How Can Pricing and Reimbursement Policies Improve Affordable Access to Medicines? Lessons Learned from European Countries

Sabine Vogler, Valérie Paris, Alessandra Ferrario, Veronika J. Wirtz, Kees de Joncheere, Peter Schneider, Hanne Bak Pedersen, et al.

Applied Health Economics and Health Policy

ISSN 1175-5652
Volume 15
Number 3

Appl Health Econ Health Policy (2017)
15:307-321
DOI 10.1007/s40258-016-0300-z

Springer

Appl Health Econ Health Policy (2017) 15:307–321
DOI 10.1007/s40258-016-0300-z

REVIEW ARTICLE

How Can Pricing and Reimbursement Policies Improve Affordable Access to Medicines? Lessons Learned from European Countries

Sabine Vogler[1] · Valérie Paris[2] · Alessandra Ferrario[3] · Veronika J. Wirtz[4] · Kees de Joncheere[5] · Peter Schneider[1] · Hanne Bak Pedersen[6] · Guillaume Dedet[6] · Zaheer-Ud-Din Babar[7]

Published online: 6 January 2017

Abstract This article discusses pharmaceutical pricing and reimbursement policies in European countries with regard to their ability to ensure affordable access to medicines. A frequently applied pricing policy is external price referencing. While it provides some benchmark for policy-makers and has been shown to be able to generate savings, it may also contribute to delay in product launch in countries where medicine prices are low. Value-based pricing has been proposed as a policy that promotes access while rewarding useful innovation; however, implementing it has proven quite challenging. For high-priced medicines, managed-entry agreements are increasingly used. These agreements allow policy-makers to manage uncertainty and obtain lower prices. They can also facilitate earlier market access in case of limited evidence about added therapeutic value of the medicine. However, these agreements raise transparency concerns due to the confidentiality clause. Tendering as used in the hospital and offpatent outpatient sectors has been proven to reduce medicine prices but it requires a robust framework and appropriate design with clear strategic goals in order to prevent shortages. These pricing and reimbursement policies are supplemented by the widespread use of Health Technology Assessment to inform decision-making, and by strategies to improve the uptake of generics, and also biosimilars. While European countries have been implementing a set of policy options, there is a lack of thorough impact assessments of several pricing and reimbursement policies on affordable access. Increased cooperation between authorities, experience sharing and improving transparency on price information, including the disclosure of confidential discounts, are opportunities to address current challenges.

Kees de Joncheere–Retired.

Electronic supplementary material The online version of this article (doi:10.1007/s40258-016-0300-z) contains supplementary material, which is available to authorized users.

✉ Sabine Vogler
sabine.vogler@goeg.at

1 WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, Pharmacoeconomics Department, Gesundheit Österreich GmbH (Austrian Public Health Institute), 1010 Vienna, Austria

2 Health Division, Organisation for Economic Co-operation and Development (OECD), 75116 Paris, France

3 LSE Health and Department of Social Policy, London School of Economics and Political Science, LondonWC2A 2AE, UK

4 Department of Global Health, Boston University School of Public Health, Boston, MA 02118, USA

5 Essential Medicines and Health Products Department (EMP), World Health Organization (WHO), 1211 Geneva 27, Switzerland

6 World Health Organization (WHO) Regional Office for Europe, Copenhagen 2100, Denmark

7 School of Pharmacy, Faculty of Medical and Health Sciences, University of Auckland, Private Mail Bag, 92019 Auckland, New Zealand

Key Points for Decision Makers

European countries apply different pharmaceutical pricing and reimbursement policies.

These policies are frequently assessed against their financial consequences and their ability to contain costs but less so in terms of access to medicines. Policies should be accompanied by regular evaluations, facilitated by the use of the appropriate methodology and access to the relevant data.

There appears to be a need for additional changes beyond traditional pharmaceutical pricing and reimbursement policies. Collaborative approaches (e.g. between countries or between regulatory authorities, pricing and reimbursement agencies) and more transparency in terms of real medicine prices, R + D costs and medicines in the pipeline are considered as possible pathways for the future.

1 Introduction

In recent years, access to essential medicines has become an issue even in the wealthiest parts of Europe. In particular, the proliferation of high-priced medicines has pushed the issue of access to new medicines high on the policy agenda of all European countries, including in high-income economies [1–4]. At the same time, pharmaceutical spending is rising again, boosted in 2014 by the entry of new hepatitis C treatments [5]. Apart from prices, payers are increasingly concerned that some of these high-priced medicines only deliver limited therapeutic-added benefits to patients [6–8].

While in most European countries all residents benefit from comprehensive coverage of healthcare costs, including costs related to medicines [9], and a major part of spending on medicines comes from public progammes, there is considerable variation in public funding on medicines between countries [10]. In addition, important variation in access to medicines exists between European countries, in particular between Western and Eastern countries. This is due to differences in marketing of medicines and their inclusion in national reimbursement lists, the country's gross domestic product, government expenditure on health, and also due to medicine prices and utilisation (for further information on differences between countries related to availability [11–14], prices [5, 15–22] and utilisation [23–30] of medicines see Appendix A1 in the Supplementary Materials).

This article provides a critical discussion of selected pharmaceutical reimbursement and pricing policies used in European countries and their ability to ensure affordable access to medicines. In line with existing frameworks [31–34], availability (marketing of a medicine in national markets) and indicators such as inclusion of medicines in reimbursement, public spending and medicine prices are considered as key determinants for affordable access to medicines. This understanding of affordable access to medicines also fits within the Universal Health Coverage and access to medicines target under Sustainable Development Goal 3 on Good Health [35].

Over the last three decades a number of initiatives have been developed to better characterise and measure the situation in countries and globally on the access to and regulation and use of medicines. These initiatives were developed in collaboration with numerous international and national organisations, academia and experts, and fed with country experiences and often consolidated in WHO documents and guidelines [36]. They normally contain a set of structure, process, output and outcome indicators. In parallel many countries developed and used their own set of indicators to more specifically measure their national situation. The latest effort has been the development of a set of 100 indicators, jointly by WHO and the World Bank, to monitor progress on UHC, and this also contains some indicators across disease programmes as well as health system development [37].

The presented findings are based on an iterative search of the published and grey literature, using the bibliographic database PubMed, alongside Google Scholar and reviewing reference lists of flagship reports (e.g. a WHO Euro report on access to new medicines [3] and the WHO Priority Medicines for Europe and the World Report, with the background chapter on pricing and reimbursement [11]). The literature search was complemented by input from co-authors, all expert on the topic. Key search terms were the names of the pricing and reimbursement policies, as listed in the WHO report on access to new medicines [3]; searches were run between 25 May and 26 June 2016. When co-authors learned about relevant updated literature that was published later, this was also included in the first draft and revised paper. In order to have access to up-to-date information about policies in Europe that might not have been covered in the literature, we included descriptive information about the existence of the discussed policies in Europe as of 2016 based on information obtained from policy surveys done with representatives of compentent authorities involved the Pharmaceutical Pricing and Reimbursement Information (PPRI) network.

To keep the review focused, this paper focuses on key policies out of the larger menu of pharmaceutical pricing and reimbursement policies, as described in the literature [3, 18, 38]. Policies included were those that have commonly been applied in European countries for several years, some of which (e.g. health technology assessment

Table 1 Policy Definitions

Policy	Definition
Health technology assessment (HTA)	A multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective health policies that are patient-focused and seek to achieve best value
External price referencing	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
	Synonyms: external reference pricing, international price referencing, international price benchmarking, international price comparisons
Parallel trade	The act of importing pharmaceuticals into one country (the 'import' country) from another (the 'export' country) and placing them on the market outside the formal channels authorised by the product's manufacturer or licensed distributors
Value-based pricing (VBP)	Setting a price according the added therapeutic value of a new product by comparison with existing treatments
	In a broad sense, VBP means that activities should be oriented, organized or funded to maximize health benefits for patients and societies. Thus, it proposes to link payments for health services, including medicines, to evidence-based assessments of value for patients, their relatives and society as a whole
Managed-entry agreement (MEA)	An arrangement between a manufacturer and payer/provider that enables access to (coverage/reimbursement of) a health technology subject to specified conditions. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximize their effective use, or limit their budget impact
Tendering	Any formal and competitive procurement procedure through which tenders (offers) are requested, received and evaluated for the procurement of goods, works or services, and as a consequence of which an award is made to the tenderer whose tender/offer is the most advantageous
Reference price system	Identical or similar medicines are clustered and are reimbursed up to a certain limit
Generic substitution	Practice of substituting a medicine, whether marketed under a trade name or generic name (branded or unbranded generic), with a less expensive medicine (e.g. branded or unbranded generic), often containing the same active ingredient(s)
International non-proprietary name (INN) prescribing	Requirements for prescribers (e.g. physicians) to prescribe medicines by its INN, i.e. the active ingredient name instead of the brand name

Definitions are based on the glossaries of the WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies and of the OECD

and external price referencing) have also been intensively discussed in literature. In addition, recently introduced policies (e.g. managed-entry agreements and horizon scanning) that have been seen as major policy options in the menu of policies for high-priced medicines are included [3]. For definitions of key policies used see Table 1.

2 Health Technology Assessments to Inform Pricing and Reimbursement Policies

In Europe, decisions about reimbursement of medicines are taken at the national level. These are often implemented through positive or negative lists, even in health systems with competing health insurers such as The Netherlands or Switzerland. Patients usually have to contribute to the costs of outpatient medicines; however, various mechanisms exist to protect patients from excessive out-of-pocket payments [9]. Typically, marketing authorisation holders have to file an application if they want their medicine to be included in the positive list of reimbursed medicines. European countries use one of the following processes to make reimbursement and pricing decisions: In some countries, health technology assessment (HTA) is used to inform reimbursement and/or pricing decisions (e.g. France, Italy, the Czech Republic, Switzerland). In other countries, HTA (and appraisal) results in a decision to reimburse a new product (with or without restrictions) or to reject funding (e.g. England, Sweden and Norway; see Appendix A2 in the Supplementary Materials on different models).

In many European countries, HTA is used either systematically for all new medicines or only for those raising specific problems such as high prices, uncertain clinical benefits or high budget impact. There are usually more than one or two HTA institutions per country (for an overview see WHO report [3]). HTA is focused on the assessment of clinical benefits but may also include economic aspects. It determines the therapeutic value of a medicine, the added therapeutic value in comparison to existing treatments, and frequently its cost-effectiveness. Medicines which are more effective than existing comparators can get a higher price, while others tend to be priced at a similar or lower level.

Medicines used in the treatment of very severe diseases and/or orphan diseases without treatment alternatives are very often accepted for reimbursement even though they do not meet the cost-effectiveness threshold [39]. This suggests that cost-effectiveness is not the only criteria taken into account by decision makers and also that the negotiation power of payers is very limited in such cases.

HTA is a tool to support prioritisation, with the aim of helping policy-makers obtain better value for money. This would arguably ensure a more rational and targeted investment of funds, thus contributing to access to cost-effective medicines. A study that compared HTA and internal price referencing suggested that HTA appears to be the superior strategy for obtaining value for money because it addresses both price and appropriate indications for the use of the medicine and the relation between additional value and additional costs [40]. Overall, no clear pattern of the impact of HTA on prices could be determined [41]. Still, policy-makers consider HTA as one of the two key tools (the other one being managed-entry agreements) to deal with new high-priced medicines [42].

3 Selected Pricing and Reimbursement Policies

Most European countries regulate the prices of medicines via a mix of instruments, applied to different market segments (outpatient/inpatient medicines, onpatent/offpatent, innovative/medicines with no added therapeutic value, etc.). Even though all these instruments have advantages and drawbacks that are described below, it is difficult to isolate the impact of any single policy on availability and affordability of medicines since countries typically use several of these policies simultaneously.

3.1 External Price Referencing

All but two (Sweden, UK) EU member states refer to the price in other countries to set the price of medicines in their own country, a practice known as external price referencing (EPR). EPR is also used in other European countries (e.g. Norway, Iceland, Switzerland and Turkey) [43]. However, the scope, relevance and methodological design vary across countries. In Denmark, for instance, EPR only applies in the hospital sector. In Germany, EPR exists in the legislation but is not used in practice [43]. EPR is typically applied to regulate the price of new products, less often in offpatent markets. This international price comparison offers a reference, or benchmark, for policy-makers, to understand where the prices proposed by the pharmaceutical industry for their country are relatively ranked. The price information achieved through EPR is frequently seen as a starting point for public payers to further negotiate and conclude agreements to reach a more acceptable and somewhat affordable price that will be funded.

The Organisation for Economic Co-operation and Development (OECD) described 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" [44]. EPR incentivises marketing authorisation holders to launch medicines first in countries with higher prices, and delay, or not to launch, in lower-priced countries. This is in order to not reduce the medicine's international reference price [38, 45–53]. Countries with lower prices or lower market volume were found to have fewer medicines available and longer delays in medicine launches [48, 54, 55]. Pharmaceutical companies have systematically delayed dossier submissions in Belgium in order to avoid the lower Belgian prices affecting other European countries [56]. While studies highlighted the ability of EPR to negatively impact the availability of medicines on the market, it remains difficult to isolate the impact of EPR from other factors, such as 'parallel trade' (see Table 1), which is a legal practice within the EU [49, 57] or pricing regulation in Germany and Italy that allow free pricing for some medicines in the first year to improve earlier market access in their country, but thus signal a high price to other EPR-applying countries. Overall, available literature on the impact of EPR is limited [41, 48]. Evaluations focused on cost-containment, showing how EPR was able to contribute to savings under specific conditions [21, 58–61], whereas aspects such as availability and uptake have not been sufficiently addressed. One study showed that, using a limited sample of new patented medicines, EPR-applying countries had, in general, lower list prices than countries not using EPR [60].

To mitigate the negative impact of EPR (and parallel trade) on availability in lower-income countries in Europe, it has been argued that public payers could keep a high 'list price' and get confidential discounts through product-specific agreements [46, 62]. This would allow the pharmaceutical industry to provide medicines at lower prices to low-income countries without negatively impacting the average reference price. While confidential arrangements (frequently subsumed under the umbrella term of managed-entry agreements (MEA), see below) have increasingly been used, also by higher-income countries as an instrument to ensure affordable access to medicines [3, 63], there is no evidence that access has improved in lower-income countries since they continue to experience delayed and limited availability. On the negative side, confidential discounts and rebates are blurring the price transparency of the market, and they limit the ability of payers to determine what a 'reasonable and fair' price would be.

3.2 Value-Based Pricing

Value-based pricing (VBP) consists of setting a price according the added therapeutic value of a new product through comparison with existing treatments. Seeking to pay for medicines in relation to the 'value' they bring to their own health system and society has been considered one approach to ensure value in pharmaceutical spending (static efficiency) and to send appropriate signals to companies for further investments in research and development (R&D; dynamic efficiency) [44].

In a narrow approach, VBP (in the context of the English National Health Service (NHS)) is defined as '[the price] that ensures that the expected health benefits [of a new technology] exceed the health predicted to be displaced elsewhere in the NHS, due to their additional cost' [64]. It thus relies on cost-effectiveness analysis and the setting of an ICER threshold beyond which a new medicine is not funded. Sweden has such a 'real' VBP system. Introduced in 2002, pricing and reimbursement processes are completely integrated, and eligibility for reimbursement is assessed against three criteria: the human value principle to guard against discrimination of individuals, the need and solidarity principle that gives priority to those in greatest need, and the cost-effectiveness principle [11, 65].

Applying a broader approach, any policy linking the price of a medicine to its added therapeutic value can be considered within the category of value-based pricing. With such a definition, many European countries use such policies [3, 39].

However, value-based pricing has proven difficult to implement, especially in therapeutic areas where no alternative treatment is available and patients suffer from severe life-threatening or debilating disease, such as oncology or rare diseases. In such cases, payers face a strong public pressure and often accept paying high prices for limited clinical benefits. To some extent, it can be argued that the value of such products cannot be reduced to clinical benefits and some analysts have developed frameworks to take other criteria into account, such as the absence of alternative treatments for orphan diseases for instance [66]. However, such frameworks do not provide any simple rule to set the price of a new medicine.

A major argument for using a value-based pricing policy is that it might create an incentive for the development of products that generate more added value [11, 65]. It could also support a new approach of policy-makers to signal more explicitly their priorities regarding which medicines would be reimbursed if they are developed as proposed in the WHO Priority Medicines for Europe and the World Study in 2004 [67]. Currently, the pharmaceutical policy framework appears to be supply-driven, and a more pro-active approach has been suggested [68, 69]. In principle, medicines with perceived high value are likely to obtain higher prices, providing a reward for innovation, which might explain the preference of the pharmaceutical industry for this policy [70]. However, VBP also presents opportunities to the pharmaceutical industry for 'gaming', in particular related to the choice of the comparator and the threshold [53]. For instance, a manufacturer will try to avoid a genericised molecule as a comparator, even if this means positioning their product as a second- or third-line therapy. In such a case, the population target will be smaller but the price premium will be set in relation to the price of an on-patent medicine. In addition, where an explicit cost-effectiveness threshold is published, marketing authorisation holders tend to price up to the threshold [71].

It has been argued that VBP would encourage access to needed medicines, in line with the prioritisation of policy-makers. Still, it can also result in limited, or delayed, access due to the resource-intensive and time-intensive character of underlying value assessments, and discussions between the authority and the manufacturer on different perceptions of value [53]. Until now, VBP has been proposed as a logical and fair policy to promote access as well as reward useful innovation; however, implementing this policy has proven very challenging.

3.3 Managed-Entry Agreement

European countries have increasingly been using MEAs to deal with high-priced medicines and uncertainty around the medicine's value [3]. These agreements take many forms such as simple confidential discounts and price–volume agreements in financial-based schemes (non-health-outcome-based schemes). These also include more sophisticated performance-based (or health-outcome-based) schemes, where the final price of a product is linked to health outcomes observed in real life. Performance-based schemes include outcome guarantees (i.e. an agreement where the manufacturer provides rebates, refunds or price adjustments if the product fails to meet the agreed outcome target), coverage with evidence development (i.e. reimbursement where additional data gathered in the context of clinical care would further clarify the impact of the medicines, and patient eligibility linked to patient registries to measure post-marketing clinical outcomes).

In some countries, the existence of such agreements is not disclosed to the public (e.g. in France), while in others the existence and the content of the agreements is public (e.g. Scotland, England and Belgium). In all cases, the final discount to payers is unknown. The EMINet survey of 2013 [72] confirmed other research [73–75] that MEAs were particularly used for specific (high-priced) indications such as cancer, and that some European countries (e.g. Italy and the UK) used them at a much higher scale than

others. It also showed that most countries opted for financial MEAs, which are easier to handle than performance-based MEAs [76]. Since that study, more MEAs have been implemented for new products, and even European countries (e.g. Bulgaria and Romania) that had not applied them before started to use them [3, 77].

For patients and the pharmaceutical industry, MEAs are an opportunity to facilitate early market access to medicines, even if added therapeutic value has not yet been fully proven. They also allow for price discrimination without changing list prices. For policy-makers, MEAs are a tool to manage uncertainty [78] and obtain lower prices than the list prices; how much lower is unknown as the prices are confidential. When performance-based MEAs have been set up, together with patients registries, for instance, this allows collecting real-life clinical data that are needed to assess the treatment effect and take a more sound decision based on more robust evidence. Still, even if updated data may urge for a discontinuation of funding (at high prices) of a medicine under a MEA, it might be difficult in reality to implement it if expectations of patients have been created [79]. Due to public pressure, funding may be continued, as observed in the cases of agalsidase alfa and agalsidase beta for Fabry disease and alglucosidase alfa for Pompe disease in The Netherlands [80].

The confidentiality of MEAs is a major drawback, particularly given the widespread use of EPR. As a result, European countries refer to the official list price of a high-priced medicine that is under MEA in several countries. It was argued that by opting for MEA payers implicitly accepting high (list) prices [81].

Despite continuously wide-spread use of MEAs, there is some [82], but comparably little, knowledge about their functioning and results in terms of improving affordability and access.

3.4 Tendering

In Europe, tendering has traditionally been applied in the hospital sector, at the level of individual hospitals and hospital groups, or through voluntary pooling of regional procurement at national level by procurement agencies (in Denmark and Norway) acting on behalf of all public hospitals [83–85]. In the outpatient offpatent sector, some European countries (e.g. Germany, The Netherlands, Slovenia and Romania) have implemented tender systems and auction elements to enhance competition (cluster-tendering) and thus achieve lower medicine prices [86–88].

National procurement agencies in Denmark (AMGROS) and Norway (LIS) have been reporting efficiency gains and lower prices through their centralised hospital tendering compared to other countries [83–85]. This is in part attributed to the shift of the balance of power in favour of the national procurement agency that procures for a much larger market as well as use of new types of tendering procedures.

Tendering in the outpatient sector has also proven its ability to considerably reduce prices through competition [88–90]. Concerns have been raised that, if tender pushed prices too low, the sustainability of the generic industry would suffer, and some companies could withdraw from the market, thus reducing competition in the longer term [91]. However, a recent study did not find any evidence Dutch offpatent market that tendered medicines would be more affected by shortages than non-tendered medicines [88]. Still, in case of shortages of tendered medicines, alternative medicines might also not be available or only at substantially higher prices. Tendering requires a clear and robust framework, as apparently observed for the tender-like system in the Danish outpatient system [88], particularly aiming at keeping several suppliers in the market, including backup strategies to deal with possible supply problems. If tendering is not well designed and based on a sound framework, there are risks of neutralisation of savings (lower prices for one medicine are met with higher prices for similar medicines), of stakeholders going to court to challenge the legal provisions, and the non-availability of medicines. These developments were observed in Belgium, which, as a result, withdrew its tendering policy for offpatent medicines [88, 92].

3.5 Generic Policies

European countries have increasingly been implementing generic policies [93, 94] (see Table 1 for definitions of generic policies listed below). They are particularly aimed at ensuring swift market entry of high-quality generics, bringing down the prices of multi-source products (offpatent originator medicines and generic medicines) and improving acceptance of generics and uptake of lower-priced medicines. As a result, generic policies are considered as a valuable instrument to generate savings for public payers that can be used to afford more expensive medicines and treat more patients. European countries use a mix of policies related to pricing, reimbursement and enhancement of uptake of generics.

Twenty-two EU member states (as of 2016) use ‘internal reference pricing’, i.e. maximum reimbursement amounts for clusters of medicines. In nine of these countries, clusters of medicines with the same active ingredient have been established, while in 13 countries a reference price is applied to therapeutic substitutes (e.g. Germany and The Netherlands) [95]. Most EU member states set the price of generics in relation to originator prices, whereas fewer

countries (e.g. Finland, Germany, Norway, Sweden and the UK) exclusively rely on competition [96]. As explained above, tendering, or an auction-like system for generics, is used by some European countries for the procurement of generics in the inpatient and, to a lesser extent, the outpatient sectors. Generic substitution by the pharmacist is allowed in 24 EU member states and is even mandatory in ten (2016 data [95]). Doctors are encouraged to prescribe using the International Non-Proprietary Name (INN) in 25 EU member states, and mandated to do so in ten of them [95]. These demand-side measures are supplemented by education and information activities targeted at patients and health professionals. Financial incentives are also applied, but to a far lesser extent. For instance, different co-payment rates for originator and generic medicines had been in place in Portugal and were abolished [97], and Austria ran a pilot of lower co-payment in one health insurance fund [98]. In recent times, more countries are moving towards mandatory generic substitution and mandatory INN prescribing instead of the voluntary form they had introduced earlier [99]. This may in fact be an approach to ensure better enforcement of the measures.

As a result, several European countries have been successful in bringing down generic prices and increasing their generic market share even if, apart from a few countries (Germany, the UK, Slovak Republic and The Netherlands) generic uptake is lower in Europe than in the USA and generic prices in European countries tend to be higher than in the USA [100]. Overall, competitive pricing policies, including tendering, as used in some Nordic European countries, appear to be more successful than other, more regulated generic policies in reducing the price levels of generics as well as of competitor originators and increasing the uptake of generics, in particular if coupled with demand-side measures [96, 101]. The quality of generics is ensured in the EU member states and neighbouring European countries, but lack of trust in the quality of generics by patients and even health professionals is still an issue [94, 102, 103]. It has been noted, for example by the Pharmaceutical Sector Inquiry of the European Commission [104], that benefits of generics were not always fully realised because of delays in market entry. Industry strategies of 'evergreening' have been observed, trying to link intellectual property issues to marketing authorisation, pricing and reimbursement of medicines [105, 106].

There is a large body of literature, including on European countries, that has confirmed the savings potential through lower prices by implementing generics policies [101, 107–109]. Evidence shows that generics have contributed to increased utilisation of medicines [101, 110]. In contrast to other policies described above, generic policies describe an area for which evidence on their effectiveness to ensure affordable access is available.

3.6 Policies on Biosimilar Medicines

Given the high prices of new biological medicines, authorities and payers have high expectations regarding offpatent successors [3]. At the time of writing, 20 biosimilar medicines have been approved in Europe [111], with substantial cost savings [112], compared to two biosimilar medicines in the USA [113]. Studies about the clinical impact of switches from originators to biosimilars are being performed in European countries [114]. The recently published first results of the Norwegian NOR SWITCH study suggested that a switch from the originator infliximab to biosimilar infliximab is safe [115].

Policies to encourage the uptake of biosimilars differ from policies to encourage the uptake of generic medicines because of the perception that biosimilar medicines should not be treated as 'generics' [116]. For instance, the prices of biosimilars are linked to originator prices, the required difference between the biosimilar and the originator price is lower compared to generics (e.g. 30% for generics and 15% for biosimilars in Croatia; and 50% for generics and 30% for biosimilars in Lithuania) [117]. While generic substitution has been widely implemented in European countries, this is not the case for biosimilar substitution at pharmacy level [118, 119]. Though European countries seem to be advanced with regard to biosimilar medicines compared to the rest of the world, overall governments in European countries appear to be still struggling to develop the best policy option mix for achieveing most benefit from biosimilar medicines. At the same time, there is the best-practice example of Norway that combines several policies (pricing, uptake enhancement and education): In the areas of biological and biosimilar medicines, Norway has been following up on its successful policy of tendering through a public procurement agency for medicines used in public hospitals [120], and closely works with the clinicians to educate and encourage them to prescribe the tendered, lower-priced medicines. Figures regarding price reductions that Norway has achieved in tenders are impressive (e.g. discounts of up to 80% between originator and biosimilar medicines) [121], and this is used to ensure that in total more patients can be treated.

4 Suggestions for Improvement

European countries developed a range of pricing and reimbursement policies, with the aim of ensuring affordable access to medicines, protecting citizens against financial hardship and generating public savings and/or to contain costs. Despite several achievements, countries continue to struggle to meet policy objectives. This is in particular the case in the context of market entry of new

high-priced medicines. Policy-makers in Europe identified an imbalance of (negotiation) power in the pharmaceutical sector, as stated in the 'Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its member states' published under the Dutch EU Presidency in June 2016 [122]. In order to address this perceived imbalance, some new approaches, including cooperation between countries and between different agencies (e.g. responsible for marketing authorisation, HTA body, pricing and reimubursement authorities), improved information sharing and data generation as well as revised incentives and frameworks, have been discussed and also partially been implemented in European countries. They aim to improve the capacity, knowledge and negotiation power of governments. They are thus intended to enable payers to take more informed decisions and to achieve negotiation results with the pharmaceutical industry that lead to a more affordable access to medicines for patients while keeping a 'healthy market'. These approaches are not policies per se, but rather processes and tools to support and further develop pharmaceutical policy.

4.1 Cooperation and Stakeholder Involvement

During the last decade, European countries have seen increased cross-national cooperation activities between public authorities at technical levels, using platforms such as the Network of Competent Authorities on Pricing and Reimbursement (CAPR) and the Phamaceutical Pricing and Reimbursement Information (PPRI) network (for information on these and further networks see Appendix A3 in the Supplementary Materials).

These networks mainly serve for building capacity and improving the exchange of experiences between authorities. Any further-reaching collaboration beyond information sharing, such as joint negotiations or joint procurement, were for some time not considered to be feasible policy options for EU member states that make the decisions about medicine prices and funding at their national levels. The sofosbuvir case, however, appeared to have been a trigger for a change. A French initiative in 2014 sought collaborative approaches with other European countries to get a lower price for sofosbuvir, but it was not successful. Some EU member states hoped that the specific 'Joint Procurement Agreement (JPA) of medical countermeasures' as of 2014 [123] (i.e. procurement of vaccines, for instance, to be prepared for an outbreak of a serious cross-border threat to health such as a pandemic) could be extended to a joint procurement of high-priced medicines against cancer, multiple sclerosis and orphan medicines. But the European Commission clarified that this would be beyond of the scope of this agreement [43]. Collaborative approaches such as joint negotiations and procurements were sought since member states wanted to increase their negotiation power in order to achieve lower prices, in return for—the predictability of—larger volumes for the pharmaceutical industry, and also to achieve earlier and improved access to medicines for lower-priced countries and small markets that were not supplied with some high-priced medicines. In this respect, the issue of 'fair prices' was also discussed since prices in lower-priced European countries were found to be as high as in higher-priced countries and thus unaffordable ([5]; see also Appendix A1 in the Supplementary Materials). Discussions also included considerations about a differential pricing policy within the EU in order to ensure that medicine prices were better linked to the economic situation of a country. A study [43] commissioned by the European Commission to explore the feasibility of differential pricing in Europe concluded that a fully-fledged differential pricing system would require addressing major obstacles, including measures to prevent leakage due to parallel trade and the wide-spread use of EPR, and political commitment of the EU member states to agreeing on principles and mechanisms.

While this far-reaching EU-wide cooperation appeared not to be implementable in the short term, a number of the countries started to cooperate in this area. For instance, in 2015, Belgium, The Netherlands and Luxembourg announced a cooperation initiative aiming to jointly negotiate with pharmaceutical companies [124], and another country (Austria) joined this cooperation platform (Beneluxa) in 2016 [125]. These collaborations appear to be at early stages and thus cannot be assessed. Joint negotiations are expected to strengthen the purchasing power of the collaborating countries, and technical cooperation in areas of HTA or horizon scanning is planned that helps governments get an improved evidence base for more informed decisions in a more resource-efficient way compared to doing this individually and separately.

In addition, joining forces in the fragmented pharmaceutical systems in European countries also requires vertical (cross-agency) cooperation in countries and at the European level. In order to overcome working in 'silos' at different stages of a the life-cycle of a medicine, awareness has been raised for enhancing national and international cooperation between different authorities along the management of market entry of new medicines (i.e. regulatory authorities, HTA organisations, pricing authorities and reimbursement agencies), possibly with the involvement of other stakeholders like the pharmaceutical industry, patients and academia [3]. Supported by a legal framework and EU funding, EUNetHTA, which is a large network of HTA organisations and public authorities, with the involvement of external stakeholders such as the pharmaceutical industry, has already been active for nearly a

decade [126]. Since 2010, the European Medicines Agency (EMA) has been offering parallel scientific advice to that of HTA bodies that allows pharmaceutical companies to receive simultaneous feedback from both regulators (EMA) and HTA bodies on their development plans for new medicines [127] and to be better able to respond to expectations of regulators and payers. Furthermore, the project of the Adaptive Pathways (adaptive licensing) of EMA foresees a staged approach to the collection of evidence and consequent licence adaptations [128]. However, it is still in the pilot phase, and the impact on pricing and reimbursement is not clear.

The involvement of patients, and, even more broadly, of citizens in priority-setting for health and social care, including aspects of pricing and reimbursement policies, has been urged for several years [67]. Patients are the 'experts' for their diseases, and they can bring in aspects of quality of life and different perspectives about medicines, for example on their observed and expected impracticalities [129]. Despite the acknowledged importance of patient involvement, this has been hardly implemented in the area of pricing and reimbursement in European countries [130]. This might also be linked to authorities' lack of knowledge and experience on how to address patients and integrate them in committees, for instance. Some examples in this field include the activities of the National Institute for Health and Care Excellence (NICE) in England [129] and the Scottish Medicines Agency [131], which have been involving the public in their processes.

4.2 Transparency

While pricing and reimbursement decisions are, as described, the responsibility of the national competent authorities in the EU member states, the EU Transparency Directive [132] obliges member states to comply with defined specifications of the processes, including time-lines and a clear definition of criteria taken into account to make reimbursement and pricing decisions of processes (e.g. justifications of the decisions and the possibility for marketing authorisation holders to appeal). This directive imposes obligations on competent authorities, not companies, and confidential arrangements between payers and companies do not fall under the scope of this regulation.

As shown, confidential discounts and further MEAs have been increasingly used, particularly for high-priced medicines. Industry has been arguing that, given the widespread use of external price referencing, price discrimination through confidential discounts was the only way to ensure affordable access to medicines (see also EFPIA [133]). Policy-makers have increasingly become aware of the impact of their confidentiality agreements on other countries, but they are in a type of prisoner's dilemma [43]. In recent years, authorities [134] increasingly joined the call of researchers and international institutions [3, 16, 48] for more price transparency. A disclosure of discounts would allow EPR-applying countries to refer to actual prices, thus lower prices and contain costs by not overpaying. But even payers that do not apply EPR, or only as a supplementary policy, reported that knowledge about real prices would be helpful to have some kind of benchmark for decision-making (information provided by PPRI network members). However, no European country has been pioneering in disclosing discounted prices [43]; in addition there is concern that lower or no discounts would be offered by the pharmaceutical industry. As a first step, since 2016 Austria has been labelling the medicines in its reimbursement list for which a discount agreement has been arranged, without disclosing the extent of the discount. Such practice is also common in Australia [135]. While a routine disclosure of discounts does not appear feasible for European countries at this time, a possible solution could lie in cooperative approaches of public authorities, as discussed in the previous section and also encouraged by the Council Conclusions in June 2016 [122] ('enhancing voluntary cooperation between member states aimed at greater transparency'). Even the cooperation of a few countries can be expected to have an impact: Given the improved knowledge and capacity of the cooperating countries, prices will likely reduce, and due to stronger purchasing power and larger markets in case of joint negotiations or even joint procurement, access can arguably be improved. Another option for countries could be to assume a certain extent of discount and thus insist on lowering the 'list price' that would be used everywhere as a starting point for negotiation.

Discussions about transparency are not only about price transparency and disclosure of discounts. To be prepared for new medicines and to develop appropriate strategies to manage their market entry (including taking priorisation in resource-restrainted settings), public authories need to know which medicines are in the pipeline. Horizon scanning and forecasting tended to be implemented rather as an academic exercise disconnected to the policy practice [3]. The horizon scanning project in Veneto, Italy [136], the English National Horizon Scanning Centre [137] and activities at the regional level with the Stockholm County Council in Sweden [138] were among the rare exeptions in Europe where horizon scanning was used to support decision-making of public authorities. While horizon scanning is not a tool to immediately ensure access to medicines or bring down prices, it surely supports the prioritisation process. The sofosbuvir case, for which policy-makers and payers of several countries were not prepared [81], could be seen as a trigger, and some countries (e.g. Norway and France) started building horizon-scanning systems [3].

Also, the above-mentioned cooperation platforms such as Beneluxa or the Nordic Pharmaceutical Forum aim to work together on horizon scanning [125, 139].

Furthermore, long-lasting discussions about knowledge of production costs, including R&D costs [69, 140], have also reached Europe. In some US states 'pharmaceutical cost transparency acts' were passed in the spring of 2016. Under these acts, it is mandatory for manufacturers to disclose their production costs for some high-priced medicines [141]. However, no concrete steps regarding a disclosure of R&D costs have yet been implemented either in Europe or in the USA.

4.3 New Funding Models

As access to new high-priced medicines has become a challenge for high-income countries in Europe as well, the ability of current pricing and reimbursement policies to ensure affordable access to medicines has been questioned. Incremental changes that are envisaged may not be enough to respond to all policy objectives, i.e. provide access, encourage innovation and ensure sustainability. There has been a call for new rules and frameworks, in particular new methods to develop and market medicines (by de-linking the price from the return on investment into R&D): While at global levels the WHO, policy-advisers and academics have been discussing new models of funding R&D for many years [142–148], this debate has only started in Europe recently, fuelled by the Dutch Presidency of the EU [4], the Review on Antimicrobial Resistance [149] and interventions at conferences (e.g. European Health Forum Gastein 2015—statement by Josef Probst, Austrian Main Association of Social Security Institution, or the PPRI Conference 2015 [81]). In September 2016, the UN High Level Panel on Access to Medicines report was published and also called for de-linking the R&D cost from the price of a medicine [150]. The Lancet Commission on Essential Medicines for UHC goes one step further in calling for an Essential Medicines Patent Pool (EMPP) by which a patent owner's refusal to license an essential medicine to the EMPP would satisfy the condition for granting a compulsory licence [151]. A medicines patent pool provides a legal mechanism through which the availability of a generic medicine can be increased and negative effects of market monopolicies be reduced.

Still within the scope of the current pricing and reimbursement framework, some European countries introduced funding models that aim at bridging the hospital and ambulatory sectors. This was done in response to the fragmentation in healthcare systems (different payers responsible for funding medicines, e.g. outpatient medicines reimbursed by social health insurance and medicines in hospitals covered by hospitals or regional authorities). This set-up incentivised payers to shift patients, treatments and thus costs between sectors. The transfer could have negative clinical outcomes, and in turn may even increase overall healthcare costs [152]. In The Netherlands, defined high-priced medicines used in hospitals are funded by the health insurers (instead of out of the hospital budget). Since 2006, Norway has been increasingly transfering the funding responsibility for a selected number of medicines (TNF-alpha inhibitors, medicines for the treatment of multiple sclerosis and anti-cancer medicines) to hospitals even if these medicines were used in the outpatient sector [3, 83]. However, to the knowledge of the authors, impact assessments as to whether these new funding approaches were able to address the observed limitations have not been made.

5 Conclusions

This article discusses selected pharmaceutical policies that aim to contribute to improving affordable access to medicines. The analysis concluded that there is an overall lack of evidence on the impact of pricing and reimbursement policies on affordable access in many settings. This is partially due to the lack of a well-established methodological evaluation framework, and the challenges in attribution, demonstrating the causual relation between the implementation of a single policy and the observed results in the availability and affordability of medicines [153, 154]. Furthermore, access to relevant data is a common limitation [151, 155].

However, an exception are policies to promote generics where there is strong evidence on price reduction resulting in substantial savings that allow investing in treating overall more patients. As other work has shown [156], an important precondition is that generic medicines in fact are lower priced than originators, quality assured and accepted by patients and health professionals. The entry of a number of biosimilars offers the opportunity to increase access to biological medicines and to contain expenditure. To take advantage of the benefits offered by biosimilars, studies such as the NOR SWITCH study [115] are essential to build trust among the medical and patient communities on the safety of switching.

In addition, the analysis showed the relevance of tools that allow prioritisation on which medicines (and patient groups) money should be spent, not only in making them more affordable through pricing policies. There is a need for improved prioritisation techniques in HTA and evaluations, and for capacity-building of technical staff. Countries pioneering in this area could support other countries through sharing of methods and techniques.

This analysis found that sharing information and exchanging experiences about policy implementation and

procurement, including failures, between policy-makers is very beneficial for countries. This allows better-informed decisions to be taken and negotiations to be more strategical. Eventually, this could increase transparency around negotiated prices if cross-border collaborations agreed to jointly negotiate and procure.

Our analysis, though limited to selected policies, covered both existing policies as well as discussions and initiatives for new models, including proposals for funding and incentivising R&D and patent pooling. While we identified a strong interest of some policy-makers and Non-Governmental Organisations in more far-reaching changes, the analysis also showed that there is still space for improvement in the development and implementation of traditional pricing and reimbursement policies, such as better enforcement of demand-side measures to promote generic uptake (e.g. generic substitution) and methodological adaptions in external price referencing (e.g. related to country baskets).

Regular reviews and evaluations of the impact of pricing and reimbursement policies, with subsequent adaption based on the findings, if necessary are critical to inform whether, or not, the policies were effective in achieving the intended aims (e.g. more affordable access to medicines). In addition, evaluations are necessary to determine areas for improvement including increased efficiencies. In particular, there is a need for impact assessments of managed-entry agreements, value-based pricing and HTA.

While this paper was limited to European policies, the conclusions about the impacts of some of the discussed policies, and possible avenues for the future are also of relevance in the global context.

Compliance with Ethical Standards

Funding No funding was received for the writing of the manuscript.

Conflict of interest SV, VP, AF, VW, KdJ, PS, HBP, GD and ZUB have no conflicts of interest to declare. All authors submitted a signed Conflict of Interest disclosure form.

Author contributions All authors fulfilled the authorship criteria. All authors are aware of the submission and are in agreement with the manuscript. SV had the lead in drafting and revising the manuscript. VP drafted the chapter on health technology assessments, KdJ drafted the section about measurement of policies, and PS drafted the Appendix on networks. AF had the lead in providing literature. VP, AF, VW, KdJ, PS, HBP, GD and ZUB critically reviewed several versions of the manuscript.

References

1. European Commission. Council conclusions on innovation for the benefit of patients (2014/C 438/06). Brussels: 6 December 2014.
2. Council of the European Union. 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. 2013.
3. WHO Regional Office for Europe. Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research. Copenhagen: 2015.
4. Ministry of Health Welfare and Sport. Summary of Medicines Plan. The Hague: 2016. Accessible at: http://english.eu2016.nl/binaries/eu2016-en/documents/publications/2016/03/1/summary-of-medicins/summary-of-medicines-plan.pdf. Accessed 14 May 2016.
5. Iyengar S, Tay-Teo K, Vogler S, Beyer P, Wiktor S, de Joncheere K, et al. Prices, costs, and affordability of new medicines for hepatitis C in 30 countries: an economic analysis. PLoS Med. 2016;13(5):e1002032.
6. Howard DH, Bach PB, Berndt ER, Conti RM. Pricing in the market for anticancer drugs. National Bureau of Economic Research. Nashville: American Economic Association; 2015.
7. Tefferi A, Kantarjian H, Rajkumar SV, Baker LH, Abkowitz JL, Adamson JW, et al. In support of a patient-driven initiative and petition to lower the high price of cancer drugs. Mayo Clin Proc. 2015;90(8):996–1000.
8. Light DW, Kantarjian H. Market spiral pricing of cancer drugs. Cancer. 2013;119(22):3900–2.
9. Paris V, Hewlett E, Auraaen A, Alexa J, Simon L. Health care coverage in OECD countries in 2012. Paris: OECD Working Paper No. 88, OECD Publishing, 2016.
10. OECD. OECD Health Statistics 2016. Paris: Organisation for Economic Co-operation and Development; released 30 June 2016.
11. Bouvy J, Vogler S. Background Paper 8.3 Pricing and Reimbursement Policies: Impacts on Innovation. In: World Health Organization, editor. Priority Medicines for Europe and the World "A Public Health Approach to Innovation" Update on 2004 Background Paper. Geneva 2013.
12. EFPIA. Patients' W.A.I.T. Indicator—Report 2011. 2011. http://www.efpia.eu/uploads/Patients_WAIT_Report_2011_FINAL_070811_1.doc. Accessed 23 June 2016.
13. Heads of Medicines Agencies. Report of Task Force of HMA. Availability of Human Medicinal Products. Madeira: 2007.
14. Leopold C, Rovira J, Habl C. Generics in small markets or for low volume medicines European Union. Vienna: EMINet, 2010.
15. Vogler S, Kilpatrick K, Babar Z-U-D. Analysis of medicine prices in New Zealand and 16 European Countries. Value Health. 2015;18(4):484–92.
16. Vogler S, Vitry A, Babar Z-U-D. Cancer drugs in 16 European countries, Australia, and New Zealand: a cross-country price comparison study. Lancet Oncol. 2016;17(1):39–47.
17. Kanavos P, Ferrario A, Vandoros S, Anderson GF. Higher US branded drug prices and spending compared to other countries may stem partly from quick uptake of new drugs. Health Aff. 2013;32(4):753–61.
18. 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.
19. Danzon PM, Furukawa MF. International prices and availability of pharmaceuticals in 2005. Health Aff. 2008;27(1):221–33.
20. 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.
21. 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.

22. Simoens S. International comparison of generic medicine prices. Curr Med Res Opin. 2007;23(11):2647–54.
23. Jönsson B, Hofmarcher T, Lindgren P, Wilking N. Comparator report on patient access to cancer medicines in Europe revisited. IHE Rep. 2016;4:228.
24. Jönsson B, Persson U, Wilking N. Innovative Treatments for cancer in Europe—value, cost, and access. Lund: IHE-Report; 2016.
25. Nolte E, Corbett J. International variation in drug usage—an exploratory analysis of the "causes" of variation. London: RAND Europe; 2014.
26. Nolte E, Newbould J, Conklin A. International variation in the usage of medicines—a review of literature. London: RAND Europe; 2010.
27. Ferech M, Coenen S, Malhotra-Kumar S, Dvorakova K, Hendrickx E, Suetens C, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe. J Antimicrob Chemother. 2006;58(2):401–7.
28. Hoebert J, Laing R, Stephens P. Pharmaceutical consumption. The world medicines situation 2011. Geneva: World Health Organisation; 2011.
29. Hoebert JM. Cross-country variation in medicines use; a pharmaceutical system perspective; 2013.
30. Hoebert JM, Souverein PC, Mantel-Teeuwisse AK, Leufkens HG, van Dijk L. Reimbursement restriction and moderate decrease in benzodiazepine use in general practice. The Annals of Family Medicine. 2012;10(1):42–9.
31. Penchansky R, Thomas JW. The concept of access: definition and relationship to consumer satisfaction. Med Care. 1981;19(2):127–40.
32. World Health Organization. Equitable access to essential medicines: a framework for collective action. 2004.
33. Management Sciences for Health. Defining and Measuring Access to Essential Drugs, Vaccines, and Health Commodities. Report of the WHO-MSH Consultative Meeting, Ferney-Voltaire, France, December 11–13, 2000 Geneva: World Health Organization. 1999. http://projects.msh.org/seam/reports/measuring_access_Dec2000.pdf. Accessed 3 June 2016.
34. Bigdeli M, Jacobs B, Tomson G, Laing R, Ghaffar A, Dujardin B, et al. Access to medicines from a health system perspective. Health policy and planning. 2012.
35. United Nations. Sustainable Developmet Goals, [28 July 2016]. https://sustainabledevelopment.un.org/. Accessed 28 June 2016.
36. World Health Organization. Essential medicines and health products. Monitoring and Evaluation 2016. http://www.who.int/medicines/areas/policy/monitoring/en/. Accessed 1 Nov 2016.
37. World Health Organization. Global Reference List of 100 Core Health Indicators. Luxembourg: World Health Organization; 2015.
38. 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 Afairs; 2012.
39. Paris V, Belloni A. Value in Pharmaceutical Pricing. OECD Health Working Papers, No. 63. Paris: OECD Publishing, 2013.
40. Drummond M, Jönsson B, Rutten F, Stargardt T. Reimbursement of pharmaceuticals: reference pricing versus health technology assessment. Eur J Health Econ. 2011;12(3):263–71.
41. World Health Organization. WHO guideline on country pharmaceutical pricing policies. Geneva: World Health Organization; 2013.
42. Zimmermann N, Vogler S, Bak Pedersen H. Policy options to deal with high-cost medicines—survey with European policymakers. J Pharm Policy Pract. 2015;8(Suppl 1):P8.
43. Vogler S, Lepuschütz L, Schneider P, Stühlinger V. Study on enhanced cross-country coordination in the area of pharmaceutical product pricing. Vienna: Gesundheit Österreich Forschungs- und Planungs GmbH; 2016.
44. OECD. Pharmaceutical Pricing Policies in a Global Market. Paris: OECD, 2008.
45. Stargardt DVT, Schreyögg J. Impact of cross-reference pricing on pharmaceutical prices. Appl Health Econ Health Policy. 2006;5(4):235–47.
46. Danzon PM, Towse A. Differential pricing for pharmaceuticals: reconciling access, R&D and patents. Int J Health Care Finance Econ. 2003;3(3):183–205.
47. Kyle MK. Pharmaceutical price controls and entry strategies. Rev Econ Stat. 2007;89(1):88–99.
48. 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.
49. Rémuzat C, Urbinati D, Mzoughi O, El Hammi E, Belgaied W, Toumi M. Overview of external reference pricing systems in Europe. J Mark Access Health Policy. 2015;3:1–11.
50. Europe Economics. External price referencing. London: Europe Economics; 2013.
51. Michel M, Toumi M. Access to orphan drugs in Europe: current and future issues. Expert Rev Pharmacoeconomics Outcomes Res. 2012;12(1):23–9.
52. Persson U, Jönsson B. The end of the international reference pricing system? Appl Health Econ Health Policy. 2016;14(1):1–8.
53. Kanavos P, Nicod E, Espin J. Short-and long-term effects of value-based pricing vs. external price referencing. 2010.
54. Danzon PM, Wang YR, Wang L. The impact of price regulation on the launch delay of new drugs—evidence from twenty-five major markets in the 1990s. Health Econ. 2005;14(3):269–92.
55. Ferrario A, Reinap M, Pedersen HB, Kanavos P. Availability of medicines in Estonia: an analysis of existing barriers and options to address them. Copenhagen: WHO, Regional Office for Europe; 2016.
56. 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.
57. Glynn D. The effects of parallel trade on affordable access to medicines. Eurohealth. 2009;15(2):1–4.
58. Merkur S, Mossialos E. A pricing policy towards the sourcing of cheaper drugs in Cyprus. Health Policy. 2007;81(2):368–75.
59. Windmeijer F, De Laat E, Douven R, Mot E. Pharmaceutical promotion and GP prescription behaviour. Health Econ. 2006;15(1):5–18.
60. 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. South Med Rev. 2012;5(1):34–41.
61. 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.
62. Towse A, Pistollato M, Mestre-Ferrandiz J, Khan Z, Kaura S, Garrison L. european union pharmaceutical markets: a case for differential pricing? Int J Econ Bus. 2015;22(2):263–75.
63. Vogler S, Zimmermann N, Habl C, Piessnegger J, Bucsics A. Discounts and rebates granted to public payers for medicines in European countries. South Med Review. 2012;5(1):38–46.
64. Claxton K. Oft, Vbp: qed? Health Econ. 2007;16(6):545–58.
65. Godman B, Gustafsson LL. A new reimbursement system for innovative pharmaceuticals combining value-based and free market pricing. Appl Health Econ Health Policy. 2013;11(1):79.
66. Process on Corporate Social Responsibility in the Field of Pharmaceuticals, Platform on Access to Medicines in Europe,

Working Group on Mechanism of Coordinated Access to Orphan Medicinal Products (MoCA-OMP). Transparent Value Framework. 2013.
67. Kaplan W, Laing R. Priority Medicines for Europe and the World. Geneva: World Health Organization; 2004.
68. Franken M, le Polain M, Cleemput I, Koopmanschap M. Similarities and differences between five European drug reimbursement systems. Int J Technol Assess Health Care. 2012;28(4):349.
69. Consultative Expert Working Group on Research and Developmen. Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) 2016. http://www.who.int/phi/cewg/en/. Accessed 26 June 2016.
70. 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. Vienna: Commissioned by the European Commission, 2014.
71. Hughes DA. Value-based pricing. Incentive for innovation or zero net benefit? Pharmacoeconomics. 2011;29(9):731–5.
72. Ferrario A, Kanavos P. Managed entry agreements for pharmaceuticals: the European experience. EMINet, 2013.
73. Adamski J, Godman B, Ofierska-Sujkowska G, Osinska B, Herholz H, Wendykowska K, et al. Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. BMC Health Serv Res. 2010;10:153.
74. Morel T, Arickx F, Befrits G, Siviero P, van der Meijden C, Xoxi E, et al. Managed entry agreements and orphan drugs: a European comparative study (2006–2012). Value Health. 2013;16(7):A391–A.
75. Garrison LP, Towse A, Briggs A, de Pouvourville G, Grueger J, Mohr PE, et al. Performance-based risk-sharing arrangements—good practices for design, implementation, and evaluation: report of the ISPOR good practices for performance-based risk-sharing arrangements task force. Value Health. 2013;16(5):703–19.
76. Neumann PJ, Chambers JD, Simon F, Meckley LM. Risk-sharing arrangements that link payment for drugs to health outcomes are proving hard to implement. Health Aff. 2011;30(12):2329–37.
77. Iskrov G, Stefanov R. Prospects of risk-sharing agreements for innovative therapies in a context of deficit spending in Bulgaria. Front Public Health. 2015;3:1–4.
78. Ferrario A, Kanavos P. Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. Soc Sci Med. 2015;124(1):39–47.
79. Parkinson B, Sermet C, Clement F, Crausaz S, Godman B, Garner S, et al. Disinvestment and value-based purchasing strategies for pharmaceuticals: an international review. Pharmacoeconomics. 2015;33(9):905–24.
80. Simoens S, Picavet E, Dooms M, Cassiman D, Morel T. Cost-effectiveness assessment of orphan drugs: a scientific and political conundrum. Appl Health Econ Health Policy. 2013;11(1):1.
81. Vogler S, Zimmermann N, Ferrario A, Wirtz VJ, de Joncheere K, Pedersen HB, et al. Pharmaceutical policies in a crisis? Challenges and solutions identified at the PPRI Conference. J Pharm Policy Pract. 2016;9(1):1.
82. Russo P, Mennini FS, Siviero PD, Rasi G. Time to market and patient access to new oncology products in Italy: a multistep pathway from European context to regional health care providers. Ann Oncol. 2010;21(10):2081–7.
83. Vogler S, Habl C, Leopold C, Mazag J, Morak S, Zimmermann N. PHIS Hospital Pharma Report. Vienna: Pharmaceutical Health Information System (PHIS); commissioned by the European Commission and the Austrian Federal Ministry of Health, 2010. http://whocc.goeg.at/Literaturliste/Dokumente/BooksReports/PHIS_HospitalPharma_Report.pdf. Accessed 15 Nov 2014.
84. Er S. PHIS Hospital Pharma Report Denmark. Vienna: Pharmaceutical Health Information System (PHIS), 2009.
85. Festöy H, Ognøy AH. PPRI pharma profile Norway. Vienna: Pharmaceutical Pricing and Reimbursement Information (PPRI); 2015.
86. Leopold C, Habl C, Vogler S. Tendering of Pharmaceuticals in EU Member States and EEA countries. Results from the country survey. Vienna: ÖBIG Forschungs- und Planungsgesellschaft mbH; 2008.
87. Dylst P, Vulto A, Simoens S. Tendering for outpatient prescription pharmaceuticals: what can be learned from current practices in Europe? Health Policy. 2011;101(2):146–52.
88. Gombocz M, Vogler S, Zimmermann N. Ausschreibungen für Arzneimittel: Erfahrungen aus anderen Ländern und Umsetzungsstrategien für Österreich [Tendering for Medicines: Experiences from other countries and implementation strategies for Austria]. Vienna: Gesundheit Österreich Forschungs- und Planungs GmbH; 2016.
89. Kanavos P. Tender systems for outpatient pharmaceuticals in the European Union: Evidence from the Netherlands and Germany. London: EMINET, January. 2012. Available at: http://www.progenerika.de/wp-content/uploads/2013/02/Anlage-2_Tendering-Report-EMINET-13OCT2012-FINAL.pdf. Accessed 30 Apr 2016.
90. Kanavos P, Seeley L, Vandoros S. Tender systems for outpatient pharmaceuticals in the European Union: Evidence from the Netherlands, Germany and Belgium. London: European Medicines Information Network (EMINet); 2009.
91. Carradinha H. Tendering short-term pricing policies and the impact on patients, governments and the sustainability of the generic medicines industry. J Generic Med Bus J Generic Med Sect. 2009;6(4):351–61.
92. VanHaeren E, Arickx F, Soete E, Bormans V, Mortier M, Leveque F. PCV162 Public tendering for off patent medicines in Belgium—the simvastatin case. Value Health. 2009;12(7):A343.
93. 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 Biosimilars Initiat (GaBI) J. 2012;1(2):93–100.
94. Dylst P, Vulto A, Simoens S. Demand-side policies to encourage the use of generic medicines: an overview. Expert Rev Pharmacoecon Outcomes Res. 2013;13(1):59–72.
95. Vogler S, Schneider P, Gombocz M. Maßnahmen der Generikaförderung in Europa [Measures to enhance generics uptake in Europe]. Vienna: Gesundheit Österreich Forschungs- und Planungs GmbH; 2016.
96. Vogler S. How large are the differences between originator and generic prices? Analysis of five molecules in 16 European countries. Farmeconomia Health Econ Ther Pathw. 2012;13(Suppl 3):29–41.
97. Vogler S, Leopold C. Access to essential medicines in Portugal. Vienna: ÖBIG Forschungs- und Planungsgesellschaft mbH; 2009.
98. Gouya G, Reichardt B, Bidner A, Weissenfels R, Wolzt M. Partial reimbursement of prescription charges for generic drugs reduces costs for both health insurances and patients [Article in German]. Wien Klin Wochenschr. 2008;120(3–4):89–95.
99. Vogler S, Zimmermann N, et al. Policy interventions related to medicines: survey of measures taken in European countries during 2010–2015. Health Policy. 2016;120(12):1363–77.
100. Danzon PM, Furukawa MF. Prices and availability of pharmaceuticals: evidence from nine countries. Health Affairs. 2003:W3–521. doi:10.1377/hlthaff.w3.521.
101. Godman B, Bennie M, Baumgärtel C, Sović-Brkičić L, Burkhardt T, Fürst J, et al. Essential to increase the use of generics

in Europe to maintain comprehensive health care? Farmeconomia Health Econ Ther Pathw. 2012;13(3S):5–20.
102. Dylst P, Vulto A, Godman B, Simoens S. Generic medicines: solutions for a sustainable drug market? Appl Health Econ Health Policy. 2013;11(5):1–7.
103. Sermet C, Andrieu V, Godman B, Van Ganse E, Haycox A, Reynier JP. Ongoing pharmaceutical reforms in France: implications for key stakeholder groups. Appl Health Econ Health Policy. 2010;8(1):7–24.
104. European Commission Competition Directorate-General. Pharmaceutical sector inquiry. Brussels: European Commission; 2009.
105. Simoens S. Generic and biosimilar medicines: quid? Farmeconomia Health Econom Ther Pathw. 2012;13(3S):3–4.
106. Dylst P, Vulto A, Simoens S. Overcoming challenges in market access of generic medicines in the European Union. J Generic Med Bus J Generic Med Sect. 2012;9(1):21–8.
107. Heinze G, Hronsky M, Reichardt B, Baumgärtel C, Müllner M, Bucsics A, et al. Potential savings in prescription drug costs for hypertension, hyperlipidemia, and diabetes mellitus by equivalent drug substitution in Austria: a nationwide cohort study. Appl Health Econ Health Policy. 2014;13(2):1–13.
108. Simoens S, De Coster S. Sustaining generic medicines markets in Europe. J Generic Med. 2006;3(4):268.
109. Cameron A, Mantel-Teeuwisse AK, Leufkens HGM, Laing RO. Switching from originator brand medicines to generic equivalents in selected developing countries: how much could be saved? Value Health. 2012;15(5):664–73.
110. Ubeda A, Cardo E, Sellés N, Broseta R, Trillo JL, Fernández-Llimós F. Antidepressant utilization in primary care in a Spanish region. Soc Psychiatry Psychiatr Epidemiol. 2007;42(3):181–8.
111. European Medicines Agency (EMA). European public assessment reports London 2106. http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=Enter+keywords&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=biosimilars&genericsKeywordSearch=Submit. Accessed 7 July 2016.
112. Schellekens H, Smolen JS, Dicato M, Rifkin RM. Safety and efficacy of biosimilars in oncology. Lancet Oncol. 2016;17(11):e502–9.
113. Food and Drug Adminstration (FDA). FDA approves Inflectra, a biosimilar to Remicade. Press release. 2016. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm494227.htm. Accessed 6 July 2016.
114. European Commission. Multi-stakeholder Workshop on Biosimilar Medicinal Products. Summary. 20 June 2016. http://ec.europa.eu/DocsRoom/documents/19302/attachments/1/translations/en/renditions/native. Accessed 3 Nov 2016.
115. Goll GL, Olsen IC, Jorgensen KK, Lorentzen M, Bolstad N, Haavardsholm EA, et al. Biosimilar Infliximab (CT-P13) Is not inferior to originator infliximab: results from a 52-week randomized switch trial in Norway. Arthritis Rheumatol. 2016;968((suppl. 10). http://acrabstracts.org/abstract/biosimilar-infliximab-ct-p13-is-not-inferior-to-originator-infliximab-results-from-a-52-week-randomized-switch-trial-in-norway/. Accessed 3 Nov 2016.
116. Mestre-Ferrandiz J, Towse A, Berdud M. Biosimilars: how can payers get long-term savings? PharmacoEconomics. 2016;34(6):609–16.
117. Vogler S, Peter S, Gombocz M, Zimmermann N. Differences in pricing policies for generic and biosimilar medicines. Value Health. 2016;19(7):A350.
118. European Biopharmaceutical Enterprises. What pricing and reimbursement policies to use for off-patent biologicals?—results from the EBE 2014 biological medicines policy survey. Generics Biosimilars Initiat J (GaBI Journal). 2015;4(1):17–24.
119. Renwick MJ, Smolina K, Gladstone EJ, Weymann D, Morgan SG. Postmarket policy considerations for biosimilar oncology drugs. Lancet Oncol. 2016;17(1):e31–8.
120. Vogler S, Zimmermann N, Leopold C, Habl C, Mazag J. Discounts and rebates granted for medicines for hospital use in five European countries. Open Pharmacoecon Health Econ J. 2013;5:1–10.
121. GaBI Online. Huge discount on biosimilar infliximab in Norway. Generics Biosimilars Initiat J (GaBI Journal). 2015. http://www.gabionline.net/Biosimilars/General/Huge-discount-on-biosimilar-infliximab-in-Norway. Accessed 3 Nov 2016.
122. Council of the European Union. Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States. 17 June 2016. http://www.consilium.europa.eu/press-releases-pdf/2016/6/47244642812_en.pdf. Accessed 3 July 2016.
123. European Commission. Medical Countermeasures that could be procured in common under the joint procurement agreement. http://ec.europa.eu/health/preparedness_response/docs/jpa_note_scope_en.pdf. Accessed 3 June 2016. Luxembourg: 2014.
124. Ministre des Affaires sociales et de la Santé publique. The Grand Duchy of Luxemburg Joins Belgium-Netherlands Initiative on Orphan Drugs, Communiqué de presse 24 September 2015 2016 [3 June 2016]. http://www.deblock.belgium.be/fr/grand-duchy-luxemburg-joins-belgium-netherlands-initiative-orphan-drugs. Accessed 3 June 2016.
125. Bundesministerium für Gesundheit [Federal Ministry of Health]. Oberhauser: Österreich tritt Benelux-Kooperation für Arzneimittelpolitik bei [Oberhauser: Austria joins the Benelux cooperation on pharmaceutical policy]. 17 June 2016. http://www.bmgf.gv.at/home/Startseite/aktuelle_Meldungen/Oberhauser_Oesterreich_tritt_Benelux_Kooperation_fuer_Arzneimittelpolitik_bei. Accessed 4 July 2016.
126. Kristensen FB, Mäkelä M, Neikter SA, Rehnqvist N, Håheim LL, Mørland B, et al. European network for Health Technology Assessment, EUnetHTA: planning, development, and implementation of a sustainable European network for Health Technology Assessment. Int J Technol Assess Health Care. 2009;25(S2):107–16.
127. European Medicines Agency (EMA). Early dialogue between regulators and health technology assessment bodies key to medicines development. EMA and multiple stakeholders to develop tools for industry. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/11/news_detail_001979.jsp&mid=WC0b01ac058004d5c1. Accessed 28 June 2016. [press release]. 28 Nov 2013.
128. European Medicines Agency (EMA). Pilot project on adaptive licensing. London: 19 March 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/03/WC500163409.pdf. Accessed 3 June 2016.
129. National Institute for Health and Care Excellence (NICE). Public involvement. London. 2016. https://www.nice.org.uk/about/nice-communities/public-involvement. Accessed 6 June 2016.
130. van Thiel G, Stolk P. Background Paper 8.5 Patient and Citizen Involvement. In: World Health Organization, editor. Priority Medicines for Europe and the World 2013 Update. Geneva; 2013.
131. Scottish Medicines Consortium. Capturing the patient and carer voice. Glasgow 2016. https://www.scottishmedicines.org.uk/Public_Involvement/Public_Involvement. Accessed 6 June 2016.
132. European Commission. Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems.

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31989L0105:en:HTML. Accessed 4 Nov 2016.
133. EFPIA. EFPIA Position Paper: Principles for application of international reference pricing systems. 16 July 2014.
134. 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 by European Social Insurance Platform (ESIP)/Association Internationale de la Mutualité (AIM) on 10 February 2011 [press release]. 2011.
135. Robertson J, Walkom EJ, Henry DA. Transparency in pricing arrangements for medicines listed on the Australian Pharmaceutical Benefits Scheme. Aust Health Rev. 2009;33(2):192–9.
136. Joppi R, Demattè L, Menti AM, Pase D, Poggiani C, Mezzalira L. The Italian horizon scanning project. Eur J Clin Pharmacol. 2009;65(8):775–81.
137. Packer C, Fung M, Stevens A. Analyzing 10 years of early awareness and alert activity in the United Kingdom. Int J Technol Assess Health Care. 2012;28(03):308–14.
138. Godman B, Paterson K, Malmström RE, Selke G, Fagot J-P, Mrak J. Improving the managed entry of new medicines: sharing experiences across Europe. Expert Rev Pharmacoecon Outcomes Res. 2012;12(4):439–41.
139. Nordic Contact Point for Priorization. Memo—Overview of Nordic collaboration within the prioritization area [27 July 2016]. https://nyemetoder.no/Documents/Nordiskkontaktpunkt/Memo-OverviewofNordiccollaboration.pdf. Accessed 27 July 2016.
140. Avorn J. The $2.6 billion pill—methodologic and policy considerations. N Engl J Med. 2015;372(20):1877–9.
141. Sullivan T. New York Introduces Pharmaceutical Cost Transparency Bill: Policy and Medicines; 18 May 2016. http://www.policymed.com/2015/05/new-york-introduces-pharmaceutical-cost-transparency-bill.html. Accessed 7 July 2016.
142. World Health Organization. Global strategy and plan of action on public health, innovation and intellectual property. Geneva: World Health Organization; 2011.
143. Velásquez G, Seuba X. Rethinking global health: a binding convention for R&D for pharmaceutical products. South Center Res Pap. 2011;42:29.
144. Jayadev A, Stiglitz J. Two ideas to increase innovation and reduce pharmaceutical costs and prices. Health Aff. 2009;28(1):w165–8.
145. Moon S, Bermudez J, t Hoen E. Innovation and access to medicines for neglected populations: could a treaty address a broken pharmaceutical R&D system? PLoS Med. 2012;9(5):e1001218.
146. Røttingen J-A, Chamas C. A new deal for global health R&D? The recommendations of the consultative expert working group on research and development (CEWG). PLoS Med. 2012;9(5):e1001219.
147. Love J, Hubbard T. Bid Idea: prizes to Stimulate R&D for New Medicines. Chi-Kent L Rev. 2007;82:1519.
148. Balasegaram M, Bréchot C, Farrar J, Heymann D, Ganguly N, Khor M, et al. A global biomedical R&D fund and mechanism for innovations of public health importance. PLoS Med. 2015;12(5):e1001831.
149. The Review on Antimicrobial Resistance. Tackling drug-resistent infections globally: final report and recommendations. London: Wellcome Trust and UK Government; 2016.
150. United Nations Secretary General's High-Level Panel on Access to Medicines. Report of the United Nations Secretary General's High-Level Panel on Access to Medicines. Promoting innovation and access to health technologies. September 2016.
151. Wirtz VJ, Hogerzeil HV, Gray AL, Bigdeli M, de Joncheere CP, Ewen MA, et al. Essential medicines for universal health coverage. Lancet. 2016. doi:10.1016/S0140-6736(16)31599-9.
152. Björkhem-Bergman L, Andersén-Karlsson E, Laing R, Diogene E, Melien O, Jirlow M, et al. Interface management of pharmacotherapy. Joint hospital and primary care drug recommendations. Eur J Clin Pharmacol. 2013;69(1):73–8.
153. Leopold C. Pharmaceutical policy analysis—a European perspective on pricing and reimbursement in challenging times. Utrecht: Utrecht University; 2014.
154. Almarsdóttir AB, Traulsen JM. Studying and evaluating pharmaceutical policy—becoming a part of the policy and consultative process. Pharm World Sci. 2006;28(1):6–12.
155. Gotham D, Onarheim KH, Barber MJ. How the MDGs gave up on measuring access to medicines. Lancet Glob Health. 2016;4(5):e296–7.
156. Kaplan WA, Ritz LS, Vitello M, Wirtz VJ. Policies to promote use of generic medicines in low and middle income countries: a review of published literature, 2000–2010. Health Policy. 2012;106(3):211–24.