EPF Draft Position on Value and Prices of Innovative Medicines 2018 – Consultation Paper

June 2018, V.3 for web-meeting

Confidential version. Please do not share!

Contents

Preface: Why this review?

This document has been prepared by the EPF Secretariat for consultation with the membership. It builds on and extends a paper published in 2016 titled “core principles from the patient perspective on the Value and pricing of innovative medicines”.

The objective of the review and update is to take account of several developments in this area since the publication of EPF’s 2016 paper; clarify EPF’s take on key concepts and terminology; and clarify and strengthen the call for action to different stakeholders.

The main changes made are as follows:

- New chapters have been added to provide context and background information. New chapters are highlighted (only in this version);
- New content has been added for some sub-chapters;
- Substantial changes and additions in the text have been given in blue text for easier reference; there are some internal explanatory footnotes, which will be removed from the final version of the paper;
- The order of the paper has been adjusted to have a more logical structure;
- The key principles have been revised and expanded.

Introduction

The European Patients' Forum's vision is that all patients with chronic and/or lifelong health conditions in the EU have access to high quality, patient-centred equitable health and social care. Access to healthcare, including to medicines, is recognised as a fundamental right and promoted as a common EU policy. Timely access to accurate diagnosis and appropriate treatment not only improves patient health and well-being but can also offset significant costs to the health and social systems as a result of avoidable exacerbation of health conditions. For patients with chronic diseases, medicines form an important, sometimes crucial, aspect of treatment. New and better medicines hold the promise of significant improvements to health or quality of life or even a new lease on life in the form of a cure. 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[i];
- *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.[1]

Inequity in access is a major cause of health inequalities.[2,3,4] Unacceptable disparities in patients' access to medicines persist, both among and within EU countries; and it can take up to 10 years for patients to access some medicines in some parts of Europe after marketing authorisation. Inequalities in access are contrary to the EU Charter of Fundamental Rights, the EU Treaties' commitment to the principle of well-being[5] and to the fundamental European values of equity, solidarity and good quality in healthcare.[6]

EU Member States have committed to the **UN Sustainable Development Goals**. The health targets under Goal 3, "Ensure healthy lives and promote wellbeing for all at all ages," calls 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.[7] But the healthcare systems of even wealthy Member States are struggling to accommodate the cost of some new medicines. Since the publication of EPF's paper in 2016, prices of medicines have continued to attract attention, in the media, in politics and society in general. They have become a high priority issue on the political agendas of EU Member States and of the European Union itself.

There is now an urgent need 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. In EPF's view, as a healthcare stakeholder representing the "end users" and beneficiaries of medicines the patient community has a role and a responsibility. We can provide a view on how to improve access by "connecting the dots" and suggesting solutions, given our experience and our reading of the

[i] Regardless of the size of a country, industry marketing strategies, expected profits or compliance with national regulations.

measures that have been put in place so far. The patient perspective is needed in defining the problems and gaps, defining the needs and priorities, and discussing new strategies to improve access for all. As an example, the four-pillars approach outlined in the EURORDIS reflection paper "Breaking the Access Deadlock to Leave No-One behind" is a consensus-based attempt to propose solutions based on existing processes that have solid legislative and regulatory foundations.[ii]

Our position starts from 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; and patients' lives cannot be measured in purely economic terms. Medicines are an essential public good and a core element of health policy.

The updated report Priority Medicines for Europe and the World (WHO, 2013), the reports of the Belgian EU presidency on Innovation and Solidarity (2010), and the Council Conclusions on Innovation for the benefit of patients (2014) have raised 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 word innovation carries with it normative connotations. We understand an innovative medicine to be a new medicine that brings added value for patients.[8] Not everything that is new can be considered innovative in this positive meaning of the word, even though the medicine's molecular structure or mechanism of action could be new. What matters is the degree to which the medicine makes a tangible (positive) difference for patients and the nature that benefit.

What is driving the cost of medicines

The industrial research and production process of new medicines is changing. On the one hand, many so-called "blockbuster medicines" have reached or are soon reaching the end of exclusivity so there is an opportunity for generic versions to become available. This is good news for patients, as generics entry can considerably lower prices paid by healthcare systems.[9] 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[10] for example for a specific form of blindness, haemophilia, sickle cell disease and muscular dystrophy. 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 differentiated, small patient groups. They are often extremely expensive.[iii][11] **Patients will only benefit from new therapies if they are accessible in a timely manner and affordable to all who need them.**

Concerned about the long-term sustainability of their health systems, in 2016 the OECD member countries endorsed a call by the French Ministry of Health for the OECD to provide a Secretariat for an *international stakeholder dialogue on access to innovative medicines and the sustainability of*

Commented [K1]: EURORDIS says: Using Luxturna as n example is out of place as related to a very specific disease. They advise to use perhaps more common therapies that are equally expensive with the potential to be extended to more common form of cancer (for example Kymriah (Novartis) and Yescarta (Kite / Gilead).
EPF: This example was included because it illustrates the dilemma of how even a relatively small number of patients treated can eat up enormous amounts of money if treatment super expensive – and in future there may well be more such cases, what happens then?
We can add another example if we can get a more precise wording.

[ii] reference and link to the paper to be added

[iii] For example, Luxturna recently approved by the FDA is a "landmark" gene therapy that treats a rare, inherited form of blindness. The one-time treatment corrects a faulty gene to improve vision. However, its price-tag is set at $850,000 [€692.140], "so daunting that its maker will offer health insurers partial rebates if the drug doesn't work and is seeking to pilot an instalment payment option". In the US, there could be 1000-2000 potential patients with the specific genetic mutation, making the total cost of treating all them $850 million to $1.7 billion. Novartis has bought the commercialisation rights for the therapy outside the US reportedly for €137 million.

pharmaceutical spending. The OECD has referred to a general feeling that there are serious system failures in pharmaceuticals, current incentives are not producing results for society, the quality of innovation is not what it should be, and too many patients do not have access. In early 2017 the OECD published a report, "New Health Technologies: Managing Access, Value and Sustainability"[12], which identified the following trends as contributing to high costs:

- An increase in "specialty" medicines that are very expensive; they account for 30-50% of pharmaceutical spending and are predicted to be main driver of spending growth in future;
- Launch prices have risen sharply, notably in cancer and in orphan drugs;
- High prices do not always correspond to high benefits for patients;
- Orphan status is being misused by some companies;
- Game-changers: 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 does not work in such cases: 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[iv];
- Cases of "price gouging" on repurposed therapies, such as the Epipen case.[13]

Initiatives at EU and international level

Several initiatives have started at European and international level to look at how pharmaceutical innovation could be improved, medicines made more accessible, and the right incentives ensured so that innovation produces results that societies want.

International perspectives: OECD, UN and WHO

In November 2015, UN Secretary-General Ban Ki-moon convened a **High-Level Panel on Access to Medicines**[14] with the objective "to review and assess proposals and recommend solutions for remedying the policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health in the context of health technologies." The *final report* of the panel[15] presented in June 2016 made rather far-reaching recommendations in three domains, linking them to the implementation of the UN Sustainable Development Goals. These include:

- Intellectual property: ensure IP protections do not pose barriers to innovation; use of TRIPS flexibilities where necessary;[v] publicly funded research should adhere to conditionalities such as transparency and return on investment.
- Incentives: more public investment in R&D; new and additional models for financing R&D (prizes, one-off grants) should be tested; governments should negotiate a binding convention on R&D for public health needs, delinking costs of research from end prices;
- Governance:

[iv] Today, the prices of hepatitis C medicines are significantly lower than initially due to competition, though it has taken some years. Moreover, prices were lowered as a result of confidential (secret) negotiations with governments though this exacerbated disparities with richer and bigger countries having better prices than smaller and poorer ones.

[v] Note on TRIPS flexibilities as regards patent rights (e.g. compulsory licensing): some countries have threatened to use it to address public health issues – and according to some media coverage, this alone may have had an effect in pressuring industry to lower prices; however, as far as we can see they have not actually been used within the EU. The EP report reminds Member States that they can be used in exceptional cases; the UN panel as above recommends their use if needed; however, most Member States would probably not consider them politically palatable options.

- Governments should review and monitor access status in their county through a human rights lens; appropriate structures to be set up with civil society participation; UN should set up independent review body and Task force to 2030 (duration of the SGDs);
- Private companies should report publicly on what they have done on access and have a strategy and governance in place for this; governments should require information from companies on the separate costs of R&D, production, marketing etc., as well as public funding they receive including tax credits and subsidies;
- WHO should maintain a cross-country registry of prices of originator and generic medicines. All (non-identifiable) data from all clinical trials should be made accessible through registries; trials protocols etc. should be made available in the public domain. Governments should establish international database for the patent status of medicines, including vaccines.

A *"Fair Pricing Forum"* organised jointly by the **World Health Organization** and the Dutch Health Ministry was held in May 2017. It debated "difficult subjects", such as the desirability or not of the concept of "value-based pricing" (as used by the industry), the need for more transparency, and de-linkage between the cost of R&D and prices of medicines. This will likely not be the last such meeting. WHO Director-General Tedros Adhanom Ghebreyesus, when taking up his post, stated his intentions to take on medicines pricing and access, possibly by using the recommendations of the UN High-Level Panel, for example by pressing industry to be transparent about all their costs including research and development, production, marketing and distribution. Recently, a report on shortage of and access to medicines and vaccines[16] has been presented and based on this Tedros has been asked to work with member countries on a *roadmap to improve access to medicines and vaccines, including activities, actions and deliverables for the period 2019–2023*. This report makes explicit reference to the UN recommendations despite these having divided country opinions.[17] The report is likely to be adopted by the World Health Assembly in May 2018.

Following the publication of the **2017 report, OECD held a public consultation and stakeholder consultation meetings** with civil society and with industry. EPF submitted a response to the OECD public consultation and participated in a civil society consultation meeting in June 2017. There has been no follow-up, however, since those meetings.[vi]

The Council and Parliament: Calls for political action

Already in 2014, Council Conclusions on "Innovation for the benefits of patients" had 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, and recalled previous Council Conclusions on the "reflection process on modern, responsive and sustainable health systems" (December 2013) and "on the economic crisis and healthcare" (June 2014), which called for cooperation on strategies to effectively manage expenditure whilst ensuring equitable access to effective medicines.

Under the Dutch presidency, the **Council conclusions on "Strengthening the balance in the pharmaceutical systems in the EU and its Member States"** were published in July 2016.[18] These

[vi] Internal note: at the time of writing – however I have been told a report will shortly be published and will update as needed .

conclusions went substantially further. The Council asked the Commission to prepare an "evidence-based analysis of the impact of the incentives (…) on innovation, as well as on the availability, *inter alia* supply shortages and deferred or missed market launches, and accessibility of medicinal products, including high priced essential medicinal products for conditions that pose a high burden for patients and health systems as well as availability of generic medicinal products." Special attention should be given to the supplementary protection certificate (SPC)[vii], the "Bolar" patent exemption[viii], and the incentives included in the EU Regulation on orphan medicines. The analysis should also address the impact of these on the development of new medicines and on pricing strategies. The final version of the Council conclusions *noted* the recommendations of the UN High-Level Panel.

The **European Parliament's own-initiative report** on "EU options for improving access to medicines" (February 2017) [19] supported the Council's call for a Commission study and calls for national and EU-wide measures *to* "guarantee the right of patients to universal, affordable, effective, safe and timely access to essential and innovative therapies". EPF contributed several amendments to the report, which asks the Commission and Council to "develop measures that ensure affordable patient access to medicines, and benefit to society, whilst avoiding any unacceptable impact on healthcare budgets", to apply horizon scanning and early dialogue (now included in the Commission's legislative proposal on *Health Technology Assessment* of January 2018), explore innovative pricing models, voluntary joint procurements and voluntary cooperation in price negotiations. The Parliament calls on the Commission and Member States to *implement* the UN High-Level Panel recommendations.

The European Commission: policy analysis

The European Commission **analysis of pharmaceutical incentives** requested by the Council is currently underway. Parts of the study has been published at the time of writing[ix], and a final report is awaited in 2018. The study will include the following elements:

- An overview of the current EU legislative instruments and incentives for investment in pharmaceutical research and development and marketing authorizations, under Directive 2001/83/EC and Regulation EC 726/2004 on medicinal products for human use; Regulation EC 141/2000 on orphan medicines; and Regulation EC 1901/2006 on paediatric medicines; and
- An evidence-based analysis of the impact of the incentives on innovation, availability (incl. shortages or delayed/missed launch), and accessibility of medicines. This should include "high priced essential medicinal products for conditions that pose a high burden for patients and health systems as well as availability of generic medicinal products."
- Use of the supplementary protection certificate, patent exemptions, particularly the "Bolar"; data exclusivity generally, and exclusivity for orphan medicines specifically.

[vii] Supplementary protection certificates (SPCs) are an intellectual property right that serve as an extension to a patent right. They apply to specific pharmaceutical and plant protection products that have been authorised by regulatory authorities. The EU wishes to provide sufficient protection for these products in the interest of public health and to encourage innovation in these areas to generate smart growth and jobs.

[viii] The principle behind the "Bolar" exemption is that generic companies should be in a position to take the necessary preparatory measures in order to be able to enter the market without delay once patent protection expires (article 10.6 of the Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use).

[ix] to be updated with references to the published studies and brief commentary for the final version

The aim of the analysis, as stated by Commission officials, is not to dismantle the incentives framework, but to understand better the links with prices and ultimately impact on access. The Commission has explained that "privileges granted by IP rights to pharmaceutical companies should translate into innovation that is accessible to people across Europe".

The overall analysis will take into account other studies published by the Commission, such as one on the economic impact of the *Paediatric Regulation* (December 2016), which looked at different aspects of the Regulation including regulatory costs and economic value to the industry as well as direct and indirect social and economic benefits; and a gap analysis for the evaluation of *orphan medicines*, having published roadmap in November 2017. (This study will take place in 2018-2019 in consultation with various stakeholders.)

Current pricing models do not support equitable access

Many stakeholders, including civil society organisations, public officials, healthcare professionals, etc., now consider that new medicines are too expensive and threaten not only equity of access but also the long-term sustainability of European health and social systems. 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 balance this by passing more of the cost of the medicines on to patients – through 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. Especially in poorer EU states, patients have lower incomes and thus higher risk of poverty due to co-payment costs for healthcare and medicines. Similarly, rationing (limiting access to a defined number of patients for economic reasons) undermines the principles of solidarity and equity. It existentially threatens the interests of the patients denied access despite medical needs.

In an effort to try to drive down the prices of medicines, Member States often use *external reference pricing (ERP).*[x,20] Whilst this may generate savings and room for shifting costs in the short term, it has significant disadvantages for patient access, particularly in poorer Member States: companies adapt their market strategies to launch products in high-paying countries first, creating delays in patients' access in other countries.

Sometimes a company may decide not to launch a product at all in a number of countries, if it is not deemed commercially worthwhile. ~~ERP may also lead to price convergence, which can disadvantage countries with already low health budgets (and average patient income), which will pay a higher price than if they did not use reference pricing~~.[21]

Differential pricing has been put forward by the industry as an alternative strategy.[22] Differential pricing is a strategy whereby price is set according to different ability to pay between countries. Until now, it has been discussed mainly in terms of "price discrimination" – a type of pricing strategy

Commented [K2]: Alternative wording proposed: "It has a number of limitations: i) prices used for ERP are list prices, which are substantially higher than actual discounted prices that are usually covered by confidentiality agreements; ii) companies adapt their market strategies to launch products in high-paying countries first, creating delays in patients' access in other countries."

Commented [K3]: Rationale: Commission study indicates that even if it has been argued (mostly by the industry) that ERP will eventually lead to convergence, no substantial reduction in price dispersion has been observed within EU countries (p. 40 of the study).

[x] Also known as "external reference pricing or international price comparison / benchmarking, is defined as the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of a medicine in a given country." It is usually limited to specific medicines, such as originator, prescription-only or new medicines. (Study on enhanced cross-country coordination in the area of pharmaceutical product pricing. Final report, December 2015; page xiv.)

adopted by companies to optimise market access. However, *differential pricing as a political strategy* driven by collaboration between Member States with the aim of improving equity of access, has been less explored.

One major barrier for differential pricing is the existence of *parallel trade*.[xi] Parallel trade is based on the principle of free movement of goods within the internal market, but it is a factor in medicine supply shortages and may lead to reduced access. EPF believes that 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. Member States would have to agree to limit external referencing for those medicines where a differential strategy would be adopted; as well as address other possible practical issues. Approaching the issue on a basis of solidarity across the EU would allow poorer Member States to benefit from lower prices with an agreement they should not be referenced by richer Member States. The lower-priced countries should commit to restrict parallel trade only between themselves.

Recently, industry has embraced the concept of "*value-based pricing*", based on the idea that prices of medicines should be linked to the health benefit they bring. It 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 as foster greater transparency and accountability of the health systems. It is also proposed that value-based pricing could provide long-term incentives for industry to develop added-value products.[23] According to a 2013 report by the OECD, many countries already apply some type of "value-based" policies in pricing and reimbursement, but the way value and cost-effectiveness determined and the different factors applied in assessment are very different in different OECD (and EU) countries. There is also no commonly accepted definition of value, and patients' views on medicines' value are still little taken into account.[24]

In our view focusing on value only is not sufficient. Added value should certainly be one consideration when considering what is a fair price for a medicine, but it should better include patients' evaluation, should not be seen as a carte blanche, and needs to be balanced with other considerations such as actual R&D costs, taking into account direct and indirect public funding; impact on the national health budgets; etc. Some degree of differentiation between countries, for example their economic situation, must also be taken into account.

The system must become more transparent

National decisions taken on pricing and reimbursement are hampered by lack of transparency on the prices of medicines, and lack of reliable information on the cost of research and development. The argument in favour of *transparency on medicines prices* is that it would make medicines pricing more realistic and more equitable. Essentially, that external reference pricing would work better if Member States could know the actual prices paid by other Member States.[25]

Commented [K4]: Proposal to delete this section. Rationale: differential pricing not shown to be a solution to high prices.
EPF proposes to keep but clarify that other measures are needed also.
EPF also proposes to keep reference to parallel trade.

Commented [K5]: Clearer wording to be added to clarify EPF does not endorse the concept of value-based pricing (+ reference to Eurordis paper)

[xi] Parallel trade is also called parallel export; it happens when a medicine originally sold under patent protection "is traded in another country without control or permission from the original patent holder ... From a legal perspective, medicines as such are no exception to the free mobility of goods in the internal market." Thus medicines from lower-priced countries are exported to higher-priced countries. (Study on enhanced cross-country coordination in the area of pharmaceutical product pricing. Final report, December 2015; page xvii)

Transparency of prices, or the process of price-setting?

The Council conclusions on Innovation for the benefit of patients (December 2014) called for more "effective sharing of information on prices of and expenditure on medicinal products, including innovative medicinal products". The EURIPID EU-funded project has set up a price database for competent authorities, although until now it only includes list prices, not actual prices. These are achieved as a result of negotiations with companies, which are confidential. Some civil society and public health stakeholders argue that there should be "no secret deals" between payers and companies, and the real prices should be shared so Member States could drive down prices.[26] The pharmaceutical industry, in turn, argues that full transparency would be counter-productive for access.[27] Until now, Member States have not agreed to share real information on prices, however.

EPF strongly believes that the system must move towards maximum transparency, for reasons of openness and accountability of the system towards patients and citizens, as well as to correct the asymmetry of information between payers and industry. This will help develop regional collaboration among Member States on pricing and reinforce the negotiation capacity of EU countries, especially small ones. It will also contribute to correct the inefficiencies of the ERP system, currently based on list prices that are usually much higher than actual prices.

Commented [K6]: Additional text proposed by France

However, we believe more knowledge is needed on what might be possible unintentional consequences on patient access, were there to be full *transparency of actual negotiated prices* in the long-term. Full transparency might put at risk access in poorer Member States, which in some cases (but not always) do achieve more affordable prices through the confidential agreements. Full transparency should only be encouraged once Member States agree on solidarity and fairness in pricing, based on the economic development of a country, excluding poorer Member States from reference pricing "baskets" and restricting parallel trade from poor to richer countries.

Commented [K7]: France: disagrees with this paragraph, "industry argument. Full transparency is needed immediately and without any condition. It is one of the conditions to improve regional collaboration on pricing among MS and to correct the current inefficiencies of ERP."
Bulgaria: makes the case for caution, against deleting this paragraph. However not against "full" transparency as long as caveat is there.
EPF suggests compromise wording (web-meeting)

Another issue is that the *processes and criteria of decision-making* on pricing and reimbursement are currently not transparent to patients. Furthermore, many EU Member States are not respecting the timeline of 180 days for decision-making under the EU Transparency Directive.[28] EPF contributed constructively to a previous attempt to review this directive. We are currently engaging with the legislative proposal on HTA which aims to accelerate the decision-making process. EPF believes the procedures and decisions on pricing and reimbursement must become more transparent and understandable to patients and citizens, and the patient perspective should be meaningfully embedded at each step. Overall there is a need for more transparency on the relationships and linkages – financial and otherwise – between all the actors in the system in order to avoid conflicts of interest.

Patients want medicines that bring added value

Recently there have been growing concerns on the part of governments, public institutions, but also medical professionals, about the added value or benefit of some new medicines. A recent example came from Ireland, which spends over €2 billion on medicines each year and the share of the healthcare budget is growing. A representative of the Irish HTA agency said the state was being asked by some companies to pay "for exceptionally expensive drugs that did not work", and that some companies "created an emotional demand, overcharging for treatment by up to 100%", and the cost

of medicines was becoming unsustainable. The body had evaluated 21 cancer medicines between January 2016 and December 2017 of which 20 were not considered cost-effective at the asking price.[xii]

The added therapeutic value of innovative medicines is debated; some sources claim that most new medicines do not add anything significant to the existing treatment options, and some may even do more harm.[29] Recent studies published in the BMJ showed that most cancer medicines approved in Europe by the EMA between 2009 and 2013 and in the US by the FDA between 2008 and 2012, were based on "flimsy or untested surrogate outcomes" without evidence of improved survival or indeed quality of life. This was the case for 57% of the EMA and 67% of FDA approvals. Furthermore, despite remaining several years on the market and having a high cost, only few of the new medicines– 15% of EMA-approved and 14% of FDA approved managed to show clinically meaningful benefits for patients.[30] 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. The cost to the public purse is mind boggling; the cost to patients who directly bear the burden of ineffective and toxic treatments, incalculable."[31]

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 recent 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." [32]

Assessing the real value of innovation: patients' perspective is key

EPF believes it is fundamentally unethical to spend limited public funds on therapies that do not have demonstrable added value. It is also unacceptable for patients to be needlessly exposed to therapies that may harm them while not providing any benefit. It is difficult to comment conclusively on assessments on specific medicines as long as it is unclear how they actually incorporated the patient's perspective of the balance between benefits and harms.

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.

***Patient involvement is still not enough embedded in research*.** Measures to assess quality of life (for example) are not yet good enough. Uncertainties about added therapeutic value call for better, earlier and more meaningful patient involvement throughout the research and development process. Patients can have a *very different perspective of benefit and risk*, different priorities (both in terms of quality-of-life factors and prioritised clinical outcomes), and different levels of acceptance of potential risks, compared to medical professionals.[33]

[xii] "Warning to control costs of medicines". Irish Examiner, 7 April 2018. www.irishexaminer.com/ireland/warning-to-control-costs-of-medicines-469210.html,

The importance of incorporating the *patient perspective in HTA* is increasingly recognised,[xiii][34] and the integration of patient-reported and patient-relevant outcome measures in HTA is considered necessary in order to arrive at an accurate assessment of a medicine's added value. But in practice, patient involvement in HTA is still very limited, and so far there is no agreement on the best method of involving patients.[35] The patient experience may be difficult to capture fully in formal quantitative measures, and therefore qualitative evidence also needs to be integrated.

Naturally several factors will play a part in the value assessment, including value for patients, value for money (cost-effectiveness) and budget impact. A company should never be able to dictate its price, even for medicines that do represent valuable innovation, if this makes the innovative medicine unaffordable and inaccessible. But ensuring meaningful patient involvement from the very start should go a long way towards ensuring that new medicines, by the time they come up for regulatory assessment, already present better added value for patients.

Adapting the system to new scientific and technological realities

Scientific advances in the area of *personalised medicine*[xiv] may have a major impact on medicines development, authorisation, pricing and reimbursement in the longer term as science moves towards more targeted populations, precision /personalised therapies, and predictive medicine. Personalised or stratified medicines, combinations, borderline products[xv], and advanced therapies will require new ways of evaluation. They will also need new ways of managing clinical use. Medicines are more and more often approved after phase II trials on small populations; even when an initial assessment shows a positive benefit-risk, it is very likely that additional data will need to be collected over time.[36]

The European Commission recently set up an expert group on Safe and Timely Access to Medicines for Patients (STAMP), [37] where experts from Member States exchange information about the experience of Member States, examine national initiatives and identify ways to use more effectively the existing EU regulatory tools with the aim of improving patients' access to medicine, in close collaboration with the European Medicines Agency.[xvi]

New concepts that are being explored include that of **adaptive pathways**.[xvii] This complex approach implies the need for more collaboration between the pharmaceutical, med-tech and IT industries, regulators, HTA, payers, medical professionals and patients. The concept of "Medicines Adaptive Pathways to Patients" (in short MAPPs, or simply "adaptive pathways") refers to a medicines development process that is flexible and iterative in nature. Typically, a medicine authorised through MAPPs will initially be licensed in a smaller, well-defined patient population for whom there is a confirmation that benefits outweigh risks. This target population is then adjusted (usually broadened)

[xiii] We do not deal extensively with HTA in this paper, because EPF has a separate position paper on HTA and is working on patient involvement in that arena.

[xiv] Definition to be added

[xv] Products where it is not clear if they fall under the definition of medicinal product or some other category (for example medical device or food supplement) for regulatory purposes.

[xvi] Reference to EMA PRIME to be added

[xvii]

as the evidence base expands. Alternatively, a conditional approval would be confirmed by additional evidence from real-world after initial authorisation.[38]

In our view, adaptive pathways should be seen as using various existing tools to the maximum advantage, including scientific advice, compassionate use, conditional approval for medicines addressing life-threatening conditions, patient registries and tools that allow collection of real-life data, and where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required. They should remain limited to conditions with important unmet medical needs and situations where it is especially difficult to collect high level evidence in a short time, and should not be seen as a new authorisation model for medicines. Early evidence then needs to be complemented with real-life data. Adaptive pathways should thus be developed hand in hand with patient registries and other tools that allow collection of real-life evidence. Patient safety and the patient perspective benefit and risk must always take precedence.

A "life-cycle" approach to evidence collection and decision-making

Many products come with high uncertainty at the time of marketing authorisation – i.e., with evidence hinting at the value the product may have, but with a lack of sufficiently comprehensive data to completely back up that estimation. Therefore, a given product may not be in a position to have "demonstrated" added value at the time of marketing authorisation but may demonstrate this over time, thanks to the ongoing collection of real-world data.

A new, collaborative mind-set, involving **early dialogue**[xviii] **between all of the stakeholders** at EU level is needed from the earliest stages of medicines research and development, building on existing examples such as the SEED and MoCA initiatives.[39] The mechanisms ensuring input from patients must be expanded and strengthened, also nationally. This will help identify anticipated benefits and value, outcomes for patients. An early dialogue will also result in a more reliable basis for pricing. It will make the process of R&D more predictable for the industry and could enable Member States and patients to have their say in the R&D processes of companies.

To manage the risks associated with uncertainties regarding the value of new medicines compared to the high prices, Member states are increasingly using a variety of tools that are collectively referred to as **managed entry agreements** (MEAs). These range from instruments with a rather narrow financial focus such as rebates and discounts linked to price-volume agreements and capping schemes, to more outcomes-focused approaches where the company is obliged to provide additional data on real-life performance of a medicine. They all have the common aim of facilitating access to new medicines in a context of uncertainty and high prices.[40] From the patient perspective, purely financial measures are problematic as they are essentially sticky-patch solutions, reflecting failures of the system. They are also focused on the short-term, and their benefits appear dependent on the secrecy of negotiations. MEAs aimed at collecting evidence of treatment outcomes over a longer time and linking pricing and reimbursement to added value are more interesting as they are aimed at managing uncertainties and at ensuring that the right patients benefit from the treatments. However, in the experience of some Member States, they are onerous to implement and costly, and are not producing

[xviii] Note to add a brief explanation of what it is

very good quality data (AIFA presentation, International symposium on the accessibility of innovative medicines, London, December 2017).

A more comprehensive, robust and smart system for collecting real-world data is needed. Systematic collection of real-world evidence is the key to the success of flexible approaches: robust systems must be in place for post-market data collection (on ADRs, changes to the benefit-risk balance, health outcomes in different patient groups). The necessary infrastructure must be put in place for systematic collection of real-world evidence, particularly through well-designed, interoperable registries, to capture treatment outcomes both successful and unsuccessful, and including off-label use. The system needs to ensure companies' compliance with their data-collection obligations; the information collected must then be made quickly available for appropriate action to be taken by regulators, industry, medical professionals and patients.

Joint price negotiations – a way forward?

In May 2015 EPF and EURORDIS published a joint letter calling on the EU's pricing and reimbursement authorities to support the scaling-up of pilots on early dialogue and to establish a "table for price negotiation" with a group of Member States, i.e., to take a collaborative European approach to negotiating the prices of medicines with pharmaceutical companies, rather than one that is fragmented.[41] We believe this would lead to better collaboration between industry and payers and, ultimately, to better access to medicines and improved health outcomes. Several regional clusters have emerged in the last two years, starting with Benelux, Austria and Ireland (BENELUXAI)[42] and now encompassing the "Valletta declaration" group (Cyprus, Greece, Ireland, Italy, Malta, Portugal, Romania, Spain, Slovenia with Croatia intending to join) and a Central Eastern Europe group (Poland, Hungary, Slovakia, Lithuania with Czech Republic as observer). However, three years since the launch of the first collaboration, no joint deals on any medicines have been achieved yet.[43]

Such a collaborative approach would only be possible if all parties accept that pricing discussions will be based on a value assessment, especially for products in areas with small populations and high uncertainties, and will be linked to post-market evidence generation. Prices would have to be flexible over time – it would need to be possible to adjust them both up and down. However, high-value cannot be a justification for an unfeasibly high price so some ceiling or range agreed in advance between the various stakeholders could be introduced for all stakeholders – particularly importantly, patients and their treating clinicians – to understand the decision-points and their implications. It should be possible also to discontinue a therapy if it does not deliver on its promise.

Commented [K8]: Suggestion to rephrase and move this section under discussion of adaptive pathways (meaning of this paragraph is not clear).

EPF: it arises from the Eurordis-EPF call for joint price negotiations, so should be here- but perhaps needs clarification.

The bigger picture

Research and development in pharmaceuticals should be geared towards unmet needs of patients and of public health, including those in the updated WHO 2014 Report on Priority Medicines. EPF believes more open debate is needed around investment in health, valuable innovation, as well as societal values and preferences and what constitutes a "fair" return on investment; such a debate implies the need for more transparency about the real costs of medicines' research and development. Patients and the public/citizens play different and complementary roles in these debates: whilst a broad discussion is needed around societal values, priorities and public health needs, when it comes

Commented [K9]: There was a suggestion to include here the definition of WHO proposed work programme on "fair price", but that definition is contested and does not fully align with the ideas discussed at the WHO/NL "Fair pricing forum" which pointed out that what is considered "fair" will depend on whom you ask; so EPF proposes to leave this definition open for the moment.

to identifying unmet needs at individual patient or disease-level, it is vital to involve patients and their organisations.

Currently commercial entities, whose priorities are driven primarily by shareholder value, are focusing on what is commercially attractive rather than public health needs per se. However, the commercially-driven model is not providing needed innovation for many critical health needs, in particular poverty-related and neglected tropical diseases as well as antibiotics.[44] A "correction" of the research priorities is needed, for example through more publicly funded research (including basic research, comparative research on existing treatments and treatment combinations, and repurposing). This public investment should be fully reflected in the price of the final medicine, which is not currently the case.

Commented [K10]: Added by France

EPF believes there is a role for developing genuine Public Private Partnerships[xix] in addressing unmet needs that can foster innovation.[45] More broadly, EPF welcomes emerging initiatives looking at alternative funding models for pharmaceutical R&D which may be particularly relevant when it comes to addressing global health needs and health equity.[46]

In addition, other issues that need to be addressed to improve cost-effectiveness of care and outcomes for patients and society include: reducing waste in health systems; tackling over-treatment and the use of inappropriate therapies or services, as well as under-treatment; improving patient adherence;[47] fighting corruption, which is an important access barrier in some Member States; and counteracting and preventing unethical practices by some companies, which should be monitored and strictly sanctioned.

Call on governments and industry to ensure access

At the end of the day, **investment in health is a political choice**. Ensuring universal access to new, innovative medicines for all those who need it is a political choice. 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.

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 possible. EPF and our members will continue to play a constructive role in helping to achieve this.

Patient organisations often work with **pharmaceutical companies** in therapeutic research and development. This is a necessary partnership, as meaningful incorporation of patients' perspectives in R&D is seen to contribute to the development of new therapies that add more value for patients. However, certain preconditions must apply in order to make this collaboration fruitful. EPF has worked, also through the EUPATI project, to develop various guidelines and tools for ethical

[xix] Brief explanation to be added

collaboration. We call on pharmaceutical companies to respect ethical guidance when involving patients in their research activities. Patient involvement must be meaningful, not tokenistic.

Companies should also commit to ethical practice *outside the field of R&D*, including transparency and good commercial practices. Practices such as "ever-greening" of patent protection and deals to prevent or 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[48] – draw attention to failures and gaps in the current system.

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, we consider this a betrayal of the partnership principle. 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. Prices of medicines cannot simply be based on strategies to maximise profit without ensuring access to all who need them. The pharmaceutical industry must "walk the talk" as a responsible health stakeholder.

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

4. 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 endpoints, and patients' views on benefits and risks.
5. 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.
6. Frameworks, structures and methodologies should be developed for meaningfully incorporating patient evidence at all stages, from early dialogue to Health Technology Assessments, relative effectiveness assessments, and pricing and reimbursement decisions taken at national level.

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. Such a framework 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 dialogue such as MoCA and SEED;
    - Transparency of the real prices negotiated by Member States and other payers;
    - Adoption of common principles and mechanisms for encouraging and rewarding innovation in order to encourage continued investment in R&D, ~~including a fair return on investment,~~ based on the evaluation of the current EU IP and incentives legal framework;

Commented [K11]: Proposed addition

Commented [K12]: Change proposed – reference to ongoing study

- Exploration of innovative models for incentivising research & development especially in neglected areas[xx;]
- Exploration of the potential of adaptive pathways, managed entry agreements and other mechanisms 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. ~~In order to ensure justifiable and ethical profit margins the companies,~~ **all costs of developing the therapy and/or acquisition** must be made transparent.
6. Pharmaceutical companies should price new medicines 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 under the Societal Challenges pillar.
9. **EU public funding for research** (Horizon 2020 and its successor; IMI) 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.

Commented [K13]: Proposal to delete

[xx] To be explained in the document – couple of examples

Notes and References

[1] Adapted from EPF position paper "Defining and Measuring Access to Healthcare: the Patients' Perspective," March 2016. Available at www.eu-patient.eu/whatwedo/Policy/access-to-healthcare/

[2] Communication from the Commission to the European Parliament, the Council, the European Economic and Social

Committee and the Committee of the Regions. "Solidarity in health: Reducing health inequalities in the EU". Brussels, 20.10.2009. COM(2009) 567 final.

[3] See EPF's position statements on health inequalities, available at our website: www.eu-patient.eu/Initatives-Policy/Policy/Health-inequalities/

[4] European Parliament resolution of 8 March 2011 on reducing health inequalities in the

EU (2010/2089(INI))

[5] Article 3, Treaty on European Union

[6] Council Conclusions on Common values and principles in European Union Health Systems (2006/C 146/01)

[7] http://www.who.int/sdg/targets/en/

[8] EPF's comments on the European Medicines Agency Strategic Framework 2020. Available at www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000292.jsp&mid=WC0b01ac05800293a4

[9] See e.g., IMS Institute (2015) "The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective."

[10] "Shaping Europe's Vision for Personalised Medicine. Strategic Research and Innovation Agenda (SRIA)". Coordination & Support Action (CSA) PerMed, June 2015. Available at www.permed2020.eu

[11] https://www.washingtonpost.com/news/wonk/wp/2018/01/03/gene-therapy-for-inherited-blindness-sets-precedent-an-850000-price-tag/?utm_term=.a41624b7dc25

[12] OECD report available online only: http://www.oecd.org/publications/managing-new-technologies-in-health-care-9789264266438-en.htm

[13] https://www.reuters.com/article/us-mylan-nl-epipen-congress/u-s-lawmakers-blast-mylan-ceo-over-sickening-epipen-price-hikes-idUSKCN11R2OG

[14] http://www.unsgaccessmeds.org/new-page/

[15] Report available at http://www.unsgaccessmeds.org/final-report/

[16] "Addressing the global shortage of, and access to, medicines and vaccines". Report by the Director-General. 12 January 2018. http://apps.who.int/gb/ebwha/pdf_files/EB142/B142_13-en.pdf

[17] https://thewire.in/external-affairs/battle-access-medicines-vaccines-who

[18] Council Conclusions on Strengthening the Balance in the Pharmaceutical Systems in the European Union and its Member States (2016/C 269/06). https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52016XG0723(03)&qid=1522063481153&from=EN

[19] Report on EU Options for Improving Access to Medicines (2016/2057(INI)), Soledad Cabezon Ruiz MEP rapporteur, document 2016/2057(INI), adopted 14.2.2017 http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//NONSGML+REPORT+A8-2017-0040+0+DOC+PDF+V0//EN

[20] For definitions and descriptions of different pricing models, please see "Study on enhanced cross-country coordination in the area of pharmaceutical product pricing", final report under contract number 2014 73 03 for the implementation of Framework Contract № EAHC/2013/Health/01 'Health economic reports – analysis and forecasting' (Lot 2), available at http://ec.europa.eu/health/systems_performance_assessment/docs/pharmaproductpricing_frep_en.pdf

[21] EC study on pharmaceutical pricing. See reference 19.

[22] "Improving Patient Access to Innovative Medicines the Framework in Which Differentiated Pricing May Offer a Solution", EFPIA 2014 position paper. Available at www.efpia.eu/uploads/Modules/Documents/pac-280214-ai6-a1-differentiated-pricing-position-paper-final.pdf

[23] "Enhancing Value in European Health Systems. The Role of Outcomes Measurement". Multi-stakeholder consensus document (2016). Available at www.eu-patient.eu/globalassets/policy/patientssafety/value-of-health-consensus-document.pdf

[24] Paris V and Belloni A (2013) "Value in pharmaceutical pricing", OECD health working papers, No. 63, OECD Publishing, pp. 11-14.

[25] EC study on pharmaceutical pricing. See reference 19.

[26] European Alliance for Responsible R&D and Affordable Medicines Joint Declaration. Available at http://medicinesalliance.eu/joint-declaration

[27] EFPIA position paper, principle 1. See reference 13.

[28] EPF statement on the European Commission's proposal for a review of the Transparency Directive, November 2012.

[29] "Added Therapeutic Value: European citizens should get their money's worth". Joint position paper by WEMOS, EPHA, SOMA and ISDB. 2014. Available at www.wemos.nl/files/Documenten%20Informatief/Bestanden%20voor%20'Medicijnen'/Position%20paper%20ATV%20Wemos%20SOMO%20EPHA%20ISDS.pdf

[30] https://www.bmj.com/content/359/bmj.j4528

[31] https://www.bmj.com/content/359/bmj.j4956

[32] "Towards a Harmonised EU Assessment of The Added Therapeutic Value of Medicines". Study for the ENVI committee. Directorate General for Internal Policies, Policy Department A: Economic and Scientific Policy, 2015, pp. 14-15. Available at www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU(2015)542219_EN.pdf

[33] See for example: "New Medicines for Serious Conditions: How patients would weigh the risks and benefits," Report of Findings from Phase 1 and 2. Genetic Alliance UK in partnership with the Welsh Institute for Health and Social Care, University of South Wales. April 2014. Available at www.geneticalliance.org.uk/docs/risks-and-benefits-2-report.pdf

[34] EU HTA Network: "Strategy for EU Cooperation on Health Technology Assessment", 2014, p. 8. Available at http://ec.europa.eu/health/technology_assessment/docs/2014_strategy_eucooperation_hta_en.pdf

[35] EPF survey: "Patient Involvement in Health Technology Assessment in Europe," 2013. Available at www.eu-patient.eu/whatwedo/Initiatives/

[36] Project ADAPT-SMART: http://adaptsmart.eu/early-access-is-it-worth-it-2/

[37] http://ec.europa.eu/health/documents/pharmaceutical-committee/stamp/index_en.htm

[38] http://adaptsmart.eu/

[39] Mechanism of Coordinated Access to Orphan Medicinal Products (MoCA); Scientific European Early Dialogue (SEED)

[40] For an overview of MEAs, see Ferrario, A and Kanavos, P (2013) "Managed entry agreements for pharmaceuticals: the European experience." EMiNet, Brussels, Belgium. Available at http://eprints.lse.ac.uk/50513/1/__Libfile_repository_Content_Ferrario%2C%20A_Ferrario_Managed_%20entry_%20agreements_2013_Ferrario_Managed_%20entry_%20agreements_2013.pdf

[41] www.eu-patient.eu/globalassets/alliance-building/eurordis-epf-letter_call-on-payers_may2015.pdf

[42] https://www.rijksoverheid.nl/actueel/nieuws/2018/02/14/ierland-wil-zich-aansluiten-bij-geneesmiddelencoalitie-beneluxa

[43] "Even facing Big Pharma together, countries still struggle to haggle", Politico, 28.3.2018

[44] Kaplan W et al., (2013) Priority Medicines for Europe and the World. 2013 update. World Health Organisation, Chapter 6.

[45] Ibid., Chapter 8.1.

[46] For example the United Nations High – Level Panel on Access to Medicines. www.unsgaccessmeds.org

[47] For a patient perspective on adherence, see "Adherence and Concordance. EPF position paper" (2015) available at www.eu-patient.eu/globalassets/policy/adherence-compliance-concordance/adherence-paper-final-rev_external.pdf

[48] "Drug Goes From $13.50 a Tablet to $750, Overnight" New York Times, 20 September 2015; "Big Price Increase for Tuberculosis Drug Is Rescinded", New York Times, 21 September 2015.