ADDRESSING POLICY FAILURES IN PHARMACEUTICALS
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POLICY BRIEF 30

Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?

Sabine Vogler
Valérie Paris
Dimitra Panteli

European Observatory on Health Systems and Policies
a partnership hosted by WHO

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What is a Policy Brief?

A policy brief is a short publication specifically designed to provide policy makers with evidence on a policy question or priority. Policy briefs

- Bring together existing evidence and present it in an accessible format
- Use systematic methods and make these transparent so that users can have confidence in the material
- Tailor the way evidence is identified and synthesised to reflect the nature of the policy question and the evidence available
- Are underpinned by a formal and rigorous open peer review process to ensure the independence of the evidence presented.

Each brief has a one page key messages section; a two page executive summary giving a succinct overview of the findings; and a 20 page review setting out the evidence. The idea is to provide instant access to key information and additional detail for those involved in drafting, informing or advising on the policy issue.

Policy briefs provide evidence for policy-makers not policy advice. They do not seek to explain or advocate a policy position but to set out clearly what is known about it. They may outline the evidence on different prospective policy options and on implementation issues, but they do not promote a particular option or act as a manual for implementation.

Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?

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Authors

Sabine Vogler, Austrian Public Health Institute

Valérie Paris, OECD

Dimitra Panteli, European Observatory on Health Systems and Policies, Department of Health Care Management, Berlin University of Technology

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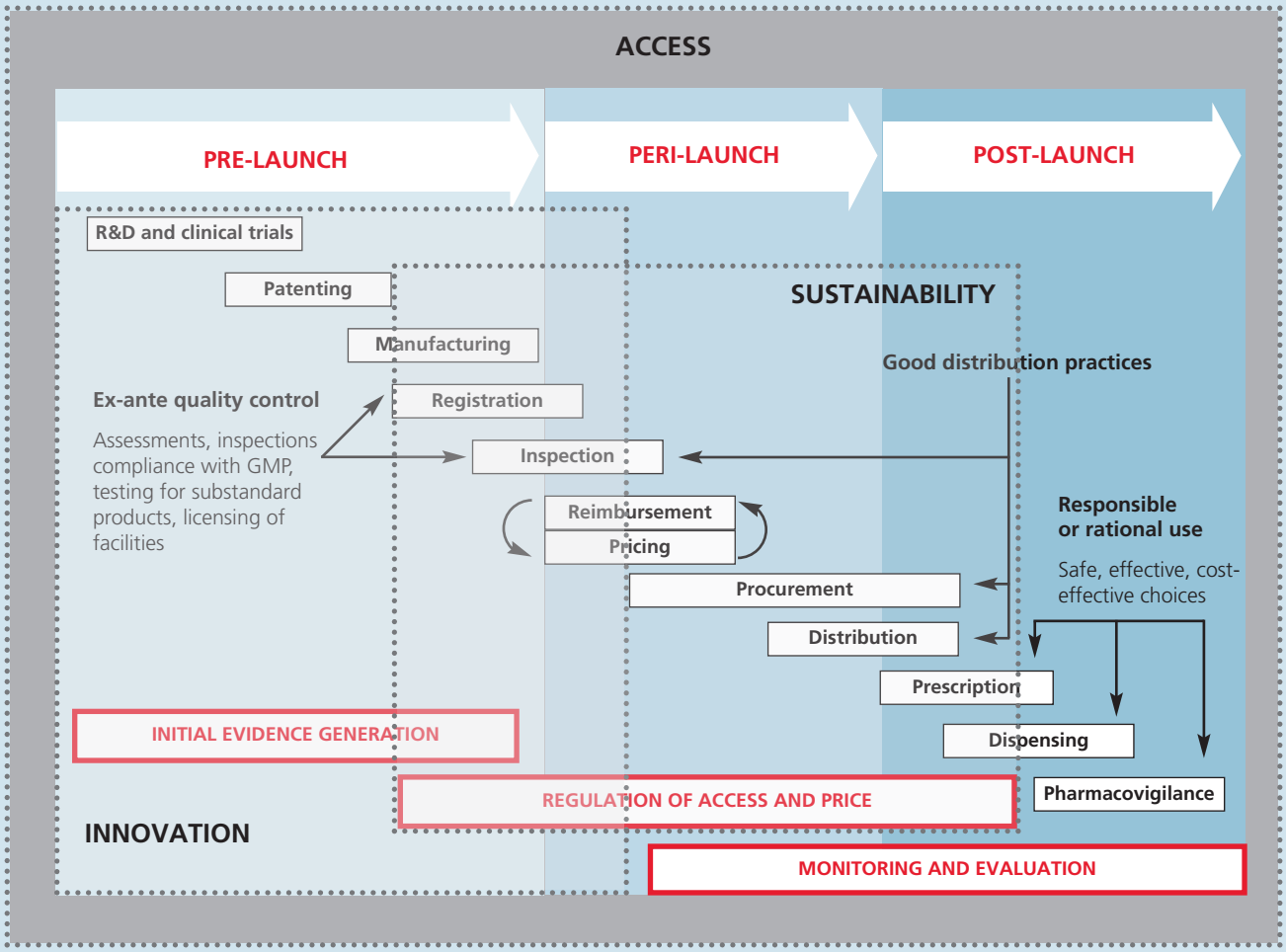
Box 1: Ensuring access to medicines: How to address policy failures in pharmaceuticals?

This series of two policy briefs on addressing market and policy failures in the pharmaceutical sector, prepared for the Austrian EU Presidency, revolves around the triple aim that health systems generally pursue:

- Ensuring access: making sure that patients have timely and affordable access to safe and effective medicines;
- Stimulating innovation: providing incentives for research that will lead to innovative medicines that effectively target real therapeutic needs;
- Safeguarding sustainability: developing the mechanisms to purchase these medicines at affordable prices in order to protect the sustainability of pharmaceutical budgets.

These objectives need to take account of the "lifecycle" of a pharmaceutical product and the different regulatory levers and policy interventions that take place over its course (see figure below). The sustainability square denotes the focus of this policy brief, while the innovation square reflects the area covered by the concurrent policy brief [1].



Source: author's and editor's own, based on [2]

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List of tables, figures and boxes

How do Policy Briefs bring the evidence together?

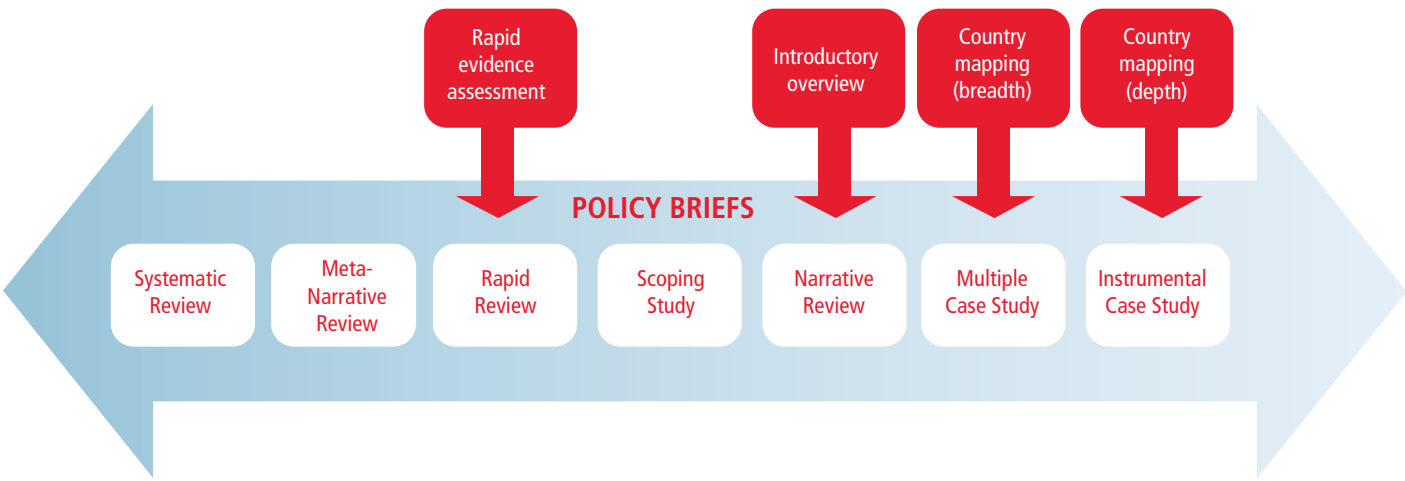
There is no one single way of collecting evidence to inform policy-making. Different approaches are appropriate for different policy issues, so the Observatory briefs draw on a mix of methodologies (see Figure A) and explain transparently the different methods used and how these have been combined. This allows users to understand the nature and limits of the evidence.

There are two main 'categories' of briefs that can be distinguished by method and further 'sub-sets' of briefs that can be mapped along a spectrum:

- **A rapid evidence assessment:** This is a targeted review of the available literature and requires authors to define key terms, set out explicit search strategies and be clear about what is excluded.
- **Comparative country mapping:** These use a case study approach and combine document reviews and consultation with appropriate technical and country experts. These fall into two groups depending on whether they prioritize depth or breadth.
- **Introductory overview:** These briefs have a different objective to the rapid evidence assessments but use a similar methodological approach. Literature is targeted and reviewed with the aim of explaining a subject to 'beginners'.

Most briefs, however, will draw upon a mix of methods and it is for this reason that a 'methods' box is included in the introduction to each brief, signalling transparently that methods are explicit, robust and replicable and showing how they are appropriate to the policy question.

Figure A: The policy brief spectrum



Source: Erica Richardson

Key terms

- **Pricing:** The act or process of determining a price, be it by a responsible authority, the manufacturer or market forces. In this policy brief we use the term to denote price-setting practices in the context of price regulation.
- **Procurement:** Process of purchasing goods, works or services (e.g. medicines) through a formal process that may or may not involve a call for tenders.
- **Reimbursement:** Covering the cost of health care services, including medicines, by a third-party payer (e.g. a public payer such as a social health insurance fund or national health service).

Key messages

- Policy-makers and purchasers increasingly face very high price tags for new medicines, and some worry that these prices challenge the financial sustainability of solidarity-based, publicly funded health care systems.
- EU Member States use a mix of policy instruments to regulate the prices and determine the reimbursement of medicines. Different policies are applied for different sectors, market segments and medicines. Some pricing, procurement and reimbursement policies are more frequently used for new, potentially high-priced medicines.
- Popular policies and tools include external price referencing, managed entry agreements, health technology assessment (HTA) and tendering, but each one of these comes with limitations.
- Adaptations of these policies, such as value-based pricing, strategic procurement and differential pricing traits, are also being explored and could be a first step in this direction.
- Further, more far-reaching measures and initiatives may also be needed to fundamentally tackle the issue of high medicine prices and to overcome information asymmetry and a lack of transparency about the real prices paid and the real development costs of medicines.
- Collaborative efforts, at both intra-country and cross-country levels, in terms of joint price negotiations and procurement and enhanced collaboration for horizon scanning and HTA appear to be promising but require strong commitment from national policy-makers.
- Pricing, reimbursement and procurement policies are important elements in the ‘tool-box’ to improve affordable access to new high-priced medicines but further interventions in other pharmaceutical policy areas may be required to supplement them.

Executive summary

In recent years some very expensive medicines have entered European markets. As a result, policy-makers are increasingly concerned about ensuring affordable patient access, while at the same time safeguarding the long-term financial sustainability of their health systems and maintaining incentives for industry to continue developing new medicines.

High pharmaceutical prices, and their potential impact on the affordability of medicines, have been high on the political agenda, at both national and European levels. This has been the case even though the pricing, reimbursement and procurement of medicines are largely a national competence of the Member States of the European Union (EU). Countries have been exploring options for improving existing pharmaceutical policies and new avenues to ensure affordable and sustainable patient access to medicines. Overall, European countries tend to use more or less the same policies to price, reimburse and procure medicines, and some of these policies are commonly and increasingly used for new, potentially high-priced medicines.

This policy brief explores the most frequently applied policies for new high-priced medicines as well as some alternative approaches. In each case, the strengths and limitations are assessed and options for improvement are studied. The brief shows that the lack of transparency on 'real' prices and development costs for medicines is a key limitation to many policies and argues that improving transparency and cooperation, both within countries and among EU Member States, is the way forward.

One of the most frequently applied pricing policies for new medicines is **external price referencing (EPR)**, which is when the price of a medicine in one country is based on the price of the same medicine in other countries. Almost all EU Member States use external price referencing for at least some medicines. The choice of comparator countries and the method of calculating the benchmark price have an impact on the prices achieved. Frequently, price benchmarks set through external price referencing are seen as a starting point for further price negotiations with marketing authorization holders, during which confidential discounts are often granted for new medicines. However, as the official list price, not the real discounted price, is referenced in EPR, it serves as an anchor in further negotiations, so payers risk overpaying. Also, EPR incentivizes marketing authorization holders to launch medicines first in countries with higher prices, and delay (or not launch) them in lower-priced countries.

There have been calls to introduce **differential pricing**, which takes into account the different ability-to-pay across countries. For the time being, this policy appears infeasible in the EU context: parallel trade and the widespread use of external price referencing have been mentioned as key barriers to its implementation. More importantly, strong political commitment from national policy-makers would be required to implement it. As a compromise, it has been suggested that differential pricing traits, such as purchasing power parity adjustments of prices in other countries, could be included in the methodology of external price referencing.

Public purchasers and payers have increasingly been concluding individual arrangements with manufacturers to 'manage' the adoption and funding of new medicines with uncertain effectiveness, unfavourable cost-effectiveness and/or high budget impact at the time of market entry. So-called **Managed Entry Agreements (MEAs)** enable the reimbursement of a new medicine tied to specific conditions. Such conditions can include simple price-volume agreements, predefined utilization pathways or expected health outcomes to be achieved. Data confidentiality is a major limitation of MEAs. While MEAs allow for agreements on prices that are lower than those officially disclosed (list prices), the exact difference in these amounts is unknown. There is also the risk that a marketing authorization holder, in anticipation of an MEA, pre-emptively asks for an inflated initial price. Furthermore, MEAs are linked to high transaction and administrative efforts and costs, and their implementation needs to be accompanied by a clear disinvestment strategy.

As a policy-informing tool, **Health Technology Assessment (HTA)** has been gaining importance across Europe. HTA agencies have been formally cooperating at the European level since 2007 and new proposed regulation aims at further intensifying and institutionalizing this collaboration. HTA is a technical evaluation tool that informs decisions on reimbursement and pricing by evaluating the clinical, economic and other consequences of new medicines. However, as such, it cannot, in isolation, make these decisions. Diverging from HTA findings, payers are sometimes willing to accept high prices for relatively low benefits, as many other considerations may be of importance when assessing the 'value' of new medicines. This is especially important for orphan diseases and cancer treatments. Consequently, **value-based pricing**, and policies considering elements of value-based pricing, have been gaining importance in some European countries for high-priced medicines.

As another supportive tool, **horizon scanning** can help countries prepare for the pricing and reimbursement of medicines that have not yet been launched. However, establishing and maintaining an effective horizon scanning system is extremely time-intensive and costly and information on medicines in the pipeline is limited. Horizon scanning as a technique is not new, but it has generally been carried out by research institutions largely disconnected from policy-making.

When the expense of some high-priced medicines cannot be borne within general public reimbursement, **specific funds** have been established in some European countries. However, as demonstrated by the case of the Cancer Drug Fund in England, such funds have opportunity costs as they divert funds from more cost-effective interventions. In addition, if cost-effectiveness is not a coverage criterion, manufacturers may be incentivized to charge higher prices leading to an increase in spending over time. Taking the experience of existing initiatives into account could help

avoid unnecessary pitfalls. **Amortization** (i.e. paying by making a number of smaller payments over a period of time) is being proposed and piloted as an alternative for medicines with extremely high price tags.

Among procurement policies, **tendering** is an approach that aims to achieve lower prices by awarding the contract to the best offer. For high-priced medicines that are mainly used in the hospital sector, individual hospitals and hospital groups often apply tendering. There has been increased collaboration at both regional and national levels, but further benefits could be achieved from cross-country collaboration in tendering (or in procurement more generally), although differences in legal provisions and regulatory procedures pose a challenge. A concern with tendering is a 'possible race to the bottom' of prices, potentially leading to a withdrawal of companies from the market and medicine shortages. It may therefore be prudent for tendering and procurement processes to be designed as part of an overall '**strategic procurement**' policy.

As an alternative to high-priced biological originator medicines, biosimilars can help contain rising expenditures. However, the **uptake of biosimilar medicines** varies considerably among European countries and is quite low in some cases. While generic substitution has been widely implemented, this is still not the case for biosimilars. Any measure to promote the uptake of biosimilar medicines will only be successful if prescribers and patients have no doubt about their quality and effectiveness.

The evidence shows that existing pricing, reimbursement and procurement policies all have their limitations and are usually not able to sufficiently address existing imbalances in the pharmaceutical sector, including information asymmetry, and other limitations in transparency. Policy-makers could therefore creatively explore new solutions and take a comprehensive approach that includes all phases in the pharmaceutical life-cycle.

Collaborations, at both intra-country and cross-country levels, are emerging as a way forward in many areas. New ideas include the establishment of a 'Clearing House' of information about real discounted prices (e.g. across the regions in Austria) and cross-country cooperations in areas of horizon scanning and of price negotiations, such as in the framework of the BeNeLuxA collaboration. Moving forward in collaborative approaches in technical areas and policies should carefully balance the competences of the European Commission and the EU Member States. It should also be strongly based on the commitment of national policy-makers, who need to unequivocally recognize its value if it is to succeed.

Policy brief

Introduction

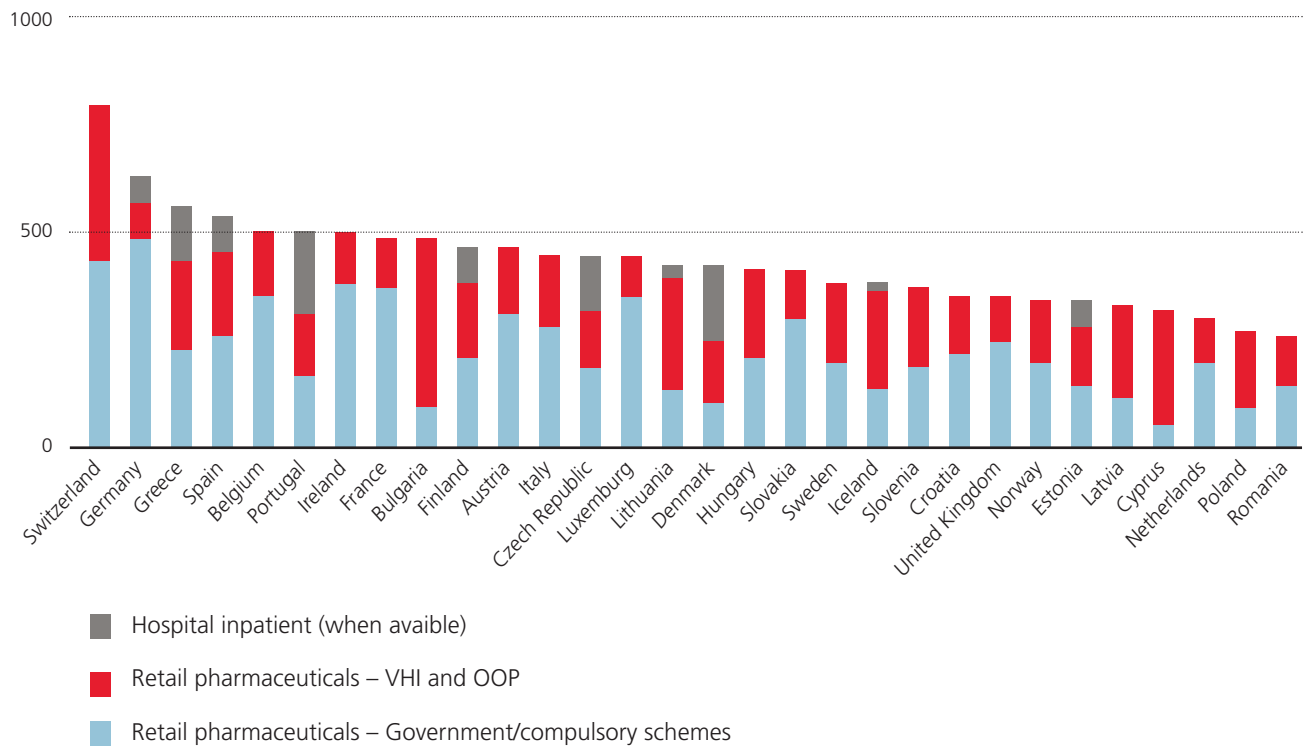
The current discussion around pharmaceutical expenditure, prices and access

In recent years policy-makers in European countries have been increasingly concerned about developments in the pharmaceutical sector that have been challenging the affordability of new medicines for lower-income countries and the financial sustainability of solidarity-based and/or publicly funded health care systems even in high-income countries [2].

This is mainly attributable to a number of new medicines that have entered European markets and are very expensive, with cancer, autoimmune and diabetes treatments being the key drivers of growth in public pharmaceutical expenditure [3], and emerging cell and gene therapies likely to drive these expenditures up even further [4].

These new medicines are mainly dispensed in the hospital setting: while policy-makers have largely been able to contain outpatient pharmaceutical expenditure, albeit at the expense of shifting expenditure to patients (Figure 1), increases have been reported from the hospital sector. For many years the inpatient pharmaceutical sector has not been the focus of policy-makers' attention [5]. This may also explain why data availability for this sector is substantially more limited than for outpatient medicines. For instance, there are no official price data published in some European countries, such as Portugal [6], and there is partial or no measurement of inpatient pharmaceutical expenditure (Figure 2). However, for a few countries where pharmaceutical expenditure data are available in the inpatient sector, we see that hospital spending has a relevant share of pharmaceutical expenditure.

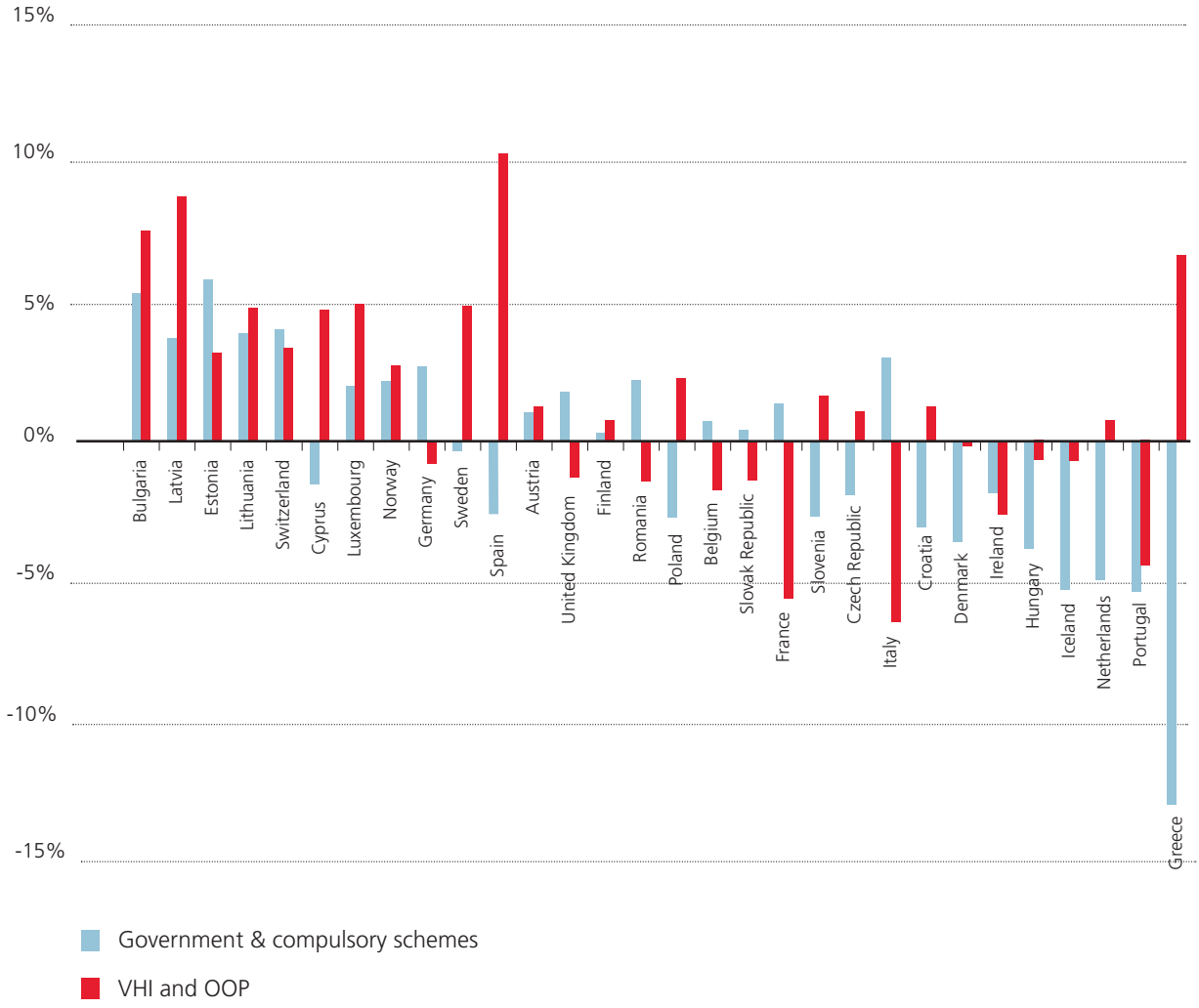
Figure 1: Pharmaceutical expenditure per capita in 2016 (Euro PPP)



Notes: VHI: voluntary health insurance; OOP: Out-of-pocket expenditures. Expenditures for medicines dispensed to hospitalized patients are only available for a few countries.

Source: [7]

Figure 2: Annual growth rate of retail pharmaceutical expenditures 2011–2016, constant prices, by financing scheme



Note: VHI: voluntary health insurance; OOP: Out-of-pocket expenditures: United Kingdom 2013-2016; Bulgaria 2012-2016. There are breaks in the series for Czech Republic, Italy and Slovakia. Countries are listed according to the annual growth rate of total retail pharmaceutical.expenditures.

Source: [7]

Policy-makers are concerned not only by the high prices of new medicines but also that some of them deliver limited or no additional therapeutic benefits to patients, which is not in keeping with their high price tags. This is an issue especially in the field of oncology and for some orphan medicines [8, 9, 10, 11]. Research has shown that some premium-priced medicines were only able to deliver marginal benefits (e.g. increase of a few days in overall survival) [12, 13, 14, 15].

These developments have pushed the issue of access to new medicines up the policy agenda in the EU (Box 2). In the search for solutions to ensure affordable and sustainable patient access, discussions have not been limited to technical issues related to pricing, reimbursement and procurement policies. Discussions have also been addressing the overall value chain and the current mechanisms to incentivize innovation. In the current intellectual property rights system, marketing authorization holders are incentivized to achieve patent-based monopolies and market exclusivity and hold them as long as possible. Manufacturers tend to justify the high prices of new medicines in this system by citing the sizeable investments that go into research and development (R&D), even though a substantial part of R&D expenditure often comes from public funding [16, 17].

Figures on R&D costs vary substantially across calculations [1, 18]. Moreover, the current incentives framework provides fertile ground for the 'orphanization' of new medicines. The pharmaceutical industry gains an important and increasing part of its revenues from orphan medicinal products [19]; these usually have considerable price tags and often follow

special rules for pricing and reimbursement. In this way, the industry has been developing and marketing medicines for very small patient populations [20], or 'niche' markets. In the United States, about one third of all successful launches of new active substances have at least one orphan designation [21]. The annual share of orphans among approvals by the European Medicines Agency (EMA) ranged from 16% to 21% between 2015 and 2017. It has been forecasted that by 2025 about 120 new orphan medicines will have been approved by the EMA with an estimated budget impact of approximately €22 billion [22].

Discussions about revisiting the regulatory framework around the pharmaceutical value chain have emerged more prominently in Europe and add to related international debates that have been ongoing for decades. A fundamental reform of how innovation is funded has been discussed under the concept of 'de-linkage', where the price of a new medicine is disconnected from its (claimed) R&D costs [23]. Furthermore, the European Commission initiated a study requested by the Council under the Dutch EU Presidency which investigated the impact of the incentives and rewards system on pharmaceutical innovation, as well as the availability and accessibility of medicinal products [24]. A 'shadow study' on this issue was commissioned by the Dutch government and is also available [25]. Despite these broader considerations, this policy brief focuses on existing and alternative approaches to pricing, reimbursement and procurement and their role in achieving sustainable access to medicines in Europe.

Box 2: Affordable access to high-priced medicines on the policy agenda in Europe and globally

Several Councils during recent European Union (EU) Presidencies have addressed the challenge of accessibility of innovation, particularly for high-priced pharmaceuticals

The 'Council conclusions on innovation for the benefit of patients' under the **Italian EU Presidency** were adopted on 1 December 2014 [26]. It was 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'. 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 …' and to 'continue to support research and information tools that aim to provide a better understanding of how pharmaceutical pricing may be applied to maximize benefits for patients and Member States' health systems and, where relevant, to minimize possible unintended negative effects on patient access and health budgets'.

The **Dutch EU Presidency** had a strong focus on ensuring the affordability of innovative medicines, tackling their high prices and seeking a 'healthy balance' in the pharmaceutical market [27]. The 'Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States', issued on 17 June 2016, called for improving transparency, and voluntary cross-country collaboration was suggested as a useful way forward. It was recognized that 'a number of Member States have expressed interest in … exploring voluntary cooperation in different areas, for example on issues related to pricing and reimbursement of medicinal products, activities aimed at 'horizon scanning', the exchange of information and knowledge, the collection and exchange of price data such as the EURIPID collaboration, and in some cases by the bringing together of facilities and resources as well as instruments for joint price negotiations [28].

The **Maltese EU Presidency** followed up on the potential of voluntary collaborations. The 'Council conclusions on encouraging Member States-driven voluntary cooperation between health systems', adopted as of 16 June 2017, called for an exchange of information between Member States on national pricing and reimbursement policies, including pricing agreements, on evidence generated in the post-marketing phase, and on criteria and processes relied on for disinvestment in health technologies [29].

In recent years, the European Commission (EC) also addressed the topic through the following initiatives and documents

- One of the five defined objectives in the 'Reflection process – Towards modern, responsive and sustainable health systems' (2013) concerned the cost-effective use of medicines [30]. Suggested actions included the consideration of 'improved cooperation on building mechanisms for increased transparency and better coordination to minimize any unintended effects that current national pricing systems may have in terms of accessibility throughout the EU' [31].
- The EC Expert Group on Safe and Timely Access to Medicines for Patients ('STAMP') was established in 2015 as a sub-group of the Pharmaceutical Committee to provide advice and expertise to Commission services on how to improve the implementation of EU Pharmaceutical legislation and speed up access to innovative and affordable medicines [32].
- The EC has been supporting collaboration in Health Technology Assessment (HTA) through the European Network for Health Technology Assessment (EUnetHTA) project since 2007 and has proposed draft legislation for the future collaboration on HTA [33].
- The European Expert Panel on effective ways of investing in health, an independent expert group advising the EC, was asked to work on an opinion regarding novel payment models for high-cost innovative medicines [34].
- In May 2017 the EC opened a formal investigation into concerns that a pharmaceutical company (Aspen Pharma) had engaged in excessive pricing concerning five life-saving cancer medicines. This is the first EC investigation into potential excessive pricing practices in the pharmaceutical industry [35].

Affordable access to new medicines is also high on the agenda of the World Health Organization (WHO) and of the Organisation for Economic Co-operation and Development (OECD)

- In 2013 WHO published the Guideline on Country Pharmaceutical Pricing Policies to support policy-makers in identifying and implementing policies to manage medicine prices [36]. In 2017, in collaboration with the Dutch Ministry of Health, Welfare and Sport, WHO held the Fair Pricing Forum to discuss challenges and the way ahead for fair pricing of essential medicines [37].
- In 2016 the French Minister of Health asked the OECD to coordinate an initiative to promote international high-level dialogue between stakeholders on access to innovative pharmaceuticals and sustainability of pharmaceutical spending. The OECD received a further request from Member countries to prepare a report that highlights the main challenges governments and other stakeholders face in ensuring appropriate access to new medicines to all those in need while maintaining incentives to innovate.

Policy levers in pricing, reimbursement and procurement

In pharmaceutical pricing, reimbursement and procurement, policy-makers have a tool-box of options, which have different consequences in terms of static and dynamic efficiency (ensuring value-for-money in the short term while keeping incentives to innovate).

In the European Union pricing, reimbursement and procurement of medicines are a competence of the Member States, but they still have to comply with the procedural specifications defined in the EU Transparency Directive (e.g. time-lines, justification for decisions and the possibility for marketing authorization holders to appeal) when making their decisions about what to cover and how much to pay for it [38].

Pricing, reimbursement and procurement decisions are separate from, and are taken after, the marketing authorization process, which has been harmonized for EU Member States and is carried out centrally by the EMA for new innovative medicines. A marketing authorization does not automatically grant public funding for a medicine; decisions about the price and (level of) reimbursement of new medicines are based on different criteria [39]. While the key evaluation criteria of marketing authorization, as defined by the EMA, are safety, quality and effectiveness, in pricing, reimbursement and procurement the medicine in question is assessed to see if it provides sufficient (added) therapeutic benefit and/or has an economic advantage over equivalent medicines already funded by the public payer. These decisions may also take into consideration budgetary constraints.

Along the life-cycle of a medicine, stakeholders engage in a number of activities, which span from development to promoting rational choices in prescribing and, in some cases, disinvestment (see Box 1). These activities can be divided into three phases: pre-launch, peri-launch and post-launch. Pricing and reimbursement policies, and supportive tools to inform policy decisions (e.g. Health Technology Assessment), are the major peri-launch activities. This policy brief will focus on policies implemented in the peri-launch phase, but will also consider, where appropriate and necessary, the whole spectrum of activities.

Policy questions

This policy brief focuses on the overall question: **How can pharmaceutical pricing, reimbursement and procurement be redesigned to ensure affordable and sustainable patient access to new medicines?**

More specifically, the following issues will be addressed:

- Which policies for pricing, reimbursement and procurement of new medicines are currently in place in EU Member States? What are their strengths and limitations?
- Which alternative approaches to these policies might help improve affordable and sustainable patient access to new medicines? Are they feasible?
- How could increased transparency on prices and cooperation between EU Member States provide a contribution to more affordable and sustainable patient access to new medicines?

This review will focus on new medicines and, geographically, on EU Member States and European Economic Area (EEA) countries. The methods and approach taken in pulling together the evidence are outlined in Box 3.

Box 3: Methods

This policy brief builds on evidence identified through a literature review as well as experiences shared by policy-makers in Europe in the context of the authors' work.

The literature review included both peer-reviewed scientific articles as well as grey literature (such as the WHO Europe report on access to new medicines [2]. To obtain more details and data, further searches were performed on specific issues. Additional evidence was identified using the bibliographic databases PubMed and Google Scholar and by reviewing the reference lists of key publications.

All the authors are closely involved in policy advice and knowledge brokering in Europe and beyond, so this policy brief also reflects the voices and key concerns of policy-makers. In particular, the policy brief draws on information and data collected from public institutions represented in Pharmaceutical Pricing and Reimbursement Information (PPRI) – a network of competent authorities responsible for pricing and reimbursement of medicines in 46, mainly European, countries [40].

This policy brief also builds on the evidence presented in previous policy briefs in the series, including those on health technology assessment (HTA) [41] and on voluntary cross-border collaboration in public procurement [42]. This policy brief was produced as a complement to a second policy brief that also explores the issue of sustainable access to affordable medicines by focusing on the issue of stimulating affordable innovation that meets patients' needs [1].

The evidence

EU Member States use a mix of policy instruments to regulate medicine prices, determine reimbursement and procure pharmaceuticals. Different policies are applied for outpatient and hospital settings, for market segments (reimbursed vs non-reimbursed medicines, on-patent vs off-patent medicines) and different groups of medicines (originator medicines with added therapeutic value vs. medicines with no added value, etc.). Authorities responsible for price setting or negotiation may consider criteria such as the (added) therapeutic benefit of a medicine (potentially in relation to its price), the price of the same medicine in other countries, or the price of similar medicines in the same country; they may also leverage the effects of competition or conclude product-specific agreements subject to defined conditions [39, 43].

Some pricing, reimbursement and procurement policies are commonly and even increasingly used for new, potentially high-priced medicines. Others are rather new and have been developed more recently to help protect financial sustainability. In the following sections, selected policies for high-priced medicines used in EU Member States are presented and discussed in relation to their benefits and limitations. The review starts with a discussion of the most commonly used policies, external price referencing (EPR) and managed entry agreements (MEAs), followed by tools to support policy-decisions (HTA and horizon scanning). Reimbursement and funding models for high-priced medicines (specific funds, amortization) and procurement approaches (tendering) are also presented, and the evidence compilation on existing policies concludes by reviewing post-launch measures that help improve the uptake of biosimilar medicines. Alternative approaches that have either been piloted or are being discussed are summarized at the very end of this brief, along with a discussion of the feasibility of their implementation in the future.

Prices are frequently based on medicine prices in other countries

A key factor that influences the price of a medicine is the price for the same product in other countries. As of 2018, 26 of the 28 EU Member States (the exceptions are Sweden and the United Kingdom), as well as Iceland, Norway and Switzerland, include external price referencing in their pricing legislation and apply it for at least some medicines [44, 45]. External price referencing is the practice of using the price(s) of a medicine in other countries to derive a benchmark or reference price for the purpose of setting or negotiating the price of the product in a given country [46]. It is different from internal price referencing (also known as internal reference pricing) that uses the prices of identical or similar medicines in the same country. Since the latter requires equivalent medicines as comparators, it is typically used in the off-patent sector. In a few countries, such as France and Germany, it is also used for new medicines with or without minor added benefits for patients. However, this policy brief focuses on on-patent high-priced medicines, so internal reference pricing is not discussed in detail.

While external price referencing is commonly used for pricing new medicines (and is less common in the off-patent market), its scope, relevance and methodological design vary across countries. Usually it is applied for pricing decisions in the outpatient sector, but in Denmark external price referencing only applies in the hospital sector. Even the 20 European countries that reported using external price referencing as the sole and main pricing policy employ additional instruments such as HTA and managed entry agreements (MEA) for reimbursement decisions, which is in line with the overall increasing use of HTA and MEA for high-priced medicines [47].

Methodological choices in external price referencing have an impact on its results (Box 4). The choice of reference countries is key and some countries tend to change these frequently [48]. In 2015 the countries most frequently referred to in the European context were France (referred to by 20 countries), Denmark, Belgium and Spain (n = 18), Italy and the United Kingdom (n = 17), as well as Austria, Germany and Slovakia (n = 16). The calculation method of the benchmark price is another major variable. The majority of countries (n = 15) take the average, or slightly modified average of the prices in comparator countries, while six countries choose the lowest price reported in the referenced countries. Given the lack of transparency about discounts granted to payers by manufacturers in confidential agreements, external price referencing refers to the official list prices. In May 2017 Austria changed its relevant regulatory framework, mandating the use of prices net of mandatory discounts required by law in external price referencing, instead of list prices [49]. Germany is the only country to report using price data that has been weighted by the estimated annual turnover of the product and the purchasing power parities of reference countries in its external price referencing methodology which is part of price negotiations between payers and manufacturers. Price data are usually supplied by the marketing authorization holder, and an increasing number of countries (n = 26) report validating this information [44, 45].

Box 4: Potential impact of changes in methodology for external price referencing on medicine prices

The 'Study on enhanced cross-country coordination in the area of pharmaceutical product pricing', commissioned by the European Commission, explored the potential impact of hypothetical methodological changes in existing external price referencing systems on financial sustainability and accessibility in all EU Member States, Iceland, Norway and Switzerland. Different scenarios were simulated against a base case (the 2015 status quo of external price referencing methodology for the outpatient sector). According to the study, price erosion after ten years of status quo would amount to an average 21.9% for the countries applying external price referencing.

The changes in methodology with the highest impact included (a) the consideration of discounted prices in other countries instead of list prices and (b) regular re-evaluations. Even if only the statutory discounts (i.e. discounts that are legally mandated and therefore public) in Germany, Greece and Ireland were taken into consideration, prices fell by 27% compared to the base case. A review with subsequent adjustment of referred prices every six months would decrease, on average, the prices in the countries using external price referencing by 6% compared to the base case, which assumes irregular revisions.

Changes to the basket of reference countries had no major impacts. Excluding the quintile of lowest income countries (as measured by GDP per capita) from all baskets slightly increased the price levels in a few other countries.

Adjusting prices according to purchasing power parities (PPP), which take into account the purchasing power in the involved countries, also changed the pattern. While a few high-income countries (particularly Switzerland) would see major increases in the level of prices set using external price referencing, prices in some lower-income countries would fall drastically, for instance by more than 40% in Bulgaria, Hungary, Poland and Romania [44].

Benefits and limitations

External price referencing provides an indication of where prices are in other countries in the form of a benchmark. This is seen as a major benefit by several policy-makers and explains the 'popularity' of this policy, particularly as a starting point for further negotiations. Another argument commonly used in this context is that external price referencing is 'easier' compared to other policies because its implementation is based on a defined framework, is technical, and does not involve any value discussions. There is some evidence that it can, in fact, contribute to cost-containment [50, 51, 52, 53, 54, 55], although this effect appears to decrease over time. Member States reported large savings on introducing external price referencing, but these declined in the longer run [44].

Major limitations concern the availability and affordability of medicines and price transparency. Delays of market launches of medicines, often of considerable duration, were observed in countries with lower price levels or market volume. In addition to market incentives, which push marketing authorization holders to launch first in markets with the highest potential, EPR provides an incentive to delay, or not launch, in lower-priced countries to avoid negative impact on prices in other countries [56, 57, 58, 59, 60, 61, 62, 63, 64].

Furthermore, the capacity of external price referencing to robustly inform policy-makers about the situation in other countries is strongly distorted by the fact that 'real' prices are often not known, since confidential discounts are frequently granted, particularly for high-priced medicines [65, 66]. There is no evidence for public payers that the promise that they would get 'the best deal' has been realized. One of the few available studies on confidential discounts confirmed that the expectation of improved access to oncology medicines in lower-income countries was not fulfilled due to higher confidential discounts: Central and Eastern European countries tended to have no or very low discounts while countries such as Italy and Spain were granted higher discounts [67]. By referencing official list prices instead of real discounted prices, payers risk overpaying. This information asymmetry also limits payers' purchasing power, for instance in a potential follow-up negotiation, since they are not on a level playing field with the marketing authorization holder who has the full picture of the prices in all countries where the medicine is marketed [68].

Several researchers and experts have argued for a pricing regime that includes supranational agreements with manufacturers and considers different income levels and ability to pay in countries leading to different prices being charged to different countries [69, 70, 71, 72, 73, 74]. More detail is presented in Box 5.

Box 5: Potential and limitations of differential pricing as a joint policy for EU Member States

Differential pricing – sometimes referred to as 'tiered pricing' or 'equity pricing' [69, 70] – consists of setting different prices for the same product in different countries. The rationale for applying differential pricing is to ensure access to essential medicines in lower income countries while providing companies with profits in higher income countries, in order to fund further investments in R&D. Different designs have been proposed. One is 'Ramsey pricing' or 'price discrimination', in which pharmaceutical companies achieve optimal pricing (from a business perspective) by differentiating prices according to purchaser demand elasticity in different market segments. It has been argued that these different prices could be achieved through confidential discounts determined and known by industry, in order to keep the level of official list prices high [75]. 'Ramsey pricing', however, is a commercial strategy used by companies, not a policy to be applied by policy-makers.

In practice, differential pricing negotiated by purchasers has been used in low- and middle-income countries, typically for certain therapeutic areas (HIV/AIDS, malaria) or specific medicines (vaccines). In these cases the purchasers were frequently international organizations (particularly UN agencies), and the differentiated prices were published [76]. While differential pricing was not always effective in ensuring access, there is evidence that for some lowest-income countries access to new medicines was improved in situations where it would otherwise have been unaffordable [76, 77, 78]. Differential pricing is not understood to be a tool for protecting financial sustainability. In fact, generic competition has proven to be more effective in bringing prices down [79, 80]. However, in recent years, differential pricing or similar policies have also been discussed and proposed in the context of higher-income countries, as a possible option to address availability and affordability issues.

Frequently mentioned barriers to the use of transparent differential pricing in Europe are the existence of parallel trade and the widespread use of external price referencing – both would undermine its impact. A study exploring the feasibility of introducing differential pricing as a policy in the EU concluded that solutions to address these limitations exist. Involved countries could agree on not using external price referencing for differentially priced medicines or modify their country baskets accordingly. Export bans and notifications, as already applied in some EU Member States that faced large waves of parallel exports, could also be imposed on the differentially priced medicines. However, the study concluded that, for the time being, differential pricing appears an unrealistic option in the EU for political reasons since it would require a strong political commitment from all EU Member States to agree on a collaborative framework and principles. Given the limited feasibility of transparent differential pricing in the EU, it has been suggested instead to include differential pricing traits, such as PPP adjustments of prices in other countries, in external price referencing methodology (see Box 4) [44].

Managed-entry agreements are increasingly used for improving access to new medicines

In light of the growing number of high-priced new medicines entering the market (some without evidence of added therapeutic value), public purchasers and payers have increasingly been concluding individual arrangements with the marketing authorization holder to 'manage' the adoption and funding of these medicines [2, 47]. In Europe the umbrella term 'managed entry agreement' (MEA) is used to describe these arrangements. An MEA is defined as 'an arrangement between a [pharmaceutical] manufacturer and payer/provider that enables access to [i.e. coverage or reimbursement of] a health technology subject to specific conditions'. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies and/or to manage the adoption of technologies in order to maximize their effective use, or limit their fiscal impact [81].

MEAs can take a variety of forms. They can be agreed as simple price discounts, price-volume agreements (i.e. the definition of a tiered repayment structure for different levels of forecast sales, with repayments, or price cuts, at the end of the defined period) or utilization capping (i.e. if more doses above a predefined threshold are required, the manufacturer provides them free of charge). These types of MEA fall under the category of so-called financial-based or non-health outcome-based MEAs. Performance-based or health outcome-based MEAs link the final price of a medicine to health outcomes observed in real life. Performance-based schemes include, for instance, 'outcome guarantees' (i.e. the manufacturer provides rebates, refunds or price adjustments if the medicine fails to meet the agreed outcome target) or 'coverage with evidence development' (i.e. the medicine is reimbursed if additional data are gathered in the context of clinical care to further clarify the effect of the medicines). Performance-based MEAs tend to be accompanied by patient registries to measure post-marketing clinical outcomes. There are different taxonomies to describe the various MEA types [81, 82, 83, 84], but the distinction between financial-based and performance-based MEAs is widely acknowledged.

Confidentiality plays a major role with regard to MEAs. While economic aspects (i.e. the actual discount or price agreed) tend to be confidential for all MEAs, in some countries further relevant information, including whether an agreement has been concluded for a given medicine, is not publicly available (e.g. France); this information is sometimes not even shared with other competent authorities not involved in this particular negotiation (e.g. the Czech Republic) [85].

As a result, we do not have a complete picture of the use of MEAs in European countries. However, MEAs are increasingly being used, particularly for cancer treatments and orphan medicines [86]. The majority of agreements concluded are financial (mainly flat discounts), but there appears to be an increasing implementation of performance-based MEAs. To illustrate the range of MEAs currently implemented, Table 1 shows examples from selected countries in Central/South Eastern Europe based on a recent survey.

Table 1: Types of MEA implemented in selected Central/South Eastern European countries

	Financial				Health outcome-based agreements		
	Discounts	Price-volume agreements	Free doses	Pay-back	Bundle and other agreements	Payment by result	Coverage with evidence development
Bulgaria	X	X		X	X		X
Croatia	X	X	X	X	X	X	
Czech Republic	X	X		X		X	
Estonia	X	X	X	X		X	
Hungary	X		X	X	X	X	
Latvia		X		X		X	
Lithuania		X		X		X	
Poland	X	X			X	X	
Romania		X				X	
Slovenia	X	X		X	X		

Source: adapted from [87]

Benefits and limitations

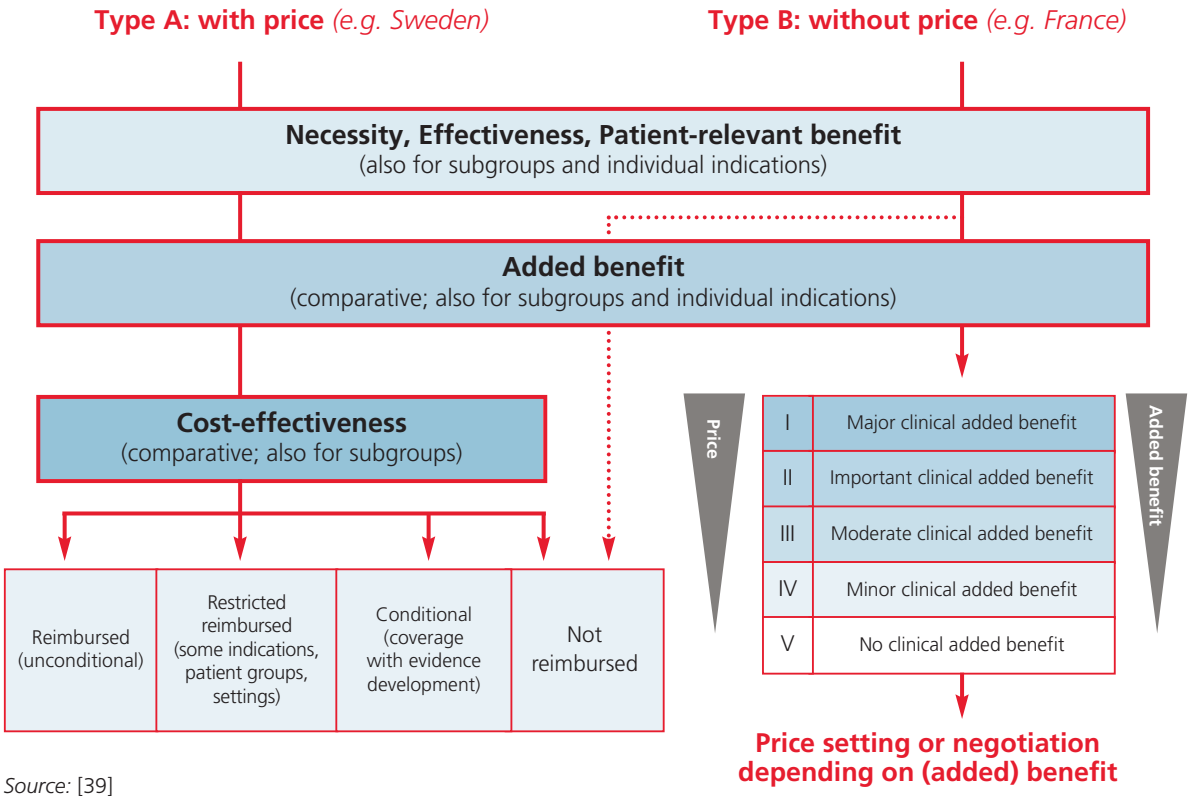
MEAs are considered an opportunity to facilitate access to high-priced medicines that would otherwise be unaffordable. They provide earlier accessibility through publicly funded health care systems (even if, as in the case of performance-based agreements, added therapeutic value has not yet been fully proven), while providing fail-safes if the medicine does not deliver. Thus, they allow the public payer to manage some uncertainty [88]. On the other hand, manufacturers are given the opportunity to price-discriminate [89, 90]. If set up appropriately (e.g. together with patient registries), performance-based MEAs enable the collection of real world clinical data that are needed to assess treatment effects and to inform sounder decisions [91].

A major limitation of MEAs is linked to the confidentiality of data. While MEAs allow for the agreement of lower prices than those published, the exact difference in these amounts is unknown. There is even the risk that a marketing authorization holder asks for a high initial price in anticipation of an MEA [83]. The issue of information asymmetry, as with external price referencing, applies here as well [68]. The official list prices of medicines under MEAs do not offer correct information. Even if the discounts and price-reducing agreements were disclosed, it would be difficult to trace back the 'real price' in complex arrangements.

Furthermore, MEAs are linked to high transaction and administrative efforts and costs [86, 92]. Their implementation therefore needs to be accompanied by a clear disinvestment strategy when updated data support the discontinuation of funding (at high prices) of a medicine under an MEA. However, a decision to that effect can still be difficult to implement if patient expectations have been created [93].

Given the limitations in access to data, there are few evaluations of MEAs [84]. While earlier access to medicines under MEAs has been demonstrated [94, 95], we lack evidence about their capacity to protect financial sustainability and mitigate uncertainty. For instance, the Belgian research institute KCE intended to perform a full evaluation of MEAs in Belgium but was unable to proceed despite an explicit commitment to respecting the confidentiality of these agreements; instead their analysis had to be based solely on public information following threats of legal action from the industry [96]. One clear limitation of performance-based MEAs is that observed outcomes are not shared among stakeholders and the scientific community. In this way, the initial goal of reducing uncertainty is not fully met. The design of performance-based agreements can probably be improved as few principles have been explicitly defined and published so far [81, 97, 92]. Policy-makers have acknowledged that they developed the specifics of their MEA approach as it was being implemented.

Figure 3: The two simplified roles for HTA



Source: [39]

HTA has a role in pricing and reimbursement of new medicines, but its institutional setting and application in decision-making differ between European countries

Health Technology Assessment (HTA) is 'a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a 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' [98]. As health technologies, pharmaceuticals are one of the main fields of application in HTA.

As a policy-informing tool, HTA has been gaining importance, particularly in its application for high-priced medicines [2]. However, not all European countries use it the same way (Figure 3, p.15). While it is used to primarily steer decisions about the level of reimbursement and/or price in some countries (e.g. France, Italy, the Czech Republic), in other countries HTA processes result in a decision on whether to reimburse a new product (with or without restrictions) or to reject funding altogether (e.g. Sweden, England, Norway) [93].

The use of HTA also varies between EU countries along other dimensions: (a) who is involved in HTA; (b) what HTA entails (methods and procedures); and (c) how HTA is applied and implemented [41]. For instance, while in some countries a governmental agency is tasked with carrying out assessments, in others more than one institution is involved in HTA, with several academic organizations being involved, whose findings are not systematically embedded in final decisions on pricing and reimbursement [41, 39].

In Europe, HTA agencies have been cooperating in the European Network for Health Technology Assessment (EUnetHTA) since its inception in 2007. The main goal has been to develop a common methodology for evaluating the clinical aspects (effectiveness or comparative effectiveness) of new technologies. The so-called "Core Models for HTA", developed by the EUnetHTA collaboration for different types of health technologies, provide practical guidance for performing health technology assessments [99]. Directive 2011/24/EU formalized the need for an EU-wide network for HTA [42]. On 31 January 2018 the European Commission published a draft regulation envisioning the centralized evaluation of clinical benefit for all new medicines and certain high-risk medical devices with a simultaneous obligation for Member States to refrain from carrying out duplicative evaluations at country level. The draft legislation [33] stresses that overall coverage recommendations (including value judgements) and final decision-making would remain a Member State competence. It further clarifies that details on the processes and methods of centralized assessment would be further regulated by the EC in due course. The proposed regulation and related discourse are discussed in the companion policy brief [1].

Benefits and limitations

HTA is crucial for providing robust data to inform reimbursement and pricing decisions, as well as treatment guidelines. However, HTA is only a technical tool, which cannot, in isolation, make decisions. For instance, countries using economic evaluation in their HTA process to make coverage decisions should in principle define a 'cost-effectiveness threshold' beyond which they would not cover products [100]. However, public payers have been reluctant to fix and publish such thresholds and have not been able so far to send clear and consistent messages about their willingness to pay for different 'attributes' of pharmaceuticals, such as rarity or severity of the disease or response to unmet need. Payers have sometimes accepted high prices for low benefits, most commonly for orphan medicines or cancer treatments [101, 102]. This creates uncertainty for future pricing or reimbursement decisions, which is a problem for both payers and pharmaceutical companies. It also creates some confusion about what payers define as 'value'. New approaches towards determining the value of health care interventions are being proposed and trialled, including multi-criteria decision analysis [103]. Such methods allow an explicit consideration of stakeholder and public preferences in trade-offs. In recent years the concept of value-based pricing, i.e. basing the price of a (new) medicine on the benefit it provides rather than 'what the market will bear' has gained in importance and application in Europe and internationally [104]. At the same time, the concept of value-based pricing has raised a lot of debate, not least because there is no widely accepted definition [105]. The idea is further described in Box 6.

Box 6: Value-based pricing

Value-based pricing, in other sectors of the economy, refers to one of the strategies firms can use to set the prices of their products. More precisely, when a company sets a price with this method, it calculates and tries to earn the *differentiated worth* of its product for a particular customer segment when compared to its competitors. Setting such a price requires (a) referring to a specific market segment; (b) identifying attributes that differentiate this product from existing competitors; and (c) understanding how consumers value this differential or how much they are willing to pay for it [106]. Market research, such as consumer surveys, can help to determine this amount. A company can, for instance, determine how much a consumer is willing to pay for a TV with a larger screen – all other things being equal – or how much a consumer values a specific brand in fashion products.

Pharmaceutical companies have been using this approach since the 2000s. Public authorities have more or less adopted this terminology, although the same words clearly have different meanings for different stakeholders. In many countries, governments or compulsory health insurance schemes are the main payers for 'covered' pharmaceuticals. Their willingness to pay (on behalf of tax-payers) for a new pharmaceutical is therefore what companies need to understand in order to propose a price that will be considered acceptable for public funding.

In practice, payers' willingness to pay is often determined through HTA. Many dimensions may potentially be taken into account when assessing the *value* of new pharmaceutical products: improvement in length and quality of life obviously plays a central role, but comfort

of use or cost-savings in other parts of the health system or gains in labour productivity for patients and carers can also be of importance. Countries most often adopt a 'health system' perspective, rather than a wider societal perspective when making coverage or pricing decisions, which means that they mainly consider costs for health care payers and added therapeutic benefits for patients (most commonly quantified by means of quality-adjusted life years – QALYs) in HTA [107].

The need for horizon scanning should not be underestimated

The case of sofosbuvir for treating hepatitis C was a turning point in the debate on pharmaceutical policies and is often referred to by policy-makers as the 'wake-up call'. It clearly demonstrated the need to be prepared for medicines in the pipeline; procurers and purchasers openly admitted that they were not ready for sofosbuvir [108].

Policy-makers were blind-sided by the marketing authorization of sofosbuvir and its high price tag, its enormous budgetary implications and the product's potential to challenge the use of existing analytical instruments such as cost-effectiveness analysis. This experience was the starting point that put horizon scanning high on the pharmaceutical policy agenda. Horizon scanning is related to neither pricing nor a specific policy per se, but it is a supportive tool to improve policy-makers' preparedness. Horizon scanning as a technique is not new but it has traditionally been carried out by research institutions, mostly as an academic exercise disconnected from policy [2]. There are few examples when horizon scanning has been used to support the decision-making of competent authorities, e.g. the horizon scanning project in Veneto, Italy [109], the English National Horizon Scanning Centre [110] and activities at the regional level in Sweden's Stockholm County Council [111]. After the sofosbuvir experience, some countries (e.g. Norway, France) started building horizon scanning systems [2], and in some of the voluntary cooperations on pharmaceutical policies between EU Member States (e.g. the BeNeLuxA collaboration, the Nordic Pharmaceutical Forum), approaches to set up a joint horizon scanning system have been discussed [42]. Recently, the Netherlands published a preliminary list of medicines in the pipeline identified through a horizon scanning mechanism [112].

Benefits and limitations

Horizon scanning is a valuable supportive tool for budget impact preparedness. As such, it supports the prioritization process for the allocation of funds. A possible concern raised by policy-makers relates to the ethics around the disclosure of information to terminally-ill patients about possible treatments still under development.

Establishing and maintaining an effective horizon scanning system is an extremely time-intensive and costly exercise. Substantial efforts have to be invested, not least because of the limitations of public information [113]. The issue of information asymmetry between authorities and industry is also critical in this context, as horizon scanning relies on the limited information that the industry provides about medicines in the pipeline.

Specific funds have been established to cover the costs of high-priced medicines

Because the costs for some new, high-priced medicines could not be borne by the existing pharmaceutical reimbursement system, specific funds have been established in some European countries to provide alternatives to established rules and enable reimbursement for defined medicines. For instance, at the beginning of 2017 Italy introduced two so-called 'funds for innovation' – one for cancer medicines and one for non-oncology medicines. These funds are each allocated €500 million from the national budget to support the regions, which normally procure and pay for medicines [114].

However, the best-known example in this area is the Cancer Drug Fund in England. The Cancer Drug Fund was introduced in October 2010. It was originally conceived as a temporary measure, until value-based pricing for medicines kicked off (this was planned for 2014, but was eventually not implemented). The aim was to give cancer patients access to medicines that are recommended by doctors but that would normally not be reimbursed by the NHS in England, either because the National Institute for Health and Care Excellence (NICE) recommended against it, or because their appraisal by NICE had not yet been carried out. While an initial fund of £50 million (€63 million) was budgeted for the first year, spending rose to well over £200 million in 2013–14 [115]. The scheme was extended for two more years and eventually reformed in 2016 [116], following severe criticism about the lack of demonstrable value of the medicines it financed [115]. Research showed that the Cancer Drug Fund did not improve access to new, cost-effective cancer medicines, but was predominantly used for medicines deemed not cost-effective [117]. Having spent a total of £1.2 billion (€1.6 billion), the Cancer Drug Fund was turned into a mechanism for 'managed access': it funds cancer medicines for up to two years, and NICE assesses them during this time [118].

Benefits and limitations

While creating a separate fund for medicines that would be otherwise unaffordable may improve access, there is a risk of funding medicines that are not cost-effective. This entails an opportunity cost for health systems, as they displace funds from more cost-effective health care interventions. In addition, in the absence of an evaluation, pharmaceutical companies could be incentivized to charge higher prices [119]. As a result, spending for such funds introduced for specific therapeutic groups tends to increase over time. Evaluating the experience of existing initiatives such as the Cancer Drug Fund in England, as well as Italian and French innovation funds, could help avoid unnecessary pitfalls.

Amortization mechanisms might help mitigate large upfront costs of innovative medicines

As well as modifying existing policies to better deal with such situations, the concept of amortization has also been recommended by researchers and piloted in individual cases of otherwise unmanageable budget impacts [120]. Amortization refers to some mechanism for paying for a large upfront cost by making a number of smaller payments over a period of time. This model is already in use for medical equipment: in the United States payers often cover the cost of the equipment in instalments, paid over the time horizon of utilization [121].

Benefits and limitations

Amortization mechanisms cannot by themselves help determine the 'right price' of new treatments. Instead, by spreading financial flows over time, they could even be 'distracting' from value-based pricing [104]. When combined with performance-based agreements, they can potentially help in aligning the cost of treatments with their long-term economic benefits, thereby allowing payers to fund innovative therapies while balancing their budgets within a single year [120, 122]. It is not yet clear whether amortization mechanisms will emerge as a viable option for managing the affordability of, for example, gene therapies on a more regular basis. The proliferation of such agreements, however, with their cumulative effect, might only postpone (or defer) sustainability issues; more experience (and thus, more pilots) will be needed before mainstream implementation can be considered [120, 122].

As a procurement approach, tendering for high-priced medicines is usually applied in the hospital sector

Tendering is one approach to procurement that is based on a formal and competitive procedure, aiming to achieve lower prices by awarding the contract to the best offer. In European countries tendering has usually been applied in the hospital sector, at both individual hospital and hospital group level, or through voluntary pooling of regional hospital procurement at the national level by procurement agencies. There has been increased collaboration in tendering and a shift from hospitals to the regional and national levels in several countries. National procurement agencies in Denmark (Amgros – see Box 7) and Norway (LIS/HINAS) have been reporting efficiency gains and lower prices through their centralized hospital tendering [123, 124, 125]. This is partially attributed to the shift in power in favour of the national procurement body, which tenders for a much larger market, as well as the use of new types of tendering procedures (Box 7). In the outpatient, off-patent sector, some European countries (e.g. Germany, the Netherlands, Slovenia, Romania) have implemented tender systems and auction elements to enhance competition [126, 127, 128]. Norway recently introduced tendering for on-patent products, notably for medicines for hepatitis C treatment, but evidence on the impact of the policy is pending.

Benefits and limitations

Tendering is a highly competitive procurement mechanism during which purchasers can use their bargaining power. There is evidence of sometimes substantial savings from lower prices that might be achieved through competition, but mainly when generics or biosimilars exist. As competition is a prerequisite for tendering, this procurement policy requires careful assessment of the feasibility of therapeutic substitution in the case of some new on-patent medicines. Overall, the success of tendering, and procurement in general, can also be linked to the prospect of reaching a larger market. Given the benefits of central procurement at the national level, further contributions to financial protection could be expected from cross-country collaboration in tendering (or in procurement more generally). However, as with any collaborative approach to the procurement of medicines, differences in legal provisions and regulatory procedures pose a challenge. While the EU Joint Procurement Agreement (JPA) on medical countermeasures offers a framework for collaboration [42, 129], the European Commission clarified in July 2015 that the scope of the JPA cannot be extended beyond vaccines and antivirals against pandemic influenza [130]. This has limited the potential for using it as an instrument to address the challenge of high-priced medicines in the future.

One of the concerns with the competitive nature of tendering is a 'possible race to the bottom' of prices, potentially leading to a withdrawal of companies from the market and subsequent medicines shortages. While it has been shown that shortages are, in several cases, attributable to other causes [131], it may be prudent to design tendering and procurement processes strategically and to maintain a 'healthy market' [132], as another possible consequence of market concentration is the risk of higher prices down the line. Finally, preferred medicines strategies linked to periodic tendering practices may mean that patients have to change their medication multiple times; problems with switching have been one of the main contributors to prescriber opposition towards tendering. In Belgium, demand shifted to non-tendered medicines following a change in physician prescribing behaviour linked to the introduction of tendering policies. This ultimately led to the halting of related efforts [128].

Box 7: Centralized procurement for public hospitals in Denmark

In 1990 the central pharmaceutical procurement agency Amgros was established as a service for the (now) five Danish regions. It is owned by the regions and procures medicines for all public hospitals. Depending on the stage of the life-cycle of a medicine (e.g. on-patent, off-patent), Amgros applies different tendering methods. Amgros has made several changes to its tender structures in order to optimize the balance between negotiating good prices, ensuring patient safety and safeguarding the availability of essential medicines. The four tender contracts used by Amgros are framework contracts, fixed volume tender contracts, regional tender contracts and contracts for new products (with tailored criteria like confidential prices). For region-specific tenders, usually one supplier wins the tender in all regions as, so far, few suppliers bid for these smaller tenders.

For the 25 years that Amgros has existed, it has reportedly saved billions of Krone for Danish public hospitals. For the year 2015, savings of approximately €314 million (approximately €6 per resident) were estimated; this was attributed to the centralized procurement structure in conjunction with the establishment of the Danish Council for the Use of Expensive Hospital Medicines. The latter has been assessing the clinical costs and benefits of expensive medicines and helps guide the selection of medicines by Amgros and clinicians [132, 133, 134].

Biosimilar medicines are considered promising cost-saving alternatives, but their uptake has not yet achieved its full potential

Biosimilar medicines are seen as a promising area because they offer a lower-priced solution to high-priced biological originator medicines [135]. As of October 2017, 36 biosimilar medicines have been approved by the EMA [136]. Although this number is high compared to the United States, the uptake of biosimilar medicines varies considerably among European countries and is below 10% for some products in certain countries [3].

Most EU Member States apply similar pricing policies to biosimilar medicines as to generics: they link the price to that of the originator medicine, although usually at a lower percentage discount than they do for generics [137]. Norway, however, has been using tenders and has achieved prices of up to 80% lower for biosimilar medicines compared to the price of originators [138]. Considering the high uptake of these medicines in Norway, it is safe to assume that substantial savings could be made elsewhere.

A study published in 2017 identified key drivers for the penetration of biosimilars in European markets. It found that incentive policies (to incentivize doctors to prescribe, pharmacists to dispense, patients to ask for biosimilars, etc.) were positively correlated to biosimilar uptake, while pharmaceutical expenditure per capita and high generic use showed a negative correlation. Biosimilar price discounts for original biologics, the number of analogues and distribution channels were not correlated with biosimilar uptake [139].

Benefits and limitations

In principle, the increased use of biosimilar medicines only has advantages as safe, effective and high-quality biological solutions are offered at lower prices. However, savings through biosimilar medicines cannot be reached solely through pricing policies. As is the case for generics, the uptake of biosimilar medicines needs to be encouraged, for instance through demand-side measures such as biosimilar switching. However, while generic substitution has been widely implemented in European countries, this is not yet the case for biosimilar substitution at the pharmacy level [140].

Any measure to promote the uptake of biosimilar medicines will only be successful if prescribers and patients have no doubt about their quality and effectiveness. While there is trust in the quality of biosimilar medicines, because they are evaluated in the marketing authorization process, limited knowledge about their effectiveness is likely to have contributed to the continued prescribing of originator biological medicines, despite the availability of biosimilars, even for new patients. Studies that investigate the safety of switching to biosimilars provide important evidence in this direction (e.g. the Norwegian NOR-SWITCH study evaluating the switch from originator infliximab to biosimilar infliximab [141].

Policy implications

Building on the discussion of benefits and limitations of individual policy tools, this section summarizes overarching barriers and limitations in the existing pharmaceuticals pricing, reimbursement and procurement framework and suggests different avenues for solutions, with different feasibility levels.

Identified barriers and limitations for the existing pharmaceutical pricing, reimbursement and procurement framework

Intransparency

A major limitation is the lack of knowledge among policy-makers and procurers about the extent of the discounts that marketing authorization holders grant to other countries. They are expected to trust the promise that they get 'a good deal' without having any possibility for verification. As shown above, the unavailability of 'real price' information in other countries has negative consequences for policies such as external price referencing. Furthermore, this information asymmetry impacts the bargaining power of public payers and procurers in price negotiations.

Another important lack of information concerns the actual costs incurred by companies for developing and producing medicines, which also limits public authorities in their price negotiations as they once again have no possibility of verifying the figures for R&D and production costs purported by marketing authorization holders. While prices are not set based directly on R&D costs, investments in R&D are always brought forward by industry as an argument for higher prices.

Intransparency does not only affect pricing. Asymmetry of information, also regarding the status and results of clinical trials, may affect the elaboration of clinical guidelines, and the choices of individual prescribers and consumers, as well as the results of HTAs.

Imbalances in negotiation power

Information asymmetry related to 'real' prices, discounts and procurement conditions, to costs for research, development and production as well as medicines in the pipeline, reflects one aspect of the imbalances in market power: national procurers and payers (and in some cases, actors at regional or provider level, e.g. hospitals) meet globally acting pharmaceutical companies that have the overview of their product portfolio worldwide.

In many countries, even higher-income countries, the staffing levels of public authorities tasked with HTA, pharmaceutical pricing, procurement and reimbursement are low. The global financial crisis has put further pressure on authorities.

Besides under-staffed authorities and over-worked civil servants, capacity-building is another issue in this area. Higher salaries in the private sector might motivate qualified experts to decide against joining public authorities.

Under these circumstances, the implementation of new policies, changes in existing policies, or initiatives to increase transparency and strengthen capacity and purchasing power, for instance through collaboration, require substantial effort and personal commitment from participating staff on top of their routine workload.

Fragmentation of the pharmaceutical sector

The limited negotiation power of some purchasers is also due to the 'small markets' they represent, which might not be attractive for industry. In addition to the 'small markets' of EU Member States with smaller populations, the fragmentation of the pharmaceutical sector within a country (different payers, or different funding mechanisms for the outpatient and inpatient sectors) can also considerably limit the bargaining power of public procurers. This fragmentation does not incentivize the exploration of collaborative procurement strategies among purchasers across the sectors for the benefit of patients. Purchasers are held accountable for containing the budget of their entity, and they thus might be inclined to argue for a shift of high-cost treatment onto the other sector.

Legal and organizational barriers

Existing legal, organizational and financial frameworks – at EU as well as at country level – may be a barrier both to implementing specific policies (e.g. legislation may only allow the use of tendering under specific conditions) and to further developing them. For example, 'parallel' trade, which is enabled through the EU legal framework on the internal market, is mentioned as a substantial obstacle for the implementation of differential pricing, but some solutions (e.g. export bans or notifications) are conceivable.

Solutions and approaches to address identified limitations

Existing pricing, reimbursement and procurement policies all have their limitations, but there are possibilities for fine-tuning these instruments and developing them further. In addition, new avenues and models could be explored. Annex 1 identifies potential levers to modify existing policies, and Annex 2 considers alternatives that expand on existing policies and introduce new concepts and elements. While there is some experience with some of the latter, no evidence on feasibility or effectiveness is yet available for others. Annexes 1 and 2 both present existing evidence and discuss requirements for the successful implementation of each approach.

In technical terms, the proposed solutions largely belong to three categories: methodological advances, collaborative approaches and consideration of the pharmaceutical life-cycle.

Methodological advances

Benefits from the existing pricing, reimbursement and procurement policies could be realized in a more effective manner if some key principles were taken into consideration. Policy-makers should ensure that policies are regularly

monitored, reviewed, evaluated and subsequently adapted and amended if deemed necessary. For new policies, this can be helpful in understanding whether they have been able to achieve their intended objectives; best practices and principles can be identified for future use, also to be shared with other countries. For instance, the development of evidence-based, validated good practice principles for MEAs would be useful. Another argument supporting the regular application of evaluations and reviews is that the effectiveness of initially successful policies may 'fade out' over time. To ensure the regularity of such reviews and the implementation of subsequent changes, an appropriate legislative framework as well as governance and administrative structures is needed.

Methodological choices within a given strategy can have an impact on its outcomes, as this review has illustrated for the example of EPR. If payers referenced to real discounted prices instead of list prices as they currently do, they could achieve lower medicine prices. Given the confidentiality of negotiated discounts, such an approach appears not to be feasible but there is the possibility to at least consider mandatory manufacturer discounts that are in the public domain in some countries. Austria changed its legislation to consider the mandatory (published) discounts in other countries. Adaptions of the methodological design of existing policies are a way forward when more far-reaching changes and new models are not yet feasible. For instance, since it is not realistic that EU Member States will agree on a fully fledged differential pricing model, individual countries could, as a unilateral measure, build PPP adjustments of prices into the EPR methodology.

Collaborative approaches

A highly promising avenue is collaboration; it can address different topics and policies, can have different intensity levels and can involve different actors. It may range from knowledge exchange about experiences with policies (good practices and less effective implementation) to technical cooperation in areas such as horizon scanning and HTA, to joint price negotiations and procurement. Collaborative approaches could be applied at both within and across countries, through bilateral and multilateral collaborations or under the framework of the European Commission (as in the area of marketing authorization in the EU). Collaborations can ensure a broader perspective along the pharmaceutical life-cycle, for instance with improved coordination between representatives of the different 'worlds' including pricing, reimbursement, procurement, HTA and marketing authorization. In recent years the establishment of several new cross-country collaborations of different formats that are related to pricing, reimbursement and procurement has been observed, and further cooperative models are likely to emerge. Frequently mentioned examples of cross-country collaboration in this area are the Valletta Declaration of Mediterranean Countries, who aim to procure jointly, and the BeNeLuxA collaboration of Belgium, the Netherlands, Luxembourg, Austria and – since the end of June 2018 – Ireland that collaborates in the areas of horizon scanning, HTA, information sharing and joint negotiations [42, 93, 142].

While moving forward in collaborative approaches (in technical areas, joint action or policies) must carefully balance the competences of the European Commission and the EU Member States and requires high and continuous commitment by national policy-makers, cooperation has proven to be an effective tool to address a number of the barriers mentioned above, such as imbalance in negotiating power, limited transparency and market fragmentation.

The recent Austrian health care reform has proposed the establishment of a 'Clearing House' for medicine prices. Through a trusted third party that collects data of discounted prices from different public purchasers and shares them in an anonymous and aggregated format, this mechanism is intended to improve price transparency while the existing framework of confidential price negotiations is still in existence. This is an example of intra-country cooperation that could be applied between countries as well.

Consideration of the pharmaceutical life-cycle

To ensure affordable and sustainable patient access to new medicines, there have been calls to interpret pharmaceutical policy as a comprehensive concept that goes beyond the core policies of pricing, reimbursement and procurement. Besides policy-supporting tools such as HTA, pre-launch activities (e.g. horizon scanning) and post-launch measures (e.g. actions to increase the uptake of biosimilar medicines) have an important role to play as accompanying levers.

More disruptive approaches challenge the current framework of incentives for innovation, mainly based on intellectual property rights and the ability to charge 'monopoly prices'. For years, there have been calls for alternative funding models that would ensure access to medicines with very low prices (closed to marginal production costs). In such 'de-linkage' models, R&D investments would be prioritized in terms of clinical needs instead of prospects of profitability. Some initiatives (e.g. the Drugs for Neglected Diseases initiative (DNDi)) have been trialled and have delivered 'proof of concept' by succeeding in developing medicines at considerably lower costs. Such models were initially designed to create incentives in therapeutic areas with high unmet needs and low prospects of profitability.

Conclusions

Currently, policy-makers in European countries use a range of measures for pricing, reimbursement and procurement out of a tool-box of available policies. In doing so, they aim to balance ensuring affordable access to medicines, long-term financial sustainability and reward for innovation. At the same time, it has become clear that existing policies have their limitations since these objectives cannot be met in several EU Member States.

This policy brief showed that, while European countries tend to use more or less the same policies to price, procure and fund medicines, they have implemented them in different configurations. There is evidence, at least for some, that the exact design of the policy can impact its results. Thus, as a first step, policy-makers could revisit the measures already in place and evaluate whether their methodology could be changed to better achieve results in line with defined policy objectives. Although the potential for improvement through such adjustments should be explored, further measures and initiatives appear to be urgently required to fundamentally tackle high prices for medicines that have a considerable impact on public pharmaceutical expenditure.

As a mainstream issue, collaborative approaches have been proposed as a way forward in many areas. In particular, measures to overcome information asymmetry and fragmentation and to strengthen the bargaining power of public payers appear to be of key importance. As demonstrated, intransparency affects several aspects of pricing and reimbursement (e.g. 'real prices', production costs, R&D costs) and could be addressed through different approaches.

The discussion of extreme price tags and their impact on budget and/or spending efficiency has moved beyond the core policy models around pricing, reimbursement and procurement. Besides technical tools to inform policy-making, such as HTA, the debate has increasingly involved the consideration of so-called pre-launch measures (e.g. horizon scanning) and post-launch measures (e.g. measures to enhance the uptake of biosimilar medicines). Furthermore, a call for creative thinking has repeatedly been made in recent years that will challenge the existing 'business models' and encourage policy-makers to change the way in which innovation is financed.

There are strong indications that a more comprehensive approach is an effective pathway to ensuring long-term sustainability. Since there is still limited evidence about some new initiatives, it is key that they are accompanied by systematic evaluations in order to allow for lesson learning and to identify best practice models to inform future policies that seek to ensure affordable and sustainable patient access to new medicines.

Annex 1

Policy options for reinforcing financial sustainability with high feasibility, building on existing measures

Policy option	Description	Evidence and experience	Prerequisites for implementation
Strategic procurement	Strategic procurement considers different options depending on the life-cycle of a medicine and its position on the market (competition).	There is evidence about the effects of strategic and less strategic procurement on cost-containment and access to medicines [132].	Capacity-building is required (WHO Europe has started some initiatives in this area [132]).
Regular price and/or reimbursement revisions	Over time, given new (clinical) evidence and other developments (e.g. competitors coming onto the market), prices and reimbursement status and extent could and should be adjusted. The element of regular revisions can be built into different pricing, reimbursement and procurement measures.	There is good evidence on the savings potential of price and reimbursement revisions (e.g. simulations in the context of EPR [44]). There are indications that regular revisions foreseen in law or regulations are not always undertaken due to resource constraints; there have been cases of payments or price reductions granted by the industry in return for non-revision. The element of regular revisions is likely built into performance-based MEAs. Experience has shown challenges for authorities and payers due to the high level of administrative resources required and costs.	Could be time-intensive: ensuring sufficient resources and, if indicated, the provision of data from other parties such as marketing authorization holders. Regular revisions (without excluding the possibility for ad hoc revisions) in law or regulation. A coordinated approach when pricing and reimbursement decisions are taken by different institutions is necessary. Needs to be built into a more specific and comprehensive disinvestment strategy (including communication to patients and the public). Ideally requires good quality patient registries with limited information gaps as the basis for the assessment (consider motivating health professionals to ensure high quality documentation).
Consideration of statutory discounts, ability-to-pay and further improvements in EPR	While the principal limitations of EPR continue to exist (particularly those related to ensuring access), appropriate methodological adjustments can contribute to savings. Even if discounts are confidential, they can be estimated (e.g. based on literature for specific therapeutic groups). Statutory discounts (i.e. mandatory discounts based on law the extent of which is published) can always be considered.	There is evidence on cost-containing effects [44, 59]. The EPR landscape in European countries shows that reference countries were selected strategically to balance between lower-priced countries and higher-priced countries (which will have price information available at an earlier stage), and that the concept of alternative (back-up) countries was considered in some cases. Different algorithms for the calculation of the reference prices are taken into account. However, there is no evidence yet on the effect of incorporating estimated confidential discounts. In 2017 Austria changed its legislation to consider mandatory (published) discounts.	It might require legal or regulatory changes, depending on each country's framework. In order to account for the different income levels in the reference countries, prices could be weighted for purchasing power parities or gross domestic product. Germany has such a provision in its EPR legislation.

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Policy option	Description	Evidence and experience	Prerequisites for implementation
Improved coordination in HTA	HTA is a useful tool for determining the value of new medicines. A more coordinated collaboration would bring benefits from synergies in this resource-intensive exercise, e.g. by reducing duplication of work.	Its possible advantages have been well documented both at national and supranational levels [42, 143].	A more coordinated collaboration on the evaluation of clinical aspects appears feasible, not only in voluntary cross-country collaboration but also in more formally coordinated collaboration at EU level (EUnetHTA). Depending on the level and set-up of collaboration, appropriate legal provisions and sufficient earmarked resources are required. The current draft legislation on strengthening HTA collaboration in Europe proposed by the EC on 31 January 2018 [33] could be a starting point. The delineation between mandatory/binding centralized items and Member State competence should be carefully considered, along with the safeguarding of methodological rigour and sufficiency of evidentiary requirements.
Increased use of biosimilar medicines	Biosimilar medicines are an effective instrument to support financial sustainability.	Good evidence on the possibility of achieving low prices through strategically well-designed policies (e.g. tendering with the prospect of sales volumes for companies), as well as the need to encourage sufficient uptake.	Possible legal issues in some countries related to tendering (e.g. a public payer not being allowed to carry out tenders on a regular basis). Important to work on measures to ensure professionals' trust in and knowledge about biosimilars in order to increase uptake.

Annex 2

Options expanding on existing experience and introducing new elements

Policy option	Description	Evidence and experience	Prerequisites for implementation
Joint procurement	Collaboration between public purchasers who join forces in negotiations, with the intention of benefiting from greater purchasing power and less information asymmetry. It does not necessarily lead to the same price for all parties involved.	Under the JPA, joint procurement for vaccines and influenza medicines can be carried out. Pilots for joint procurement under the BeNeLuxA initiative have started.	There are major challenges with regard to divergent legal, regulatory and organizational procedures. Once these have been successfully overcome, the model might offer good opportunities, providing large markets.
'Clearing House' to inform about real discounted prices	A mechanism (e.g. a web platform run by a trusted third party) that collects data on discounted prices of different (national/cross-country) purchasers. It shares the data in an anonymous and aggregated format (e.g. a range of minimum, maximum, average, median, etc.).	These mechanisms are rare but there is some evidence available: for the vaccine price database of the Vaccine Product, Price and Procurement (V3P) mechanism run by WHO, WHO Member States provide data via a web interface. The V3P price database allows for country analyses and evaluations over time but it does not disclose the countries that delivered the data [144]. Over the years the number of participating countries has been increasing [145]. A 'Clearing House' that received anonymous data was developed for an independent research project aiming to assess the use and extent of discounts for high-priced medicines in some high-income countries [66]. In Austria the establishment of a 'Clearing House' as a cross-regional measure is foreseen as part of the health reform process.	Besides technical requirements (e.g. a protected web-interface), the success of a 'Clearing House' strongly depends on the commitment of the participating data providers. Their willingness to regularly deliver data is linked to an understanding of the benefits of the approach. If the 'Clearing House' knows the data providers, a high level of trust is vital. A 'Clearing House' potentially has some feasibility for realization since it helps reduce information asymmetry without necessarily breaching contracts.
Good-practice (performance-based) MEAs	When MEAs are implemented, they should follow defined principles and guidelines. Such agreements can also serve purposes beyond cost-containment, such as the generation of real world data.	While MEAs have gained in importance over time, their development has not been accompanied by systematic evaluation and guidelines for implementation. There are only a few scientific papers that suggest some related principles. In autumn 2017 KCE offered a proposal for good practice in (performance-based) MEAs [96].	Designing guidelines as non-binding recommendations for countries would increase their feasibility for compliance. It is important to have accompanying measures, such as capacity-building activities in good practice for countries with little experience in MEAs. The establishment of cross-country joint patient registries would be a challenging but helpful activity in this area for reimbursement purposes.

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Policy option	Description	Evidence and experience	Prerequisites for implementation
Coordinated collaboration alongside the life-cycle	Improvement in the exchange of information between different authorities and bodies at different points of the life-cycle of a medicine (e.g. regulators that decide on marketing authorization, HTA bodies, pricing authorities, reimbursement authorities/payers). This aims to identify and then undertake possible changes in the processes of data collection. Data needed at later stages, e.g. for pricing, could be identified and communicated to the marketing authorization holder at an earlier stage. This collaboration can be organized both nationally and at European level.	Until recently, the different regulatory processes along the life-cycle of a medicine appeared to be separate, with no or very limited interaction. Under the Dutch EU Presidency a meeting was organized to bring together relevant actors to aid understanding of different perspectives. Such exchanges of information have gained some momentum. For instance, considering information that is of interest for pricing and reimbursement during early scientific advice (which is a service of European and national regulators to marketing authorization holders planning to apply for marketing authorization) has been discussed. In April 2016 the German marketing authorization and benefit assessment authorities (BfArm, Paul Ehrlich Institute and Federal Joint Committee) reached an agreement on collaboration and knowledge exchange on joint scientific advice for manufacturers. There appears to be no structured process to sufficiently coordinate those who collect real-world evidence.	It requires an authority/body to take the lead and organize the process. A more formal and structured approach might be required (e.g. a survey to assess the different information needs of policy-makers).
De-linkage and new research funding models	The implementation of alternative funding models for R&D that allow low medicine prices – very low, close to marginal costs. This would include a greater involvement of public funders in research, including the support of public-private partnerships, as well as exploring the feasibility of models such as patent pools for Europe and 'prizes'.	Proposals for change in the research funding models for medicines have been discussed for more than 20 years, and some initiatives have been started, with promising results. For instance, the Drugs for Neglected Diseases initiative (DNDi) is considered a good model [146]; it has shown that in the non-profit setting, effective medicines can be developed at considerably lower cost. However, most of the discussions and initiatives have aimed to ensure medicine accessibility in low- and middle-income countries. Experience and evidence has yet to be collected for Europe. In the Netherlands, the 'Fair Medicine' initiative to organize a non-profit partnership for the development of medicines was established. The UN Secretary General's High-Level Panel on Access to Medicines presented recommendations for "remedying the policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health in the context of health technologies" [18], and in the EU the Expert Panel on effective ways to invest in Health explored new payment models for high-cost innovative medicines [34].	It requires long-term investments from public funders and collaboration across sectors. Legal challenges in the European framework would need to be identified, and solutions sought.
Differential pricing ('equity pricing')	Pricing policy for more than one country (e.g. all EU Member States). First, policy-makers of the involved countries determine a uniform price and then adjust it in accordance with the income levels and ability-to-pay of the countries involved.	Evidence from low- and middle-income countries globally: a policy to ensure access but not a policy for cost-containment (see Box 5). No experience in Europe.	Legal issues (including solutions to preclude parallel trade for these medicines) would have to be solved, along with the potential undermining effects of EPR (see Box 5). This policy could only be used in combination with other pricing policies that help define the uniform price that will be used as the basis for differentiation. Significant political will to agree on principles and mechanisms for differential pricing, including willingness for transparency around differentially set prices, would be needed. Implementation strategies could be explored through pilots, for example for one product under differential pricing between a few countries.

Notes: EC = European Commission; DNDi = Drugs for Neglected Diseases initiative; EPR = external price referencing; HTA = Health Technology Assessment; IP = intellectual property; JPA = Joint Procurement Agreement; MEA = Managed Entry Agreement; R&D = research and development; UN = United Nations; V3P = Vaccine Product, Price, and Procurement; WHO = World Health Organization

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World Health Organization
Regional Office for Europe
UN City, Marmorvej 51,
DK-2100 Copenhagen Ø,
Denmark
Tel.: +45 39 17 17 17
Fax: +45 39 17 18 18
E-mail: postmaster@euro.who.int
web site: www.euro.who.int

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