore F (2014)[60]:

13.3.1 Dual pricing (Art. 101 TFEU) – *GlaxoSmithKline (GSK I, Spain)*[61]

In GSK I the Spanish subsidiary – a company without dominant position – entered into agreements with 75 different wholesalers, fixing different prices for the same products: prices were lower for wholesalers selling products exclusively in Spain (a low price country) and higher prices for wholesalers exporting and selling these same products in MS with higher price levels for pharmaceuticals. This strategy by Glaxo SmithKline's subsidiary intended to impede parallel trade.

The Courts' ruling in GSK I can be summarised as follows:

- ➔ Agreements with wholesalers in low-price countries, providing for different prices – depending on whether wholesalers will export some of the products to high-price countries – are **in principle a restriction of competition** by object[62], and might impede free movement of goods, thus **violate EU competition law**.
- ➔ However, such **agreements might be justified** in individual cases, **if advantages for consumers outweigh its anti-competitive effects, fulfilling the requirements for an exemption under Art. 101 (3) TFEU with regard to the specific features of the pharmaceutical sector**.

According to Hancher L (2010), '*this judgment will have significant repercussions for future Commission policy. In the past, the Commission has always contended that, while it was broadly sympathetic to the claims of the research-based industry that divergent national price and profit regulations that give rise to parallel trade could threaten their capacity for innovation and their global competitiveness, its hands were tied by the jurisprudence of the Courts, which supported parallel trade as an important stimulus to completing the internal pharmaceuticals market.*'[63]

---

[60] See supra note 48.

[61] *GSK I (GlaxoSmithKline Services Unlimited v. Commission ao)*, joined Cases C-501/06 P, C-306/01, C-354/01 and C-513/06 P, C-515/06 P and C-519/06 P [2009] ECR I-0929l.

[62] With respect to parallel trade, the Court has already held that, in principle, agreements aimed at prohibiting or limiting parallel trade have as their object the prevention of competition (see, to that effect, Case 19/77 Miller International Schallplatten v Commission [1978] ECR 131, paragraphs 7 and 18, and Joined Cases 32/78, 36/78 to 82/78 BMW Belgium and Others v Commission [1979] ECR 2435, paragraphs 20 to 28 and 31). 60 As observed by the Advocate General in point 155 of her Opinion, that principle, according to which an agreement aimed at limiting parallel trade is a 'restriction of competition by object', applies to the pharmaceuticals sector.

[63] Hancher L (2010), supra note 31, at p. 664.

13.3.2 Supply quota restrictions

In reacting to the phenomenon of parallel trade, pharmaceutical companies started to supply wholesalers in one MS with only about enough products to cover domestic sales (supply quota restriction). Thus, by implementing supply quota restrictions, **wholesalers in one MS shall not have excess amounts of pharmaceuticals to export in higher price countries** and to engage in parallel trade or export. Such restrictions typically happen in low-price countries such as Spain or Greece and in amount in its effect to an **export ban** to Member States with higher price levels.

For an assessment of such a strategy under EU competition law it matters whether the company restricting supply is in a dominant position. The following case law analysis therefore distinguishes the case *Lélos v. Glaxo-SmithKline (GSK II)*[64] that deals with a company in a **dominant position** from the case *Adalat*[65] dealing with a company in a **non-dominant position**.

Supply quota restrictions of a company in a dominant position (Art. 102 TFEU) – *Lélos v. GlaxoSmithKline II (Greece)*[66]

In this case the Greek Appeal Court (‘*Trimeles Efeteio Athinon*’) turned to the ECJ, inquiring ‘*whether there is an abuse of a dominant position contrary to Art. 82 EC [now: Art. 102 TFEU] if a pharmaceuticals company occupying such a position on the national market for certain medicinal products* ***refuses to meet orders sent to it by wholesalers on account of the fact that those wholesalers are involved in parallel exports*** *of those products to other Member States*.’

The ECJ’s key findings in GSK II are basically the following:

- ➔ **Parallel trade does have positive effects** on prices and thus for consumers in **parallel importing states**, which must be considered.[67]
- ➔ ‘[I]*t should be noted, on one hand, that the control exercised by Member States over selling prices or the reimbursement of medicinal products does not entirely remove the prices of those products from the law of supply and demand.*’[68]
- ➔ ‘*Where a medicine is protected by a patent which confers a temporary monopoly on its holder, the* ***price competition which may exist between a producer***

---

[64] Judgement of the Court (Grand Chamber) in Joined Cases C-468/06 to C-478/06, *Sot. Lélos kai Sia EE (and Others) v. GlaxoSmithKline AEVE* [2008] ECR I-7139, see also supra note 16.

[65] Judgement of the Court in Joined Cases C-2/01 P and C-3/01 P, *Bundesverband der Arzneimittel-Imorteure (and Others) v. Bayer AG* [2004] ECR I-64 – ‘*Adalat*’ or ‘*Adalate*’

[66] See supra note 16.

[67] ‘[…] [E]*ven in Member States where the prices of medicines are subject to State regulation, parallel trade is liable to exert pressure on prices and, consequently to create financial benefits not only for the social health insurance funds, but equally for the patients concerned*, […]. […][T]*here can be no escape from the prohibition laid down in Article 82 EC for the practices of an undertaking in a dominant position which are aimed at avoiding all parallel exports from a Member State to other Member States, practices which, by partitioning the national markets, neutralise the benefits of effective competition in terms of the supply and the prices that those exports would obtain for final consumers in the other Member States.*’, supra note 16, points 56 and 66.

[68] Supra note 16, point 61.

and its distributors, or between parallel traders and national distributors**, is, until the expiry of that patent, **the only form of competition which can be envisaged[69].'

➔ **Member States' price regulation** in the pharmaceuticals sector '*is one of the factors **liable to create opportunities for parallel trade***'.[70]

➔ The ECJ explicitly stated that it is aware of the **risk** that competition policy and market rules in combination with national pricing policies might **lead companies not to place its medicines on the market at all in a Member State, where the prices of those products are set at a relatively low level,** thereby jeopardizing consumer interests. Thus, it concluded, '*a company must nevertheless be in a position to take **steps** that are **reasonable and in proportion to the need to protect its own commercial interests***.'[71]

➔ **Reasonable and Proportionate Measure Test**:
Courts therefore have to assess in every individual case, '*whether the refusal by a pharmaceuticals company to supply wholesalers involved in parallel exports constitutes a **reasonable and proportionate measure** in relation to the threat that those exports represent to its **legitimate commercial interests**, it must be ascertained whether the orders of the wholesalers are out of the ordinary*.'[72]

Following this reasoning, a **dominant company may refuse to supply exporters** (in higher price countries) **out of the ordinary supply** to respond to different pricing areas, caused by MS' deviating policies.

Even though the ECJ **stresses that parallel trade does have a positive effect on consumers (i.e. in parallel importing states)**, and thus principally upheld a positive attitude towards parallel trade as the only remedy for competition in a patented market, **it acknowledged existing legitimate commercial interests of a company** in taking **reasonable** and **proportionate measures to minimise parallel trade**.

The Court stated that **supply quota restrictions by a dominant company** – even though potentially being abusive – **might be justified if reasonable and proportionate in order to pursue legitimate commercial interests**. By applying this test, national authorities as well as national courts will have to assess **suitability** and **necessity** of the restriction and **balance harms** and **efficiencies**. However, the case leaves much uncertainty about how to '*properly assess and enhance competition on innovation in this sector in order to achieve the greatest benefit for the public*.'[73]

---

[69] Supra note 16, point 64.

[70] Supra note 16, point 67.

[71] Supra note 16, points 68 and 69.

[72] Supra note 16, point 70.

[73] Nguyen T, Minssen T, Groussot X, The Rule of Reason under Article 82 EC After Sot Lelos kai Sia, 6 July 2009, electronic copy available at: papers.ssrn.com/sol3/papers.cfm?abstract_id=1431010, at p. 21: '*This uncertainty is inter alia reflected by the fact that both the pharmaceutical industry and the parallel traders have claimed for victory after the ruling*.'

Supply quota restrictions in non-dominant position (Art. 101 TFEU – *Adalat*)[74]

Bayer AG – the parent company of subsidiaries in all EU MS – has manufactured and marketed under the trade name '**Adalat**' or 'Adalate' a range of medicines with the active ingredient nifedipine to treat **cardiovascular disease**. [75]

In most MS, the price of Adalat is directly or indirectly fixed by national health authorities. Between 1989 and 1993 the prices fixed by the Spanish or French health services were, on average, 40 % lower than prices in the UK.

Exploiting these price differences, wholesalers in **Spain** (starting in 1989) and in **France** (starting in 1991) began exporting Adalat to the UK, causing an alleged loss of sales for the UK subsidiary of Bayer (according to Bayer sales in the UK fell by almost half from 1989 to 1993 because of these parallel imports, causing a loss of turnover of 230 Mio DM).

As a result, Bayer started to change its delivery policy and began to **cease fulfilling all the increasingly large orders placed by wholesalers in Spain and France**.

The Commission thus started an administrative investigation procedure, finally leading to the decision that **Bayer Spain and Bayer France infringed Art. 85 (1) EC** [now: Art. 101 (1) TFEU], by imposing an export ban on Spanish and French wholesalers. The Commission adopted a decision, requiring Bayer to change its policy infringing Art. 81 (1) EC [now: Art. 101 (1) TFEU] and imposed a fine of 3 Mio Ecus on Bayer.

This Commission decision has been challenged and brought before the General Court and the ECJ, finally leading to court rulings, both annulling the Commission's decision.[76]

As Liberatore states: '[i]*t follows from this case law that, provided he does so without abusing a dominant position, and there is no concurrence of wills between* […] [the company] *and its wholesalers* [implying an agreement in the sense of Art. 101 (1) TFEU], ***a manufacturer may adopt the supply policy which he considers necessary, even if by the very nature of its aim, for example, to hinder parallel imports****, the implementation of that policy may entail restrictions on competition and affect trade between Member States*.'[77]

However, since both, the General Court as well as the ECJ mainly assessed whether there has been an agreement in accordance to Art. 81 EC [now: Art. 101 TFEU], no

---

[74] Supra note 64.

[75] See supra note 64, points 1 to 4.

[76] Findings of the Court, supra note 64: point 140. '*By these pleas, the appellants are seeking to challenge the assessment by the Court of First Instance that the Commission could not effectively rely on the case-law precedents referred to in order to call into question the analysis which led the Court of First Instance to conclude that in this case acquiescence of the wholesalers in Bayer's new policy was not established (paragraph 159 of the judgment under appeal).*' and point 141. '*In that respect, it is important to note that this case raises the question of the existence of an agreement prohibited by Article 85(1) of the Treaty. The mere concomitant existence of an agreement which is in itself neutral and a measure restricting competition that has been imposed unilaterally does not amount to an agreement prohibited by that provision. Thus, the mere fact that a measure adopted by a manufacturer, which has the object or effect of restricting competition, falls within the context of continuous business relations between the manufacturer and its wholesalers is not sufficient for a finding that such an agreement exists.*"

[77] Liberatrore F (2014), supra note 48, at p. 354.

further information on ECJ's attitude towards parallel trade in general or its effects has been provided.

13.3.3 Product life cycle management (Art. 102 TFEU) – *AstraZeneca*[78]

Product life cycle strategies are relevant in the context of generic medicines, intending to delay or prevent market authorization of these products and parallel trade. In the *AstraZeneca* case, the Commission imposed a fine of EUR 60 million on AstraZeneca AB and AstraZeneca plc for having abused the patent system and the procedures for marketing pharmaceutical products in order to prevent or delay the arrival of competing generic medicines on the market and to impede parallel trade.[79]

As Liberatore F (2014) states: '*It follows from the General Court's reasoning that, when there is* ***no other documented explanation for the withdrawal of a marketing authorization****, this* ***may be assumed to have the sole purpose of restricting parallel trade and is therefore abusive****. Accordingly, a* ***dominant company*** *comes under a positive obligation to ensure that its marketing authorizations are maintained so that it is easier for parallel imports to continue*.'[80]

13.3.4 Reaction in MS' laws to parallel trade (Art. 34 to 36 TFEU)

It would be beyond the scope of this legal analysis to scrutinise all MS's laws related to parallel trade of medicines. However, some legal effects shall be pointed out exemplarily. Basically, it can be observed that **MS** (predominantly) **affected by parallel exports** increasingly start to issue export bans on medicines within the past years, whereas **MS benefiting from parallel imports** implemented supply strategies promoting the sale of imported medicines from lower-priced countries (e.g. according to § 129 (1) 2. of the German Social Security Act (Sozialgesetzbuch (SGB), (V)), pharmacies are obliged to preferably sell imported medicines, if the prices for these products are at least 15 Euro (or 15 %) below pharmacy retail price). The following overview focuses on recent developments, mainly in countries affected by parallel exports of medicines.

Distinct measures of MS

Allegedly, MS affected by parallel exports have to deal with shortages of certain medicines. ECJ rulings allowing pharmaceutical companies to execute quota restrictions in specific cases and if '*legitimate commercial interests*' justify these restrictions, should also be considered in this context (see GSK II above). In reaction to this problem, MS concerned issued laws, allowing the competent authorities to issue **export bans** on medicines affected.

In December 2013, Member of European Parliament (MEP) Thomas Ulmer officially raised the issue of the **Greek export** ban on certain medicines in reaction to allegedly existing shortages of specific medicines due to parallel exports.[81] Other countries such

---

[78] Judgement of the Court (First Chamber), Case C-457/10 P [2012], *AstraZeneca AB, AstraZeneca plc v. European Commission*.

[79] Commission Decision C(2005) 1757 of 15 June 2005.

[80] Liberatore F (2014), supra note 48, at p 356.

[81] Question for written answer E-013769/13 to the Commission, 4 December 2013, OJ C 263/234, 12.8.2014.

as **Hungary**, **Bulgaria**, **Slovakia**, the **Czech Republic**, **Romania**, **Estonia**, **Poland, Portugal, Spain** and **Italy** have either already implemented or drafted similar laws.

These laws typically provide for a **mandatory notification** of medicine agencies, if reimbursed medicines are exported or if there is a disruption of supply. The agency then usually has the right to (temporarily) object to exports within a certain time limit, if quantities of the medicine are insufficient to meet demand, could lead to a (temporary) shortage or if the shortage could pose a serious threat to the health and life of patients.

The European Commission officially answered the question raised by Thomas Ulmer by stating that each complaint and information needs to be examined on a case by case basis, examining whether the export ban violates Art. 34-36 TFEU. Regarding Greece, the Commission so far reported on 3 February 2014 that '*the problems with Greece have been resolved in the course of contacts the Commission had with Greece. The Commission examines all complaints it receives and if the problems remain unresolved it could refer a case to the Court of Justice*.'

In **Bulgaria** the export notification/authorisation procedure, criticised by the European Commission for infringement of free movement of goods, has been scrutinised by the Bulgarian **constitutional court**. The Court found that the **grounds on which the competent medicine agency could object to exports violate the Bulgarian constitutional principles of equal treatment of market players and proportionality**. The court basically stated that the lack of specific and quantifiable criteria is disproportionate and not suited to ensure security and sufficiency of local supplies. However, the requirement for notifying medicines agencies about exports has not been revoked.[82]

In **Italy**, a recent law provides that **essential medicines** must always be available. Besides, the Italian Medicine Agency (AIFA) and the Italian Ministry of Health plan to publish a weekly list of medicines short of supply. However, in the course of drafting the new law it has been criticised that the term 'shortage' is not clear at all. Does it refer only to cases, in which there is no therapeutic alternative? The United Kingdom and France also implemented laws providing for mandatory lists of medicine shortages.

---

[82] Melck B, Parallel-export bans: Member states in collision course with EU regulations?, HIS blog, December 11, 2014, referring to legal provisions in **Slovakia**, **Bulgaria**, the **Czech Republic**, **Hungary**, **Romania**, **Estonia** and **Poland** available at: http://blog.ihs.com/parallel-export-bans%3A-member-states-in-collision-course-with-eu-regulations (accessed: 1 June 2015), European Federation of Pharmaceutical Industries (Efpia), Policy proposals to minimise medicine supply shortages in Europe, 25 March 2014, referring to specific legal provisions in **Bulgaria**, **Czech Republic**, **France**, **Greece**, **Hungary**, **Poland**, **Portugal**, **Romania**, **Slovakia** and **Spain**, available at: http://www.efpia.eu/uploads/Modules/Documents/pac-280214-ai6-a2-shortages-position-paper-final.pdf (accessed: 1 June 2015), Fessenko D, Issaev S, **Bulgarian Constitutional Court** repeals grounds for blocking parallel exports of medicines, February 2015, available at http://www.kinstellar.com/insights/detail/202/bulgarian-constitutional-court-repeals-grounds-for-blocking-parallel-exports-of-medicines (accessed: 1 June 2015), PharmDedict, **Bulgaria**: restrictions on the export of medicinal products, available at: http://pharmdedict.com/bulgaria-restrictions-on-the-export-of-pharmaceutical-products/ (accessed: 1 June 2015), Biro H, Baker & McKenzie, New law introduces supply obligation and export ban on medicines, August 19, 2013, referring to **Hungary**, available at: http://www.lexology.com/library/detail.aspx?g=d9db6589-f73e-4b34-90a3-22c182bffdd4 (accessed: 1 June 2015), Lucchini C, Medicines shortages: an European overview? A clear definition of the terms shortages and a measurable scope of the problem are required to prevent patient's discomforts, Pharma world magazine 4 April 2014, referring to legal provisions in the **United Kingdom**, **France**, **Greece**, **Poland**, **Spain** and **Italy**, available at: http://www.pharmaworldmagazine.com/medicines-shortages-an-european-overview/ (accessed: 1 June 2015), Liptáková J, Chamber of Pharmacists proposes tightening rules on re-export of medicines, Parallel Trade in Drugs plagues **Slovakia**, The Slovak Spectator, 7 October 2013, available at http://spectator.sme.sk/c/20048436/parallel-trade-in-drugs-plagues-slovakia.html (accessed 1 June 2015).

With these (temporary) **notification or authorisation laws on exports** of medicines, parallel trade (i.e. parallel export) as alleged primary cause of medicine shortages shall be combated. However, the phenomenon of medicine shortages in European countries needs to be further analysed. Recent studies show that **parallel trade is by far not the sole cause for medicine shortages in Europe**.[83] Rather, there are several **predictable and unpredictable** causes for shortages, e.g. unpredictable: manufacturing problems, raw material shortages, non-compliance with regulatory standards, unexpected demand or natural disasters, epidemics, packaging shortages, etc. or predictable: product discontinuation, industry consolidation, rationing / quotas, limited manufacturing capacity, etc.[84] Besides, causes can be located at the **supply side** (e.g., manufacturing difficulties, unavailability of raw materials, natural disaster, etc.) or at the **demand side** (e.g., unexpected increase in demand, unforeseen shifts in clinical practice, parallel trade etc.)[85].

The European Association of Hospital Pharmacists (EAHP) published a survey on the medicines shortage problem in Europe in 2014. According to this survey with 600 responses from hospital pharmacists in 34 countries, 86% reported that medicines shortages are a '*current problem in the hospital they work in*.'[86] In 2012, Gray and Manasse as well as Pauwels et al. identify shortages of medicines as a **complex global challenge**, not only in developing countries, but also in the US, Canada, Australia and European countries.[87] Besides, Pauwels et al conclude that '**[p]*roduction problems*** *seem the leading cause of shortages in European countries* […]' and that there '[i]*s a strong link between production problems and market attractiveness*'[88].

The fact that the US, where parallel trade is no issue, is affected by this problem as well, recent studies on causes for medicine shortages in Europe stress that parallel trade cannot be the sole / main cause. **Thus, uncoordinated mandatory notification regimes and export notification / authorisation laws in European countries could be analysed as to whether these measures are well suited and proportionate** for combating this serious health risk and for securing safe supply for patients in Europe.

Recent studies rather indicate that the manifold reasons for medicine shortages call for a joint European policy to combat this **cross-border health threat**[89]: one of the find-

---

[83] Pauwels K, Huys I, Casteels M, Simoens St, Drug shortages in European countries; a trade-off between market attractiveness and cost containment?, *BMC Health Services Research*, 2014, 14:438.

[84] For a detailed list of reasons for drug shortages according to a study conducted in Europe see Birgli AG, An Evaluation of Medicines Shortages in Europe with a more in-depth review of these in France, Greece, Poland, Spain, and the United Kingdom, July 2013, available at: http://static.correofarmaceutico.com/docs/2013/10/21/evaluation.pdf.

[85] Supra note 82 at p. 1.

[86] The survey is available at: http://www.eahp.eu/practice-and-policy/medicines-shortages.

[87] Gray A, Manasse H, Shortages of medicines: a complex global challenge, *Bulletin of the World Health Organization*, 2012; 90: 158-158A as well as Pauwels K et al, supra note 82.

[88] Supra note 82 at p 8.

[89] For the US, several legislative acts have been passed in order to fight drug shortages. Besides, the FDA developed a Strategic Plan for Preventing and Mitigating Drug Shortages in October 2013 (see http://www.fda.gov/Drugs/DrugSafety/DrugShortages/). FDA in close cooperation with pharmaceutical manufacturers publishes a drug shortage database (http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm) and helps to mitigate the underlying causes. According to FDA statistics, progress in fighting drug shortages has been made from 2011 to 2014: see http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm441579.htm (accessed 1 June 2015).

ings in a recent Study was that '[…] *availability problems are not limited to small markets and an effective response to availability problems would need to take into account more than just issues relating to authorisation and* ***focus on the EU as a whole***.'[90]

The EC Pharmaceutical Committee published a number of legal tools for national authorities in case of shortages, intending to ensure adequate supply (e.g. according to Article 126a of Directive 2001/83 EC: '*In the absence of a marketing authorisation or of a pending application for a medicinal product authorised in another Member State in accordance with this Directive, a Member State may for justified public health reasons authorise the placing on the market of the said medicinal product.*')[91]. Besides, the **EMA** publishes a **catalogue on medicine shortages** that affect or are likely to affect more than one European Union (EU) Member State[92] and published a **reflection paper on medicinal product supply shortages**[93]. In its reflection paper, the EMA indicates, that the problem of shortages in some cases already represented a **serious health-threat**[94], comprising of **shortages of essential, life-saving medicines**: '*In some cases defective medicines had to be left on the market to prevent shortages of life saving medicines as there is no available alternative and risks to a possible exposure with the defective product are considered less than those linked to the unavailability of the product*.'

So far, initiatives at EU level seem to be not sufficiently comprehensive enough, and responses to the medicines shortages are predominantly undertaken by competent national authorities that use different approaches (e.g. including differing definitions of 'shortage', etc.).

Parallel trade, MS's patent protection and compulsory licensing in the EU

Under the WTO/TRIPS agreement there exists the option of **compulsory or voluntary licensing**, i.e. breaking the patent holder's right to exclude others, if the **patent holder was given the possibility of voluntary licensing, receives adequate remuneration** and **does have the right to legal review**.[95] For 'national emergencies', 'other

---

[90] Matrix insight, Study on the Availability of Medicinal Products for Human Use, Specific Request EAHC/2011/Health/01 Lot 1, 21 December 2012, final report available at: http://ehtpa.eu/pdf/Matrix_report.pdf at p. 6.

[91] For a comprehensive overview of legal tools, possible remedies and communication see European Commission, Pharmaceutical Committee (PHARM 610), Subject: Shortages of medicinal products due to quality or manufacturing issues, 22 October 2012, available at: http://ec.europa.eu/health/files/committee/69meeting/pharm610_shortages.pdf. http://ec.europa.eu/health/files/committee/69meeting/pharm610_shortages.pdf

[92] See: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000376.jsp&mid=WC0b01ac05807477a6

[93] See EMA, Reflection paper on medicinal product supply shortages caused by manufacturing/Good Manufacturing Practice Compliance problems, 22 November 2012, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/11/WC500135113.pdf.

[94] For a definition of 'serious cross-border health threat' see Art. 3 Decision No 1082/2013/EU of the European Parliament and of the Council of 22 October 2013 on serious cross-border threats to health and repealing Decision No 2119/98/EC, OJ L 293/5 5.11.2013.

[95] The TRIPS Agreement lists a number of conditions for issuing compulsory licenses, in Article 31. In particular: normally the person or company applying for a license has to have **tried to negotiate** a voluntary license with the patent holder on reasonable commercial terms. Only if that fails or if there is an **emergency** (e.g. anti-competitive practices, other national emergencies) a compulsory license can be issued. Even if a compulsory license (e.g. without agreement of the patent holder) has been issued, the **patent owner has to receive payment**. The TRIPS Agreement says '*the right holder shall be paid adequate remuneration in the circumstances of each case, taking into account the economic value of the authorization*', but it does not define '*adequate remuneration*' or '*economic value*', leaving this decision to the competent authorities

circumstances of extreme urgency', 'public non-commercial use' (or 'government use') or anti-competitive practices, there is no need to try first for a voluntary licence. The EU and its MS **voluntarily** declared that they would not use this system for imports (i.e. from non-EU countries).

In line with these international provisions, the EU and its Member States use **compulsory licensing measures in order to fight violations of market or competition rules** - thereby giving competition rules and free movement of goods privilege over intellectual property protection. In a human rights sense, this attitude also favours public interest and equal access to scarce medicines to comprehensive protection of intellectual property rights. In Case C-7/97 Oscar Bronner GmbH&Co. KG v. Mediaprint Zeitungs-und Zeitschriftenverlag GmbH&Co. KG, the Advocate General Jacobs stated that a compulsory license *can be granted 'in terms of competition policy only in cases in which the dominant undertaking has a genuine stranglehold on the related market'*.[96]

Thereby, EU free market rules: Art. 29, 34, 35 and 36 as well as EU competition rules: Art. 101 and 102 would set the scope for compulsory licensing measures, for EU MS' authorities aiming at achieving and promoting access to medicines for all. Consequently, any compulsory licensing measure will be scrutinised under EU free market and competition rules. As Tudor (2012) summarises after analysing recent ECJ case law, any **compulsory licensing decision** must

- **not interfere with free movement of goods** within the EU, even if MS's authorities have filed the decision; however,
  - in case of **voluntary placement** (final outcome is an agreement between companies), the patent right holder and producer may not block any re-entry of that good (produced in another EU MS) and **parallel trade** within the EU may not be inhibited;
  - in case of **involuntary**, compulsory licensing (compulsory licensing is the decision of public authorities), parallel import of that good from a competitor may be blocked (unless there is an economic link between the patentee and the compulsory licensee);
- a dominant position alone does not justify any compulsory licensing;

of the country concerned. Besides, a compulsory license under the TRIPS agreement **can never be an exclusive** one. Thus, the patent owner still has the same rights (e.g. the patent-holder can continue to produce), but is in competition with the holder of the compulsory license. Over all, any compulsory licensing should be **subject to legal review** in the country. – see https://www.wto.org/english/tratop_e/trips_e/public_health_faq_e.htm.

[96] Trudor J, Compulsory Licensing in the European Union, *Geo. Mason J. Int'L Com. Law*, Vol 4:2, 2012, pp 222-258, at p. 225: '*There is significant contention, however, that there is a growing divide between the United States and the European Union on how to handle competition matters (i.e., 'antitrust' in the United States). In regard to this division, the United States is more likely to defend intellectual property rights than the European Union which is more likely to protect competition interests. For example, the European Union is more likely to consider the interests of potential licensors (e.g., intellectual property holders) and licensees in contrast to United States courts. In addition, the showing of a dominant position – the equivalent to the concept of market power in the United States – has a lower threshold in Europe than in the United States. Thus, it is easier to show a competition rules/antitrust violation in Europe. Therefore, the European Union is more likely to grant a compulsory license than the United States courts. Since 1988, this trend in the European Union has become more significant*.'; in the context of human rights see also id. at p. 227.

- **only if a company in a dominant position abuses this position**, compulsory licensing might be justified (e.g. if any abuse leads to a violation of public interests, i.e. access to medicines or any risk to public health).[97]

However, since these basic principles only result from EU case law and only specific fields are explicitly regulated (e.g. Directive 98/44/EC on the legal protection of biotechnological inventions[98]), there is no harmonised regulatory EU-approach so far.

13.4 Secondary EU law interfering with the pharmaceutical (pricing) market: Transparency Directive[99]

In some fields the EU has implemented certain common standards. In order to authorise safe, effective and high quality medicines, the **EU issued common rules for marketing authorisation** of pharmaceuticals. Thus, rules to obtain marketing authorisation are harmonised for the European market. However, as already pointed out, there are no common, coordinated price building mechanisms in the EU and in this sense there is no coordinated European internal market for pharmaceuticals. According to **Art. 168 (7) TFEU, the Member States are responsible for organising their healthcare systems**, including mechanisms for reimbursement and pricing decisions. '*For instance, Member States usually evaluate the cost-effectiveness of authorised medicines, or their relative efficacy as well as the short- and long-term effectiveness compared to other products in the same therapeutic class, in order to determine their price, funding and utilisation in the framework of their health insurance system*.'[100]

Even after obtaining marketing authorisation according to European legislation, Member States can further regulate whether and how a medicine can finally be put on the market. Since **such practices lead to a distortion of the internal market and competition**, these **measures need to fulfil certain basic conditions of procedural transparency** according to primary EU law (Art. 114 TFEU), providing the legal basis for approximation of MS' laws Thus, based on Art. 114 TFEU as well as settled ECJ case law relating to procedural conditions, the Council Transparency Directive has entered into force in 1989[101]. It is the attempt to move towards a **better coordinated** and **genuine single market in the field of pharmaceuticals through secondary legislation at EU level.** The manner in which national policies operate as well as criteria on which they are based in this sector shall be better aligned.

The directive provides for national authorities to **operate within specific time limits** (from 90 to 180 days)[102] and to publish **price lists** as well as a list of pharmaceuticals

---

[97] Supra note 95, pp. 255-257; For an overview of recent European Union Compulsory Licenses see KEI, Research Note: Recent European Union Compulsory Licenses, March 1, 2014, available at keionline.org/sites/default/files/Annex_B_European_Union_Compulsory_Licenses_1Mar2014_8_5x11_0.pdf (accessed: November 16, 2015).

[98] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, OJ L 213/13, 30.7.1998, Article 12.

[99] Council Directive of 21 December 1989 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, OJ L 40/8, 11.2.89.

[100] See 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 system, COM(2012) 84 final, 2012/0035 (COD), at p. 2.

[101] Directive 89/105/EC, supra note 98.

[102] Directive 89/105/EC, supra note 98, Article 3, 1.

with increased prices within this period of time.[103] Any MS imposing a **price freeze** on all or certain products shall review conditions for this freeze at least once a year.[104] If a MS adopts a system of direct or indirect controls on the profitability of persons responsible for placing medicines on the market, specific information has to be published and the Commission has to be informed.[105] Specific procedural requirements are provided for, if a medicine is covered by the national health insurance system only after the competent authorities have decided to include a product in a **positive** or **negative list**.[106] These procedural requirements imply the availability of a remedy involving effective legal protection and the possibility to **appeal to a judicial body**, not simply an administrative one.[107]

Since 1989 the directive has neither been amended nor changed. However, since then, the European **pharmaceutical market has changed significantly** (e.g. in the field of generic medicines or the development of HTA strategies). For this reason and to implement ECJ case law[108], signalling legal uncertainties and reduced transparency of national pricing and reimbursement measures, the Commission issued a proposal for a revised directive in March 2012.[109]

The revised proposal basically retained the key principles of the 1989 directive, but additionally

- seeked to **clarify the scope of the directive** (no application to measures involving public procurement and voluntary contractual agreements with companies),
- clarified that **time limits** for pricing and reimbursement decisions **include all procedural steps leading to the decision**, including HTA where applicable,
- provided for **shorter time limits** for pricing and reimbursement decisions,
- provided for states' non-interference of **patent** and **safety issues** in the context of pricing and reimbursement decisions and
- for **different instruments to facilitate dialogue** on the implementation of the Directive and to ensure its effective enforcement.[110]

The revised proposal has been criticised, especially since time limits provided had been too short and allegedly impossible for Member States to implement. Therefore, the Commission issued a revised version in 2013, providing for

- longer time limits for pricing and reimbursement decisions,
- revised remedies procedures and provisions for penalty payments and
- less strict reporting requirements for MS' authorities.[111]

---

[103] Directive 89/105/EC, supra note 98, Article 3.

[104] Directive 89/105/EC, supra note 98, Article 4.

[105] Directive 89/105/'EC, supra note 98, Article 5.

[106] Directive 89/105/EC, supra note 98, Articles 6 and 7.

[107] Commission v. Austria Case C-352/07 of 2 April 2009 and Hervey T & McHale J (2004), supra note 15, at p. 324.

[108] Including: Case C-424/99 of 27 November 2001, Commission v. Austria, Case C-229/00 of 12 June 2003, Commission v. Finland, Case C-245/03 of 20 January 2005, Merck, Sharp & Dohme, Case C-296/03 of 20 January 2005, GlaxoSmithKline, Case C-317/05 of 26 October 2006, Pohl-Boskamp, Case C-311/07 of 17 July 2008, Commission v. Austria Case C-352/07 of 2 April 2009, Menarini and joined cases C-353/07 to C-356/07, C-365/07 to C-367/07 and C-400/07.

[109] Supra note 99.

[110] See Overview of the main legal elements, supra note 98, at p. 6.

[111] See e.g. Website of the UK Parliament: www.publications.parliament.uk/pa/cm201415/cmselect/cmeuleg/219-xxxii/21910.htm (accessed: 5 May 2015).

Besides, the European Parliament further amended the proposal, providing for further development of the **EURIPID price information database**.[112]

Nevertheless, in March 2015, the **Commission withdrew the proposal since a number of MS still opposed the revised version and no agreement has been reached**.[113]

For now, it would be premature to outline any way forward. However, the removal of the revised version indicates that **any further coordination approach in the field of pharmaceutical pricing and reimbursement through secondary legislation is difficult to attain**. According to the information provided by the Minister to the UK Parliament, MS still oppose to any further coordination approach, arguing with **missing subsidiarity** and **proportionality** of such initiatives.[114]

Since pricing policies are not coordinated within the EU (neither the current version nor the revised and removed version of the Transparency Directive provide for procedural provisions in this context), such practices might have unintended effects, possibly not thoroughly assessed by MS while using EPR: '*While the ERP mechanism may provide useful benchmarks for price negotiations between governments and producers, some stakeholders have voiced concerns about ERP being applied* ***without taking into consideration the socioeconomic features of each country*** *and in particular over the fact that reference prices affected by such emergency measures may influence the price level in other MS or in third countries*.'[115]

13.5 Regulation related to differential pricing

The EC launched regulation related to differential pricing, however to provide a framework for differential pricing between the EU and non-EU countries in the area of external trade.

The **Council Regulation (EC) No 953/2003** of 26 May 2003 to avoid trade diversion into the European Union of certain key medicines (currently under revision: 2014/0165 (COD)) has been introduced to support the principle of tiered pricing between the EU

---

[112] See '*(15a) Member States should ensure the public availability of documents and information in an appropriate publication, in accordance with national practice, which could include electronic and online format. They should also ensure that the information delivered is understandable and supplied in a reasonable quantity. The Commission and the Member States should also examine how to continue to co-operate on the functioning of the EURIPID price information database, which provides EU-wide added value in terms of price transparency*.', available at http://www.europarl.europa.eu/sides/getDoc.do?type=REPORT&reference=A7-2013-0015&language=EN.

[113] OJ, C 80/08, Volume 58, 7 March 2015; see also: supra note 110: '*7.9 The Minister notes the lack of progress made in Council working group discussions since 2013. At the last meeting, in June 2014, he adds: 'A number of Member States continued to raise significant concerns about the amended proposal, particularly relating to issues of subsidiarity and proportionality, and because it was felt to be imposing a one-size-fits-all approach to varied national pricing and reimbursement policies. The UK position had remained more positive than those of most other delegations, although we also had some major concerns that still needed to be addressed, such as about the time limits for decisions on pricing and how these are calculated. 'Whilst progress had been expected with the Italian Presidency of the Council, none of [the] meetings that had been scheduled since June 2014 took place.'* '

[114] Supra note 110.

[115] Commission Staff Working Document, Pharmaceutical Industry: A Strategic Sector for the European Economy, SWD(2014) 216 final/2, 1 August 2014, p. 10

MS and low- and middle income countries. This regulation provides for safeguards to prevent leaking of tiered products from low- and middle-income countries outside Europe into the EU: Authorised tiered priced products are marked with a logo. The manufacturer basically has two options to achieve the differential price: a certain percentage of the average ex-factory price charged in high-priced countries (e.g.: 25%) or the direct production costs plus a certain percentage (e.g. 15%). These tiered priced products with logo are then subject to specific trade rules.

Some specific mechanisms of the Council Regulation, even if relevant for the area of external trade, could be another point of reference to provide technical solutions related to the implementation of DP within the EU.

13.6 Conclusions

There are **several constraints** in EU law that prevent the introduction of an EU-wide coordinated DP scheme. Even though the EU strives at realising a free, internal market in the pharmaceutical sector with equal and affordable access to medicines in all MS, the EU does not have the legal power to regulate the market after market authorisation of medicines has been obtained. In accordance with Art. 168 (7) TFEU, MS have the competence to regulate pricing and reimbursement of medicines, which is justified by MS by the specific nature and tradition of their health care systems. This leads to a highly diverse market for pharmaceuticals with split competences and considerable price differences between MS.

Due to this diversity of the EU pharmaceutical market, and patent-exhaustion after first sale, **parallel trade** results, leading – at least short-term – to reduced prices for consumers in importing MS with high price levels, but potentially threaten supply in MS with low price levels for pharmaceuticals. In addition, pharmaceutical companies' or wholesalers' revenues in high-price countries allegedly decrease, possibly leading to higher prices and reduced investments in R&D.

For this reason, **pharmaceutical companies have developed several strategies** in order to diminish effects of parallel trade, i.e. dual pricing strategies, supply quota restrictions and specific life cycle management policies. These strategies have been scrutinised by European Commission and the ECJ and have in some cases been classified as anti-competitive. The ECJ ruled that agreements of pharmaceutical companies with wholesalers in low-price countries providing for different prices– depending on whether wholesalers would export products to high-price countries – violate EU competition law, but might be justified under certain circumstances and if advantages for consumers outweigh its anti-competitive effects.[116] Besides, the ECJ ruled that a company in a dominant position may refuse to supply out of ordinary exporters' orders in higher price countries, if these measures are proportionate and reasonable, thereby acknowledging existing legitimate commercial interests of pharmaceutical companies.[117] If a company does not abuse a dominant position, a manufacturer may adopt a supply policy, which he considers necessary, even if by the very nature of its aim, the implementation may restrict competition.[118] However, the Commission and the ECJ criticised pharmaceutical

[116] See *GSK I*, supra note 60.

[117] See *GSK II*, supra note 16.

[118] See *Adalat*, supra note 64.

companies' strategy to delay market entry of generic products by using different life cycle management strategies.[119]

These rulings show that the ECJ on the one hand still stresses positive effects of parallel imports, but on the other hand acknowledges legitimate commercial interests of pharmaceutical companies, if **reasonable and proportionate strategies** are applied or **if consumer interests outweigh its anti-competitive effects**. But even though the ECJ provides some guidelines on possibilities for pharmaceutical companies to diminish negative effects of parallel trade, these rulings leave many open questions, e.g. how to apply the reasonability and proportionality test, leading to **legal uncertainty**, e.g. what is specifically meant by a pharmaceutical company's 'legitimate commercial interest', which concrete market conditions in terms of concrete quantifiable criteria have to be fulfilled in order to justify limits in supply and how shall they be determined or how to determine best consumer interests? Thus, **through its competition policy, European Institutions have some possibilities to react to the effects of different MS pricing and reimbursement policies in the field of medicines on undertakings**. However, these measures do not seem to support the healthcare objective of equal and affordable access to patented medicines in all MS.

Consequently, the European Commission built on already **existing legislative opportunities** in order to further advance coordination of MS' pricing and reimbursement policies. However, above described experiences with the delayed and finally removed revision of the Transparency Directive indicated that it is difficult to direct MS' pricing strategies through secondary legislation. Any **legislative coordination initiative** in this field would have to be well argued, based on **'*qualitative and, wherever possible, quantitative indicators*' to convince MS that this objective can be better achieved at Union level**.[120]

Besides, recent activities of MS, i.e. **(temporary) export bans and authorisation / notification procedures** will have to be scrutinised under Articles 34 to 36. It will be necessary to analyse measures taken by MS in relation to a specific product for necessity (public health and access to medicines) and proportionality (reasonable, quantifiable criteria).

Alternatively, initiatives through the so called '**Open Method of Coordination (OMC)**' sometimes might be more successful than legislative initiatives; specifically in fields traditionally not assigned to the European level by MS. The Lisbon Summit introduces this policy of 'spreading best practice and achieving greater convergence towards the main EU goals. According to the Conclusions, this involves: fixing guidelines (with specific timetables); establishing quantitative and qualitative indicators and benchmarks (against the best in the World); national and regional targets; and periodic monitoring, evaluation and peer review organised as mutual learning processes.[121]

---

[119] See *AstraZeneca*, supra note 77.

[120] See the Protocol (No 2) on the Application of the Principles of Subsidiarity and Proportionality, supra note 23.

[121] European Commission, Joint report on social protection and social inclusion 2007: social inclusion, pensions, healthcare and long-term care', Directorate-General for Employment, Social Affairs and Equal Opportunities (2007), available at *ec.europa.eu/social/BlobServlet?docId=2014&langId=en*; see also: Greer S, Vanhercke B, The hard politics of soft law; the case of health, in Mossialos E, Permanand G, Beaten R and Hervey T (Eds.), *Health Systems Governance in Europe, The Role of European Union Law and Policy*, European Observatory on Health Systems and Policy, Cambridge University Press, New York (2010), pp. 186-230, at p. 193-197.

Indeed, there are several points of reference for the Commission to provide sound guidance for MS and to promote transparency of pricing and reimbursement measures or to assess necessary (temporary) export bans and authorisation / notification procedures, e.g. **to provide information and qualitative or quantitative data on effects of different price levels within the EU on consumers and patients** (especially in relation to Directive 2011/24/EU on the application of patients' rights in cross-border healthcare), the **Joint Procurement Agreement of medical countermeasures** that provides a legal framework for joint procurement and specific mechanisms of the **EU Regulation (COM(2014) 319 final) related to differential pricing** for external trade that might provide **guidance** for intra-EU use.

14 Annex 14: Examples of EU coordination mechanisms – Detailed information

14.1 EU Emission Trading System

14.1.1 Practice

The EU Emission Trading System (ETS) aims to reduce emissions of man-made greenhouse gases in the EU by putting a limit on the overall emissions of carbon-dioxide in high-emitting sectors. All 28 EU Member States plus Iceland, Norway and Liechtenstein participate in the EU ETS [20]. Emission Trading is based on the idea of Ronald H Coase who stated that negative externalities of the market (emission of greenhouse gases) can be efficiently internalised if the property rights to a common good (clean air) are clearly specified [21]. In the case of emission, all members of the society are entitled to clean fresh air and manufacturers have to release that right through freely traded certificates.

The EU launched ETS in 2005 as the cornerstone of its strategy for cutting emissions of carbon dioxide (CO_2) and other gases at least costs. In contrast to traditional 'command and control' regulation, emissions trading make use of market forces to find the most efficient way of reducing emissions. A market distributes scarce resources according to signals expressed in relative prices. By limiting the overall volume of greenhouse gases that can be emitted each combined with the issue of emission certificates, the EU puts a price on carbon and thereby giving a financial value to each ton of emissions saved. EU ETS incentivises to invest in clean technologies and low-carbon solutions which is strengthened furthermore by allowing companies to buy credits from emission-saving projects around the world [20].

The Emission Trading Directive (2003/87/EC) for establishing the EU ETS was adopted in 2003, and free trade of certificates was put into existence in 2005. Since its introduction, EU ETS has experienced three trading periods. The first trading period took place between 2005 and 2007 and was used for 'learning by doing'. Although the EU has established the world's biggest carbon market the price of first-period allowance fell to close to zero. The main reason was the excessive amount of allowances due to exaggerating emission reports of the Member States. Therefore, in the second trading period between 2008 and 2012, the number of allowances was reduced by 6.5 percent annually. However, this period coincided with the economic downturn after the credit crunch leading to a surplus of unused allowances. The third period started in 2013 and will last until 2020, and it is accompanied by further reforms [20].

The EU ETS covers emission of three different greenhouse gases in certain sectors which constitute 45% of total greenhouse gas emissions from the 28 EU countries. These are carbon dioxide (CO_2) from power plants, a wide range of energy-intensive industry sectors and commercial airlines, Nitrous oxide (N_2O) from production of nitric, adipic, glyoxal and glyoxlic acids and Perfluorocarbons (PFCs) from aluminium production. From 2013 onwards, the cap on emissions from power stations and other fixed installations is reduced by 1.74 percent every year, summing up to a total reduction of 21 percent in 2020 from these sectors compared to the 2005. A separate cap is applied to the aviation sector which is 5 percent below the average annual level of emissions in the years 2004-2006 [20].

Emissions certificates are allocated through two mechanisms: (1) Auctioning; Businesses have to buy their allowances at auctions. (2) Free allocation; businesses receive their allowance for free. Which type of mechanism applies depends on the sector, in

which the business is operating, but in the recent trading period there was a shift towards auctioning and free auctioning should phase out completely by 2027 [20].

14.1.2 Costs

Costs for participating in the EU ETS can be divided into 3 broad categories: (1) Costs of obtaining emission allowances (excluding the price of the allowances) (2) Costs of monitoring, verifying and reporting emissions and (3) costs of managing the portfolio of allocated emission allowances. Most of costs are not proportional to the size of the emission or the size of the allocation, making the EU ETS particularly burdensome for small emitters [22].

In 2005, the Commission conducted a survey among Member States to evaluate the costs for participation in the EU ETS for smaller installations. The survey revealed that most countries do not have much detailed information on the costs of participation. The estimated costs of the EU ETS participation for smaller installations are reported in the table below [23].

Table A10: Costs estimates of EU Emission Trading System

Country	Cost reported
Germany	EUR 12,500.00 to more than EUR 20,000.00 per installation
Denmark	Total recurring costs of at least EUR 4,300.00 – EUR 7,000.00 per installation covering costs of registration with the administration, monitoring, verification etc. Depending on complexity of the installation
Sweden	Total recurring costs of EUR 2,100.00 – 5,000.00 per installation in phase I and EUR 1,400.00 – EUR 2,600.00 per installation in phase II
United Kingdom	Total administrative costs EUR 3,675.00 - EUR 4,415.00

Source: Research by GÖ FP

A range of studies aimed to assess administrative compliance costs under EU ETS. The Emissions Trading Group (ETG) Working Group 5/6 gathered data on (1) staff costs, (2) non-staff costs (3) total indicative costs and (4) one-off costs and estimated the total annual costs per installation in Phase I at GBP 27,000.00 [24]. The National Audit office conducted a survey, in which companies reported total annual costs of GBP 35,000.00, composed of monitoring and reporting (GBP 26,000.00) and average annual verification costs (GBP 9,000.00) [25]. In an impact assessment of the Emission Trading Scheme the European Commission stated that the range of estimated administrative costs for operators range varies between EUR 2,000.00 to EUR 15,000.00 per year, and for authorities between EUR 3,000.00 and EUR 10,000.00 per site and year [26]. King et al. (2010) estimate the average administrative burden of the EU ETS to be around GBP 16,400.00 (including one-off costs and fees). If wider administrative costs are included the average can increase to GBP 21,000.00. In their assessment, the authors found a significant variation from sector to sector. From the operator's perspective, the costs of the extension of the EU ETS in 2008 were estimated at EUR 3.05 Mio. for operational expenditure, EUR 6.727 Mio. for human resources and associated costs, and EUR 1.881 Mio for administrative expenditures other than human resources, summing up to EUR 11.658 Mio. [27].

14.1.3 Benefits

Evaluating emission trading schemes it must be done cautiously because it is important to distinguish between the inherent strengths or weaknesses of emission trading (from theoretical viewpoints) and those contingent matters of performance which are rather related to (1) the particular design of characteristics of the scheme, (2) its fit with the context of application or (3) the intensity by which the pollution abatement is enforced. Every Emission Trading system operates with quite different strengths and weaknesses in different context and its different design [28].

Coverage: The centralised function of the European Commission facilitated the introduction of the coordination mechanisms on a large scale, covering all 28 EU Member States plus Iceland, Norway and Liechtenstein. Under the EU ETS, individual countries are responsible for emissions monitoring, reporting verification and enforcement under the ETC. The European Commission contributed to the success of implementation by approving national budgets, establishing common registry protocols and providing information and technical assistance [29].

Reducing uncertainty: The joint implementation (JI) and the clean development mechanism (CDM) within the EU ETS enable participants in the schemes to undertake emission-saving investments in other countries and credit these savings towards their emission targets. CDM covers projects in countries without and emission target under the Kyoto Protocol i.e. developing nations, whereas JI applies to projects in countries that have agreed on an emission target i.e. other industrialised countries and countries with economies in transient. Efforts in JI and CDM are rewarded with credits known as 'emission reduction units' (ERU) and can be converted 1:1 to emission certificates[122]. The EU ETS creates a stable environment for investors in emerging markets for JI and CDM projects and encourages more investment in such projects and promotes the transfer of environmentally sound technologies.

Compatibility: The EU ETS is compatible with schemes in other countries that have ratified the Kyoto protocol. The market for trading certificates can be readily expended if countries agree to recognise allowances issued by the other. In a major step towards an international emission trading system, the European Commission and Australia have agreed, that by mid2018 the schemes from both continents will be fully linked. Negotiations are also under way with Switzerland on linking the EU ETS.

14.1.4 Limitations

The EU ETS was designed as the largest emission trading scheme in the world and the first application of emission trading on a large scale, making it an ambitions and highly challenging policy experiment. Due to the lack of comparable experience in this field, the implementation was sometimes characterised by a learning-by-doing process.

National Allocations Plans vs. central coordinating organisation: The market mechanism distributes goods on signals the participants send and receive. Emission trading schemes are designed markets, where the demand and the supply are dependent on government decisions. Demand is driven by the coverage of the system, whereas supply is determined by the volume of allowance allocation. In order to derive the cap of emissions certificates, every member state was required to develop a national allocation plan

[122] Excepted are nuclear energy projects, afforestation or reforestation activities and projects involving the destruction of industrial gases.

(NAP). Since countries feared a competitiveness loss of their national industries due to higher production costs and the lack of date at the installation level, the calculation of NAPs lead to substantial over-allocation of emission allowances in the first period. Therefore the EC took a stronger role in the in the second period to provide a higher overall stringency of the allocation caps [29, 30].

Inclusion of Transport: In the beginning, the EU ETS scheme was limited to four emission intensive sectors: (1) energy activities (2) production and processing of ferrous metals (3) mineral industry and (4) other industries [30]. However, the transport sector, which accounts for a large fraction of emissions, was not included. Only in the third trading period, some steps were made in this direction, by including aviation, but not road transport. It was argued that the inclusion of road transport would increase the cost of certificates and the marginal abatement cost, and therefore could have a negative impact on the competitive advantage. Also problems related to limited effectiveness of emission trading for road transport where identified [31].

Emission banking: The actual system does not consider the possibility to 'save' not-consumed allowanced and transfer them to later periods. This supplementary regulation is known as emission banking and breaks through the stringency of the EU ETS by offering additional freedom to participants in the system. Seller of certificates would not be required to find purchasers of their licenses within a certain period, if the price of this allowance is relatively low [32]. Emission banking can also contribute to reduce price volatility, which hampers investment decisions of economic agents [30]. In order to prevent excessive storage of emission allowances, demurrage can be applied to older certificates.

Stand-alone policy: In theory, emission trading is a cost-efficient tool to internalise negative market externalities. However, in practice it is not clear how much of the emission reductions are attributable to emission trading. In Europe, due to the economic crisis and the lower economic activity, emissions were reduced substantially [33]. Also for the 1995 introduced 'Clean Air Act' some authors claim that the reduction of Sulfur dioxide (SO_2) emission by electric utilities was unrelated to emission trading but to other factors [34].

14.2 Common Agricultural Policy (CAP)

14.2.1 Practice

The Common Agricultural Policy (CAP) is not one policy but rather a set of policies aimed at raising farm incomes in the EU, which have radically changed over time. The early CAP was established as price floor for many major farm products like grains, dairy products, beef, veal and sugar. The prices held above world prices through a system of import tariffs which changed daily according to world market conditions and direct purchases as the last resort. The goal of the early CAP was to ensure that imports never pushed EU prices below the price floor. Price supports have huge distributional consequences from the producer and consumer perspective. The benefits of price supports mainly go to larger farms, because they produce a lot and – due to economics of scale – tend to produce more efficiently i.e. at lower costs. Since the owners of large farms tend to be rich, the benefits of a price floor are systematically biased in favour of larger and wealthier producers. Furthermore, price floors are paid for by consumers, because they have to pay the higher price for food. As poor families spent a higher fraction of their income on food, prices are more important to their budget and, price floors are therefore a regressive consumption tax [35].

In the first years after its introduction CAP as price floor worked quite well and provided higher and stable prices food. Although these artificial higher prices were paid by consumers, it was not criticised by them, because as the average income in that time rose faster than food prices. However, in this period agriculture witnessed revolutionary advances which boosted yields and created a cascade of unintended consequences as CP rewarded output. Budget, food disposal and farm income problems as well as 'factory farming' and harming the prospects of developing nations are the most notable references. Breaking the link between the payments and overproduction was considered as solution to that problem and therefore payments were gradually decoupled i.e. the size of the payment was not related to the produced amount [35]. The MacSharry Reform in mid-1992 and the Fischler reform in 2003 brought substantial changes, moving from a production-oriented policy towards single-farm payment, decoupling the production from subsidies [36]. The money was paid directly to the owner of the farmland regardless of whether the owner was a farmer or not. The only requirement was to continue farming.

Today's CAP has two pillars: the first concerns direct payments and the cost of the remaining price supports, and the second pillar is the so-called 'Rural Development'. Council Regulation 1234/2007 established a common organisation of agricultural markets which main framework was also retained for the new CAP Period from 2014 till 2020. However, the new CAP design pursues a more holistic approach with better targeted instruments of the first pillar, complemented by regionally tailor-made and voluntary measures of the second pillar [37]. The common rules regulate the EU internal agricultural markets through market interventions (public intervention or aid for the private storage), special intervention measures (exceptional market supports in crisis), quota schemes (fixed national production quotas for sugar) and aid schemes for several sectors (e.g. programmes promoting the consumption of fruit and milk in schools). For instance, the production of sugar beets (with the EU being the world's leading producer of beet sugar) is regulated via a production quota that is divided between nineteen EU Member States. Farmers receive for quota sugar beets from sugar factories a minimum fixed price whereas out-of-quota sugar beet has to be sold at market prices. A EU reference price for white sugar was fixed, and, if EU market prices fall below 85% of the reference price, private storage aid can be activated [38].

14.2.2 Costs

Evaluating the costs of CAP is a difficult task because there do not exist many publications on that topic. In a study published in 2007, DG AGRI estimated that CAP cause on the producer level Germany 480.37 million Euro total administrative costs. This corresponds to 1,298 Euro average administrative costs per producer/famer at. When distributing the total administrative costs to acreage, the administrative costs amount to 28 Euro per ha. The relation between total CAP payments and total administrative costs is 9.3%. The most burdensome subject in CAP at producer level is the application for the decoupled payment which constitutes 98.3% of all administrative costs [39]. On the operator's level no data on the costs on running this allocation mechanism is available.

14.2.3 Benefits

Ensuring the safety and quality of food: Due to climate change, oil shortages the availability of quality land and water, some parts of the world experience food shortages. Since its introduction CAP has contributed to ensure food security for European citizens. It also helps to guarantee that Europe's consumers get food that meets quality requirements. For instance, organic farmers and food producers are encouraged to use the EU organic logo where at least 95% of the product's ingredients have been organically

produced and it complies with the rules of an official inspection scheme. This benefit has been regularly recognised by European citizens, which think that agriculture and rural areas are an important matter for the future of the EU [40].

14.2.4 Limitations

Duration of decision finding in political sensitive areas: The evolution of CAP reveals a central problem: a coordination mechanism in a politically sensitive area – as food and nutrition clearly for various reasons clearly is – can take long time and large efforts the larger the group is. The original coordination mechanisms worked well for a low (rather homogenous) number of countries in the beginning, but over time (and several enlargements later) it became a subject for many quarrels among EU members.

Impeding the signal function of prices requires regular adjustments: Experience from the 70's and 80's showed that due to CAP the prices lost its function as signal for relative scarcity. High prices resulted in 'wheat, beef, and butter mountains' which either rotted or sold as animal feed. The policy of exporting the food 'surplus' abroad created a foreign trade problem and had severe consequences on producers in other countries. The evolution of CAP showed that any coordination mechanism needs to be adjusted for transformations which occur within the system and is at best a snapshot of an ongoing adjustment process [35].

Complexity: Although the logic behind CAP claims to be simple i.e. raising farm incomes in the EU, the set of policies with which this aim should be achieved, has become more and more complex. This is reflected in the fact that the average European citizens does little know about agricultural or agricultural policy [41]. A centralised coordination mechanism of the complexity of CAP bears the risk that Europeans citizens alienate from an issue which affects them fundamentally.

15 Annex 15: Stakeholder review

15.1 Methodology

The contractor was asked to perform a stakeholder review for this study as defined under the Call for tender n. EAHC/2013/Health/01 for concluding Multiple Framework Contracts with reopening of competition to support the implementation of the Health Programme (2008-2013) and the Health Programme (2014-2020) for large reports.

The key elements of such a stakeholder review were defined by the EC as follows

- Minimum 20 stakeholders, up to 60 stakeholders to be suggested, to be approved by Chafea/DG SANCO;
- Comments from stakeholders to be collected in writing, to be presented to Chafea/DG SANCO;
- One face-to-face meeting needed with Chafea/DG SANCO;
- The review shall include a stakeholder meeting with minimum of 20 stakeholders in Luxembourg or Brussels;
- Duration: maximum 8 weeks.

Thus, the Tender Specifications asked for two elements of the stakeholder review: a written review, and a stakeholder review meeting.

According to the Tender Specifications of the Study on 'Enhanced cross-country coordination in the area of pharmaceutical product pricing', the stakeholder review shall be 'open to participation of EU-level representatives from patients, public payers and medical industry'.

In the proposal, the contractor proposed the following criteria for a representative selection of stakeholders:

- Extending stakeholder groups beyond the Tender Specifications: Based on the experience of a previous piece of research ('Study of the policy mix for the reimbursement of medicinal products' by Vogler et al. 2014), the contractor proposed to also include the stakeholder groups of consumers, competent authorities for pricing and reimbursement and healthcare professionals such as doctors and pharmacists. Industry should be represented by different industry branches focusing on different types of medicines, e.g., research-based pharmaceutical industry (also considering biotech industry), generics and biosimilar industry, and self-medication industry. Medical devices were not considered as within the scope of the consultation since the study targets only pricing policies for medicines.
- EU-level representativeness: The contractor considered stakeholder representatives from the European associations as primary target for the stakeholder review. They are the key contact points, and should therefore to be addressed for the 'full' stakeholder review (both comments in writing and at the meeting). However, with a view of addressing up to 60 stakeholders (as requested in the Tender Specifications), the European institutions would be not sufficient. Therefore, some representatives from the Member States, but active in the associations, should also be involved in the stakeholder review. The contractor was of the opinion that the decision on whom to nominate should be with the European associations, and thus suggested going through the European associations for their nominations (where applicable).

Based on these considerations, the contractor proposed a differentiated approach for the written review and the stakeholder review meeting: We were convinced that a high number of high-quality stakeholder responses on the draft findings would provide an

added value to the project. However, to allow for a constructive dialogue during the meeting, offering enough time for the representatives of the stakeholder groups to address all relevant topics during the stakeholder meeting, the contractor suggested to limit the number of participants in the meeting to around 20-25 stakeholders, whereas the remaining stakeholders have the possibility to comment in writing. The stakeholder representatives to be invited to the meeting should primarily come from affiliations to the European associations, plus some Member State' representatives from associations and competent authorities for pricing and reimbursement / public payers. Our rationale for proposing this was that the same approach was applied for the Working Groups of the Platform 'Access to Medicines in Europe' under the Process on Corporate Social Responsibility in the Field of Pharmaceuticals.

We also suggested the principle of 'one institution – one voice/representative' so that the consulted stakeholders would be invited to provide their comments in their role as representatives of the institutions they represent. As a result, we suggested accepting one coordinated response per institution (either European association or national stakeholder organisation) in the written stakeholder review.

These principles were presented in the proposal, presented at the kick-off meeting in Brussels on 19 December 2014 and confirmed in a revised inception report accepted by the EC in January 2015.

In line with these principles, the contractor proposed a list of stakeholders to be invited for the stakeholder review meeting. We discussed this list of stakeholders with the EC at the kick-off meeting in Brussels on 19 December 2014. In principle, the list was accepted, and it was expanded thanks to some further suggestions of the EC. The finally agreed list of stakeholders to be invited to the stakeholder review meeting was confirmed through EC's approval of the inception report in January 2015.

For the written review, participants were invited to provide their feed-back in a 'feedback template', divided into 'general comments' and 'specific comments' related to specific parts (sentences / paragraphs) of the draft report.

While it was expected that all participants of the stakeholder review meeting had read and were familiar with the draft report, the meeting was still opened with a presentation of the key findings of the draft report. The presentation of the results was accompanied by a summary of major comments, sometimes contradictory, of the written comments. Following the discussion of the presentation, some specific questions were discussed:

- EPR – A tool for access to medicines and/or cost-containment
  - How can EPR be designed to be improved in order to be able to possibly work as instrument towards increased access to medicines and increased cost containment? (e.g. Improvement in the formulae, in the MS coordination – cf. proposals for cooperation in the study)
- DP – A tool for increasing access to medicines
  - Should a DP scheme be developed in the European Union, and if yes – how? (e.g. how to differentiate prices, limitations, MS coordination)
- Ways forward for the future
  - What is missing?
  - Proposals for (future) research and for policy-making?

The meeting was held under the Chatham House Rules.

15.2 Results

15.2.1 Participation

We sent the draft interim report on 10 August 2015 to a total of 51 institutions, thereof 13 stakeholders (associations / interest groups)[123], 32 Member State institutions (pricing authorities), and 6 DP experts (that had been available for interviews). We received written feedback from a total of 23 institutions, thereof 7 stakeholders, 16 Member States institutions from 15 Member states, and 2 DP experts. Written feedback was received between 14 August and 7 September 2015. The lengths of the written comments varied between nearly 50 pages and one paragraph. If shorter comments were provided, stakeholders did not use the feed-back template.

A total of 34 people participated in the stakeholder review meeting held in Brussels on 17 September 2015. In addition of representatives of DG SANTÉ and further Directorate-Generals of the European Commission and permanent representatives of following EU Presidencies, 11 stakeholder representatives and 11 Member State representatives (two of them also represented a stakeholder perspective) attended the meeting. For further information about the participation in the stakeholder review see Table A11.

Table A11: Stakeholder review process

Stakeholder / Member State	Written comments (between 14 August and 7 September)	Participation in the workshop (17 September 2015)
European Social Insurance Platform (ESIP)		✓
Association Internationale de la Mutualité (AIM)	✓	✓
Bureau Européen des Unions de Consommateurs (BEUC) and national associations	✓	✓
Health Action International (HAI)	✓	✓
European Patient Forum (EPF) and national associations		✓
European Public Health Alliance (EPHA)	✓	✓
European Federation of Pharmaceutical Industries and Associations (EFPIA) and national associations	✓	✓
European generic and biosimilar medicines Association (EGA) and national associations	✓	✓
European Association for Bioindustries (EUROPABIO)		
Association Européenne des Spécialités Pharmaceutiques Grand Public (AESGP)		✓

[123] The report was shared with associations and interest groups on European level, who were allowed circulating the draft report within the boundaries of their national associations.

Stakeholder / Member State	Written comments (between 14 August and 7 September)	Participation in the workshop (17 September 2015)
European Association of Hospital Pharmacists (EAHP)		✓
Comité permanent des médicins européens (CPME) & n. assoc.	✓	✓
Euripid		✓
Austria		
Belgium		✓
Bulgaria		
Croatia	✓	
Cyprus		
Czech Republic		✓
Denmark		
Estonia		
Finland	✓	
France		✓
Germany	✓	✓
Greece		✓
Hungary	✓	✓
Iceland		
Ireland	✓	
Italy		
Latvia		✓
Lithuania	✓	
Luxemburg		
Malta	✓	✓
The Netherlands		✓
Norway	✓	
Poland		
Portugal		
Romania		
Slovakia	✓	✓
Slovenia	✓	
Spain	✓	✓
Sweden	✓	
Switzerland	✓	
Turkey	✓	
United Kingdom	✓	
DP experts	✓	

Dutch representative also represented ESIP, Hungarian representative also represented EURIPID

15.2.2 Written stakeholder review

Overall, different approaches in commenting the draft reports were observed between comments provided by stakeholders (associations / interest groups as defined above) and those of Member States. Since Member States representatives had already been involved in the survey about their EPR systems, they understood the sharing of the draft report as an opportunity to validate and confirm the information about their country. Comments of stakeholders, overall, were thus not country specific but more general. In some cases, the general comments provided did not necessarily refer to the draft report, but were general statements related to EPR, DP and/or pharmaceutical policies.

Among others, the study aimed to start the discussion about improvements for EPR and exploring alternative pricing possibilities, including DP. This 'pedagogic exercise' was apparently successful since the contractor received several comments, particularly from Member States, that the study helps to increase their understanding about DP. Both stakeholders and Member States expressed their pleasure to see the launch of a critical discussion about limitations of EPR by the EC through the commissioning of this report.

The different parts of the report were addressed in different frequencies. Most comments probably related to the validation of the country-specific information about EPR (usually confirming that this information was correct). For the remaining non-country specific information, considerably more comments referred to the EPR section compared to the DP section. No stakeholder comments related to the legal analysis[124]. One stakeholder critically addressed the methodology of the simulations, proposing to run a dynamic instead of a static model.

General comments related to EPR were as follows:

- Several comments concerned the limitations of EPR that were generally acknowledged by both stakeholders and Member States.
- It was suggested that the non-availability of medicines should be further stressed. One stakeholder recommended considering it in the simulations, in connection with the disclosure of discounts.
- Several comments referred to the role of EPR within the menu of policy options. Stakeholders but also, to a lesser extent, Member States comments stressed that EPR should be not used as a single tool, but also and particularly with other (pricing) policies. Further, it was commented that pricing is only one part of the tools to ensure equitable access to medicines while containing costs.
- One stakeholder addressed the scope of this policy, stating that EPR should not be used for generics.

The most controversial issue related to EPR (but also addressed again in the DP sections) concerned transparency. While one stakeholder stated that elements of price information, in particular discounts, rebates, and managed-entry agreements, should be kept confidential, as this was understood as part of the business, other stakeholders and Member States opted for (full) disclosure of these price reductions.

These controversial approaches were also reflected in more specific comments related to two of the four proposals to improve EPR.

[124] However, some conclusions resulting from the legal analysis (with regard to the Council Regulation (EC) 953/2013 to trade diversion into the EU of certain key medicines (EU tiered pricing regulation)) were challenged.

The first proposal concerned an extended price database, and this appeared to be the part of the report that attracted most comments. Most comments related quite specifically to the already existing database Euripid. Member States confirmed the usefulness of that database as a supporting tool for doing EPR. Stakeholders who did not have access to the Euripid database raised concern about possible methodological limitations of that database. It was suggested that a price database should not contain price data calculated on average margins (e.g. ex-factory prices based on average wholesale margins). Stakeholders without access to the Euripid database called for a price database open to either all stakeholders or to industry only which was suggested be invited to validate the prices in Euripid. Some stakeholders and Member States addressed again the issue of confidential discounted prices, and called for the inclusion of discounts in a price database.

While there were controversial views between the commenters about confidentiality, the proposal of the study authors to consider at least published mandatory discounts in EPR was only addressed by one commenter representing a stakeholder. This proposal was challenged since mandatory discounts were seen as a temporary measure only[125].

No explicit written comments were made with regard to regular price monitoring, and only few comments related to a coordinated EPR formulae. Overall, the proposal of weighting prices by the income / wealth of the countries was welcome by several commenters, both stakeholders and Member States representatives.

General comments related to DP were as follows:

- One industry stakeholder challenged the definition for DP that was applied in the study. In line with the Tender Specifications to study a government policy measure, the study elaborated about DP in a format as a coordination measure applied by Member States, and did not consider 'Ramsey pricing' or 'price differentiation'. The stakeholder would have preferred to further include an assessment of current price differentiation by industry through granting confidential discounts to public payers.
- However, the applied definition might apparently not have been clear enough since another stakeholder expressed the concern that differential pricing could run the risk of being first and foremost used as a commercial strategy allowing pharmaceutical industry to maximise their profits.
- Some stakeholders from consumers/patients side confirmed findings of the literature reported in the study that other instruments, in particular generic competition might be more effective, not only related to cost-containment, but also for ensuring long-term access to medicines.
- Some commenters (both stakeholders and Member States) expressed concern about the feasibility of a DP scheme in Europe and doubt whether there might be sufficient political will.
- In this respect, some reflections were made of what would be the most appropriate price to start with in the DP model. One stakeholder challenged the proposal made in the report to design the DP model in a way that higher-income countries would not pay more with DP than without DP.

[125] The study authors do not agree. There are examples of mandatory discounts in European countries that have been in place for some years (e.g. Italy, Spain).

- It was felt by an industry representative that the issue of parallel trade was not sufficiently explicitly highlighted in the study.
- Concern was addressed that the Member States might be under pressure to reimburse a differentially priced product.

References related to further examples of DP initiatives were made, and it was suggested considering drawing conclusions from literature related to risks and benefits of donations.

Few specific comments were made with regard to the outline that the authors were asked to develop on how a DP scheme in Europe might look like:

- The authors were asked by a commenter (Member State) to elaborate further on the organisational aspects of a DP model in Europe.
- Another commenter (stakeholder) challenged the proposal that orphan medicines might not be a good example for a DP pilot due to their specific character.

Overall comments, not directly linked to EPR or DP, reflected the different views of power between stakeholders and Member States. While a commenter from an international organisation considered Member States in their current role as 'price takers', industry referred to the authorities as 'price setters'. Some commenters raised questions about how to establish a 'fair' EPR and DP scheme ('what is a 'fair price' for all) and about the cost of research (and their funding: 'Do societies have to pay the cost of research'). Further, the study only concerned two of the three objectives as defined in the European processes such as the Pharmaceutical Forum (see Chapter 2 on Background), i.e. access to equitable medicines and cost-containment/financial sustainability. Stakeholders felt that, though acknowledging that this was not the scope of the study, industry perspective in general and the objective of reward for innovation should also be taken into consideration.

15.2.3 Stakeholder review meeting

Some of the issues that had been raised in the written review were also addressed during the stakeholder review meeting. These included:

- The issue of transparency that was debated controversially between stakeholders (in addition, the idea was raised that different levels of transparency with regard to different target groups might be in palace).
- The definition of DP (the definition of a government-fledged DP system was challenged).
- The difficulties related to defining a starting price were discussed.
- Limitations of EPR were again highlighted.
- The importance of political will as a prerequisite for starting a new pricing policy such as differential pricing was stressed.
- The scope of EPR (one stakeholder repeated that EPR should not be used for generics).
- Stakeholders asked to elaborate on the industry perspective in general and the objective of reward for innovation.
- It was repeated that prices are not the only component of pharmaceutical policies.
- The importance of other tools and policies was stressed. In particular compulsory licensing and TRIPS flexibilities were mentioned, as well as generic policies, where appropriate. Further, the importance of horizon scanning and HTA was also highlighted.

Since the stakeholder review meeting was designed in a way to allow addressing further issues (beyond the scope of the study), the following topics were debated in the meeting:

- One stakeholder mentioned the importance of managed-entry agreements, and considered them as an appropriate policy option to address current challenges, however limited capacity in countries was identified.
- Clarity on the mandate of the representatives who jointly procure on behalf of authorities was defined as a prerequisite for meaningful negotiations from industry's perspective.
- Increased pressure from the public about new treatments can influence 'technical' assessments.
- Though limitations of EPR and DP were seen, these policies should not be stopped but adjusted in a way that the ideas and elements were changed.
- Stakeholders and Member States representatives stressed the need to have a better understanding about the cost of research.

The following suggestions were made during the stakeholder review meeting:

- Improving the capacity of procurers to negotiate and to become price setters;
- Policy-makers should define what the health care system is willing, and can afford, to pay, and should then communicate this to industry (thus moving from an offer-based to a demand-based system);
- Need for finding new ways of financing;
- Moving away from the focus on medicine prices to a more comprehensive consideration of the treatments;
- Opening up the discussion on parallel trade related to medicines;
- Considering also the impact of pricing policies on the distribution (wholesale and pharmacies);
- Collaboration between countries shall consider discussing further areas of cooperation beyond pricing issues;
- Citizens and consumers should be increasingly involved;
- The EC was asked to support Member States, in disseminating information about upcoming products and technologies, and by helping countries in building capacity related to price negotiations;
- It was suggested to start research and practical pilots on the methodology for defining a 'fair' price;
- An independent review on the cost of research was requested;
- Stakeholders would highly appreciate a continuation of a multi-stakeholder dialogue as it was done in the stakeholder review meeting (the meeting was seen as a step in the right direction for enhancing dialogue and coordination).

15.2.4 Follow-up on the stakeholder review

This stakeholder review report aims to strike a balance between providing information of relevant comments of stakeholders and Member States and ensuring threshold of confidentiality.

The contractor considered all comments provided by the stakeholders and Member States in writing and in the course of the meeting and duly revisited the text of the draft report where considered appropriate.

16 Annex 16: Peer review

16.1 List of peer reviewers

The following tables provides an overview of the peer reviewers contacted in line with the methodology agreed with EC and decided in chapter 3.5.2.

Table A12: List of possible peer reviewers

Name	Institution	Country	Status
Babar, Zaheer-Ud-Din	University of Auckland	New Zealand	Written review received
Brekke, Kurt	Norwegian School of Economics	Norway	Declined to review for time constraints
Busse, Reinhard **Panteli, Dimitra**	University of Technology Berlin	Germany	Written review received
Danzon, Patricia	University of Pennsylva-nia	United States	Did not review for time constraints
Docteur, Elizabeth	Elizabeth Docteur Con-sulting	United States	Written review received
Espin, Jaime	Andalusian School of Public Health	Spain	Written review received
Glynn, Dermot	Europe Economics	United Kingdom	Written review received
Henry, David	University of Toronto	Canada	Declined to review for time constraints
Hollis, Aidan	University of Calgary	Canada	Written review received
Kanavos, Panos	London School of Economics	United Kingdom	Did not review for time constraints
Kyle, Margaret	Toulouse School of Economics	France	Written review received
Laing, Richard	Boston University	USA	Declined to review for time constraints
Morgan, Steve	University of British Co-lombia	Canada	Written review received
Rovira, Joan	University of Barcelona	Spain	Written review received
Stargardt, Tom	University of Hamburg	Germany	Declined to review for time constraints
Toumi, Mondher	University of Aix-Marseille	France	Did not review for time constraints
Towse, Adrian	Office of Health Economics	United Kingdom	Did not review for time constraints

16.2 Outcome of the peer review

The response of the peer reviewers to the report was very positive. More comments were related to EPR than to DP. Several comments reiterated the limitations of EPR and asked the authors to spell them out more explicitly.

Some comments were made to invite the authors for further specifications and explanations (e.g. related to the definition of DP, to statutory discounts), and comments included practical suggestions related to editing.

Content-wise, it was suggested by a few reviewers to acknowledge and explain how the pharmaceutical industry acts strategically in response to pharmaceutical pricing mechanisms, in particular EPR. The issue of the pharmaceutical research, currently being linked to pricing policies, was addressed by some reviewers, and authors were asked to highlight the characteristics of R&D as a public good, and the role of public funding of biomedical research. Several reviewers regretted that further policies besides EPR and DP were beyond the scope of the study. They would have welcomed a discussion about value-based pricing and HTA in the report. Overall, reviewers were concerned about the premium-priced medicines that challenged the financial sustainability of publicly funded health care systems and urged for developing alternative models to fund innovation. Most peer reviewers acknowledged a need for more transparency (while arguing about the difficulty to achieve a disclosure of discounts), and were rather positive to the implementation of a DP scheme or DP-like features.

17 Annex 17: References of the Annex

[1] Toumi M, Rémuzat C, Vataire A-L, Urbinati D. External reference pricing of medicinal products: simulation-based considerations for cross-country coordination. Final Report. European Commission, 2014.

[2] Babar ZUD, Atif M. Differential pricing of pharmaceuticals: a bibliometric review of the literature. Journal of Pharmaceutical Health Services Research. 2014;5(3): 149-56.

[3] Bundesministerium für wirtschaftliche Entwicklung und Zusammenarbeit. Bringing Medicines to Low-Income Markets: A guide to creating inclusive business models for pharmaceutical companies. 2012.

[4] Glaxo Smith Kline Communications and Government Affairs. GSK Public Policy Position: Tiered Pricing Approaches for Vaccines. 2014.

[5] Steinbrook R. Thailand and the compulsory licensing of efavirenz. New England Journal of Medicine. 2007;356(6): 544.

[6] Yadav P. Differential pricing of pharmaceuticals: Review of current knowledge, new findings and ideas for action. A study conducted for the UK Department for International Development (DFID). Zaragoza: MIT Zaragoza International Logistics Program, 2010.

[7] Global Health Progress. Novo Nordisk: Differential Pricing on Insulin. Available from: http://www.globalhealthprogress.org/programs/novo-nordisk-differential-pricing-insulin. 2015.

[8] Mossialos E, Dukes G. Affordably priced new drugs for poor populations: Approaches for a global solution. International Journal of Risk & Safety in Medicine. 2001;14(1): 1-29.

[9] Vogler S, Schneider P. Vergütung der Arzneimitteldistribution in den europäischen Ländern. Vienna: Gesundheit Österreich Forschung und Planung GmbH (GÖ FP), 2015 (unpublished).

[10] Vogler S, Kilpatrick K, Babar ZUD. Analysis of Medicine Prices in New Zealand and 16 European Countries. Value in Health. 2015;18(4): 484-492.

[11] Kanavos PG, Vandoros S. Determinants of branded prescription medicine prices in OECD countries. Health Economics Policy and Law. 2011;6(3): 337.

[12] 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. 2010.

[13] Gesundheit Österreich GmbH (Austrian Health Institute). Pharma Price Information (PPI) service. Further information available from: www.goeg.at/en/PPI. Vienna.

[14] Europe Economics. External Reference Pricing. London: Europe Economics, 2013.

[15] Konijn P. Pharmaceutical products-comparative price levels in 33 European countries in 2005. Statistics in focus: Economy and finance. 2007;45: 1977-0316.

[16] Leopold C, Mantel-Teeuwisse AK, Seyfang L, Vogler S, de Joncheere K, Laing RO, et al. Impact of External Price Referencing on Medicine Prices-A Price Comparison Among 14 European Countries. Southern Med Review. 2012;5(1).

[17] Leopold C, Mantel-Teeuwisse AK, Vogler S, de Joncheere K, Laing RO, Leufkens HGM. 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: 209-16.

[18] Danzon PM, Furukawa MF. Prices and availability of pharmaceuticals: evidence from nine countries. Health Affairs. 2003: W3-521.

[19] Danzon PM, Furukawa MF. International prices and availability of pharmaceuticals in 2005. Health Affairs. 2008;27(1): 221-33.

[20] European Commission. The EU Emission Trading System (EU ETS). http://ec.europa.eu/clima/publications/docs/factsheet_ets_en.pdf. Accessed 18. Juni 2015. 2013.

[21] Coase RH. The Problem of social cost. JL & econ. 1960;3: 1.

[22] Ruokonen J. Developing the EU Emission Trading Scheme: an analysis of key issues for the nordic countries. Commissioned by the Nordic Council of ministers. 2007.

[23] Graus W, Voogt M. Report under the Project "Review of EU Emission Trading Scheme". Commissioned by European Commission. 2007.

[24] Emission Trading Group (ETG). Administrative Cost of the Emissions Trading Scheme to Participants. A Working Group 5/6 Study, September 2008. 2008.

[25] National Audit Office (NAO). European Union Emissions Trading Scheme. 2009.

[26] European Commission. Impact Assessement of Directive of the European Parliament and of the Council amending Directive 2003/87/EC so as to improve and extend the EU greenhouse gas emission allowance trading system. 2008.

[27] European Commission. Proposal for a Directive of the European Parliament and of the Council amending Directive 2003/87/EC so as to improve and extend the greenhouse gas emission allowance trading system of the Community. 2008.

[28] Baldwin R. Regulation lite: the rise of emissions trading. Law and Financial Markets Review. 2008;2(3): 262-78.

[29] Ellerman AD. The EU's Emissions Trading Scheme: A Proto-Type Global System? Harvard Project on International Climate Agreements. 2008.

[30] Kettner C, Köppl A, Schleicher S. The EU Emission Trading Scheme: Insights from the first trading years with a focus on price volatility. WIFO Working Papers, 2010.

[31] Desbarats J. An Analysis of the Obstacles to Inclusion of Road Transport Emissions in the European Union's Emissions Trading Scheme. Institute for European Environmental Policy: London, UK. 2009.

[32] Fritsch M, Wein T, Ewers H-J. Marktversagen und Wirtschaftspolitik: mikroökonomische Grundlagen staatlichen Handelns; Munich: Vahlen; 2005.

[33] Borkent B, Gilbert A, Klaasen E, Neelis M, Block K. Dynamic Allocation for the EU Emission Trading Scheme. Commissioned by the Dutch Ministry of Infrastructure & Environment and the Dutch Ministry of Economic Affairs. Utrecht: ECOFYS, 2014.

[34] Ellerman AD, Montero J-P. The declining trend in sulfur dioxide emissions: Implications for allowance prices. Journal of Environmental Economics and Management. 1998;36(1): 26-45.

[35] Baldwin R, Wyplosz C. The Economics of European Integration: New York: McGraw-Hill; 2009.

[36] Swinnen JF. The perfect storm: The political economy of the Fischler reforms of the common agricultural policy: Ceps; 2008.

[37] European Commission. Overview of Cap Reform 2014-2020. Agricultural Policy Perspectives Brief. 2013(5).

[38] European Commission Agricultural and Rural Development. Sugar. http://ec.europa.eu/agriculture/sugar/index_en.htm. Accessed 18 June 2015. 2014.

[39] European Commission DG AGRI. Study to assess the administrative burden on farms arising from the CAP-Final report. Brussels, Directorate-General for Agriculture and Rural Development (DG Agri). 2007.

[40] Special Eurobarometer. Europeans, Agriculture and the Common Agricultural Policy. European Commission. 2008.

[41] Special Eurobarometer. Europeans, Agriculture and the common agricultural policy (CAP). AGRI ECD. 2014.

EW-01-15-894-EN-N

Publications Office

doi: 10.2875/631265