POSITION PAPER:

THE VALUE AND PRICING OF INNOVATIVE MEDICINES

EPF European Patients Forum

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INTRODUCTION

This position paper was developed by the European Patients' Forum, a pan-European cross-disease umbrella patient organisation, in consultation with its membership. It builds on a statement first published in 2016 titled "Core principles from the patient perspective on the value and pricing of innovative medicines". Since 2016, the prices of medicines have emerged as a high priority both on the political agendas of EU Member States and of the European Union itself, as well as internationally. This paper has therefore been reviewed and updated to take account of the many developments. New content has been added to provide context and background. EPF's stance on certain concepts and terminology have been clarified and, though the spirit of our principles remains the same, the call for action to different stakeholders has been strengthened.

This paper will inform our advocacy activities vis a vis the new European institutions: the Commission and the Parliament, as well as Member States and health stakeholders. Access to medicines is a priority of the new European Commission for 2019-2024. It features explicitly in the mission letter of the new Commissioner for Health, Stella Kyriakides and includes for the first time a mandate to work for affordability of and access to medicines to meet needs. This work will include addressing medicine shortages as well as cost, whilst balancing these priorities with the requirement to support European pharmaceutical industry.[1] Given the current challenges relating to the COVID-19 pandemic, collaboration between public and private stakeholders in supporting the needed research ***and*** the affordability and accessibility of a new treatment or vaccination, when it comes on the market, is more vital than ever. EPF will engage proactively with the Commission, members of the European Parliament and the Member States to put forward a robust patient perspective[2] in the intense policy debates to come.

EPF's position is based on the premise that health is a fundamental right and a critical investment in the well-being, economic development and cohesiveness of society. Medicines are not consumer goods like any others; patients' lives cannot be measured in purely economic terms. Medicines are an essential public good and a core element of health policy.

SUMMARY

BACKGROUND

All patients in the EU should have timely access to high-quality, patient-centred, equitable healthcare and other support. Timely and accurate diagnosis and appropriate treatment not only improve patients' health and quality of life, but may also offset significant costs to the health and social systems as a result of avoidable worsening of chronic conditions. For many patients with chronic diseases, medicines form a key aspect of treatment. New and better medicines hold the promise of significant improvements to health or quality of life, and even a new lease of life in the form of a cure. Vast progress has been achieved in many disease-areas, notably in HIV/AIDS with antiretroviral therapies and much improved treatment regimes; certain cancers, such as chronic myeloid leukaemia where five-year survival has risen from less than 20% to over 90%; and Hepatitis C, where 90% of treated patients can be cured with a relatively short course of treatment.[3]

Access to healthcare, including medicines, is a fundamental patients' right. Patients will only benefit from innovative therapies if they are available in a timely manner, accessible and affordable to all who need them. Access to medicines can be framed in similar terms as access to healthcare generally, following EPF's principle of equitable access based on needs not means:

- ***Availability:*** the medicine needs to be available in the market;[4]
- ***Affordability:*** patients should not suffer financial hardship as a result of seeking treatment, and healthcare systems should not suffer financial hardship as a result of seeking to provide treatment for their citizens;
- ***Adequacy:*** the medicine should be safe, of high quality and effective;
- ***Appropriateness:*** the medicine needs to be appropriate for patients' needs;
- ***Accessibility:*** the medicine should be distributed through reachable channels, without geographical or time barriers.[5]

The European Union and the EU Member States are committed to achieving the **UN Sustainable Development Goals.** The health targets under Goal 3 "ensuring healthy lives and promote wellbeing for all at all ages" call for universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all by 2030.[6] But the healthcare systems of even wealthy EU Member States are struggling to accommodate the cost of some new medicines, and many Member States fear this will undermine their ability to continue to provide universal health coverage in future.

ACCESS TO MEDICINES IS AN URGENT HEALTH INEQUALITY ISSUE

Inequity in access to medicines is a major cause of health inequalities.[7,8] Unacceptable disparities in patients' access persist, both among and within EU countries; it can take years for patients to access some medicines in some parts of Europe after the granting of marketing authorisation.[9] In some cases, especially for cancer medicines, the delay can take years even in the richest countries.[10] Inequalities in access to medicines are contrary to the EU Charter of Fundamental Rights, the EU Treaties' commitment to the principle of well-being[11] and to the fundamental European values of equity, solidarity and good quality in healthcare.[12]

Healthcare systems are confronted by conflicting aims – providing equitable access to innovative medicines, whilst preventing an unacceptable escalation of costs. Unfortunately, too often they try to do this by passing more of the cost on to patients by restricting reimbursement or increasing co-payments – strategies which are not only unacceptable from an equity perspective but also counterproductive, as they worsen health outcomes and exacerbate societal inequalities.[13] Especially in poorer EU states, patients are at higher risk of poverty due to co-payment costs for healthcare and medicines. Similarly, rationing on economic grounds undermines solidarity and equity and threatens the interests, and sometimes lives, of the patients denied access despite medical needs.

Many civil society organisations, public officials, and healthcare professionals consider that new medicines are often too expensive and threaten not only equity of access but also the long-term sustainability of European health and social systems. Although the affordability of medicines has long been a concern for developing countries, it is today global and also affects high-income countries and extends even to older medicines whose patents have expired, such as insulin for diabetes.[14,15]

There is now an urgent need to **work collectively to identify effective solutions at EU level**, and to take concrete steps to ensure that all patients across Europe have access to high-quality, affordable treatments based on their need, not means, without jeopardizing the sustainability of European healthcare systems.

EUROPEAN UNION POLICY

Access to innovative medicines really emerged on to the EU's political agenda in 2014, with **Council Conclusions** on "Innovation for the benefits of patients" that expressed concern that "very high prices of some innovative medicinal products in relation to their benefit to patients" were having an impact on public health expenditure. The Dutch presidency in 2016 took the issue forward with Council conclusions on "Strengthening the balance in the pharmaceutical systems in the EU and its Member States" that went substantially further.[16] The Commission was tasked with preparing an evidence-based analysis of the impact of pharmaceutical incentives on innovation, availability and accessibility of medicines.

The **European Commission** published its first commissioned overview of incentives in 2018.[17] The study by Copenhagen Economics discussed various incentives in great detail and concluded that whilst existing IP rights and incentives stimulate innovation by creating an attractive environment for industry, they do delay the entry of generics, thus pushing up total spending. The report did not make recommendations. As part of the overall reflection, the Commission also published a study on the EU paediatric medicines regulation.[18] New EU rules on Supplementary Protection Certificates (SPC), following the European Commission's proposal to amend Regulation (EC) No 469/2009, were adopted in early May 2019 and will apply from 2022. EU pharmaceutical companies will be able to manufacture certain generic and biosimilar products for export to non-EU markets while the SPC is still in place in the EU, and stockpile them for six months to sell in Europe as soon as the patent extension expires.[19]

The **European Parliament** issued its own-initiative report in 2017 titled "EU options for improving access to medicines." The report called for measures to "guarantee the right of patients to universal, affordable, effective, safe and timely access to essential and innovative therapies."[20] EPF contributed to the report in which calls for action include collaboration on horizon scanning and early dialogue (subsequently included in the HTA legislative proposal), exploring innovative pricing models, voluntary joint procurements and cooperation in price negotiations. The report also called on the Commission and Member States to implement the UNHigh-Level Panel recommendations (see below).

The **new European Commission** under Ursula von der Leyen, which took office in December 2019, will be developing an overall Industrial Strategy. A critical part of this will focus on medicines, with the Commission due to publish its planned pharmaceutical strategy towards the end of 2020. A roadmap was expected to be published in early March 2020 but was delayed by the COVID-19 crisis. As part of the strategy, the Commission is likely to review the Orphan and Paediatric Regulations as well as the base pharmaceutical legislation dating from 2001. It also envisages non-legislative actions on tackling medicine shortages and to enhance EU cooperation on assessing the cost-effectiveness of medicines, pricing and reimbursement.

INTERNATIONAL POLICY

A number of initiatives both at European and global level form a complex, interlinked mix of research and policy. This section briefly outlines recent developments, many of which EPF has participated in.

UNITED NATIONS HIGH LEVEL PANEL ON ACCESS TO MEDICINES

Access to medicines emerged prominently on the global agenda with the 2015-16 **UN High-Level Panel on Access to Medicines,** whose final report[21] made recommendations in the domains of intellectual property, incentives and governance, linking them to the implementation of the Sustainable Development Goals. The Panel's recommendations included ensuring that intellectual protections do not block innovation, that countries should use TRIPS flexibilities where necessary,[22] and putting conditionalities for publicly funded research on transparency and return on investment. It recommends more public investment in R&D, testing new and additional models for financing, and that costs of research should be de-linked from prices. Further, it calls for public reporting on the actions of governments including their strategy to increase access and the governance structures in place; and publicly available information on the costs of R&D, production, marketing and the contribution of public funding to the development of a medicine.

OECD REPORTS ON ACCESS TO MEDICINES

In 2016, the member countries of the Organisation for Economic Co-operation and Development (OECD) – which include EU Member States – endorsed a call by the French Ministry of Health for an international stakeholder dialogue on access to innovative medicines and the sustainability of pharmaceutical spending. EPF submitted a response to the public consultation of OECD and participated in a civil society consultation meeting in June 2017. The OECD's report, **New health technologies: managing access, value and sustainability**, published in 2017,[23] identified the following key trends:

- A growing proportion of "specialty" medicines account for 30-50% of pharmaceutical spending and are predicted to be a main driver of spending growth in future;
- Launch prices have risen sharply in some areas, notably in cancer and orphan medicines;
- High prices do not always correspond to high benefits for patients;
- Orphan incentives are being misused by some companies;
- Emerging "Game-changers" for which the current cost-effectiveness model does not work. Hepatitis C treatments were a genuine therapeutic breakthrough and were deemed cost-effective on an individual basis – but because of the high number of potential patients to be treated, the usual "value for money" logic did not work: countries could not afford them, and patients were denied access – but the company made back 25 times the initial outlay in R&D in less than two years according to OECD data;[24]
- Cases of excessive pricing of generic, sometimes repurposed, medicines.[25]

A second report in 2018 on pharmaceutical innovation and access to medicines[26] concluded that the failures in the system are complex and due to many interrelated factors. It noted that pharmaceutical spending can present good value by reducing other healthcare costs, but sustainable access is a concern. It outlined five principles to improve access: (1) increasing the value of spending; (2) ensuring access in countries at different levels of development; (3) supporting a rules-based system, with transparent criteria that create a more predictable environment; (4) increasing competition, in both on-patent and off-patent markets; and (5) promoting better communication and dialogue between payers, policymakers, industry, and the general public to increase trust.

The OECD examined various policy options, including making the R&D process more efficient and less costly; collaboration on HTA, price negotiations, procurement and horizon-scanning; more effective use of real-world data in medicines evaluation; defining explicit criteria for pricing and reimbursement; optimising the use of managed entry agreements; developing new targeted incentives; and various ways to increase transparency for better informed policy decisions.

WORLD HEALTH ORGANIZATION INITIATIVES

A **WHO technical report on prices of cancer medicines** (2018) contributed further to the debate. Prices of cancer medicines are higher than for other medicines and their costs are 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.[27]

The WHO report proposed several options for expanding access, including strengthening pricing policies; improving transparency around pricing and the costs of research, development and production of medicines; and realignment of incentives. The report countered claims that the high cost of research and development leads to high prices, and called attention to various commercial practices that delay generic medicines' entry on to the markets.

The first **Fair Pricing Forum** was organised in 2017 by WHO in collaboration with the Dutch Ministry of Health. EPF was among the participating NGOs. The report[28] from the Forum outlined several possible actions, such as the establishment of national priorities on medicines, pooling resources, actions to promote generics, and improving transparency on R&D costs and prices. It also proposed voluntary cooperation between payers especially of countries with similar health systems. WHO can facilitate joint activities, such as health technology assessment and horizon scanning, as well as support global collaboration to share information.

The 2017 Fair Pricing Forum defined 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 medicines. In this context, fairness implies positive incentives/benefits for all stakeholders, including purchasers and those involved in the research and development and manufacture of medicines."[29] This definition is undergoing a review and a public consultation was launched following the second Fair Pricing Forum in Johannesburg. EPF submitted a response to the consultation.[30]

WHO is now convening two technical working groups to determine achievable policy options for the short and medium term, one investigating technical options to ensure pricing approaches are sensitive to health systems' ability to pay and the need to ensure universal coverage and the other exploring different models for incentivising health innovation. The working groups will report to the 2021 Fair Pricing Forum.[31]

In May 2019 the World Health Assembly adopted a **resolution on improving the transparency of markets for medicines, vaccines and other health products.**[32] The resolution asks Member States and WHO to create systems to collect and share information about prices, sales, patents, public and private R&D costs, subsidies and other items, and to continue to organise a biennial Fair Pricing Forum. Although some countries blocked the including of wording on the transparency of clinical trial costs, the adoption of this resolution indicated that countries globally recognised a need and were willing to mandate the WHO to act in this area. Access to medicines and implementation of the WHO resolution are high on the priority list of the **WHO European Regional Office** under its new Director, Hans Kluge.[33]

EPF'S CONSIDERATIONS ON FAIR PRICING

This section outlines EPF's considerations on pricing of innovative medicines, recalling the principles outlined in the beginning chapter of this paper – availability, accessibility, affordability, appropriateness and adequacy. EPF considers that decisions on prices of such medicines need to reflect several factors, and the patient perspective should be integral.

PRICES SHOULD CONSIDER VALUE FOR PATIENTS, BALANCED WITH OTHER CONSIDERATIONS

While companies often justify high prices with the high cost of research and development, the real costs are not known and estimates range very widely.[34] Recently, the concept of ***value-based pricing*** has gained attention as part of the discourse on value-based healthcare. The concept is based on the idea that prices of medicines should be linked to the health benefit they bring. This is framed by broader discussions on the need to measure health outcomes, generally motivated by the desire to improve the quality and adequacy of care as well transparency and accountability. It is also proposed that value-based pricing could provide long-term incentives for industry to develop added-value products.[35] However, EPF does not subscribe to the concept of value-based pricing, for several reasons. Firstly, there is no commonly accepted definition of value, and patients' views on medicines' value are still insufficiently taken into account.[36] Secondly, new treatments often come onto the market with considerable promise but also uncertainty about their value for patients – a question we will discuss below. Finally, in our view, focusing on value alone ignores other important considerations, such as affordability.

We do agree that more open debate with all stakeholders, including organisations representing patients, their families and carers, is needed around investment in health, valuable innovation, as well as societal values and preferences and what constitutes a "fair" price" or acceptable return on investment.

EPF believes that the added value of a new medicines for patients should be a strong factor when considering what is a fair price, but it must be assessed in the context of other factors, such as the costs of R&D, direct and indirect contributions from public funding into developing a medicine; affordability to patients; and impact on national health budgets, to ensure that medicines are accessible to all.

TRANSPARENCY OF PRICES

Debating a fair price implies the need for more information about the real costs of medicines' research and development. National decisions taken on pricing and reimbursement are hampered by lack of transparency.[37] The EU-funded project, EURIPID, which includes a price database and guidance on external reference pricing,[38] for example suffers from the key weakness that it does not have access to real prices, which are the result of confidential negotiations. External reference pricing[39] could overcome at least some of its weaknesses if Member States could know the actual prices paid by other Member States.[40,41] Transparency has been a fairly consistent policy recommendation, including of the WHO 2017 Fair Pricing Forum and the 2018 OECD report. However, there are also cautions: full transparency could undermine ***differential pricing***. The OECD thus puts forward various options to try and manage its undesirable effects.[42]

EPF strongly believes that the system must move towards more transparency, for reasons of openness and accountability of the system towards patients and citizens, as well as to correct asymmetries of information between payers and industry. This should support regional collaboration among Member States on pricing and reinforce the negotiation capacity of EU countries, especially small ones.

However, we agree that more knowledge is needed on possible unintentional consequences of full transparency of actual negotiated prices in the long-term. In some specific cases, full transparency might put at risk access in poorer Member States, which in some cases – though not always – do achieve more affordable prices through the confidential agreements. Member States should agree on ***solidarity and fairness in pricing***, excluding poorer Member States from reference pricing "baskets" and restricting parallel trade from poor to richer countries where it threatens supply for the local population. This would require a political rethink of Internal Market constraints, with specific consideration of medicines as a common good that is not like other products.

TRANSPARENCY OF DECISION-MAKING

Lack of transparency undermines trust, legitimacy and accountability in medicines policy. One particular issue is that the ***processes and criteria of decision-making*** along the medicines pathway from marketing authorisation through to health technology assessment, pricing and reimbursement are currently not transparent, especially to patients. The procedures, decisions and criteria used in decision-making must become more transparent and understandable to patients and citizens. The patient perspective must be meaningfully embedded at each step, with patient representatives involved in decision-making.[43] The ***results of all clinical trials***, whether positive, negative, inconclusive or stopped early, must be made publicly available to improve the evidence-base on which critical decisions are made.[44] Overall, there is also a need for more transparency on the relationships and linkages, including financial ones, between all the actors in the system in order to manage potential conflicts of interest and strengthen trust.

DIFFERENCES IN COUNTRIES' CAPACITY TO PAY

Some ***degree of differentiation*** between countries, based on their economic situation, should be taken into account. Currently, in an effort to try to drive down the prices of medicines, Member States often use external reference pricing as described above. Whilst this may generate savings and room for shifting costs in the short term, it has a number of limitations. For example, companies tend to launch first in higher-paying countries and delay, or not launch at all, in a country if it is not deemed commercially worthwhile.[45] ***Differential pricing*** has been put forward as an alternative.[46] This is a strategy whereby prices are set according to countries' different paying capacities. Until now, it has been discussed mainly in terms of "price discrimination" – a type of pricing strategy adopted by companies to optimise market access. However, as a ***political strategy*** driven by collaboration between Member States with the aim of improving equity of access, it has been less explored. One major barrier to differential pricing is the existence of parallel trade,[47] which is based on the principle of free movement of goods within the EU Internal Market but can have adverse effects on availability. The European Commission's report on incentives, while it did not address parallel trade specifically, stated that "the feasibility of parallel trade is likely to have a significant impact on the price setting and launching behaviour of pharmaceutical companies." A second barrier is that Member States would have to agree to limit their external referencing for certain medicines. Approaching the issue on a basis of solidarity across the EU would allow poorer Member States to benefit from lower prices, with an agreement that these should not be referenced by richer Member States. The lower-priced countries should commit to restrict parallel trade only between themselves.

EPF believes that while differential pricing should not be seen as the only or main solution to high prices, it has potential to improve access in low-income countries and for that reason should be further explored from a political perspective. Possible consequences of increasing transparency on the feasibility for differentiating prices should be taken into account, if it might affect patient access. Member States should prioritise the interests of patients and public health over the Internal Market and take action to limit the negative impacts of parallel trade where necessary, on grounds of public health.

PATIENTS ARE CENTRAL TO ENSURING NEW MEDICINES BRING ADDED VALUE

Patients and the public play different and complementary roles in debates on pricing and access. A broad public discussion is needed around societal values, priorities and public health needs; but when it comes to identifying unmet needs of individual patients or for particular diseases, the patients' perspective is indispensable. The patient community has a critical role and responsibility as a healthcare stakeholder group representing the end users and beneficiaries of medicines. The patient perspective is needed in defining the problems and gaps, identifying patients' needs and priorities, and discussing new strategies to improve access for all.[48] Patient organisations can provide a view on how to improve access by "connecting the dots" and suggesting solutions, given our experience and our reading of the measures that have been put in place thus far.

WHAT IS INNOVATION?

The 2010 Belgian EU presidency started a debate with its theme "Innovation and Solidarity", which resulted in the 2013 updated report on priority medicines.[49,50] The 2014 Council Conclusions on "Innovation for the benefit of patients" raised further concerns about access and questioned the nature of innovation. What does "innovative" mean; what should be considered "valuable" innovation; and how should valuable innovation be adequately incentivised and rewarded?

In EPF's view, the term "innovation" carries normative connotations. We understand an innovative medicine to be a new medicine that brings real and concrete added value for patients.[51] Not everything that is new can be considered innovative in this positive meaning of the word; what matters is the degree to which the medicine makes a tangible, positive, difference for patients and the nature that benefit.

Can the current system deliver real innovation? Undoubtedly, in many cases, it has done so – there have been many important success stories for patients and for society. Vastly improved outcomes have been seen in many cancers, for example, thanks to new therapies. But, also, in some areas the answer would seem to be: not very much, or only very incrementally. There have also been growing concerns on the part of governments, public institutions, but also medical professionals, about the added value of some new medicines.[52,53] Several studies have found that a significant proportion of new medicines cannot demonstrate important clinical benefit, even after several years on the market.[54,55]

A cancer patient commented that such figures "should give pause for thought to those lobbying for accelerated access to new cancer medicines, including patient organisations.[56] In January 2018, the European Commission's Expert Panel on effective ways of investing in Health (EXPH) issued recommendations for addressing the uncertainties around the benefits of new medicines, improving patients' timely access to valuable medicines, exploring innovative payment models, and steering rewards for innovation especially towards unmet needs and neglected areas. It also called for methodologies to measure the social value of medicines and to use these methods systematically in, for instance, health technology assessment.[57]

ASSESSING THE REAL VALUE OF INNOVATION: PATIENTS' PERSPECTIVE IS KEY

The concept of "added therapeutic value" is at the heart of the current discussions around medicines pricing. It refers to a therapeutic advantage offered by a new medicine compared to existing ones.

However, there is no universally agreed definition of the concept. A 2015 European Parliament study defined it as "the incremental 'therapeutic value' brought by a new drug or intervention compared with the best available treatment options already on the market. The therapeutic value can be defined in terms of patient-relevant endpoints and relevant levels of effectiveness, efficacy, and safety." [58]

Patients' engagement is vital – both from a moral perspective, because the decisions directly impact patients' lives and well-being, but also from a practical perspective, because **a meaningful definition of "value" and "added therapeutic value" is only possible with the involvement of patients.** It is arguably unethical to spend limited public funds on therapies that do not have demonstrable added value, whilst it is also unethical for patients to be needlessly exposed to therapies that may harm them while not providing any benefit. It is difficult, however, to comment conclusively on assessments on specific medicines, as long as it is unclear how the patient perspective was incorporated in them.

Meaningful patient engagement is far from being a reality in research. Many clinical trials still do not include outcomes that matter to patients, including quality of life. Existing measures to capture those outcomes are not yet good enough. Uncertainties about added therapeutic value highlight the need for better, earlier, and more meaningful patient involvement in setting research priorities and throughout the research and development process.

Patients can have different priorities in terms of quality of life and prioritised clinical outcomes, and different levels of acceptance of risk, compared to researchers, medical professionals or regulators.[59] The EPF-co-led project PARADIGM is driving good practice in patient engagement in pharmaceutical research; the EU Innovative Medicines Initiative (IMI) adopted a progressive strategy to involve patients in deciding the research agenda and facilitating meaningful patient engagement in relevant projects, which should be adopted by its successor programme. However, there is a need to go beyond individual good practices and mainstream a partnership approach in research.

The importance of incorporating the **patient perspective in health technology assessment** is increasingly recognised,[60,61] with patient-reported and patient-relevant outcome measures in HTA considered necessary – but in practice, patient involvement in HTA is still very limited. So far there is no consensus on the best methods of involving patients.[62] The patient's experience of living with a condition and with different treatments may be difficult to capture fully in formal quantitative measures, and therefore qualitative evidence also needs to be integrated. Regrettably, the EU legislative proposal on HTA did not fully take on board recommendations for patient involvement, given the cumulative experience and added value shown in the EU regulatory context.[63]

EPF calls for both industry and academic researchers to work towards embedding meaningful patient involvement in the R&D process, following existing best practice guidance[64] to ensure that by the time new medicines are submitted to regulatory assessment, they can demonstrably present better added value for patients. Similarly, national HTA bodies should ensure that patients are fully included in the HTA process, in line with EPF's recommendations.[65]

ADAPTING TO SCIENTIFIC AND TECHNOLOGICAL PROGRESS

The landscape of research and development of new medicines is changing rapidly. On the one hand, many "blockbuster" medicines reaching the end of their protection periods opens up opportunities for generic and biosimilar versions to become available. This is good news for patients, as generics entry can considerably lower prices paid by healthcare systems.[66] On the other hand, scientific knowledge is advancing fast. New, potentially ground-breaking, discoveries are being made, such as cures from chronic infection, advances in the fields of immuno-oncology, and in personalised medicine and gene therapies.[67] This is also good, as it promises more effective and personalised solutions to patients' needs. Yet, these new treatments are usually "specialty" and focused on small, differentiated patient groups. They are often very expensive.[68]

Scientific advances in the area of personalised or precision medicine[69] may have a major impact on medicines development, authorisation, pricing and reimbursement in the longer term as science moves towards more targeted populations, precision therapies, and predictive medicine. Personalised or stratified medicines, combinations, borderline products,[70] and advanced therapies will require new ways of evaluation. They will also need new ways of managing clinical use.

Many new products, especially those developed for small populations, involve uncertainty regarding their long-term effectiveness at the time of marketing authorisation – the evidence promises added value, but not enough comprehensive data are available to back up the estimation. Such products may demonstrate their added value over time, thanks to the ongoing collection of real-world data. There may still be a solid case for authorising them because ofurgent unmet needs of patients, given a positive benefit-risk balance.

Medicines are more and more often approved after phase II trials on small populations. Thus, even when an initial assessment shows a positive benefit-risk balance, additional data will need to be collected from real-world use to confirm or otherwise an initial conditional approval.[71]

The **European Medicines Agency** has several tools at its disposal. Its PRIority MEdicines scheme (PRIME) aims to improve efficiency of R&D in diseases where patients have limited or no treatment options. It provides enhanced regulatory support to candidates.[72] Discussions around adaptivepathways[73] seem to have stalled, but it is increasingly recognised that medicines of the future will require different regulatory approaches and much closer collaboration between the industry, regulators, HTA, payers, patients, and medical professionals.[74] Repurposing old medicines for new conditions offers another avenue, particularly as genomic analysis becomes more sophisticated. The European Commission's expert group on Safe and Timely Access to Medicines for Patients (STAMP) explored ways to use existing EU regulatory tools to improve patients' access to medicines, focusing, in particular, on repurposing medicines.[75] There is a need to align evidence requirements between regulatory assessment and marketing authorisation on the one hand, and health economic/relative effectiveness assessment and pricing and reimbursement decisions on the other hand. This will help identify anticipated benefits, value and outcomes for patients. Early dialogue[76] with all stakeholders can help align the evidence requirements between different actors, make the process of R&D more predictable, and enable Member States and patients to have more input in the R&D process.

REAL-WORLD DATA ON OUTCOMES THAT MATTER TO PATIENTS

Systematic collection of real-world data is key to evidence-based decision-making on medicines. It is needed both to identify adverse reactions that might affect the benefit-risk balance of a medicine over time and to capture treatment outcomes, both successful and unsuccessful. **Well-designed, interoperable disease registries that collect data on those outcomes that matter most to patients** are of key importance. Regulators and payers should ensure companies comply with their data-collection obligations, and the information collected should be made quickly available to regulators, medical professionals, industry and patients, so that appropriate actions can be taken. Governments should also collect data on the incidence, prevalence, mortality, quality of life and overall survival by disease-area, as well as the cost of treatments. From a patient perspective, Managed Entry Agreements that collect real-world data of treatment outcomes over a longer time and link this to pricing and reimbursement to added value can be interesting, as they are aimed at managing uncertainties and ensuring that the right patients benefit from the treatments. However, MEAs can be onerous and costly to implement, and are not suitable for all medicines.[77,78]

EPF believes a more comprehensive, robust and smart approach for collecting real-world data is needed, with full involvement of patients in the process. A new, collaborative mind-set, involving early dialogue between all of the stakeholders at EU level is needed from the earliest stages of medicines research and development, building on existing examples.[79] Mechanisms for patient input must be expanded and strengthened, both at EU level and nationally. Patients' privacy, confidentiality and rights must be fully respected in the development of frameworks for collection and use of real-world data.[80]

MORE COUNTRY COLLABORATION ON PRICE NEGOTIATIONS

Governments should see funding for health as an investment that will contribute to greater economic benefits, for example by enabling more health sector jobs in the public and private sectors, in addition to keeping the population healthy. Greater investment in R&D prioritization should result in development of products that respond to public health needs." More cooperative approaches would be helpful, for example with governments sharing information on pricing, and gaining greater leverage when negotiating prices. In 2015, EPF and EURORDIS published a joint letter calling on pricing and reimbursement authorities to take a collaborative European approach to overcome fragmented negotiations with pharmaceutical companies.[81] Since then, several regional clusters have emerged, including Beneluxal, the Valletta Declaration, and the Central Eastern Europe group. The International Horizon Scanning Initiative, launched in October 2019 by nine countries, seeks to identify innovative medicines before they come on the market and is expecting first results around end of 2020.[82] These initiatives are at an early stage but may show concrete results in time.[83] To date, they remain somewhat opaque to patient organisations, and it is not clear to what extent the patient voice is heard in these exchanges.

REALIGNMENT OF R&D INCENTIVES

Research and development in pharmaceuticals should be geared towards unmet needs of patients and of public health, as already stated in 2014 by the WHO report on Priority Medicines for Europe and the World. Since then, much attention has been devoted to exploring the potential of alternative business models, including in the UN Panel and the WHO Fair Pricing Forum. Currently commercial entities, whose priorities must be driven primarily by shareholder value, are focusing on what is commercially attractive rather than public health needs per se. However, this model is not delivering needed innovation for many critical health needs, in particular poverty-related and neglected diseases as well as antibiotics.[84,85] Research priorities can be steered, for example, through more publicly funded research (including basic research, comparative research on existing treatments and treatment combinations, and repurposing), and by explicit agreement on what the public health priorities are.

The WHO Fair Pricing Forum noted that achieving fairer pricing of new medicines will challenge the current model of R&D. "Governments would need to take a bigger role in investing in R&D, including via public-private partnerships, and conditions should be attached to research funding to ensure public investment is "explicitly taken account of in pricing discussions and the results are made publicly available." De-linking costs of R&D from medicines prices are being explored in various context. At present, the concept and consequences are not yet fully understood, and this is not possible without knowledge of what inputs feed into pricing decisions, and of how different elements contribute – investment into research and development, commercial acquisitions, marketing, etc. – that is, more transparency. As the WHO notes: "Before de-linkage models

are pursued, better definitions of the inputs into price setting are needed, noting that R&D has to be paid for in order to have the necessary medicines and health technologies."

EPF believes there is a role for developing genuine Public Private Partnerships in addressing unmet needs that can foster innovation. More broadly, EPF welcomes emerging initiatives looking at alternative viable funding models for pharmaceutical R&D, which are particularly relevant when it comes to addressing health needs and health equity globally.[86]

In addition, other issues that need to be addressed in parallel to improve overall cost-effectiveness of care and outcomes for patients include reducing waste in health systems; tackling over-treatment and under-treatment; improving patient adherence; fighting corruption, which is an important access barrier in some Member States; and preventing unethical commercial practices.[87]

CALL ON GOVERNMENTS AND INDUSTRY TO ENSURE EQUITABLE ACCESS

Investment in health and ensuring universal access to new, innovative medicines for all those who need them are political choices. EPF urges decision-makers to reject the "zero-sum-game" approach, whereby health budgets are regarded as fixed and immutable, and take positive action to realise an inclusive society that values health and makes it a political priority. This includes ensuring sustainable investment in health, including healthcare, health promotion and prevention, as called for in EPF's Roadmap on Universal Health Coverage.[88]

We are convinced that investment in valuable innovation will result in a virtuous circle, whereby better health outcomes will eventually contribute to balancing the short-term financial impact of the investment, and possibly even generate greater efficiencies and savings in the entire economy in the long term. We therefore call on European decision-makers and stakeholders to put patients' health first and ensure EPF's core principles on value and pricing of innovative medicines are applied to the fullest extent. EPF and our members will continue to play a constructive role in helping to achieve this.

Companies, in turn, should commit to ethical practice within and also outside the field of R&D, including transparency and good commercial practices. Practices such as "ever-greening" of patent protection and deals to delay the entry of generic products onto the market, and "price-gouging" – whereby certain companies acquired old, neglected drugs and turned them into costly 'new' drugs – are not acceptable and should be sanctioned.

Patient organisations often work with pharmaceutical companies in therapeutic research and development. Given that meaningful incorporation of patients' perspectives in R&D contributes to the development of new therapies that add more value for patients, this partnership is as important as it is delicate. Certain preconditions must apply in order to make collaboration fruitful. EPF has worked, inter alia through the EUPATI and PARADIGM projects, to develop guidelines and tools for ethical collaboration.[89] We call on pharmaceutical companies to respect ethical guidance when involving patients in their research activities. Patient involvement must be meaningful, not tokenistic.

If patients partner with industry in order to develop new and better treatments, but at the end of the day, the same patients cannot have access to these treatments because they are too expensive for the public health systems, this is a break of the fundamentals of the partnership principle. Prices of medicines cannot simply be based on strategies to maximise profit without ensuring access to all who need them. Industry should ensure the end products of its R&D provide added value for patients and that they are priced so they are affordable to patients and to health systems whilst providing reasonable returns on investment.

EPF CORE PRINCIPLES AND RECOMMENDATIONS FOR THE VALUE AND PRICING OF INNOVATIVE MEDICINES

EPF CORE PRINCIPLES AND RECOMMENDATIONS

HEALTH AND ACCESS TO INNOVATIVE MEDICINES

1. Health is a fundamental right ***as well as*** a critical investment in the well-being, economic development and cohesiveness of society.
2. Medicines are not a consumer good like any other; and patients' lives cannot be measured in purely economic terms. Medicines are an essential public good and a core element of health policy.
3. Patients' needs go beyond medicines and include other therapeutic options, social and community services and peer support. Innovation should be encouraged in this wider sense,encompassing better ways of structuring and delivering integrated health and social care; more efficiency and effectiveness; social innovation; and the development and effective use of new user-driven technologies.

THE CENTRALITY OF PATIENTS

1. A common understanding is needed on the concepts of "innovation", "value" and "added therapeutic value." Patients' views should be central to this understanding, including patients' perceptions of quality of life, patient-relevant clinical and quality-of-life endpoints, and patients' views on benefit/risk.
2. Patients should be recognised as an essential stakeholder group in medicines pricing and value assessment, and the patient perspective should be at the heart of every assessment.
3. Investment is needed in frameworks, structures and methodologies for meaningfully incorporating patients at all stages, from setting research priorities to clinical research, regulatory assessment, Health Technology Assessments, and pricing and reimbursement decisions.

CALL FOR ACTION TO EU MEMBER STATES, EUROPEAN COMMISSION AND PHARMACEUTICAL INDUSTRY

1. The European Commission should implement the European Parliament's call to set up a ***High Level Strategic Dialogue*** co-ordinated by the Commission, which should build on the achievements of the High-Level pharmaceutical Forum and include patient organisations, to reflect and establish concrete and comprehensive strategies to achieve a framework for fair and equitable access in the short, medium and long term.
2. ***A framework for fair and equitable access*** should maximise societal benefit and patient access whilst avoiding unacceptable impact on healthcare budgets should be developed at EU level, through a consultative process led by governments with the participation of all stakeholders including patients. Such a framework should encompass at least the following elements:
    - Closer collaboration by Member States on price negotiations and scaling-up of pilots on early dialogues;
    - Transparency of real prices, at least to Member States and other payers in their negotiations with industry;
    - Adoption of common principles and mechanisms for encouraging and rewarding innovation in order to encourage continued investment in R&D, based on the evaluation of the current EU IP and incentives legal framework;
    - Exploration of innovative models for incentivising research & development especially in areas of high unmet need;
    - Exploration of the potential of optimal use of mechanisms such as adaptive pathways, managed entry agreements and others for optimising access and determination of value;
    - More thorough exploration of differential pricing mechanisms, barriers and potential solutions to dealing with practical issues such as parallel trade;
    - Common EU principles for calculating a fair price, taking into account the specifics of each Member State.
3. ***Pricing and reimbursement authorities*** should be transparent about their decisions, how these are made, what criteria are used, and who is involved in the process. Information explaining decisions should be available in an easily accessible and understandable format that addresses the specific questions of patients and the public.
4. ***Cooperation between Member States*** on medicines pricing should take place on the basis of cross-EU solidarity and include meaningful involvement of patient organisations as well as an appropriate level of transparency towards patients and the public.
5. ***The real costs of developing the therapy and/or acquisition*** must be made transparent, including contributions from public investments, infrastructure, etc.
6. ***Pharmaceutical companies*** should price new medicines fairly and responsibly to ensure that they are accessible and affordable. Pricing should consider inter alia a country's relative capacity to pay; budget impact; the extent of public funding that contributed to the development of a medicine; and the need to ensure universal access.
7. The ***European Commission should collect and analyse data and provide public reports on access to medicines and access barriers faced by patients*** in different EU member states, including medicine shortages, bad commercial practices and price increases including of "repurposed" products, and other barriers.
8. The ***EU should foster research and incentives based on patients' unmet needs*** including under-represented patients (such as women, older people, children). Adequate ***EU investment in biomedical research*** should be secured in the future 9th Framework Programme, and funding for patient organisations' involvement in research projects should be ensured.
9. EU public funding for research should focus on patients' unmet needs and ***should build in a return on the public investment*** with conditions such as affordable and equitable access, non-exclusive licencing and open access publication of results. Open data requirements should be strengthened and incentivised.
10. ***Transparency of the entire system*** must be improved, including transparency of research, registration and publication of all clinical trials, and transparency of financial and other links between the industry and public institutions, healthcare professionals, academic researchers and non-governmental organisations.

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This is a position paper of the European Patients' Forum, an umbrella organisation of patients' organisations across Europe and across disease-areas. Our 74 members include disease-specific patient groups active at EU level and national coalitions of patients.

Our position paper and its key messages have been developed in a consultative process together with our members. We would like to express our special thanks to our membership for their support and dedication to this work.

Please visit www.eu-patient.eu/Members/The-EPF-Members for a full list of all EPF members.

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EPF is committed to transparency and independence in all aspects of our work in accordance with our Code of Ethics and Framework for working with funding partners. In keeping with our commitment to transparency, you can find out how EPF works with its sponsors, including our ethical guidelines and complete financial information on our website:
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