ECL ACCESS TO MEDICINES TASK FORCE

WHAT IS A FAIR PRICE?

Cancer leagues' reflections on fair pricing and fair price of cancer medicines

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ABOUT ECL ACCESS TO MEDICINES TASK FORCE

Established in 2016, the ECL Access to Medicines Task Force aims to make safe and effective medicines available to all cancer patients in Europe, by insisting on accessibility, availability, affordability and increased transparency related to medicine prices, ultimately leading to sustainability of healthcare systems. The Task Force strongly believes in the power of constructive dialogue. We urge all stakeholders to push for accessibility to high quality treatments, improving both survival and the quality of life of cancer patients. ECL Task Force connects 30 national/regional cancer societies in 25 European counties, representing over 500 million Europeans.

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Opinions expressed in this paper reflect the position of the ECL Access to Medicines Task Force collectively. Some opinions may not reflect the views of the individual Task Force's members, nor the views of their respective organisations.

EXECUTIVE SUMMARY

In this paper, the ECL Access to Medicines Task Force analyses concepts related to cancer medicines pricing as such, and the notion of 'fair pricing' in particular.

The paper discusses the inherent market failure in healthcare services and the dilemma between the delivery of quality cancer care for all European patients, addressing the growing demand, rising costs and unmet medical need while securing the sustainability of health systems. The paper examines the differences and implications of cost-based and value-based pricing models of medicines, putting in contrast their benefits and disadvantages and elaborating on the role of transparency in the pharmaceutical market.

Based on the analysis, the paper states that a standardised value-based approach to pricing and reimbursement is desirable, because it addresses the fundamental information need of health systems (*'is the treatment worth it?'*). However, this approach should be combined with the notion of affordability (*'can we afford it?'*). Additionally, a third relevant question is: *'is there a reasonable relationship between the cost of bringing the product to market and the price?'*

The Paper concludes that strategies for obtaining fairer and more transparent prices and price approval criteria as well as enhanced international collaboration are needed across Europe. It also offers a new definition of a fair price, as perceived by the ECL Access to Medicines Task Force and suggests ways forward for policy makers and pharmaceutical companies on how to achieve it.

WHAT IS A FAIR PRICE?

A 'fair price' is justifiable, predictable and cost-effective within the aims and priorities of the healthcare systems and the available budget.

At the same time, a fair pricing policy that takes into account the ethical and financial dimensions of patient access to care, affordability and sustainability of healthcare systems should be encouraged and rewarded.*

Whereas *'justifiable'* means a price that reflects the documented and clinically relevant benefit of the medicine, and a reasonable relationship between the cost of bringing the product to market (including R&D, production, marketing) and the price.

Whereas *'predictable'* relates to the need for health payers, policy makers and systems to be able to predict the total costs and of investing in the treatment.

'Cost-effective(ness) could be a common criterion for evaluating whether the price seems 'justifiable', as it links benefits with costs in a systematic way and provides a comparable decision-making tool across healthcare interventions.

Finally, *'affordability'* addresses the financial side of the sustainability of health systems.

A prerequisite for obtaining fairer prices is a higher level of transparency and access to information about end-user prices, documentation of product value and the cost of developing and bringing the pharmaceutical product to market, as well as reimbursement decision-making processes.

* The definition can only be interpreted in the context of the recitals.

WHAT SHOULD STAKEHOLDERS DO NEXT?

The ECL Access to Medicines Task Force suggests establishing a **High-Level Working Group on fair pricing** facilitated by the European Commission which would connect all relevant stakeholders, including public authorities, payers, patients, public health NGOs, academia and the industry in order to define a fair price and identify opportunities and challenges connected to different pricing models.

POLICY MAKERS AND PAYERS SHOULD:

1. Expand existing structures, e.g., the EURIPID database, to share information on net prices of medicines and strive toward full implementation of the WHA Resolution on improving the transparency of markets for medicines, vaccines and other health products.
2. Pool resources and enhance collaboration throughout the entire medicines access pathway, to prepare health systems for (i) the arrival of new medicines and technologies, (ii) conducting high quality Health Technology Assessment (HTA) and (iii) sharing information about prices and pricing and reimbursement strategies, in order to enhance countries' ability to (a) prioritise medicines with higher clinical value, (b) review and adjust prices based on new evidence, and (c) effectively negotiate the prices of medicines.
3. Provide structures, control systems and incentives to either reward socially responsible and highly ethical industrial behaviour or punish unethical behaviour;
4. Review regulatory incentives where they may lead to unaffordability of products (e.g., orphan medicines) and ensure that awards for innovation do not lead to a lack of competition and monopolistic prices.
5. Attach conditionalities to both national and European public funding (e.g., Horizon Europe, Innovative Medicines Initiative - IMI) and ensure that public investment in R&D is accounted for and that medicines resulting from publicly funded research are available for a fair and affordable price.

6. Ensure that criteria and processes for priority setting in health care are explicit, transparent and that there is a clear link between priorities, national pricing policies and practices, and the actual price of medicines. Furthermore, pricing and reimbursement authorities should be transparent about their decisions, how they are made, what criteria are used and who is involved in the process.

7. Make fair pricing and affordability of new treatments a core element of the upcoming Europe's Beating Cancer Plan, the New Pharmaceutical Strategy for Europe and other relevant EU policy and legislative activities.

PHARMACEUTICAL COMPANIES SHOULD:

1. Price new medicines fairly and responsibly to ensure that they are accessible and affordable. Pharmaceutical companies should incorporate responsibility for access and sustainability (CSR) of healthcare systems as part of their market access and pricing strategies for pharmaceuticals), as seen within other commercial areas.

2. Apply a higher degree of cost-consciousness (i.e., lowering the cost of bringing the product to market) throughout the product value chain.

3. Be transparent about the costs of bringing the product to market as well as end-user prices (by disclosing these figures to relevant stakeholders, e.g., public authorities).

4. Include HTA and payer considerations early-on in the product development.

5. Incorporate an ethical charter and guidelines within the product development and pricing processes.

6. Focus on steering R&D investments toward areas with higher unmet need and develop pharmaceutical products with added value for patients and public health.

CONTENTS

INTRODUCTION

In recent years, prices of cancer medicines have become subject to an increasing concern among health policy makers and payers in Europe, as well as other parts of the world. The ageing populations and an increasing need for healthcare services combined with an increase in the societal cost of providing care cause budgetary and affordability constraints for most health systems. However, these worries arising from the experienced growth of the health system expenditures on cancer medicines cannot be justified by the rising incidence of cancer alone.

All patients have the right to optimal treatment, regardless of their financial means, gender, age or nationality. Nevertheless, at the current rate of healthcare spending, it may not be possible to provide access to health care for the entire population in the near future.[1] This situation calls for strategies to obtain economically sustainable health care and healthcare systems, including predictability about input prices (e.g., the cost of personnel, buildings, equipment and medicines), and better knowledge about the value for money of different treatment options.

In this paper, the ECL Access to Medicines Task Force analyses concepts related to cancer medicines pricing as such, and the notion of *'fair pricing'* in particular. The aim of the paper is to discuss:

i. the different notions related to the pricing and prices of cancer medicines;

ii. the different options available for sustained decision-making by health policy makers in relation to pharmaceutical pricing; and

iii. the barriers and facilitators of the various policy suggestions provided in the literature under the umbrella of *'fair pricing'*.

MARKET FAILURE IN THE SUPPLY OF CANCER MEDICINES

According to the neoclassical economic theory, it may be claimed that just like the price of other goods and services, the *'fair'* price of healthcare goods is formed as a result of an *'invisible hand'* automatically regulating the demand and supply.[2] In this perfect market situation, demand will fall if the price increases and supply will increase if the price increases, and the 'fair' price will be set as a result of an equilibrium between the demand and supply forces. Thus, competition between suppliers keeps the price down.

However, for many reasons, the market for health services fails to work this way.[3]

First, the pharmaceutical market is characterised by an *asymmetry of information* between the market actors. Health services are complex and while health professionals have the knowledge and access to the relevant information about the specific diagnoses and health services they offer, patients and the public do not. A similar situation applies to suppliers/providers of health products and payers/policy makers who act on behalf of patients. Within cancer care, asymmetry of information and the lack of market transparency are particularly pronounced, as cancer cases are very complex and diverse, making it difficult to generalise from a case-to-case basis.

Second, the healthcare market is often characterised by an *inelasticity of demand*. Unlike goods and services whose demand and supply are sensitive to price changes, (i.e., the demand falls if the price increases), the demand for many health services, such as cancer treatments, will still be high under increasing prices. The reason for this is that cancer is mostly a life-threatening disease and its treatment is needed urgently.

Third, one may also argue that *the demand for cancer medicines may even increase despite increasing prices*. The reasons for this higher demand include i. a growing incidence of cancer; ii. a high unmet need for cancer treatment; and iii. the launch of many new treatments which may have a promising potential for improving patient outcomes. Additionally, many cancer medicines are relatively new and under patient protection. Hence, prices may be kept high as long as the patent lasts.

Finally, the market for health care is *elastic to the differences in patients' income*. Because of lower income, some patients may postpone their treatment, even when suffering from highly symptomatic diseases. This is especially noticeable in health services financed or co-financed directly by patients themselves. Generally, with a few exceptions, health services in Europe are considered a 'public good' and access to health care is an entitlement. Although in some European countries certain cancer medicines may be subject to patient co-payment, the majority of cancer treatment is financed through taxation or through mandatory health insurance built on the principle of solidarity.

Therefore, the aim of ensuring sufficient and equitable access to cancer care whilst solving the increasing challenge of affordability is in the hands of health payers and policy makers. Throughout Europe, there is a great disparity in the availability of and access to different cancer therapies, with unaffordability being one of the main reasons.[4]

THE GROWTH IN CANCER CARE SPENDING, UNMET MEDICAL NEED AND ITS BURDEN ON HEALTH SYSTEMS

GROWING PRICES OF CANCER MEDICINES

In recent years, pharmaceutical companies' pricing policies and, in particular, high prices of cancer medicines have become subject to an increasing concern among health policy makers, payers and other stakeholders in Europe, as well as other parts of the world. These concerns arise from the experienced growth in the expenditure related to cancer treatments which cannot be justified by the rising incidence of cancer alone.

The growth in the prices of cancer medicines has exceeded the growth in total cancer spending and new cancer medicines coming to the market at a high price were identified as important drivers of the growth in cancer care expenditure.[5] The WHO Report on pricing of medicines states that globally between 2012 and 2019 the expenditure on cancer medicines grew at higher rates than the growth rates of people newly diagnosed with cancer, 5.3–8.7% and 2.6–2.8% per year, respectively. During the same period, the global per-capita expenditure on cancer medicines has been about 2- to 8-fold above the overall per-capita expenditure.[6]

The WHO Technical Report on pricing of cancer medicines and its impacts further recognised that prices of cancer medicines were higher than for other indications and their costs were growing at a faster rate, resulting in lack of access to treatment for many patients worldwide and hampering the capacity of governments to provide affordable access for all.[7]

In addition, there is evidence that the revenue of pharmaceutical companies on cancer medicines has increased in the past decade while, at the same time, treatment per patient for new cancer medicines has come at a high price, becoming unaffordable due to budget constraints.[8]

Current demographic changes have led to a rising incidence of cancer and other non-communicable diseases (NCDs). Together with the rising cost of cancer treatments, this can pose a direct threat to patient access and the sustainability of healthcare systems in the near future. Hence, we experience an increasing demand for cancer care and an increasing financial burden for the health systems. With an expected global economic recession due to the current COVID-19 crisis, addressing the issue of sustainability of health systems becomes even more critical than before.

FAST ACCESS TO NEW EXPENSIVE MEDICINES WITH AN UNCERTAIN ADDED THERAPEUTIC BENEFIT

In order to enable timely patient access to new and innovative cancer medicines, the European Medicines Agency (EMA) has lowered its regulatory requirements for pharmaceutical companies related to the demonstration of added therapeutic value and its documentation, compared to other disease areas (e.g., diabetes). An example of this is the PRIME scheme and the conditional market approval.[9] This means that many new medicines or new indications for existing treatments can obtain faster marketing authorisation in Europe based on relatively small clinical studies with a short observation time for the evaluation of the medicine's efficacy and safety (Phase II trial).

Moreover, there is evidence that only few cancer medicines get regulatory approval based on 'hard endpoints', such as prolonged survival.[10] A study of the EMA's decisions about granting marketing authorisations between 2009-2013 found that out of the 48 cancer drugs approved for 68 indications only 24 (35%) of the indications demonstrated an extended survival (median 2.7 months). Furthermore, in less than half of these 24 indications, the effect size was clinically meaningful. Additionally, only 10% of the 68 indications demonstrated an improvement in health-related quality of life for patients.[11] Therefore, according to this study, most cancer medicines entered the market without any evidence of longer survival or improved quality of life.

Although there are good reasons for faster regulatory approval of new medicines in some cases, it may also unintentionally lead to incomplete information about the treatment's efficacy and safety and potentially lead to inefficient health decisions or difficulties in setting a fair price. As a result, when pharmaceutical companies apply for reimbursement in individual countries, which have different structures and requirements for reimbursement, they may do so without robust documentation related to the medicine's clinical and patient-reported efficacy and safety. At the same time, new cancer medicines often come at an extremely high price.

In Germany in 2011, the Institute for Quality and Efficiency in Health Care (IQWiG) introduced the demonstration of an added clinical benefit as a requirement for pharmaceutical companies ahead of the price negotiations of newly approved medicines. Eight years after the introduction of this approach, the Institute found that only 25% of the reviewed products actually met the requirement of an incremental clinical benefit. For 58% of the medicines, no meaningful benefit over existing standard of care was demonstrated.[12]

A study published in May 2020 analysed the correlation between the monthly treatment cost and the clinical benefit of 65 new oncology medicines approved for solid tumours and various types of blood cancer in the USA, Switzerland, England, Germany, and France. The authors evaluated the clinical benefit of each drug using the validated frameworks of the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Although prices of medicines were twice as high in the USA than in the participating European countries, there were still significant differences between the prices in Europe, e.g., lower prices in France and Germany than those in England and Switzerland. The study found that, with the exception of one of the frameworks used in the French case, there was no correlation between the clinical benefit of the medicine and its price. The authors stated that the establishment of a clearer link between the price and the effectiveness of the product is crucial for adequate patient access to cancer treatments in the years to come.[13]

LACK OF TRANSPARENCY IN MEDICINE PRICES

There is a lack of transparency throughout the pharmaceutical system, including a lack of transparent pricing components, reimbursement criteria and the actual (net) prices of medicines in different European countries. Transparency is often praised by stakeholders as a way to ensure fairer prices and bring public accountability in the predominantly secretive pharmaceutical sector.[14]

The 2019 WHO resolution on 'Improving the transparency of markets for medicines, vaccines and other health-products'[15] recommended public transparency on real medicine prices in the spirit of good governance and Member States were advised to take appropriate measures to publicly share information on net prices of health products. The ECL believes that this is an important step to restore the balance in pricing and reimbursement negotiations between governments/payers and multinational pharmaceutical companies. Currently, there exists an informational asymmetry, where pharmaceutical companies may have knowledge about the prices of products globally, but national payers do not have access to such data beyond their borders.[16]

Other aspects of transparency (R&D costs, marketing costs, subsidies, incentives and patent status) were vaguely mentioned in the resolution and transparency of the results of clinical studies has disappeared completely compared to the initial draft. **ECL believes that increased transparency about related costs would build patients' and taxpayers' trust in health decision-making of public agencies and payers. In addition, access to full clinical studies reports would provide the opportunity for independent research and detailed evaluations of related harms and adverse events. It would reassure the wider health community about the added value and safety of authorised products.[17]**

CALL FOR FAIR MEDICINES PRICES

The market failure in health care and the unsustainable situation in the pricing and prices of cancer medicines calls for action. Which type of action is to be directed towards which stakeholder involved in pricing is subject to a debate among researchers, payers, policy makers, patients, consumers, and the pharmaceutical industry. Many solutions to achieve greater transparency, better regulation and enhanced international collaboration are already on the agenda of many decision-makers and stakeholders.

Since 2017, the WHO has become a platform to host the biennial multi-stakeholder Fair Pricing Forum. The 2017 Forum touched upon solutions, such as the pooling of resources and voluntary cooperation between payers in medicines pricing, including horizon scanning, HTA and information-sharing. Importantly, the Forum also set the first working definition of a 'fair price' as 'one that is affordable for health systems and patients and that at the same time provides sufficient market incentive for industry to invest in innovation and the production of quality essential health products.' In 2019, following the second Fair Pricing Forum this definition was put under review and a new one is yet to be defined.[18]

It is safe to say that the whole idea of a market price as a 'fair price' in cancer care can be contested. The nature of cancer as a life-threatening disease means that fair pricing could be interpreted as pricing that enables access for as many patients as possible, or pricing based on how effective the medicine is at treating individual patients' disease.

In the following chapters, the paper briefly describes the pathway from product development to patient access of medicines and discusses the notions of 'price', 'pricing', 'transparency', 'cost-effectiveness', 'affordability', 'therapeutic value' and others. The paper includes examples of the various fair pricing definitions and pricing strategies, including arguments about cost-based and value-based pricing options.

PRICING, PRICE AND PATIENT ACCESS

Initially, it is important to distinguish between 'pricing' and 'price' and outline the 'patient access pathway' for medicines.

'Pricing' is a strategy – or a set of strategies - used by pharmaceutical companies to optimise their prices and profits in the ever-changing markets. Pricing could also refer to the way that legislators and payers regulate the price of products.

'Price' is the market (list) price of an individual medicine which is usually put forward to the authorities (payers) responsible for (public) reimbursement decisions. It may also be the actual (end-user/net) price that the purchasers end-up paying for the product (after discount is applied). Currently, list prices are publicly available while most net prices remain confidential.

PROCESS FROM THE DEVELOPMENT TO PATIENT ACCESS

Figure 1. The process from product development to patient access (ECL 2020)

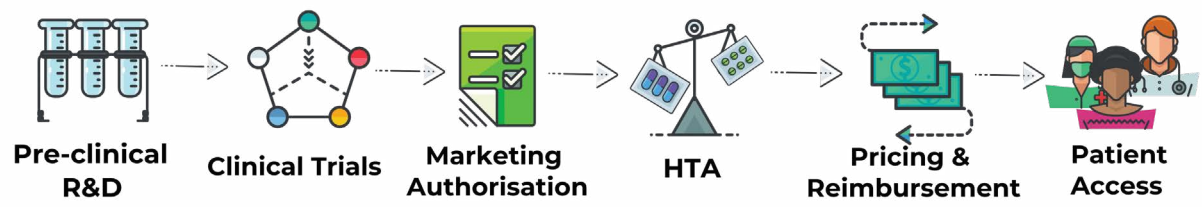


Figure 1 shows, in a simplified manner, the process from research and development of medicines to patient access.

The R&D process starts with discovery and pre-clinical studies and continues to clinical patient trials in a smaller scale (Phase II) and larger scale

(Phase III), aiming at testing efficacy and patient safety. When the product is on the market, Phase IV studies may be carried out to evaluate real-life effectiveness, safety, patient compliance etc.[19]

Companies make assumptions about the price and the pricing approaches of medicines very early in the development phase. These assumptions may provide input to the decision of whether to invest in the development and marketing of the product. Likewise, decisions about how to incorporate both regulatory and HTA criteria in the trials may be made early in the development process. The evidence required by the regulatory authorities providing the marketing authorisation and payers deciding whether or not the product should be reimbursed uses results data from clinical trials together with local real-world data (e.g., related to epidemiology, demography, effectiveness, resource use, and unit costs).[20] **Therefore, early dialogue between the developers and the authorities about data requirements is crucial in order to meet the demands for market approval and reimbursement.**

In Europe, the marketing authorisation of cancer medicines is granted by the European Commission based on the recommendation of the European Medicines Agency (EMA). After getting the marketing authorisation, the company can sell the product in all EU countries. However, the decision about reimbursement is provided at a national, regional, local or hospital level, by different organisations and under different criteria.

To decide whether or not to reimburse a product, some countries and payers use full HTA criteria (including clinical and non-clinical aspects, such as economic, ethical and organisational evidence). Others, only use a selection of these criteria (e.g., clinical benefit and budget impact). Some of these criteria may be *explicit* and publicly available. For example, the type of outcomes to be documented (added clinical benefit, cost-effectiveness, clinical benefit, etc.) or the decision-criteria (e.g., the threshold for the willingness to pay for a life year/ quality adjusted life year in England or the ASMR rating in France).* However, some criteria are only *implicit*. It could happen that reimbursement is not provided or is only provided to a subgroup of patients because of the impact the decision may have on the health budget. On the other hand, reimbursement can be granted despite not meeting the explicit criteria, because medical need is considered more important. The decision about reimbursement is also influenced by the price negotiations between pharmaceutical companies and payers. In some cases, reimbursement may take place only after additional (confidential) discounts are added to the price. Therefore, there is a difference between the actual and the list price.

It is important to note that the time period between marketing authorisation at the EU-level and reimbursement at the national level varies a great deal throughout Europe. For several reasons (including e.g., the capacity to evaluate and pay, buy larger volumes and health system readiness), pharmaceutical companies typically do not launch (apply for reimbursement) their products in all EU Member States at once but start with larger and wealthier markets (e.g., the UK, France, Germany, Italy).[21] In addition, the lack of robust evidence regarding the safety and efficacy of novel products, their hefty price tags and staff shortages in the national bodies often result in lengthy pricing and reimbursement processes. Therefore, it may take a couple of years before the product actually reaches patients.

* ASMR rating = the lower the rating of the drug in terms of added clinical benefit, the higher the requirement for price negotiation/deduction

PRICING STRATEGIES

A pharmaceutical company defines a viable price range by assessing the product from the market perspective, (i.e., patient population, number of alternative treatments available etc.), and the company perspective, (i.e., associated costs and return on investment).[22] In general, the market perspective determines the upper achievable limit for what the market will bear and the company perspective sets the lowest acceptable price that will still yield the required return on investment.
Traditionally, companies have been setting medicine prices on a 'cost plus profit margin' basis. In **'cost-based pricing'**, prices should reflect costs (such as R&D, marketing and production costs), profit mark up and R&D investment risk. Hence, an increase in price can only be justified by a change in costs or profit.

However, during the last decades, **'value-based pricing'** has become increasingly incorporated in pharmaceutical product development and pricing strategies, as well as in the criteria for reimbursement. 'Value-based pricing' is based on a patient and payer relevant (incremental) value of the product, (e.g., a health gain of the new drug compared to the current treatment). Any increase in price can be justified by an increase in units of 'health' compared to the available treatment available. It is crucial that the demonstration of added value is considered already in the product development, so that data on payer and patient relevant outcomes are available at the time of reimbursement.

In the absence of data related to costs and value of novel products, **'what the market will bear'** pricing is commonly used. It refers to the balance between the maximum price achievable in a given market and the lowest price required in view of costs and desired returns. The literature provides various examples of how to keep the price as close to the upper limit as possible. For example, launch in high price-indications first and then subsequently in other indications, making sure that an appropriate reference product is chosen for the product and perhaps change of comparator through shifting ATC class etc.[23]

Other strategies, including the 'competition-based pricing' and **'reference-pricing'**, are strategies that are used when the product is on the market. Competition-based pricing is used by sellers (pharmaceutical companies or wholesalers) according to the price of competitive products, (e.g., the price may be reduced in order to gain market shares from competitors). Reference-pricing, regularly used by payer authorities, compares list prices in different countries, under which one country compares the prices to a basket of other selected countries (external) or nationally (internal).

Which strategy companies actually choose depends on the specific market situation and related regulation, supply and demand, and competition. As stated before, prices vary greatly from one country to another. For instance, monthly costs of new cancer medicines in the United States could be two times higher compared to European countries.[24] This can be partly explained by free price setting in the USA, compared to the European market regulated by HTA or other criteria, which may keep prices at a lower level. In addition, discounts and rebates realised are results of negotiations and often provided on basis of the quantities purchased, i.e., larger markets (e.g., France) are able to purchase medicines at a cheaper price than smaller markets (e.g., Malta).

In addition, it is crucial to stress the impact of intellectual property (IP) protection on the price of medicines and understand that companies have a monopoly on the development and sale of novel cancer treatments. According to the European Patent Office (EPO), pharmaceuticals and biotechnology belong to the most patent intensive industries. Even after the patent expiry, market entry and uptake of generics and biosimilars often remain slow. In extreme cases, some companies tried to postpone market entry of generics

and biosimilars by closing 'pay-for-delay' deals between originator and generic manufacturers, while keeping prices at a high level.[25] Finally, research suggests that medicines for life-threatening, highly symptomatic acute diseases with lower prevalence are less price-sensitive than medicines for chronic diseases where prices may fall with increasing demand. This corresponds well to the development of the demand and prices of oncology products.[26]

COST-BASED VS. VALUE-BASED PRICING

This chapters discusses the opportunities and challenges connected to the two main approaches in pricing, 'cost-based' and 'value-based'.

As stated above, **'cost-based pricing'** should reflect costs (including R&D, marketing and production costs), profit mark up and R&D investment risk. Technically, an increase in price can only be justified by a change in costs. This also means that companies will solely compete based on costs, hence drawing low-cost suppliers into the market.

There are several shortcomings connected to the cost-based approach. Firstly, as stated by the WHO,[27] there is a risk that the cost-based approach may prevent access to cancer medicines as companies may withdraw their products from the market or never even enter a market which is using cost as reimbursement criteria. If a company cannot compete with other companies based on costs, such market may not be sufficiently attractive to launch the product. Secondly, this pricing approach does not provide incentives for innovation, which are highly needed for cancer patients. Thirdly, it does not encourage companies to demonstrate product's added value. Therefore, it would be the responsibility of public authorities to evaluate the value compared to other available alternatives or it would be necessary to add it as an addition requirement for marketing authorisation. The **'value-based pricing'** strategy has the advantage that, in principle, it is aligned with the aims of health care and (public) healthcare systems: *'to get as much 'health' for the population as possible… with the budget available'*. Hence, if the company can sufficiently document the incremental value of the medicine in terms of 'relevant' health gain at a price that lie within healthcare systems' willingness to pay for this particular health gain,* the price can be approved and reimbursed. In addition, this model has the potential to encourage the pharmaceutical industry to be innovative and develop new products, which are relevant to patients.

Generally, value-based approach may drive up the cost of the individual R&D projects, as the demonstration of clinically relevant endpoints (overall survival) requires a higher number of patients in the trials. At the same time, focus on value may lead to less clinical trials as products that are not likely to have relevant incremental value to patients will not be developed and marketed.

* Often applied as an incremental cost per quality-adjusted life-year (QALY) gained, but it can be other outcomes measures as well.

In addition, methods for value assessment, comparative efficacy, (real-life) effectiveness, cost-effectiveness and the documentation of the evidence are complex. As previously mentioned, many new oncology products receive marketing authorisation based on scarce documentation, for instance based on small clinical trials (Phase II) with surrogate endpoints. For payers to know the real size of the effect that they pay for, post-marketing (real-life) observational studies are needed. These studies may take 3-5 years to conduct and create a gap for decision-makers between the time of investment in the medicine and availability of sufficient information about its effectiveness, safety and patient compliance. Therefore, better documentation based on the analysis of real-life data and the link between surrogate outcomes (e.g., disease-free survival) and hard outcomes (e.g., overall survival) presented at the time of application for marketing authorisation is at the heart of the new EMA Regulatory Science Strategy.[28]

Value-based approach also requires health policy makers to become more explicit about what their aims are. They should be able to describe the outcomes that are relevant for the specific patient population, how much they are willing to pay for the health gain and their priorities in terms of healthcare budgets. However, methods and evaluation of value-related analyses require specific skills which may not be sufficiently available in every country. Therefore, it is necessary to enhance international consensus and collaboration and pool resources to deliver high quality assessments throughout the patient access pathway. This approach has been supported by a number of stakeholders including patient and public health organisations as well as national and international policy makers. Nevertheless, such cooperation in horizon scanning, HTA, price information-sharing, negotiations and joint procurement is still relatively new and its full potential is yet to be seen.

Value-based pricing has the potential to provide the right incentives for suppliers as well as ensure that payers focus on reimbursing treatments that provide more health rather than on medicines which are less costly to produce. Nevertheless, the remaining challenges are (i) to agree on the priorities (unmet need), outcomes, comparators, assessment methods and approaches that ensure access to high quality treatments for patients who need them, and (ii) to generate sufficient evidence to support the value claims.

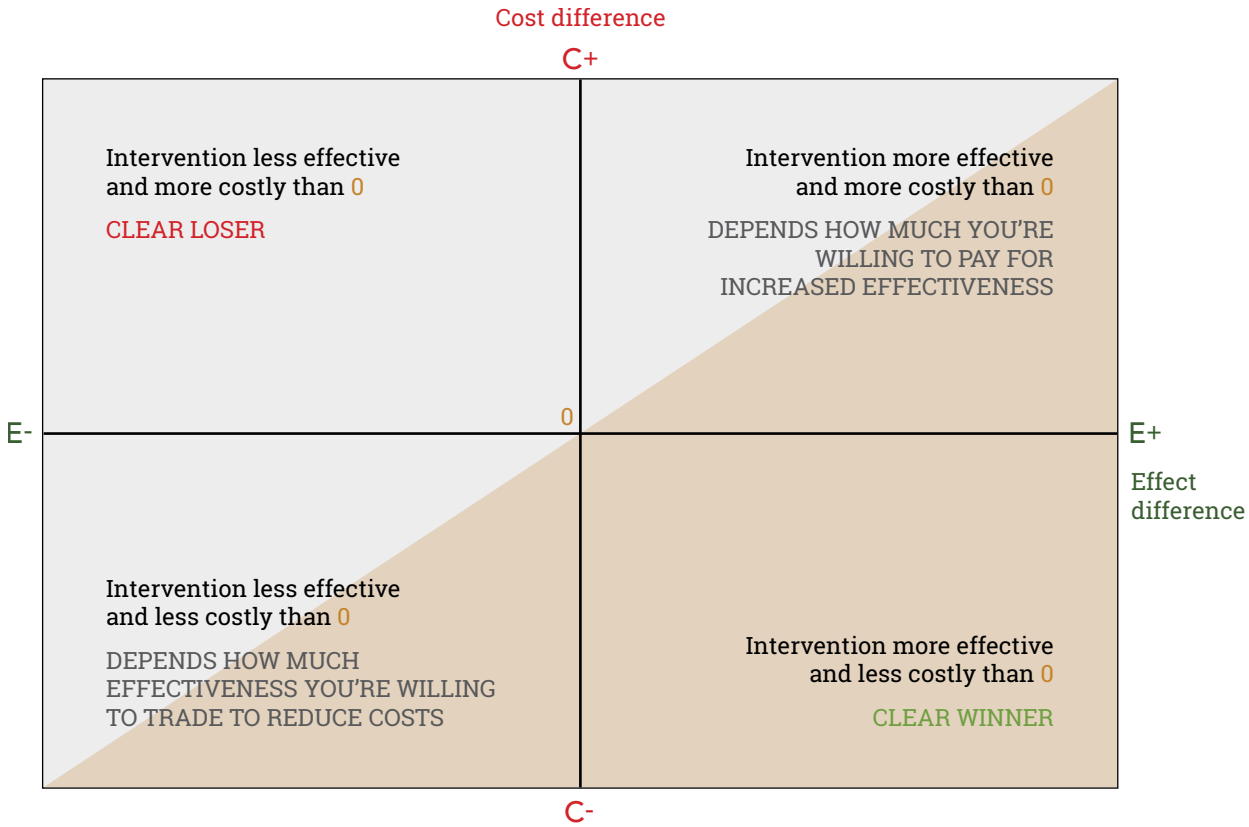
We can conclude that any definition of a 'fair price' should be linked to value. However, there might be a dilemma between value (cost-effectiveness, clinical benefit etc.) and affordability and, at the same time, the price should not be completely disconnected from cost related to the product's development. Therefore, in the following chapter, the paper provides a rationale for combining the two pricing approaches.

THE DILEMMA BETWEEN COST-EFFECTIVENESS, BUDGET IMPACT AND AFFORDABILITY

The fundamentals of welfare economics, such as health economics, are that resources are constrained and therefore any choice we make has direct consequences in the form of alternative costs. This means that resources we spend on cancer care cannot be spent on treatment for other disease areas and therefore, there is a need to prioritise.

The idea behind using societal cost-effectiveness as a decision criterion is that it can answer a question essential to all health systems: Is the drug worth it? Does it provide more value for money than what is already available? As the effect measured (e.g., life years gained or QALYs) should be the same across all diseases, it can be used to inform decisions and set priorities in health care, which is highly needed under budgetary constraints.

Figure 2. The cost-effectiveness plane



Drummond et al (1987)

Figure 2 shows of the most-known features in health economic evaluation, the 'cost-effectiveness plane'.[29] This is a (theoretical) decision-making framework for payers and other health decision-makers. The vertical line shows the incremental differences in costs and the horizontal line shows the incremental differences in effect of a new intervention in comparison with

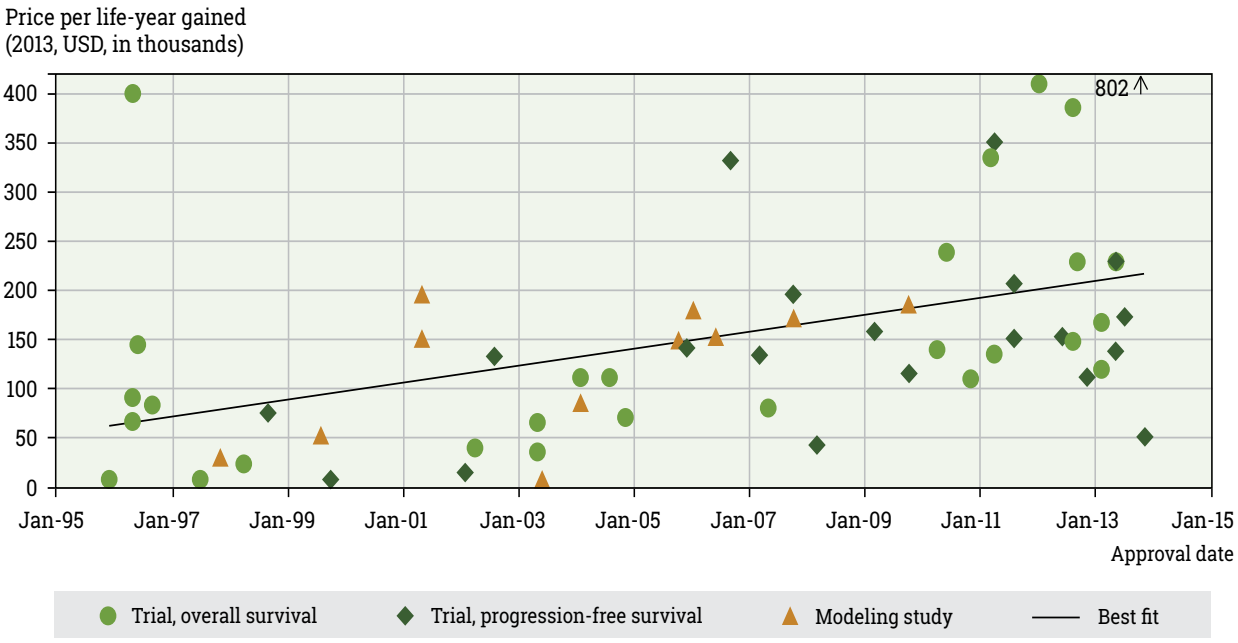
the standard of care or other a similar intervention. There is no decision problem in the upper left quadrant – here the intervention is less effective and more costly, so this intervention should clearly not be introduced. On the other hand, in the right lower quadrant, the intervention is more effective and less costly, hence it should be introduced.

The real decision challenge occurs in the two other quadrants. Here, the intervention is either less effective and less costly and incremental 'health' (effectiveness) must be traded for lower costs or it is more effective and more costly and more 'health' can only be obtained at a higher cost. In cancer, at the time of reimbursement, many interventions can be found in the right upper quadrant, as they come as more expensive, and promise to be more effective than the current standard of care. However, as previously stated, new cancer medicines are regularly launched without hard evidence about their effect, and therefore their placement in the right upper quadrant may be questionable.

WILLINGNESS-TO-PAY THRESHOLD

An incremental cost-effectiveness ratio of a medicine may lie within the explicit or implicit threshold of healthcare systems' willingness to pay for a health gain (e.g., QALY). However, in the end, reimbursement may still be refused because of the impact the medicine's price might have on the healthcare budget. The reason for this is a lack of explicit criteria that relate to affordability.[30] In the USA, as can be seen in the fitted line in figure 3 below, the price-per life year gained at the time of FDA approval has increased tremendously during the 20-year period shown.

Figure 3. Price per life-year gained vs. FDA approval date for oncology products, 1995-2013



Source: OECD 2017.

In Europe, there are indications that the willingness to pay in the form of ICER thresholds may have gone up as well. For example, for seven years, until 2009, the National Institute for Health and Care Excellence (NICE) in the UK had an explicit threshold range of £20,000-30,000 per QALY gained. However, NICE changed its position for some patient groups and introduced differential thresholds. These include £50,000 per QALY gained for 'end-of-life' treatment for late-stage terminal diseases for small populations, introduced in 2009 and a threshold of £100,000-300,000 per QALY gained for treatment for rare diseases.[31] Both margins are relevant for cancer patients.

There is a dilemma between cost-effectiveness and budget impact/affordability. The cost per incremental QALY gained (ICER) or other approaches like the IQWiG additional clinical benefit, the ESMO-MCBS etc. – whether or not they include costs or have an economic threshold – are not sufficient decision-making criteria to address the affordability issue. In light of demographic challenges and rising cancer incidence in Europe, affordability of cancer care is increasingly becoming an issue.

Therefore, paying for value-based criteria (addressing a high unmet need, effectiveness, clinical benefit or cost-effectiveness) should be addressed in the context of a budget impact.

Some medicines pricing models have already tried to address this challenge. For instance, there is an interesting suggestion to combine the two reimbursement criteria, cost-effectiveness and budget impact, from Prof. Lieven Annemans[32] and other multifaceted approaches combining value-based pricing with various strategies aiming at lowering the budget impact (see overview on page 25-31).

For example, the International Association of Mutual Benefit Societies (AIM) suggests the introduction of a European maximum price calculation model,[33] and Prof. Suerie Moon suggests introducing both 'price floors' (minimum costs and prices) and 'price ceilings' (maximum price/budget impact) in order to improve affordability and predictability of prices.[34]

Another approach to decrease the budgetary impact is to encourage companies to look for subgroups of patients where the medicine is most effective, i.e., for those patients who have the largest 'capacity to benefit' from the products. In the so called **'indication-based pricing'**, indications eligible for reimbursement could be narrowed and the budgetary impact brought down. However, while using this approach encourages continued investigation in different populations and potential reduction of waste in health care, it also carries the risk of 'salami slicing' of patient populations to enable higher prices to be charged per treatment.[35]

However, if and how these strategies may work in practice are yet to be seen.

THE ROLE OF TRANSPARENCY

PRICE TRANSPARENCY

As stated, the lack of transparency and asymmetry of information leads to market failure in health care and is part of the reason why regulation of the healthcare market is highly necessary.[36] This becomes even more visible within the pharmaceutical market as most sellers of medicines are private companies operating globally whereas most purchasers are national, regional or local. Thus, there is a lack of balance between the selling and buying negotiating powers in the current market.[37]

In the literature and policy documents, the pharmaceutical industry has often been criticised for its lack of transparency regarding the actual (end-user/net) prices *vis à vis* list prices of medicines and of the processes leading to the actual price. In Europe, because of the relatively strong reimbursement regulation in outpatient medicines, this lack of transparency seems most apparent in hospital medicines, including for cancer. In some countries, the prices of medicines may also be negotiated between a marketer and an individual hospital.

End-user prices for cancer medicines are generally not disclosed to the payers and policy makers beyond their jurisdiction. They are kept confidential from taxpayers (general public). Research showed that actual prices, after the application of confidential discounts, are often significantly different from the list price and that there are significant differences both within - and between - the European countries.[38]

This is also why **'reference-pricing'**, used as a price approval criterion, does not seem to work as intended. External referencing is usually based on the list price in the reference countries and not on the actual price. So, if e.g., Estonia references Latvia and Lithuania, the Estonian authorities will only approve the price if it is the same or lower than the average of the list prices of the two reference countries.

COST TRANSPARENCY

Furthermore, as elaborated above, evidence shows that there is no clear link between pharmaceutical R&D costs, production and marketing costs, profits, nor added-value and the prices of cancer medicines[39] and pricing seems to be according to the 'what the market will bear' principle. Therefore, many payers and policy makers and stakeholders call for more transparency of pharmaceutical costs and profits.

The application of a transparent cost-based model, where information about the costs of R&D, production, marketing, profit mark-up etc. is made available to the payers, has been discussed by several authors. One challenge is the great deal of complexity in displaying all costs from early R&D and marketing processes in companies operating globally. The actual costs of getting medicinal products to the patients are dependent on the

number of markets entered, as marketing and production costs decrease with increasing number of sales. In addition, the fact that companies indirectly allocate their investment losses of R&D failures to the price of other products adds to the complexity of the cost-based equation. Therefore, realistic methods and processes for calculation and demonstration of costs of getting the product to market are needed.

TRANSPARENCY OF REIMBURSEMENT DOCUMENTATION AND CRITERIA

Full transparency of clinical studies data is crucial to enable further research into the efficacy and safety of products after their marketing authorisation. Such data can help determine the added value of treatment in real-life setting across different populations and potential divestment into treatments that have proved harmful or obsolete. Value documentation most often needs both clinical trial data, local real-life data about the population and local unit costs. Such data are collected outside the trials and often years after. It often also needs to be based on a model that can simulate the lifetime of the patient population beyond the observation time for clinical trial data (e.g., this is required to make a long-term cost-effectiveness analysis with QALYs). Therefore, transparency of how clinical, epidemiological and economic data were collected and how statistical and simulation-based models were developed and used in the documentation of value is also warranted.

There is also a lack of transparency of pricing and reimbursement criteria set by public payers in different European countries. Although a lot of international collaboration and networking has been initiated to standardise evaluation methods and payer organisational structures (e.g., EUNetHTA, Beneluxa, EURIPID etc.), there may still be as many different ways and principles for organising these decision-making processes and criteria as there are countries. Although this may to a certain extent be due to lack of harmonisation between countries, it is also a lack of transparency of local decision-making.

THE ROLE OF TRANSPARENCY IN A FAIR PRICE, WHERE TO START?

While many stakeholders call for more transparency into costs and prices of medicines, pharmaceutical companies are very reluctant to disclose them, as they believe it might potentially jeopardise their business strategy. On the one hand, some argue that disclosure of prices may lead to collusive agreements between sellers about prices, resulting in price increases. This can also trigger 'gaming' where one company, despite the collusive agreements, may unexpectedly decrease the price which will lead to fierce price competition driving some companies out of the market and thus inhibiting patient access to certain treatments.[40] On the other hand, more transparency of the cost components of a price and the actual prices has the potential to build payer, patient and consumer's trust when applied to the pharmaceutical system, as all components of the price would be clearly stated and understandable.

ECL believes that transparency on actual prices of medicines is an important step to restore the balance in pricing and reimbursement negotiations between payers and multinational pharmaceutical companies. Therefore, several cancer societies established the European Fair Pricing Network (EFPN), a collaborative entity of cancer societies and research institutes, which aims to conduct more research into actual price levels of cancer medicines throughout Europe. In addition, increased transparency about related costs would build patients' and taxpayers' trust in health decision-making of public agencies and payers.

The ECL Access to Medicines Task Force published numerous recommendations in relations to increasing transparency in the pharmaceutical market.[41] They are directed towards the regulatory authorities and support enhanced international collaboration in this area. ECL recommends to:

1. Use the EURIPID database to share net prices of medicines;
2. Enhance cooperation between the European Medicines Agency (EMA) and national authorities towards transparent and robust criteria for marketing authorisation, aligned with criteria for HTA and reimbursement;
3. Support open science and make sure research results of all clinical studies and collected real world data (RWD) are publicly available in order to enable further studies and better decision-making in health;
4. Make sure regulatory incentives (e.g., orphan designation) and related or other patent protection are transparent and prevent/penalise their misuse (e.g., salami slicing, pay-for delay agreements);
5. Insist on greater accountability and reporting on investments of public funding in R&D (including tax breaks, staff and other in-kind support);
6. Support the pooling of resources and international cooperation between European countries in order to prepare health systems for (i) the arrival of new medicines and technologies, (ii) conducting high quality HTA; and (iii) sharing information about prices and pricing and reimbursement strategies, in order to enhance countries' ability to (a) prioritise medicines with higher clinical value, (b) review and adjust prices based on new evidence, and (c) effectively negotiate the prices of medicines.
7. Conduct a study on the role of price transparency, indicating ways forward to support the key elements of the WHO Transparency Resolution,[42] with particular attention to robust state-of-the-art methods for the calculation of R&D and production costs in the pharmaceutical sector, and suggest ways forward toward Europe-wide implementation of the WHO Transparency Resolution.

Both scientific and policy-driven literature present various options for new business models under which prices and costs become more transparent and the drug price justified.

For example, AIM suggest that a 'fair' pricing policy should reflect and promote transparency but should not depend on it. In the absence of concrete data related to the company's R&D investment, AIM suggest introducing a 'lump sum' of e.g., 250 million EUR for the development of a medicine which should be allocated within the fair price calculation. If a company should claim a larger R&D investment, it would need to deliver supporting evidence. This could be a solution which encourages increased transparency but does not demand a complete disclosure of cost information.

ECL believes that, if increased cost transparency would be a requirement for reimbursement, the pharmaceutical industry could be persuaded to put the ethical flag higher throughout the value chain, from product discovery to the patient access pathway. There could be 'hard' incentives, such as legislation or regulatory approaches demanding more transparency and excluding or penalising companies who do not comply with the requirements. There could also be 'soft' incentives such as rewarding transparency of documentation, prices and costs (e.g., pharmaceutical companies could be encouraged to incorporate responsibility for access and sustainability (CSR) of healthcare systems as part of their market access and pricing strategies for pharmaceuticals), as seen within other commercial areas.

ECL's FAIR PRICE DEFINITION

The notion of a fair price has been discussed by the members of the ECL Access to Medicines Task Force since its very beginning. The Task Force's 2016 Declaration of Intent[43] stated that:

- *Cancer societies of this task force state that all effective and innovative cancer treatments now and in the future should be accessible to patients. Patients cannot suffer from a dysfunctional system and/or unsustainable financial and pricing arrangement in the prescription of medicines.*
- *Medicine prices should be sustainable and proportionate to real cost of research and development and added therapeutic value.*
- *Cancer medicines that have a distinctive therapeutic added value should reach patients in a timely manner, in the safest way and at affordable prices.*

The Let's Talk Access White Paper[44] published in 2018 offered the following definition of a fair price:

- *ECL Access to Medicines Task Force believes that a fair price is transparent, understandable, cost-effective, affordable, and based on objective factors such as R&D investment, delivery, marketing and sales costs, and a clearly defined profit margin connected to the therapeutic value. Fair prices are profitable enough to ensure innovation as well as sustainable.*

In 2019, the Task Force submitted a response to the WHO's consultation related to the definition of a fair price, stating that:

- *A fair price is transparent, understandable, affordable, proportionate and based on objective factors such as R&D investment, delivery, marketing and sales costs, and a clearly defined profit margin connected to the proven therapeutic value (if available compared to other treatments). Fair price is profitable enough to steer innovation in the long term but does not pose a threat to the sustainability of healthcare systems.*
- *The Task Force further underlined: 'Need for the responsibility of health system to ensure the best possible health of the population within the available budget. Need for affordability criteria and sufficient market incentives. Transparency in price setting is key in creating understanding of prices of medicines and enables accountability and is therefore a key component of the definition. The component of therapeutic value should be added to the equation by a clearly defined margin based on available evidence, compared to existing treatment alternatives.'*

Subsequently, the Task Force agreed that there is a need to further analyse the development of prices, different pricing approaches and transparency of costs, prices, and processes. Based on the findings, the Task Force would formulate a new definition of a fair price.

Following the conclusions drawn in this paper, the ECL Access to Medicines Task Force introduces a new definition of a fair price:

A 'fair price' is justifiable, predictable and cost-effective within the aims and priorities of the healthcare systems and the available budget.

At the same time, a fair pricing policy that takes into account the ethical and financial dimensions of patient access to care, affordability and sustainability of healthcare systems should be encouraged and rewarded.*

Whereas *'justifiable'* means a price that reflects the documented and clinically relevant benefit of the medicine, and a reasonable relationship between the cost of bringing the product to market (including R&D, production, marketing) and the price.

Whereas *'predictable'* relates to the need for health payers, policy makers and systems to be able to predict the total costs and of investing in the treatment.

'Cost-effective(ness) could be a common criterion for evaluating whether the price seems 'justifiable', as it links benefits with costs in a systematic way and provides a comparable decision-making tool across healthcare interventions.

Finally, *'affordability'* addresses the financial side of the sustainability of health systems.

A prerequisite for obtaining fairer prices is a higher level of transparency and access to information about end-user prices, documentation of product value and the cost of developing and bringing the pharmaceutical product to market, as well as reimbursement decision-making processes.

* The definition can only be interpreted in the context of the recitals.

FAIR PRICE: THE STAKEHOLDER VIEW

INTERNATIONAL ORGANISATIONS

The **UN High-Level Panel on Access to Medicines** put the topic of access to medicines on the global agenda in 2015, linking the topic to Sustainable Development Goals (SDGs) and the notion of Universal Health Coverage (UHC). The panel endorsed the use of compulsory licensing where necessary and suggested putting conditionalities for publicly funded research in relation to the product affordability. Further, it called for publicly available information on the costs of R&D, production, marketing and the contribution of public funding to the development of a medicines.[45]

The **World Health Organization (WHO)** plays a key role in the fair pricing debate. The WHO technical report on prices of cancer medicines suggested several options to enhance affordability and accessibility of cancer medicines. These include:

- Designing differential pricing sensitive to health systems ability to pay;*
- Enhancing systems ability to review and adjust prices and withdraw funding of superseded and less cost-effective medicines;
- Sharing information on prices and disclosing net transaction prices to relevant stakeholders;
- Reporting the cost of R&D and production, including any source of public funding;
- Pooling national resources and enhancing international collaboration; etc.[46]

Since 2017, the WHO holds biennial Fair Pricing Forum and in 2020 it established dedicated working groups to explore pricing approaches sensitive to health systems' ability to pay and to incentivise innovation while preventing posing threats to the affordability of medicines.[47]

In 2019, the World Health Assembly adopted a resolution on improving the transparency of markets for medicines, vaccines and other health products. The Resolution urged Member States to take appropriate measures to publicly share information on net prices and take appropriate steps to improve transparency in R&D costs, marketing costs, subsidies and incentives and patent status of health products.

The **Organisation for Economic Co-operation and Development (OECD)** published a report in 2017 on new health technologies: managing access, value and sustainability. The report identified an increase in the launch prices of medicines, particularly in cancer and orphan indications and their misalignment with the added value they bring to patients and R&D expenditures.[48] A 2020 report addressing challenges in access to oncology medicines stressed concerns of OECD countries (including EU Member States) about i. the uncertainty of clinical benefit of new cancer medicines; ii. the complexity of reimbursing combination therapies; and iii. the rising expenditure in cancer medicines and growing cancer incidence. The

* It is important to note that price differentiation combined with disclosed prices may create parallel import and encourages collusive price agreements between suppliers. Furthermore, fierce price competition may drive suppliers out of the market [Brassel, Rozanova, Towse (2019), The WHO technical report on the pricing of cancer medicines: missing a central role for value assessment. Research Paper, Office of Health Economics]

report suggested several policy actions, including enhanced monitoring of real-world evidence (RWE) and price adjustment where appropriate, and the harmonisation of outcomes measures, data aggregation, and information-sharing among payers and countries, particularly in the case of rare conditions.[49]

EUROPEAN INSTITUTIONS

Issues concerning access to innovative medicines and their pricing and affordability have been regularly on the table of the EU institutions in the past decade. The 2014 **Council** Conclusions on 'Innovation for the benefits of patients' expressed concern about the negative impact the very high prices of some innovative medicinal products were having on public health expenditure.[50] In 2016, the Dutch presidency further elaborated on the issue in the Council Conclusions on 'Strengthening the balance in the pharmaceutical systems in the EU and its Member States', calling for enhanced cooperation in medicines evaluation and pricing between Member States and asking the European Commission to prepare an evidence-based analysis of the impact of pharmaceutical incentives on innovation, availability and affordability of medicines.[51]

The **European Parliament** issued an own initiative report in 2017 on 'EU options for improving access to medicines' and called for measures to guarantee the right of patients to universal, affordable, effective, safe and timely access to essential and innovative therapies.[52]

The **European Commission** published the first incentives review in 2018.[53] A specific report related to orphan and paediatric medicines is underway. In 2018, the Commission also published a draft regulation on European HTA cooperation[54] which would help Member States pool resources to evaluate the cost-effectiveness and added value of new medicines and medical devices, which would enable them to make well-informed pricing and reimbursement decisions at the national level. The file is still open and under discussion, as Member States have diverging opinions about the appropriate level of harmonisation of methods and uptake of joint clinical assessments.

The EU-funded **EURIPID** project is a voluntary cooperation between European countries on building up and maintaining a database with information on national prices and pricing regulations of medicinal products. Currently, it mainly contains information about list prices of medicines and guidance on external reference pricing. Nevertheless, if there is sufficient political will, there might be a potential to expand the database and include more information about net prices and pricing practices.[55]

In the 2019-2024 legislature, we can expect further elaboration on affordable access and fair pricing, particularly as part of the New Pharmaceutical Strategy for Europe[56] and Europe's Beating Cancer Plan[57] which are both to be published in the form of Commission Communication by the end of 2020. In this mandate, the Commission is likely to review the orphan and paediatric medicines regulations which may have an impact on the availability and affordability of these products. It also aims to propose non-legislative actions on tackling medicine shortages and enhance the role of the EMA and EU cooperation on assessing the cost-effectiveness of medicines and pharmaceutical pricing and reimbursement.

PAYERS AND POLICY MAKERS

Although there are fundamental differences between the universal health systems in the Nordic countries, the UK, France, Cyprus etc. and the insurance-based systems in Germany, Austria, The Czech Republic, the Netherlands, Belgium or Spain, they do have something in common.

In most European health systems, national or regional public payers and policy makers must ensure that their populations have access to sufficient and timely health care of sufficient quality. The health care provided must be equitable, safe, and at the same time, affordable for the payers within the budget available to them. Therefore, it is in their clear interest that the health services they invest in provide as much health as possible for the money available. For payers, a 'fair price' should be justifiable, predictable, cost-effective within the aims and priorities of the healthcare system and the available budget.

The **AIM**, organisation connecting non-profit health payers and insurance funds, introduced a pricing model which added a 'lump sum' of 250 million EUR for the development of a medicine which should be allocated within the fair price calculation. If a company claimed larger R&D investment, they would need to deliver supporting evidence. This model encourages increased transparency but does not depend on full disclosure of information.

Payers, policy makers, and legislators have a very large stake in fair pricing. However, without international collaboration on standardisation of price approval criteria, HTA methods, and evaluation competences, fairer prices and pricing approaches will not be achieved. Since 2015, Europe witnessed a wave of creation of voluntary inter-governmental initiatives, such as the **Beneluxa** and the **Valletta Declaration**, which contribute to knowledge-sharing on best practices and method harmonisation in horizon scanning, HTA, and medicines pricing and reimbursement.

ACADEMIA

The available literature offers numerous models developed by academics to achieve sustainable pricing of medicines. Recently published models include:

Prof. Lieven Annemans developed a value-based pricing model which takes affordability into account and suggests combining cost-effectiveness criteria (incremental cost per QALY gained) with budget impact criteria by adjusting the cost-effectiveness threshold under which reimbursement is provided according to the expected budget impact of the medicine.[58]

Dr. Carin Uyl de Groot suggested calculating a maximum price for novel anti-cancer medicines using an algorithm which combines the R&D costs and new medicine costs (manufacturing, sales, marketing and overheads) with a profit margin which is linked to the clinical benefit, the number of patent years after registration and the number of patients worldwide. This maximum price should be set and controlled by a central organisation in the EU. The suggested approach incorporates transparency, maximum price and links potential profit directly with product value.[59]

Prof. Surrie Moon suggest introducing both a price floor (minimum costs of bringing the medicine product to market) and a price ceiling in a maximum price and budget impact that the payers will approve.[60]

Prof. Fatima Suleman suggested a 'de-linkage' strategy where the risk of R&D failure and the R&D component of the prices is paid for separately and in other ways than through the price of the pharmaceutical. This could be done using a push mechanism e.g., through direct public funding of pharmaceutical development or a 'pull' mechanism where the rewards are delivered only after the product development goals have been reached. These approaches address transparency and link costs of bringing the product to market.[61]

Dr. Gilberto Lopes suggested a multifaceted approach for sustainable cancer care which includes a combination of various strategies addressed by different stakeholders. These include changes in regulatory requirements, increased efficiency of healthcare systems, implementation of value-based pricing and measurable outcomes, managed entry agreements, targeting drugs to specific populations, use of cheaper biosimilars, and price differentiation according to ability to pay.[62]

PATIENTS, HEALTHCARE PROFESSIONALS AND CIVIL SOCIETY

European Patients' Forum (EPF), a European umbrella representing 75 chronic disease patient organisations, recently published a paper about the value and pricing of innovative medicines. EPF highlighted the need for: i. common understanding of 'value' and 'innovation'; ii. setting up a high-level multi-stakeholder dialogue about medicines prices and pricing; iii. knowledge exchange about real prices of medicines among public authorities; iv. adopting common principles for the calculation of a fair price; and v. enhanced international cooperation throughout medicines access pathway with a meaningful ionvolvement of patients in the decision-making process.[63]

EURORDIS, a global network connecting over 900 rare disease patient organisation have published a position paper on equitable access to rare disease treatments in Europe. The paper underlined an unsustainable economic model that fuels mistrust between payers and companies and stressed that orphan medicines pose many different challenges to national authorities, as they increasingly tend to reach marketing authorisation with higher levels of uncertainty on efficacy and safety due to small patient population in clinical studies and are often launched at a high price. The paper states that maintaining such an approach is fundamentally unsustainable, and that industry associations, leading corporate players and the investor community must take a firm stance towards a fairer pricing strategy and business model. EURORDIS recommends focusing on early dialogue about added value between developers and public authorities and setting of a transparent framework for the determination of prices based on costs, value and policy-defined priorities, supported by a set of well-defined and well-accepted criteria.[64]

Doctors without Borders (MSF), an international medical humanitarian organisation, believe that this lack of transparency gives pharmaceutical corporations the upper hand in price negotiations, keeping prices as high as possible while overstretched health systems and people in need of lifesaving medicines lose out. MSF point out that there is currently no direct connection between the costs of pharmaceutical R&D and manufacturing, and the prices of medicines. For

instance, MSF report that price transparency for HIV antiretroviral drugs has enabled competition and fair price negotiations. In fact, the price of HIV treatment has dropped dramatically – from around US$10,000 per person per year in 2001 to around $100 today – enabling treatment scale-up to over 22 million people living with HIV/AIDS and saving millions of lives. Regarding the definition of a fair price, MSF believe that two key components are essential: the notion of ability to pay (affordability),[65] and full price transparency of all R&D expenditure, of manufacturing costs, and of how the price is decided.

Health Action International (HAI), a global network of organisations, academics, healthcare professionals and policymakers focusing on improving access to medicines and responsible medicine use, published a comprehensive set of policy recommendations on improving access to innovation in the EU. HAI, among others, focuses on i. tackling the misuse of patents and other IP protection and its impact on affordability of medicines; ii. ensuring publicly funded products are available at affordable prices; iii. enabling full transparency on medicines prices and R&D costs.[66]

PHARMACEUTICAL INDUSTRY

The mission of pharmaceutical companies is to operate to maximise their profit in an ever-changing competitive global market for the benefit of their shareholders. They do so by consistently adapting their strategies to the needs and demands of the various market stakeholders. This includes the product development strategies, market access strategies, marketing strategies and their pricing strategies. This means that they adapt and respond to payer policies and system changes as well as incentives provided to them. A challenge for the industry is that it carries the investment risk and, when there are development failures, (e.g., when the clinical trial does not meet its primary end-points), the companies need to find ways to compensate for their investment loss. This could happen for instance through increased sales of other products or increased prices.

In order for payers to be able to pay for new treatments, industry advocates for several novel pricing approaches. Most of which provide conditional reimbursement, where payment depend on number of patients or other criteria. These include models stated in Figure 4. Apart from the ones already elaborated on above, these include:

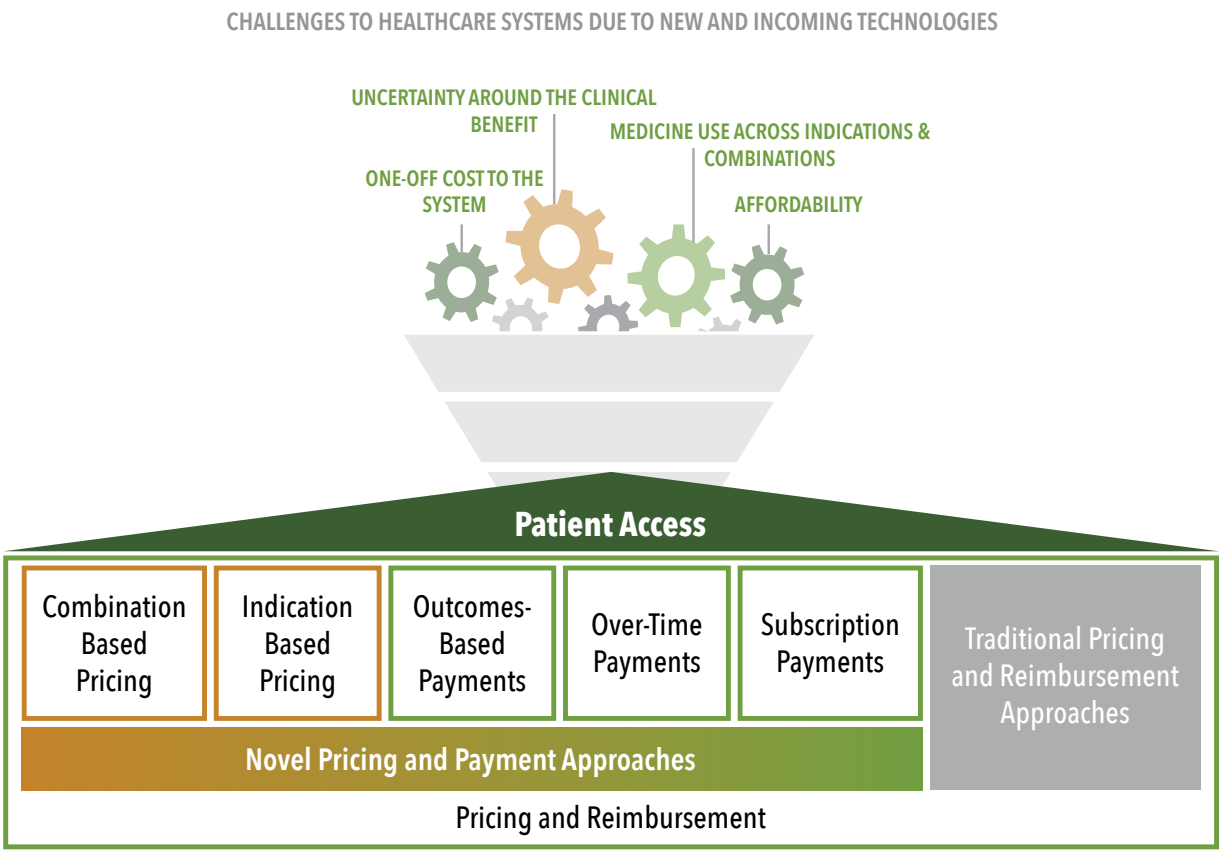
'Combination-based pricing' addresses the fact that many novel cancer treatment strategies are based on the combination of different therapies and the clinical effect of one therapy cannot be isolated from the effect of the other therapies in the combined treatment. Therefore, there is a suggestion to price the treatments in combination.

'Indication-based pricing' suggests that the value of a medicine may vary across indications, and therefore, the price should reflect the observed value across indications, i.e., be higher in indications where the value is higher and vice versa.

'Outcome-based payments' are payments conditioned by a positive result or outcome of the treatment, so there is an observation period and the outcomes may or may not be demonstrated after this period.[67]

'Over-time payments' mean that payments are made over a longer (fixed period) and not up-front. Sometimes these types of payments could be linked to the outcome. Subscription payments are payments up-front decoupled from the number of patients treated.

Figure 4: EFPIA's suggestions for novel pricing and payment models



Source: EFPIA 2020

These suggestions could be part of the **'managed entry agreements' (MEA)** mentioned by WHO which defines them as 'an arrangement between a manufacturer and payer/provider that enables access to coverage/reimbursement of a health technology subject to specified conditions… " or "as risk sharing arrangements'.[68] The WHO distinguishes between two types of MEAs - financial-based and performance-based. MEAs are increasingly used in relation to payment for new cancer medicines. According to the WHO, however, most MEAs implemented in Europe are financial-based. Generally, implementing MEAs – especially performance/outcomes-based ones – can be challenging because they require good governance, data collection design and infrastructure which may not yet be available. However, whether these novel pricing and payments initiatives could provide solutions for better affordability is yet to be evaluated.

CONCLUSION & WAYS FORWARD

The inherent market failure for health services is particularly pronounced in cancer medicines. There is a dilemma between the wish to address unmet medical need, with fast access to new cancer medicines, and the current situation with the lack of robust evidence regarding new treatments' safety and efficacy, growing cancer incidence, increasing prices per patient, increasing total costs and budget impact of cancer medicines which poses challenges to the affordability and sustainability of health systems. With an expected global economic recession due to the current COVID-19 crisis, addressing the issue of sustainability of health systems becomes even more critical than before.

Strategies for obtaining fairer and more transparent prices together with enhanced international collaboration are needed across Europe.

WHAT IS A FAIR PRICE?

In theory, a standardised value-based approach to pricing and reimbursement is desirable, because it addresses the fundamental information need of health systems (*'is the treatment worth it?*). However, this approach should be combined with the notion of affordability (*'can we afford it?*). Additionally, a third relevant question is: *'is there a reasonable relationship between the cost of bringing the product to market and the price?'*

Therefore, the ECL Access to Medicines Task Force suggests the following definition of a 'fair price':

A 'fair price' is justifiable, predictable and cost-effective within the aims and priorities of the healthcare systems and the available budget.

At the same time, a fair pricing policy that takes into account the ethical and financial dimensions of patient access to care, affordability and sustainability of healthcare systems should be encouraged and rewarded.*

Whereas *'justifiable'* means a price that reflects the documented and clinically relevant benefit of the medicine, and a reasonable relationship between the cost of bringing the product to market (including R&D, production, marketing) and the price.

Whereas *'predictable'* relates to the need for health payers, policy makers and systems to be able to predict the total costs and of investing in the treatment.

'Cost-effective'(ness) could be a common criterion for evaluating whether the price seems 'justifiable', as it links benefits with costs in a systematic way and provides a comparable decision-making tool across healthcare interventions.

Finally, *'affordability'* addresses the financial side of the sustainability of health systems.

A prerequisite for obtaining fairer prices is a higher level of transparency and access to information about end-user prices, documentation of product value and the cost of developing and bringing the pharmaceutical product to market, as well as reimbursement decision-making processes.

* The definition can only be interpreted in the context of the recitals.

WHAT SHOULD STAKEHOLDERS DO NEXT?

The ECL Access to Medicines Task Force suggests establishing a **High-Level Working Group on fair pricing** facilitated by the European Commission which would connect all relevant stakeholders, including public authorities, payers, patients, public health NGOs, academia and the industry in order to define a fair price and identify opportunities and challenges connected to different pricing models.

POLICY MAKERS AND PAYERS SHOULD:

1. Expand existing structures, e.g., the EURIPID database, to share information on net prices of medicines and strive toward full implementation of the WHA Resolution on improving the transparency of markets for medicines, vaccines and other health products.
2. Pool resources and enhance collaboration throughout the entire medicines access pathway, to prepare health systems for (i) the arrival of new medicines and technologies, (ii) conducting high quality Health Technology Assessment (HTA) and (iii) sharing information about prices and pricing and reimbursement strategies, in order to enhance countries' ability to (a) prioritise medicines with higher clinical value, (b) review and adjust prices based on new evidence, and (c) effectively negotiate the prices of medicines.
3. Provide structures, control systems and incentives to either reward socially responsible and highly ethical industrial behaviour or punish unethical behaviour;
4. Review regulatory incentives where they may lead to unaffordability of products (e.g., orphan medicines) and ensure that awards for innovation do not lead to a lack of competition and monopolistic prices.
5. Attach conditionalities to both national and European public funding (e.g., Horizon Europe, Innovative Medicines Initiative - IMI) and ensure that public investment in R&D is accounted for and that medicines resulting from publicly funded research are available for a fair and affordable price.
6. Ensure that criteria and processes for priority setting in health care are explicit, transparent and that there is a clear link between priorities, national pricing policies and practices, and the actual price of medicines. Furthermore, pricing and reimbursement authorities should be transparent about their decisions, how they are made, what criteria are used and who is involved in the process.
7. Make fair pricing and affordability of new treatments a core element of the upcoming Europe's Beating Cancer Plan, the New Pharmaceutical Strategy for Europe and other relevant EU policy and legislative activities.

PHARMACEUTICAL COMPANIES SHOULD:

1. Price new medicines fairly and responsibly to ensure that they are accessible and affordable. Pharmaceutical companies should incorporate responsibility for access and sustainability (CSR) of healthcare systems as part of their market access and pricing strategies for pharmaceuticals), as seen within other commercial areas.
2. Apply a higher degree of cost-consciousness (i.e., lowering the cost of bringing the product to market) throughout the product value chain.
3. Be transparent about the costs of bringing the product to market as well as end-user prices (by disclosing these figures to relevant stakeholders, e.g., public authorities).
4. Include HTA and payer considerations early-on in the product development.
5. Incorporate an ethical charter and guidelines within the product development and pricing processes.
6. Focus on steering R&D investments toward areas with higher unmet need and develop pharmaceutical products with added value for patients and public health.

TERMINOLOGY

- Actual (net) price = a price of a medicine paid by the end user, after all discounts and rebates are applied; this price is often not disclosed and remains confidential between the payer and the company.
- Asymmetry of information = a situation where some actors have access to more information than others, e.g., health professionals have the knowledge and access to relevant information about the specific diagnoses and health services they offer, patients and the public do not have the same information, or payers only know prices for a certain product in their own country and companies know all prices globally.
- Beneluxa = a voluntary collaboration between the governments of Belgium, the Netherlands, Luxembourg, Austria and Ireland which aims for sustainable access to, and appropriate use of, medicines in the participating countries by enhanced collaboration in horizon scanning, health technology assessment, pricing and reimbursement, and information and policy experience sharing.
- Compulsory licensing = when a government allows someone else to produce a patented product or process without the consent of the patent owner or plans to use the patent-protected invention itself.
- Conditional Marketing Authorisation (CMA) = For products intended for use in emergency situations, less comprehensive pharmaceutical and non-clinical data may also be accepted to approve the product. CMA can be granted when the benefit-risk balance of the product is (i) positive; (ii) it is likely that the applicant will be able to provide comprehensive data; (iii) unmet medical needs will be fulfilled; (iv) the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to need for further data.
- Cost-based pricing = a medicines pricing model which reflects costs (including R&D, marketing and production costs), profit mark up and R&D investment risk.
- De-linkage = a proposed model for development of new pharmaceuticals where "de-link" refers to isolating cost of R&D from the price, financing the R&D cost from other sources
- Demand = the quantity of a good that consumers are willing and able to purchase at various prices during a given period of time.
- Elasticity of demand = the degree to which the demand for a good changes as its price changes.
- ESMO-MCBS = ESMO Magnitude of Clinical Benefit Scale is a tool developed by European Society of Medical Oncology (ESMO) which uses a rational, structured and consistent approach to derive a relative ranking of the magnitude of clinically meaningful benefit that can be expected from anti-cancer treatments, helping to frame the appropriate use of limited public and personal resources to deliver cost effective and affordable cancer care.
- EUNetHTA = European Network for Health Technology Assessment (EUNetHTA) is an EU-funded joint action between European HTA bodies who work together to facilitate efficient use of HTA resources, create a sustainable system of HTA knowledge sharing and promote of good practice in HTA methods and processes.
- EURIPID = an EU-funded voluntary and strictly non-profit cooperation between mostly European countries on building up and maintaining a database with information on national prices and pricing regulations of medicinal products in a standardised format.
- Hard endpoint vs. surrogate endpoint = a 'hard' endpoint - or a clinical endpoint is an aspect of a patient's clinical or health status that is measured to assess the benefit or harm of a treatment. A clinical endpoint describes a valid measure of clinical benefit due to treatment: the impact of treatment on how a patient

feels, functions and survives. Clinical endpoints may be a clinical event (e.g., mortality,) a composite of several events, a measure of clinical status, or health related quality of life (HRQoL). A surrogate endpoint is an endpoint that is intended to replace clinical endpoint of interest that cannot be observed in a trial - it is a variable that provides an indirect measurement of an effect in situations where direct measurement of clinical effect is not feasible in a reasonable timeframe. A surrogate endpoint is expected to predict the effect of therapy (either benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. In many cases, an effect on a surrogate endpoint will not per se be of any benefit to the patient (biomarkers are typical examples). A surrogate endpoint may be a biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint may also be a clinical endpoint that is used to replace the endpoint of interest, such as an intermediate clinical endpoint.

- Health Technology Assessment (HTA) = a systematic evaluation of properties, effects, and/or impacts of health technology. It is a multidisciplinary process to evaluate the clinical, social, economic, organisational and ethical issues of a health intervention or health technology. HTA measures the added value of a new health technology compared to existing ones.
- ICER = The incremental cost-effectiveness ratio (ICER) is a statistic used in cost effectiveness analysis to summarise the cost-effectiveness of a health care intervention. It is defined by the difference in cost between two possible interventions, divided by the difference in their effect.
- Indication-based pricing = setting different prices for the same product across indications or in distinct patient sub-populations.
- Input prices = all the costs that go into producing a good or service.
- IQWiG = The Institute for Quality and Efficiency in Healthcare (IQWiG) is a German agency responsible for assessing the quality and efficiency of medical treatments, including drugs, non-drug interventions, diagnostic and screening methods, and treatment and disease management.
- List price = a publicly available price set by the manufacturer of a medicine in a specific market (country).
- Managed Entry Agreements (MEAs) = arrangements between companies and healthcare payers that allow for coverage of new medicines while managing uncertainty around their financial impact or performance. MEAs usually include a confidentiality clause preventing public disclosure of price information.
- Marketing authorisation = a regulatory approval for market access granted by the European Commission based on an evaluation of the European Medicines Agency (EMA).
- Medicine access pathway = a process from the early development of a product up to the point where it is administered to the patient; the process includes R&D, manufacturing, HTA, pricing and reimbursement and subsequent availability for the patient.
- NICE = The National Institute for Health and Care Excellence (NICE) is a UK agency which provides evidence-based guidance and advice for health, public health and social care practitioners within the UK National Health Service (NHS).
- Orphan medicine = a product intended for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 people in the European Union.
- Patient outcomes = Patient-centered outcomes are results (end points) of health care that can be obtained from a healthcare professional's ability to care for their patients and their patient's families in ways that are meaningful, valuable and helpful to the patient.

- Payers/Purchasers = health maintenance organisations, insurance companies, management services organisation, or any other entity that pays for or arranges for the payment of any health care or medical care service, procedure, or product.
- Price equilibrium = the market price where the quantity of goods supplied is equal to the quantity of goods demanded. This is the point at which the demand and supply curves in the market intersect.
- Price negotiations = an actual price discussion between manufacturers and payers.
- Pricing / Price setting = establishment of a price by the company based on a set of different components.
- Pricing components = aspects shaping the price of a product; these may include costs of R&D, manufacturing, marketing, added clinical value, profit margin, etc.
- PRIME = a scheme launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need. The scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier.
- Provider = an individual health professional or a health facility organisation licensed to provide health care diagnosis and treatment services including medication, surgery and medical devices.
- QALY = The quality-adjusted life year (QALY) is a generic measure of disease burden, including both the quality and the quantity of life lived. It is used in economic evaluation to assess the value of medical interventions.
- Reference pricing = the external reference pricing (ERP) is the practice of regulating the price of a medication in one country, by comparing with the price in a "basket" of other reference countries. Internal reference pricing is when the price of one drug is compared to the domestic price of therapeutically related medicine.
- Reimbursement = a positive decision by a payer to approve a price set by/with the pharmaceutical company.
- Supplier = a person, or agency or any company that offers medical products.
- Supply = a fundamental economic concept that describes the total amount of a specific good or service that is available to consumers.
- Valletta Declaration = an alliance of EU member states (Malta, Cyprus, Greece, Italy, Spain, Portugal, Romania and Ireland) which aims to explore strategies to jointly negotiate prices with the pharmaceutical industry.
- Value-based pricing = a pricing strategy which sets prices primarily, but not exclusively, according to the perceived or estimated value of a product or service to the customer rather than cost associated with the production of the medicine.

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