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EXPERT PANEL ON EFFECTIVE WAYS OF INVESTING IN HEALTH

(EXPH)

Opinion on Innovative payment models for high-cost innovative medicines

The EXPH adopted this opinion at the [to be inserted][h] plenary of [to be inserted]

About the EXpert Panel on effective ways of investing in Health (EXPH)

Sound and timely scientific advice is an essential requirement for the Commission to pursue modern, responsive and sustainable health systems. To this end, the Commission has set up a multidisciplinary and independent Expert Panel which provides advice on effective ways of investing in health (Commission Decision 2012/C 198/06).

The core element of the Expert Panel's mission is to provide the Commission with sound and independent advice in the form of opinions in response to questions (mandates) submitted by the Commission on matters related to health care modernisation, responsiveness, and sustainability. The advice does not bind the Commission.

The areas of competence of the Expert Panel include, and are not limited to, primary care, hospital care, pharmaceuticals, research and development, prevention and promotion, links with the social protection sector, cross-border issues, system financing, information systems and patient registers, health inequalities, etc.

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https://ec.europa.eu/health/expert_panel/experts/members_en

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SUMMARY

The growth of pharmaceutical expenditures due to new high-cost innovative medicines, under the current institutional framework, creates financial challenges to health systems.
The recognition that the current path of growth cannot be continued indefinitely leads to the search of new ways to ensure that innovation "that matters" is produced, that patients have access to innovation and that health systems are financially sustainable.
This context leads to the discussion of innovative payment models for new drugs that improves the way the three above-mentioned objectives are met.
It is unlikely that a single payment model will be optimal for all situations. Some broad principles should be observed when defining specific payment models for innovative medicines and deciding on rewarding R&D in pharmaceutical products:

- Greater price and cost transparency, including the acknowledgement that high prices (high costs to payers) may or may not have underlying high costs of R&D.
- Revisit the rules of protecting innovation through patent law and market exclusivity, as other mechanisms to promote and reward high-value innovations can and should be devised. This is particularly true when clear areas of neglected attention can be identified in a consensual way. The patent system is the current best option for decentralized innovation efforts when consumers are price sensitive, but not necessarily otherwise. This opens space to explore new models of promoting innovation that will encompass novel payment models which may or may not be associated with different rules in R&D funding (say, making use of prize-awarding mechanisms)
- Develop methodologies to measure the social value of pharmaceutical products
- Have an assessment of exercise of market power in each price negotiation, as a result of insurance protection set by health systems, reducing the role of consumer's price sensitivity in limiting price increases of new products under patent protection.
- Set better rewards for higher therapeutic value added, so that innovation efforts are directed to the more relevant areas.
- Payment systems should evolve in the direction of paying for acquisition of a service (treatment) and not of a product (pill).
- Explore non-linear payment systems, including bundling, differentiation across geographies and across indications.
- Create dialogue platforms involving all relevant stakeholders.

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1. BACKGROUND

The emergence of high-price innovative medicines, implying high costs for health care payers, is exerting strong financial pressure on health systems. Over the years, health care payers and pharmaceutical companies have explored different ways of defining payment for new products that ensures three main objectives: quick access of patients to more effective new drugs, that provides adequate incentives to R&D efforts (both in rewarding R&D and guiding efforts to areas of higher social value) and that keeps health systems financially sustainable.

Recent years have seen an growing number of new medicines with price increases that led health authorities and health care payers to question the implications for the financial sustainability of health systems. Detailed information on prices of new pharmaceuticals in different countries is often not available as they result from secret price negotiations. Howard et al. (2015) document price increases in the anticancer drugs market of about 10% a year in the past 20 years, after controlling for increased benefits (survival). Cost changes are deemed unlikely to be behind the price increases. The main explanation offered by Howard et al. (2015) for the high prices is based on the roles of health insurance in making patients insensitive to drug prices (allowing companies to increase prices without losing demand) and of anchor effects of previous prices (by which a price increase over a previous high price is tacitly deemed as natural, even if the reference point comes from other, non-competing, pharmaceutical products).

The response to this trend has been the search for new payment models between health care payers and pharmaceutical companies. The new payment models have been generally termed Managed Entry Agreements and have a wide variety of formulations. A crucial question is whether, or not, any of these, or a subset of them, will deliver a solution to the three objectives outlined.

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2. TERMS OF REFERENCE

The Expert Panel on effective ways of investing in Health is requested to analyse the following:

(a) What is the current role of the national pricing and reimbursement authorities to improve access on innovative medicines? Is there a scope to explore new ways of setting prices for specialty medicines in terms of improving access, while taking in to account the costs, the benefits, the budget impact and the future return on investment on a transparent way? How to deal with polypharmacy/ combination of treatments? What are the existing frameworks for such dynamic payment models? Any experience from other economy sectors (transport or telecommunications) that can potentially be applied to medicines?

(b) How can the use and uptake of medicines impact the health care costs? Can this be reflected on price setting i.e. reward for the right behaviour? Ways to monitor the adherence to treatment? What is the importance of choosing the right outcomes to measure the performance? What is the role of RWD for innovative payment models and are there any prerequisites to develop such system? Is it possible to develop a common definition for RWD from all different perspectives (regulators, HTA bodies, payers, pharmacovigilance etc.)?

(c) Is there a theoretical framework for the interpretation of the results and outcomes? Is there a framework of health system performance assessment in the area of pharmaceuticals and possible areas for future work? Is there a scope to improve resilience and cooperation between those bodies that are involved in the decision making process? What type of synergies can be developed between the payers, HTA bodies and regulators in the EU?

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3. OPINION

3.1. The challenges to health systems

Health systems in Europe face common challenges: non-communicable diseases dominate the disease burden (depression and heart disease are leading causes to healthy life years lost), infectious diseases such as HIV and tuberculosis remain a challenge to control, antibiotic resistant organisms are emerging, people live longer and have less children, people migrate within and between countries and cities grow bigger, primary health care systems lack preventive services, public health capacities are outdated, health care rising costs require ever more funding, etc.

In a more systematic way, health systems come under pressure from different sources: technological innovation and arrival of new products asking high prices, professional differentiation, population needs and demand, and demographic and epidemiological transition.

In the European Union, Member States are experiencing challenges in delivering financially sustainable health care. Those challenges translate into concerns about access to health care (EXPH, 2016b). One of the areas of concern is access to medicines, which faces conflicting objectives for the role of prices as they provide incentives for development of new products and influence affordability (and access of patients to treatment), an issue discussed in detail below.

It is by now well documented that expenditure with new molecules has outpaced the growth of GDP or the growth of other health care expenditures. Several factors contribute to the current concern regarding access by patients to new pharmaceuticals. Lower economic growth (meaning less available resources), health systems built to answer acute health problems and not for prevention and management of chronic conditions (meaning that more costly and less adequate care is provided), and the increasing prices asked for the new products are among the main drivers of the concern with the growth in health expenditures.

The growth in new pharmaceuticals is a composite of growth in new molecules being available and the price increases compared to previous therapeutic alternatives. To

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address the growth in pharmaceutical spending associated with new pharmaceutical products we need to inquire about the relative strength of both "quantity" and "price" dynamics and their drivers.

3.2. The challenges to innovative payment models

3.2.1. Current practice of pricing new pharmaceutical products

3.2.1.1. General scenery

There is little systematic knowledge on pharmaceutical markets, optimal R&D levels and pricing and marketing strategies by companies. Pharmaceutical companies have been found to be high performers for their investors. Merger activity between pharmaceutical companies was significant in the past three decades, reducing the number and increasing the size of companies engaging in across-the-board development of new products. Companies' expenditure breakdown by category often reveals that R&D costs represents a much smaller share than promotion and marketing costs (Mossialos, 2017).

Several arrangements to set prices and access conditions for new medicines have been experimented by the national authorities in charge of pricing and reimbursement decisions. A common, general, denomination for these arrangements is outcomes-based managed entry agreements (also known as market entry agreements or market access agreements).

The several forms and variants of these agreements deal with different aspects, such as hidden price discounts (of value to companies as such discounts bypass international referencing practices used in many health systems), uncertainty about the performance of the product in real-world context, asymmetric information about product quality between companies and health care payers, etc. (See Morgan, Vogler and Wagner, 2017, for a more detailed description of the role of these agreements).

Most countries conduct benefit or cost-benefit assessments, with different degrees of transparency and detail, before they negotiate with companies on prices taking the price-reference system into consideration.

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Box 1

Example: "highly innovative product" status in the Czech Republic

Some countries have more-or-less defined criteria for assigning of the status of the "Highly Innovative Product - HIP". In the Czech Republic the criteria involve: incidence of serious adverse events decreases at least 40%, reduces serious drug interaction by at least 40%, implies substantial reduction in mortality and prolongation of median survival of more than 2 years, or, in the case of patients where predicted survival is less than 24 months, to extend the life expectancy of at least 50%, at least about 6 months etc. Based on this, only "specialized care facilities" are assigned, where the "HIP" may be used, and these facilities then negotiate the pricing with Health insurance companies/Sickness funds.

Temporary as well as definitive pricing (for every strength of a drug etc.) is then performed (in Czech Republic as the lowest price determined from a "reference basket"). Payment for packing a highly innovative product is fixed at the lowest foreign or Czech producer price of that product in adequate strength and pack sizes with some possible variations. This price then stays in place until the HIP is replaced by a fully comparable cheaper or a more effective one.

The differentiation of price setting for intramural (hospital) and extramural settings is an issue of concern. Some countries decide then which drugs to take "in quarantine" (within the context of risk sharing, managed entry agreements etc.) due to uncertainties of benefit or unfavourable (incremental) cost-benefit or cost-effectiveness ratio, delaying immediate access to the new pharmaceutical products by patients in exchange for a more informed decision and more appropriate price and associated spending.

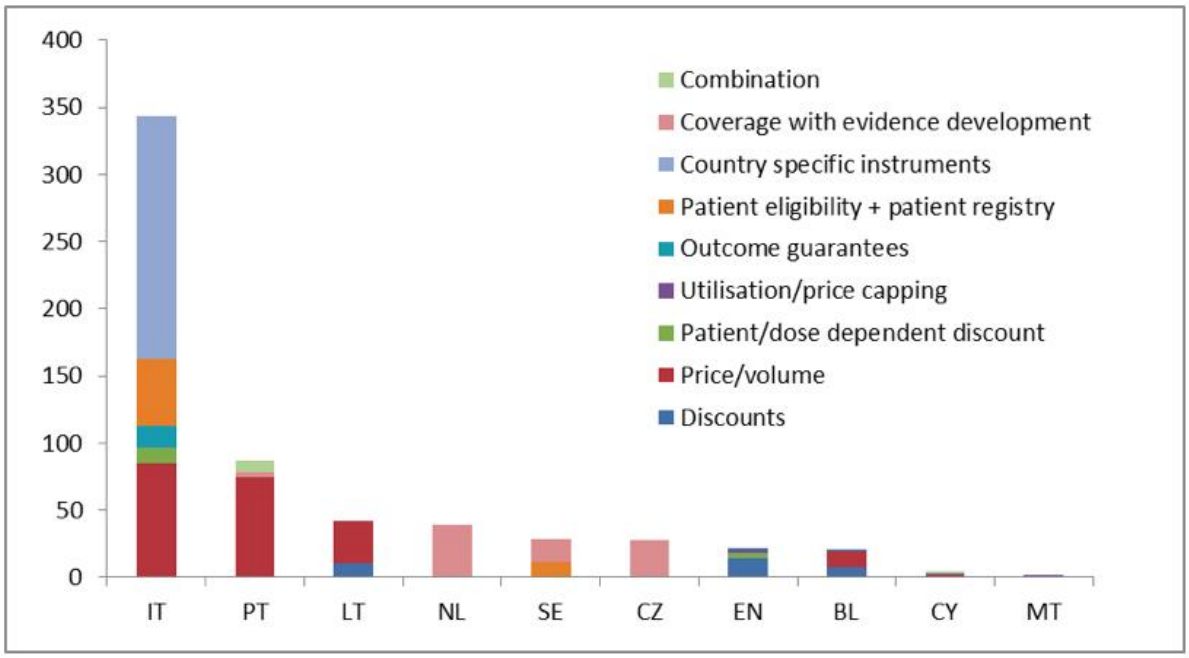
With respect to policy interventions in this area, the recent survey by Vogler et al. (2016) covered over 550 pharmaceutical measures surveyed in 32 European countries (for the period 2010–2015). The most frequent measures adopted by health care payers were price reductions and changes in co-payments. Unsurprisingly, countries strongly hit by the crisis tended to make more policy changes than the others, aiming to curb pharmaceutical expenditures growth.

Unfortunately, neither the arrangements (price-based vs. clinical-outcome based) nor the outcomes (improvement in certainties of clinical benefit, improvement in cost-benefit

ratio) in many of the new payment models being used are made public. This undermines the international price-reference system in Europe, used by most countries in some form.

The number of MEAs carried out by each country varies considerably as does the type of MEA. The scope and breadth of MEAs is country-dependent.

Figure 1: Number of MEA per country and type



Source: Figure 9.3 in Ferrario and Kanavos (2013),

Different prices across countries and different prices across indications for the same product (which may carry different commercial names according to indication) are additional tools available on a European (or transnational) perspective. The discussion of differential pricing across indications and/or countries relies on the (implicit) view that rewards to innovation should take place through higher prices. From economic analysis, the basis for such price differentiation results from different demand price elasticities (how use of the product is related to its price) and the objective of funding a certain amount of R&D (common to all users and countries). The R&D cost of developing a new pharmaceutical product is independent of how many countries decide to use it and for how many indications the product is adopted. Revenues from all sources (indications and

countries) contribute to reward the R&D effort. If an average price across indications (or across countries) is set, then letting firms adjust individual indication prices to meet the average price would also lead to the pricing structure that is best from the social point of view, given the decision to pay for innovation through prices. The technical argument for differential pricing to be social-welfare improving is conditional on having a certain level of R&D cost to be covered. Without some reference level for the average price across indications and/or countries, allowing differential pricing does not have necessarily the same social welfare implications.

There is also a crucial role for the possibilities of arbitrage, exploiting price differences. Arbitrage means buying at the lower price to use it on the "market" of higher price (where "market" can be a different indication or a different geography/country).

The practice of different prices across geographies or indications often creates discomfort with policy makers, opinion makers and, ultimately, the population. The exact conditions of its existence, the scope for its application and the social welfare implications need to be carefully defined, assessed and explained to the several shareholders, often in an international context.

Only some countries will have the ability to manage these agreements, and oversee the results. Replication in every country will be challenging for small countries due to costs of setting and using monitoring mechanisms. There are clear economies of scale in the management of entry agreements for new pharmaceutical products.

An important aspect is to clearly identify what are the problems that need to be solved, as the broad question of how to set payment models for high-price innovative medicines allows for different interpretations.

There are two main issues: how to deal with uncertainty about the value of the new product and how to set its price.

The great majority of discussions have the focus on the first problem. The concerns of that line of discussion are one or several of the following: do not pay for little value added, avoid setting high price for low value added products when at moment of setting the price true value at population level is not know, ensure patient access (at least for

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some patients), avoid payers' budget disruption and reward more the innovations that bring more value. Implicitly, the discussion takes as granted that health technology assessment together with a threshold approach for incremental cost-effectiveness ratio (or a variant of it) is the adequate institutional setting, allowing firms to set prices with considerable freedom as long as these prices allow the threshold to be met.

The second problem starts where the first problem stops. Current institutional mechanisms do not make any assessment of market power exercise (ability of firms to set high prices without hurting the level of demand they face, that is, without losing sales), which is more likely in the case of pharmaceutical products due insurance protection and R&D protection through patents. Insurance protection decouples who benefits from the use of the product and who pays for it. Patent protection implies that there are no close competing products.

The challenge is not how to find financial funds to match the high prices asked for the new pharmaceutical products. It is rather to question whether, or not, such high prices are really the result of well functioning system of rewards to innovation.

The use of managed-entry agreements provides a way to have early introduction of new products "managing" the information flow. The basic issue addressed is typically related to evidence required to take final decisions, later on when more information has become available.

This means that managed entry agreements are not designed to address the issues of high prices as a result of exercise of market power by pharmaceutical companies.

Figure 2 illustrates the difference between the two issues. Take four elements of the value chain: R&D costs incurred to discover the new product (the blue bottom box in each column), production, marketing and all other costs that take place to bring the R&D outcome to patients (the green second-to-bottom box), the margin retained by the company (purple second-to-top box) and the net value accrued to the health system (defined as the total value minus the price paid, and represented by the orange top box in each column).

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Column (1) in Figure 2 shows a typical distribution of values in a new product in the economy (not necessarily in the health sector). The price paid by consumers is given by the sum of bottom three components. The price splits the net value defined as value to consumers (total height of column (1)) minus costs (sum of the bottom two boxes) between payer and producer. Sizes of boxes have no meaning in this illustrative example.

Column (2) introduces uncertainty, on the left side there is a low value product and on the right side a high value product. Costs are similar whether a low or a high value product is used, to simplify the presentation of the argument. Normal working of the market would set a low price on the first case, as consumers need it to be willing to buy the product, and a high price on the second case, as the highest willingness-to-pay by consumers allows firms to set a higher price without losing sales. The pharmaceutical market with health insurance (public or private) introduces the issue of a payer / health system defining the price without knowledge of whether it is on the left or the right column. Setting an average price leads to paying more than the value if the low-value product is in the end revealed to be the true one, while under-rewarding, in relative terms, the innovator if there is a high-value product (which may undermine the dynamic incentives to invest in R&D).

Column (3) has the same uncertainty. Now the price is set by companies under the constraint of net value for the payer to be at least some non-negative amount (in the case of pharmaceuticals, cannot be lower than the value of an alternative treatment). This leads to a rise in price, which can be substantial if the difference between a high-value (right) and low-value (left) product is large. Thus, incentives for the company to invest in R&D in a way that the "right side" occurs are stronger than previously. Column (4) has almost similar value in both cases, and the same approach to define prices just favours high prices, with little gain in guiding efforts of R&D towards one or the other (and does not matter much in terms of value in the end). Column (5) reduces the price paid in comparison to column (4) by some mechanism. By making the price to the company almost equal in both R&D outcomes (high-value or low-value innovation) does

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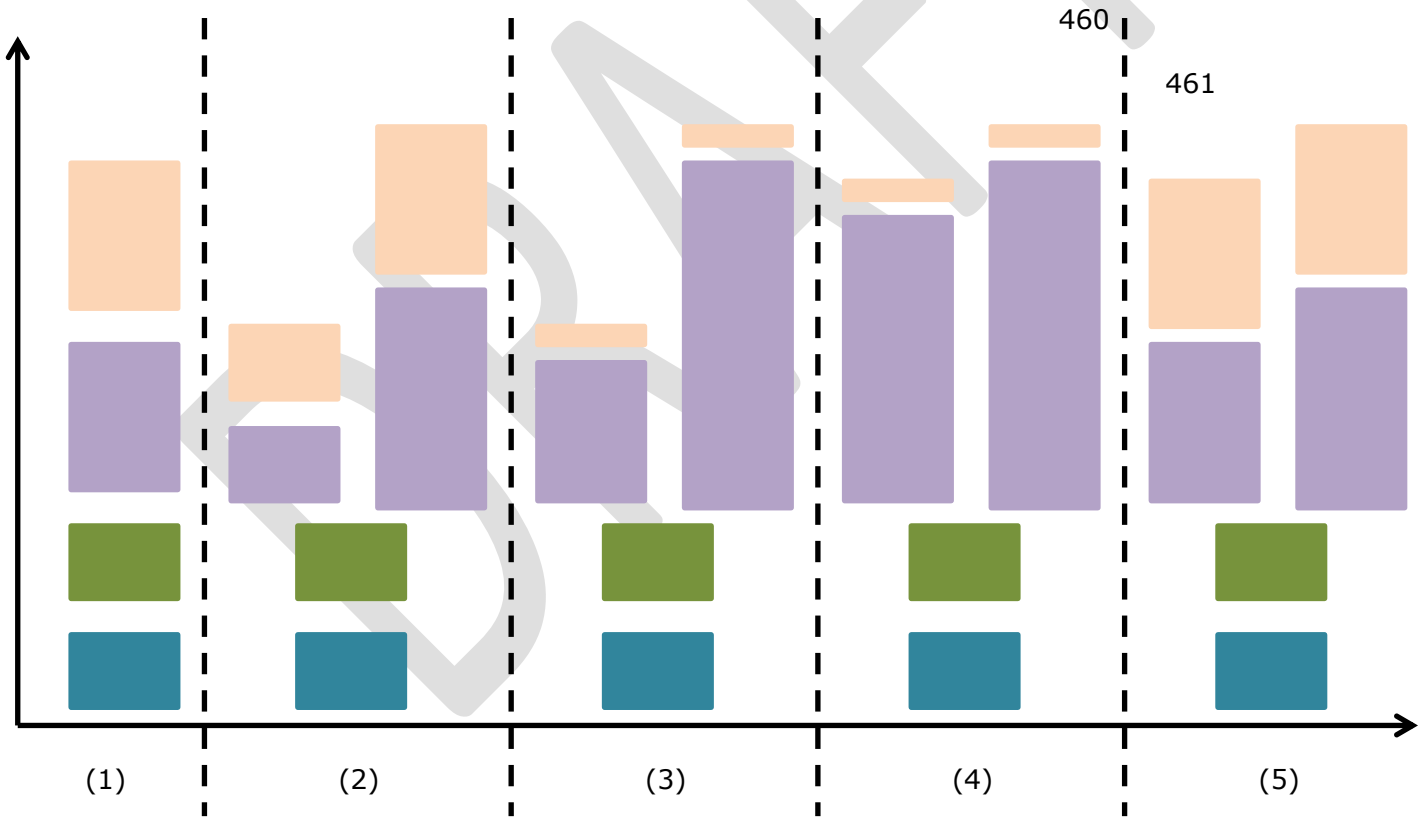
not provide a strong signal for the company to obtain the right-side case instead of the left side. On the other hand, it contains price and has a lower expenditure, at the risk of having a lower-valued innovation.

Thus, the payment model has to balance these different blocks. And knowledge of all of them is crucial to have a full view of the problem. The managed entry agreements focus on ways to deal with the uncertainty (for each column 2-5, the difference between left and right side), neglecting the split of value between payer and company (the two top boxes).

Figure 2

Illustrative example of value split under uncertainty about final value of product



Legend: Blue – R&D costs; green – production and commercialization costs; Violet – margin to companies; orange – surplus to health care payers

Note: Size of green and blue boxes kept constant for simplicity. Only relative size of Violet and orange boxes are discussed.

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3.2.1.2.Innovative payment models for new products

Value-based pricing

"Value-based pricing" stands for the assessment of the therapeutic value of medicines and the according pricing deduced from the clinical value. "Value-based pricing" can lead to the reduction of prices for medicines with no or limited added value and increase the price for medicines with high value, which in turn may encourage manufacturers to focus their R&D on therapeutic drugs with superior value (World Health Organization (WHO) 2016). A concern emerges from this: the relative incentive to R&D, resulting from paying a price that approaches the value of benefits, transfers most of value generated to companies, affecting negatively the financial sustainability of health systems. This issue is discussed at length below.

"Value-based pricing" has become a widespread term to designate prices set according to principles of value-based health care. The essential driving force behind value-based health care is the need to have value measurement of outcomes that matter for patients. The main operational implication is that health care without value for patients should not be paid for. This does not automatically translate into a pricing rule for new products. The notion of "value-based pricing" for new pharmaceutical products rests on the attractive and intuitively simple principle of paying more for products that deliver more value. Thus, some sort of price discrimination according to value generated seems to underlie some of the discussion of pricing in value-based health care. The value-based health care framework is consistent with the different ways of setting prices and with the different roles of prices in the context of pharmaceutical innovation. In particular, it does not follow from the principles of value-based health care that maximum prices for a new pharmaceutical product should be set equal to the value added it brings over existing therapeutic alternatives or pre-existing practice in treatment.

The principle itself of setting prices according to some automatic rule that allows the price of a new product to appropriate all, or most, of the value it brings does not follow form the value-based health care approach.

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This argument is of different nature from other motives to have reservations about value-based pricing for new pharmaceutical products, such as the uncertainty regarding the definition and the measurement of value.

The main attractiveness of paying new products according to value in some way results from the R&D incentives it provides, not from the access effects it entails. It gears innovation in the direction of more relevant products and needs of patients.

Box 2

The Swedish pharmaceutical reimbursement system

In Sweden, since the beginning of the century, reimbursement is linked to cost-effectiveness shown by the new product and other elements of value can be taken into account.

Several features of the value-based pricing system in Sweden are worth mentioning. It takes a societal perspective, allowing the decisions to avoid the silo mentality (savings due to cost offset in other areas are considered). It has a clear anchor point for the value of a Quality Adjusted Life Year. The use of a threshold approach for inclusion in the coverage of the public health system implies that budget implications are open ended. The budget will have to accommodate any new product that meets the threshold condition. The Pharmaceutical Benefits Board (LFN) is the entity in charge.

A major feature in the Swedish system is the centrality of cost-effectiveness as a criterion, with negotiations being, presumably, non-existent: "We look upon the prices as an integrated part of the cost-effectiveness analysis. If the price is too high there will no cost-effectiveness." Companies can reapply and present a lower price to ensure cost-effectiveness.

Basic motives behind this approach: inability to efficiently set prices, least-regulation approach and reward innovations bringing more valued innovations.

Source of information: http://www.lfn.se

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Managed-entry agreements

"Value-based pricing" is an umbrella term for a variety of purchasing strategies outside the traditional models of volume-based purchasing (The Network for excellence in Health Innvovation (NEHI) 2017). For the time being there is little knowledge whether, or not, value-based pricing yields its promised benefits (World Health Organization (WHO) 2016).

Managed Entry Agreements (MEAs) are increasingly used in many European countries.[1] Under MEA, various forms of confidential agreements between pharmaceutical manufacturers and payers (hospitals, social insurances) are subsumed, which are mainly negotiated when there is uncertainty on the actual clinical benefit of the medicines, but high public expenditures are required. Although they have been applied in many countries for several years, there is no public knowledge available whether they meet the associated expectations (a contribution to the reduction of uncertainty on actual benefit, amount of cost reductions and/or access of patients to these drugs) (Grössmann, Wild et al. 2016).

Given the solidarity of public funding of health care, the increased demand for evidence about the experiences made with and the expectations met by MEA seems quite legitimate (Morgan, Vogler et al. 2017; Wild, Zechmeister-Koss et al. 2017). A recent accounts of MEAs due to KCE (2017), the Belgian HTA institute, and Ferrario et al. (2017), which the latter focusing on Central and Eastern Europe countries.

In principle, the Managed Entry Agreements differ in whether they refer to the prices (rebates and discounts, "free" of delivery medication, price-volume agreements, budget limits) or they are based on the clinical outcome (conditional reimbursement under documentation in registers, performance-based payment/payment by result): here England and Italy are the countries with the most experience with MEAs.

The properties expected from each type of agreement depend on the particular context and on the specific rules adopted in the agreement. This class of payment models is not

[1] Recent reviews of managed-entry agreements is provided by KCE (2017) and Ferrario et al. (2017).

without problems and they may even introduce inefficiencies. One example is the moral hazard effect of the so-called risk-sharing agreements. Whenever a payment occurs only if successful treatment is achieved, decision makers in the health system will have an incentive to put too many patients into treatment as treatment failure will not have a direct financial cost to them. As the financial cost of failures passes through to prices of successful treatments by companies, health systems may end up with too many patients under treatment under a higher price, driving up health care expenditures (Barros, 2011).

To companies, MEAs offer the additional benefit of setting confidential effective prices, breaking the link of external reference pricing (a policy that relies on publicly available listed prices of pharmaceutical prices in reference countries). The confidentiality of prices brings countries to a situation that is usually termed prisoner's dilemma. Individually it is optimal to sign agreements of prices that are confidential, while globally countries could be better off by keeping a coordinated action on price determination for pharmaceuticals.

There are arguments both in favour and against MEAS. On the advantages side one may have the following:[2] (a) reduce uncertainty about the real value of medicines, if additional data (real-life data) are collected under those agreements (however, these data are not necessarily published); (b) prevent the complete exclusion from the reimbursement of expensive medicines with (still) uncertain clinical benefit and thus grant access to medicines, so that the patient's hopes do not have to be disappointed; and, (c) keep the budget under control because they contain discount rules.

These agreements may also bring disadvantages, with the following ones being listed in the existing literature:[3] MEAs (a) provide access to medicines with uncertain clinical benefit and - at a later stage - it is difficult to argue against patients why they are not reimbursed anymore (dynamic consistency problem); (b) are associated with additional costs for implementation, especially when they are based on the clinical outcome data;

[2] See Ferrario and Kanavos (2013); Ferrario and Kanavos (2015); Grössmann, Wild et al. 2016; Morgan, Vogler et al. 2017; The Network for excellence in Health Innvovation (NEHI) 2017; Wild, Zechmeister-Koss et al. (2017)

[3] See footnote 1.

(c) require well-functioning IT support, and (d) undermine the current system of international price comparison ("External Price Referencing / EPR"), since MEAs usually contain confidential agreements on discounts, while EPR is only referenced to list prices, since the discounted confidential prices are not known. As a result of the confidential agreements, the payers believe to have completed a good deal, although there is no objective evidence on the basis of comparisons due to lack of comparative data from the other countries.

MEAs should only be used when HTA identifies issues or concerns about key outcomes and/or costs and/or organizational/budget impacts that are material to a reimbursement decision. They provide patient access and can be useful to manage technology diffusion and optimize use. However, they are administratively complex and may be difficult to negotiate and their effectiveness has yet to be evaluated. Moreover, they are designed to address the issue of uncertainty about the value of the effectiveness of the drug and not the (high) price tag or the rising pharmaceutical expenditure.

Areas of innovation

Additional to the higher growth of medicines expenditure relative to income growth and overall health expenditure growth, other concerns are present. The (lack of) development of medicines for small groups, which may raise fairness issues, is one concern. Another one is that current incentives reward companies to develop mainly new medicines of little advantage rather than developing superior medicines as long as having a new product brings with it the (implicit) promise of a high price.

Only 1 in 10 drugs brought to the market is considered a true innovation and important therapeutic gain defined by clinical advantages for patients. Vice versa 9 in 10 drugs have no or only marginal clinical advantages for patients (Light and Warburton 2011; Godman, Oortwijn et al. 2016; Schwabe and Paffrath 2016; Techniker Krankenkasse 2016).

In oncology – a clinical field of special interest due to the many new drugs (30% of all new approvals, 12-14 each year), high cost-intensity and many drugs with marginal benefit even expressed by Clinical Societies (ESMO (Cherny, Sullivan et al. 2015) , ASCO

(Schnipper, Davidson et al. 2015), NCCN (Nardi, Wolfson et al. 2016)) - an analysis of all drugs out approved between 2009 and mid 2016 (n=134) showed that only 22 (18%) increased overall survival by more than 3 months (Grössmann and Wild 2017), while for 37 drugs (27%) neither data for progression-free survival nor for overall survival was available at the time of approval.

New payment models that reward any new drug irrespective of the therapeutic value they bring can, in fact, be detrimental to the social value of R&D efforts compared with alternative discoveries.

Not only governments are concerned with developments (huge drug prices and few drugs with more than marginal benefits) that the given regulatory system to set incentives is not delivering innovation but rather leading to exploitation (e.g. orphan designations), but also public institutions and non-governmental organizations (NGOs) express their concerns. Among such public institutions we can refer to the European Social Insurance Platform (ESIP) (European Social Insurance Platform (ESIP) 2016) and the European Hospital & Healthcare Federation (HOPE) (European Hospital & Healthcare Federation (HOPE) 2017). From the NGOs group, we have Health Action International (HAI): Keys to improving access & Innovation of needed Medicines (Health Action International (HAI) 2016) and European Public Health Alliance (EPHA) (European Public Health Alliance (EPHA) 2017). Even Medical Societies start to express their concerns and provide support to distinguish between drugs of no or marginal benefit and those of true value to the patients.[4]

Managed Entry agreements can be analyzed by type of instrument (say, outcome guarantees, price capping, patient/dose dependent discount, price/volume contracts, etc.) or by type of impact (say, treatment interruption if drug is not effective according to pre-established targets, application of discount if drug is not effective or less effective than expected, cap on number of doses/total cost reimbursed per after which the manufacturer assumes the cost, etc.).

[4] For example, the European Society of Medical Oncology (ESMO) (Cherny, Sullivan et al. 2015), the American Society of Clinical Oncology (ASCO) (Schnipper, Davidson et al. 2015), and the National Comprehensive Cancer Network (NCCN) (Nardi, Wolfson et al. 2016).

MEAs should not become a quick-fix solution to introduce expensive drugs but be integrated into a process of managed introduction of new medicines which starts from horizon scanning activities, moves to forecasting, HTA assessment, pricing and reimbursement, and continues with post-marketing studies and surveillance.

MEAs include price-volume agreements (PVAs), outcome guarantee, coverage with evidence development (CED), and disease management programmes.

A variety of names have been used to describe MEAs (e.g. risk-sharing agreements (RSAs), performance-based agreements (PBAs), patient access schemes (PAS), etc. Three-quarters (75%) of all the agreements in the study countries aimed to address budget impact, either alone (42%) or in combination with cost effectiveness (16%), use (15%) or both (2%). In some countries, Italy, Portugal, Lithuania, the Czech Republic, and Belgium there was a strong focus on budget impact. While in others, Sweden, the Netherlands and the UK, cost effectiveness seems to be the driving force when deciding to engage in a MEA. Further, Italy, the Czech Republic and Belgium, limit access of certain medicines to eligible patients in an attempt to manage budget impact and use. Managing budget impact is one the main objectives of MEAs in Belgium, the Czech Republic, Italy, Lithuania, Portugal, and the UK.

This is reflected in the design of MEAs in these countries which includes features of PVAs, budget caps, and a compensation mechanism in Belgium, limited access through specialised healthcare centres in the Czech Republic, PVAs, discounts and conditional treatment continuation in Italy, PVAs, payback, and expenditure cap in Lithuania, PVAs in Portugal, and discounts, dose capping, initial free doses in the UK. The first is to grant reimbursement for a limited time period during which additional evidence on the drug effectiveness will be collected and to update the reimbursement decision afterwards based on the new cost-effectiveness results.

The diversity of contracts and agreements can be organized according to different taxonomies. Figure 1 provides one possible taxonomy, proposed in Ferrario and Kanavos

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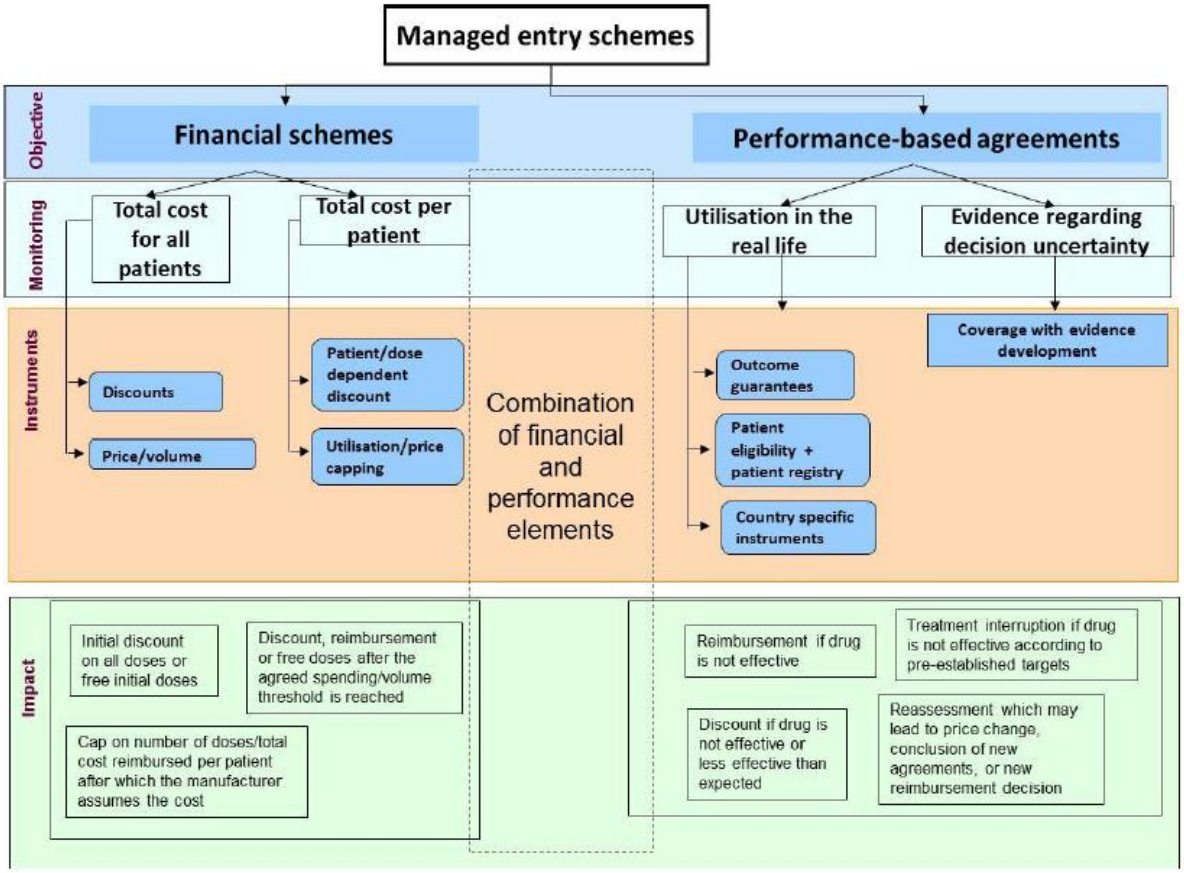
(2013).[5] A synthesis of the literature on the taxonomy of MEAs is provided in KCE (2017). Typically, taxonomies cross in different ways four key elements of MEAs: (1) financial-based versus health outcomes-based agreements; (2) population level versus patient level agreements; (3) performance-related measurement, or not; (4) role attributed to further information/evidence on product characteristics.

Figure 3:
A taxonomy of Managed Entry Agreements



Source: Ferrario and Kanavos (2013)

3.2.1.3.Strategic analysis of MEAs

The MEAs anticipate access to the new product at the cost of delaying some steps of the standard analysis. The anticipation of entry decreases one type of problem, delayed access – a good new product reaches sooner the patients. As elements such efficacy and safety are measured along the way, a different problem emerges – the use of products that have an efficacy level that under normal conditions would not lead them to be

[5] Two alternative typologies are presented in apêndix. The central features do not differ considerable across typologies.

approved. As withdrawal may be difficult, as would be seen as cutting access to a product by the population, unless serious issues of safety become apparent, the anticipation substitutes one type of problem by another. Of course, an automatic and credible rule of withdrawing the product when standards are not met would allow anticipation while also reducing the risks of the second problem. The key aspect is credibility of such mechanism.

From a literature perspective there seems to be a general agreement that MEAs can, under certain conditions, help to address post-licencing uncertainty and enable patient early access to innovative treatments. In general, MEAs offer flexibility in dealing with new and often expensive technologies, which are characterised by significant levels of uncertainty about their effects. Still, as described previously, there is an element of exercise of market power present in the high prices asked that is not addressed by MEAs by design.

The use of MEAs can be characterized in strategic terms, using a strengths-weaknesses-opportunities-threats approach, described in detail in Ferrario and Kanavos (2013). The variety in types of MEAs results from the particular aim in each case (according to whether it is the financial budget impact or the uncertainty in the information from clinical evidence, or eventually both, a different type will be used). A review of strengths and weaknesses of each type of MEA can also be found in KCE (2017). The ability of MEAs to bring useful information in practice seems to fall short of expectations. Aspects that seem to contribute to this finding are the short time span of the use of MEAs, the small number of patients typically involve, and selection of patients receiving the pharmaceutical product (after being approved) included in the MEA. The discussion, still, does not address the crucial issue of price determination mechanisms.

The strong points of MEAs are different for distinct stakeholders (health care payer, patients, companies), as each focus on a different main objective (for example, respectively, budget control, access, obtaining reimbursement with a non-disclosed price). On the weaknesses side, the main one identified in Ferrario and Kanavos (2013) and in KCE (2017) is the absence of support to the expected gains. Another major

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weakness is the costs associated, which seem to have been larger than anticipated by health care payers (monitoring requirements do require specialized resources from both sides, health care payers and companies). The non-disclosure conditions on the exact terms and results of MEAs, part of the agreements set, lead to lack of transparency and difficulties in assessing whether or not objectives are achieved.

Opportunities identified range from use of additional information on real-use characteristics of new products (ranking high in health care payer perspective) to faster access (ranking high in patients' perspective) and to public image benefits (ranking high in companies' perspective). From these, it has become clear over time that information obtained is smaller than expected, and opportunities related to it were hard to materialize.

On the threats, it is becoming clear that heterogeneity in MEAs, across and within countries health systems, makes difficult to have an integrated approach at the health care payer level. In addition, both price setting and data collection (evidence) by companies may adjust to the conditions required by the MEAs. Quick examples are upward price adjustments by companies under the expectation that discounts will be part of the MEA and leaving data (evidence) collection to later stages, within the context of the MEA. That is, the starting points of the initial MEAs may not be representative of future MEAs, as economic agents adjust to their existence. On the side of pharmaceutical companies, as health care payers require further information and monitoring systems, costs of engaging in MEAs can escalate.

Overall, the SWOT analysis of Ferrario and Kanavos (2013) does change in its main messages with more recent information on MEAs, with the broad message being centred in the complexities and heterogeneity of MEAs bringing less information and higher management costs that were presumably predicted.

3.2.2. Health system performance

The health system performance of current payment models has concentrated on the overall growth in pharmaceutical expenditure, putting pressure on third-party payers, whatever their nature (public, private or non-profit entities).

Expenditure by payers is a combination of several elements: how many products are included in the health insurance coverage (public or private)? How much are patients sharing the costs at the moment of use? Are there limits to consumption set by payers? How fast prices are rising and what mechanisms counteract on the ability of companies to raise prices of their products? How institutional mechanisms facilitate high prices by companies?

For example, the accepted association between value and prices has led to a practice of indication-slicing to secure higher prices, as once a price set for an indication, typically the more cost-effective one to command a larger price, an umbrella extension of prices is beneficial to manufacturers and non-discriminatory to patients (although, at very high cost to health care payers).

Health system performance in the use of pharmaceuticals can also be addressed in terms of future health and system challenges, to contribute to better health outcomes through equitable improvements in access, quality, coverage, and use of pharmaceutical products and related services.

Pharmaceutical systems strengthening is the process of identifying and implementing strategies and actions that achieve coordinated and sustainable improvements in the critical components of a pharmaceutical system to enhance responsive and resilient system performance for achieving better health outcomes. The critical components of a pharmaceutical system are its core functions, structures, the supporting health system resources, and an enabling policy, legal, and governance framework)

Following the list of components for the measurement framework of health systems, the following aspects can be considered as relevant dimensions: (a) Policy, laws and governance; (b) Regulatory systems; (c) Pharmaceutical services; (d) Human resources; (e) Financing; (f) Information and (g) Innovation, research and development, manufacturing, trade.

The impact of medicines on health care costs occurs through three main channels: prices, quantities (consumption levels) and cost off-set (when spending more in pharmaceutical products implies spending less in other types of care).

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The difficulties of the current payment models to health systems performance became apparent with the first case of a high volume – high price drug (Sovaldi), which was a pre-announcement of forthcoming drugs asking for a very high price and not restricted to a small number of patients.

3.3. Properties for payment models of innovative medicines

3.3.1. Role of directing R&D

Payment systems for innovative pharmaceutical products have to provide the correct signals, from a social point of view, for private R&D investments. As stated in EXPH (2016b) "*Creating incentives for and rewarding innovation involves two approaches: a) compensation for the costs of developing a new product; and b) compensation for the value of the innovation to encourage the development of products that are more highly valued than others because they address a more important therapeutic gap.*"

This view has several implications about the several roles performed by payment systems in fostering innovation and what are desirable features of innovation that should be incentivized. A first consideration is that new payment models should implicitly direct R&D efforts to development of breakthrough products that can be considered disruptive innovation, and not just incremental innovation. The opinion in EXPH (2016a) introduces a notion of disruptive innovation in health care suited for the European health systems, "disruptive innovation" in health care as "a type of innovation that creates new networks and new organisations based on a new set of values, involving new players, which makes it possible to health improve outcomes and other valuable goals, such as equity and efficiency. This innovation displaces older systems and ways of doing things" (EXPH, 2016a, p.23).

Thus, payment systems that reward truly innovative products may have to be flexible enough to adjust for novel ways and cultures of providing care. Within the context of new pharmaceutical products this is made possible due to the research frontier that combines products for specific areas and for the combination of diagnostic and treatment products. In sum, new payment models need to reward more innovate and disruptive products

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than incremental ones. The difference in rewards will drive efforts towards more valuable innovations (to society).

But since truly disruptive innovation is mostly unpredictable in its effects, it is not feasible to define ex-ante a payment model general enough that can be optimal in all future contingencies. This raises a problem of "what comes first" as incentives for R&D efforts that may lead to disruptive innovation depend on the payment model that will be adopted, which in turn may be a function of R&D efforts. Still, some principles should be present in the payment model.

Payment should be made for products that are worthwhile. In this assessment, the value-based health care approach provides a methodology to measurement of results that matter to patients that should pursued. Note that identification of relevant dimensions of benefits and the definition of measurement approaches do not force a particular mechanism for price determination to be adopted.

Another principle to consider is that new payment models should not be based on paying for R&D costs incurred. Payment models that are solely based on costs incurred provide an incentive to companies to inflate costs as a way to secure higher payments. A "cost plus" approach to pricing would not respect the principle above of providing incentives for new products with high benefits to patients. As it will be argued below, cost transparency is important though not as the way to build the price that rewards innovation.[6]

Taking the principle that payment models need to be related to "outcomes that matter" for patients, it follows that no general pricing rule can be set ex-ante. The payment model must then establish a procedure that will lead to a price. Such procedure may involve sophisticated methods to define "what matters" for patients and which payers are willing to pay for, and may involve price adjustments over time, as information about the true value of the product is revealed. The use of contracts for payment may replace a simple price announcement.

[6] The properties of this type of payment model are presented, for example, in Laffont and Tirole (1993).

3.3.2. Role of affordability to health systems and to patients

Health systems pursue several objectives, which can be summarized in universality, equity, sustainability and high quality of health care services. For both equity and sustainability, affordability of new products is key. Affordability implies that prices asked are within financial means (of the payer and/or of the patient). In the context of public health care systems with limited budgets, affordability means that budget funds diverted to pay for the new product do not exhaust the budget or imply strong, and harmful, reductions of healthcare services elsewhere in the health sector. For private insurance models of financing health care, affordability translates into the ability of the insurer to pass-through increased costs to contributions of citizens (insurance premiums, wage-related contributions, etc.).

Affordability results from the health system design and value of payments that have to be done by payers (public health systems, private insurers, or copayments and out-of-pocket payments by patients). Payments to providers of health care, including pharmaceutical companies selling drugs, will cover their costs and their profit margins.

Higher affordability to institutional payers can be achieved shifting costs to patients through higher cost sharing rules (which, in turn, decreases affordability to patients). Affordability to institutional payers can also be achieved by limiting the volume of patients to be treated, which results in access issues and eventually too much rationing in access to treatment. Thus, a balance between affordability to institutional payers and to patients needs to be achieved. The innovative payment models have to achieve this balance.

A more subtle point is the avoidance of multiple payers, as double health insurance coverage (say, by health insurers and by public hospitals) may lead to cost-shifting strategies from one payer to the other, with the likely effect of increasing overall costs. This is an issue that is not specific to pharmaceutical expenditure, though it may also arise here.

One popular theme in the discussion on access to new pharmaceutical products is the call to drop the "silo mentality". This has two main arguments by performing efficiency

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assessments of health technologies and interventions, health systems can discard those of low efficiency, freeing up resources to be used elsewhere in the health system, most notably in paying for access to new pharmaceutical products. This means substation of spending across areas ("silos") in the same temporal moment. The second argument is that by spending today in pharmaceutical products that avoid future need of health care, such expenditure is seen as an investment that brings lower expenditure in the future in other areas. There is an intertemporal substitution in spending across areas ("silos") of health care. Both arguments highlight the point that efficient use of resource may imply higher expenditure in new pharmaceutical products by health systems and that resources to pay for it may result from avoidable expenditure elsewhere in the health system.

These arguments, however, do not call for a particular system of price determination for new pharmaceutical products and do not call for a continued rising in the prices of new pharmaceutical products.

It is consensual that new pharmaceutical products must be subject to a rigorous control regarding efficacy, safety and quality. It is becoming widespread the view that efficiency considerations of new products is also to be assessed. Under the efficiency heading one includes also programs aimed at better prescribing patterns.

The use of generics and biosimilars is often regarded as a contributing element to lower the financial pressure on health care payers. In that line of argument, they open budget space to pay the new innovative products.

All these areas for public policy interventions have merit though they arguably do not address the fundamental tension on the pricing of new pharmaceutical products between access and innovation incentives. In particular, the mechanisms driving up prices are not addressed by policy measures regarding generics and biosimilars. These policy measures have merit on their own and should be pursued under the objective of reaching the best possible use of scarce available resources.

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3.3.3. The role of intergenerational transfers

Innovative pharmaceutical products benefit from patent protection. After the patent expires, these products can be produced and sold by any manufacturer that complies with the established safety and quality rules. This brings competition to the market, and lowers the price of drugs. The costs of R&D are recouped during the patent period. Thus, future patients will not contribute to the payment of R&D costs. This corresponds to an intergenerational transfer. Of course, if the life cycle of the new drug is approximately equal to the patent duration, no such intergenerational transfer takes place.

Another intertemporal effect is associated with too much current use of products leading to antimicrobial resistance, resulting in higher treatments costs for future generations. This "externality cost" is disregarded in current payment models. New payment models should explicitly recognize their properties and implications in terms of intergenerational transfers. On payment models for new antimicrobials, the report on the issue by European Commission (2017, p. 16) clearly lays down the market failure associated with the negative global effect of antimicrobial resistance from large-scale usage of new products. The report advocates an improvement in health technology assessment methodologies. These are likely to require complementary insights from a broader health system design as to incorporate adequately the need to internalize the impact on resistance from consumption while preserving patients' access to antimicrobials.

3.3.4. The balance between objectives and instruments

The payment model has to satisfy several objectives at the same time: ensure affordability of new products to institutional payers and patients, reward innovation, cover costs of companies, promote efficient use and efficient production, etc.

The traditional payment model based on defining a single price per unit of drug, linear price model, has only one instrument to achieve the several objectives. When conflicts between objectives exist, a trade-off between them will determine the optimal price value.

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Another route is to increase the set of instruments available. Innovative payment models should use a more comprehensive set of instruments than the traditional linear price model.

Although intellectual property protection has been the cornerstone to foster innovation by private companies, in medicines as well as across the economy, it can be questioned whether it can or should be replaced or complemented by other ways to reward innovation in the health care field (say, prizes for discoveries, followed by a immediate-generics strategy). The definition of preferential areas is, of course, debatable in the choices it makes and these may change over time. Areas with both a) an increasing burden of disease, and b) more amenable to have substantial breakthrough gains in therapeutic value added are natural candidates to be included in novel ways to promote R&D. But sometimes unexpected innovation with high impact emerges from unexpected places. At least, considering other ways to reward innovation would free prices from being the single way to meet such objectives at the same time.

3.3.5. Framing health system design options

Pharmaceutical companies have proved to be quite adaptable to the economic environment they face. They have adjusted to the new incentives to develop orphan drugs. Some may even argue they adjusted too much, as many drugs are now presented initially as indicated for a few number of patients in which they are highly effective (and thus command a high price), benefiting from orphan drugs' special treatment. Later, expansion on indications to use of the product bring scale to activity.

The value-based healthcare trend brings the measurement of benefits (outcomes) of health interventions, including medicines, to the frontline. By focusing on measuring benefits and arguing with payment according to value, companies are able to set attention of payers into the logic of paying ever more under the approach that any price that guarantees that cost-effectiveness is below a pre-defined threshold is fair. The argument implicitly assumes that "pricing by the threshold" is the adequate way to set prices. Allowing the discussion of benefits to dominate attention leads to intellectual

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capture of payers, restricting attention to a pre-determined model of payment that has revealed the property of inducing high prices.

The focus on incentives to R&D investment (and thus higher prices for better, more valuable innovation) should not lead automatically to the highest price possible as chosen by companies. The approach of unchecked pricing behaviour for products under patent (meaning not being assesses as exercise of market power by competition authorities), common in most industries, breaks down here. The limit on very high prices for innovative products in other industries results from sensitivity of consumers' demand to price – at very high prices some, or many, consumers will stop using the service or consuming the product. In health care, the existence of health insurance protection (public or private) eliminates, or decreases considerably, the role of demand sensitivity to price (at the gain of the value of insurance protection). The implication is that the standard conditions under which innovation and its pricing takes place in other industries is not met in the case of pharmaceutical innovation, once the drug is approved for reimbursement. The health system design to deal with high-price innovative medicines has to mimic (some of) the results that would occur under "standard market conditions". This clearly sets the discussion at the level of health system design, which provides the background for firms' decisions, rather than interfering directly with firms' internal decisions (regarding prices and R&D efforts).

One example of the importance of adequately framing the price determination process is given by the rule that if a product meets a certain criterion (a certain threshold for incremental cost-effectiveness) then it must be approved for reimbursement, where cost to the payer applying this rule is given by the price asked by the company, leads to a focus on presenting an ever-expanding set of benefits to the new pharmaceutical product. This increases the room for a higher cost to the payer, that is a higher price asked by the company.

The direct implication is that defining payment models for high-cost innovative medicines is an issue of health system design, not an issue of finding a particular contract for prices of a particular drug.

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3.3.6. Governance

The creation and use of new payment models raises governance challenges that cannot be overlooked. Crucial elements are the monitoring procedures and the negotiation power on behalf of the public good.

The MEAs experience shows the relevance of these two issues. The general use of more complex payment models for new pharmaceutical products will imply changes in health system design. Some of the changes will likely create challenges in terms of political feasibility, including the delisting of products that do not materialize initial expectations based on preliminary evidence. Even if predicted in the payment model, removing products from coverage may face the opposition of patients, even at the light of smaller effects than promised.

The issue that pharmaceutical products are seldom delisted points to the importance of the political risks of not being able to remove a product once included in the coverage package of a health care payer. The "uncertainty motive" for using MEAs should, statistically lead to some products being delists. This bias towards inertia after inclusion is apparently a persistent phenomenon. The alternative interpretation for non-delisting of products is that all products are highly innovative, in which case the question being why there was not enough information about it during the assessment by health care payers.

Some health systems, the ones not based on a single (or major) health care payer, face an additional issue of coordination across payers, which can eventually be accused of collusion if information about payment models and values is shared and alignment of models is coordinated.

The governance model for new payment models has to provide a clear definition of information to be collected, open standards for outcome measurement, decision rules about it, openness of information, registries and ownership of data. All these matters may require important changes in the legal and institutional settings of health systems.

3.4. The instruments

The definition of innovative payment models for new pharmaceutical products needs to consider both existing and novel instruments. Prices have been the main instrument in the payment model, complemented recently with more sophisticated contracts.

The first line of development is, therefore, contracts that use more flexible pricing models, including conditional payment for results, fines for negative results, etc. Examples of instruments along this line are two-part prices, non-linear prices (such as different prices conditional to volume, or to different patient characteristics) and conditional market-entry agreements.

A second line of development is to use different ways to set prices and change the institutional setting in which prices are formed. Examples of this line are actions that increase the bargaining power of payers in price negotiations, like joint procurement or the eventual use of legal rights around patents, invoking public health concerns. The initiatives on joint procurement intend to build bargaining power in the negotiation of prices, doing it by two different forces. On the one hand, joint procurement aggregates demand from several countries (or purchasing entities), becoming a more relevant partner to the pharmaceutical companies than each on its own. On the other hand, joint procurement uses a more pressing mechanism to obtain prices (at least, in comparison with the implicit approach to price determination associated with meeting a cost-effectiveness threshold).

A third line of development is to use different instruments to reward innovation, such as innovation procurement, public-private initiatives, etc.

The main concern is to explore new ways of setting prices for specialty medicines in terms of improving access, while taking in to account the costs, the benefits, the budget impact and the future return on R&D investment on a transparent manner.

3.4.1. Prices (multi-indication, tier pricing, bundling, etc.)

3.4.1.1.Non-linear prices

The use of non-linear prices (that is, payment models that do not restrict payment to a price value per unit of the product) is present in other sectors. The consideration of non-linear price structures adds instruments to structure the payment that increase flexibility to address the several objectives present in the definition new payment models.

Combination of pharmaceutical treatments, commanding a higher price than individual products, was observed in several cases. This raises the issue of how to deal with such

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situations. This question has a strong analogy with the theory of pricing bundles. The new element is the combination of treatments with original components from different companies. The more relevant point is whenever the combination of existing products is presented as innovation, as way to obtain higher prices only.

The combination of existing products may have extra value to patients (from convenience or from an increase in treatment compliance, for example). Costs of production do not change considerably by setting a joint product and as individual products' prices are already rewarding innovation, having a higher price for the bundle of products is a mere transfer of value to companies (its affects on R&D incentives are non-existent or minor compared with individual prices).

The analogy with other economic sectors suggests that experience from these other sectors (transport or telecommunications) can potentially inform the development of payment models for new medicines. The analogy is, however, incomplete because health insurance – financial protection of patients from the random costs of health care regarding moment and amount - is a distinctive feature that isolates to a considerable extent payers from the price. The objective of universal access itself is shared with other economy sectors (e.g. third party liability insurance or home insurance, telecommunications and other utilities). Also the objective of providing insurance against adverse events is shared with other economy sectors. Still, the combination of insurance, consumption demand under considerable delegation (agency relationship) to a considerable extent and universal access as policy objective is fairly unique to health care. The fact that in other sectors, like telecommunications, innovation can be quality increasing and price (cost) reducing over time shows the distance in context to the health care sector, where innovation has traditionally been price increasing. Nonetheless, some ideas can be borrowed from those other sectors: price differentials across different and distinguishable groups of users can be welfare enhancing under certain conditions (further discussed below).

Prices that reflect economic opportunity cost should be pursued. In the absence of innovation, competition drives prices to their economic opportunity of production. With

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innovation, patent protection is given and prices above (marginal) cost of production are allowed.

Limits to market power exercise in other sectors of the economy in general results from price elasticity of demand (reduction of consumption that becomes very significant at high prices). Health insurance eliminates (or strongly) decreases the price elasticity of demand (which tends to be low anyway). Other mechanisms to address exercise of market power need to be found. Health Technology Assessment has become predominant internationally. HTA has as by-product a decision rule that implicitly promotes high prices – by taking the price asked by the pharmaceutical company as the cost to the health authority, a rule that includes in coverage of the health system products that have a cost-effectiveness below a pre-defined threshold allows firms to raise the price up to a level close to that threshold even if a lower value would provide also a profitable margin to the company. There is a need to distinguish the HTA assessment (on clinical) and HTA appraisal (or pricing).

If there is a certain R&D amount to be funded across markets/countries that differ in their characteristics, differential pricing is adequate but levels of prices need to be the minimum required to collect the amount to be funded. Resulting optimal rule is based on price sensitivity, which is influenced by each country's health system rules.

Monopoly pricing has the same relative price structure as the one selected by a regulatory entity but goes for higher prices (that is, in both cases users with a smaller price elasticity will face a higher price, as there is less loss of consumption for these users). Thus, optimal pricing from a social point of view coincides in the structure of prices but not in price levels.

A crucial question is "What to pay?". It is not enough that R&D is done and a new product is discovered. It needs to provide evidence of benefit. Often, there is uncertainty about the value of new products, so there is room for real world evidence (RWD) to improve knowledge on market characteristics. But the use of RWD has its own shortcomings.

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The optimal time profile of prices would be low prices after discovery of valuable product and provide reward to innovation without distorting prices or decisions. But this would undermine rewards for R&D and consequently dynamic incentives for new discoveries (as already discussed above).

As we do not have a competitive market for new pharmaceuticals due to existence of patents, the analysis needs to be set in terms of bilateral (or multilateral) price negotiations. This brings the relevance to focus on the features that determine the bargaining power of each side. The automatic rule of the incremental cost-effectiveness ratio (ICER) where "costs" are set by the prices asked to the payer gives bargaining power to Governments.

A different, though related point, is that the "very costly" nature of new pharmaceutical treatments is not unavoidable. Very high prices do not follow automatically from R&D costs and such very high prices cannot be taken as exogenously determined.

The justification of high prices based on the high underlying R&D costs is often unchecked (as none or very little information is released by companies on the costs of R&D, which include opportunity costs of investment and failed attempts to obtain the innovation).

The pharmaceutical industry alleges that high prices are unavoidable given the expense of R&D to bring new medicines to the market. Several (sponsor-based as well as independent) analyses tried to shed some light on the actual R&D expenditures a basis for transparent price-building. The German Association of Research-Based Pharmaceutical Companies (https://www.vfa.de/) estimates US$1-1.6 billion (Verband de Forshenden Pharmaunternehmen (VfA) 2016), depending on calculating the cash needed to develop one drug or to – additionally – include the "capitalized" cost including investments in aborted projects and lost profits elsewhere. A recent estimate from Prasad and Mallankody (2017) sets the (median) cost to develop a cancer drug at US$793.6 million, after accounting for the opportunity cost of capital invested, a figure significantly lower than prior estimates (though a large interval of possible values was found, with costs ranging from US$219.1 to US$2827.1 million).

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Knowledge of R&D costs would help to scrutinize the extent of exercise of market power. A simple hypothetical example illustrates the relevance of this element. Suppose a new drug takes 5 billion euro to develop (this is a value that exceeds several estimates of the average cost of developing a new drug, including the returns to investment over time and failed attempts to obtain the innovation). Suppose it allows to treat 100 million people worldwide over the life-cycle of the product. A simple computation leads to an amount of 50€ per patient – year to cover the R&D costs. Even if the new product reaches only 10 million patients over the full life-cycle of the product, the price tag for R&D alone would be 500€, still far from the 5, sometimes 6, digits prices being asked for some of the new products. Naturally, shorter periods of monopoly of an innovation require a higher price per period to obtain the same revenue. Though, whenever the shorter period results from another, better, innovation being introduced, it would be normal competition in the market place, as firms bear the risk of other companies replacing them.

A different case may be considered for antibiotics, as resistance to them bring negative effects from consumption. This may call for higher prices or for strategies to limit use to the truly necessary situations.

The economics of price differentiation across markets (and indications) suggests it can both improve patients' access and be a strategy to increase revenues to companies. The conditions under which price differentiation increases both affordability and access need to be clarified.

3.4.1.2.Price transparency

There are several claims that price setting should be more transparent and should not be left to industry alone.

A clear view on the issue of price transparency was already present in the EXPH (2016b) "Opinion on access to health services in the European Union": *"Creating greater transparency around the costs of pharmaceutical products and the price of medicines would provide better grounds for assessing affordability, equitable access, fairness in pricing and incentives to develop new medicines.* (p.79)

The belief that that low prices are slowing the process of drug development worldwide is contradicted with the major companies have changed their business model years ago by stopping to discover new drugs themselves and buying into the discoveries of other, smaller companies specialized early development of molecules. So called Partnered Development Programs focus on the discovery and development of molecules in small Biotech companies and processed (commercialized) towards market authorization by large pharmaceutical companies.[7]

3.4.1.3. From paying pills to paying services

Market entry agreements can be the first step towards more elaborated strategies to commission health care services from private providers. New payment models based on outcomes (value-based health care), with bundled payments that may include bonus and penalties related to positive and negative outcomes defined in a contract, mark a change to simply paying for a product. This brings acquisition of medicines becoming closer to commissioning of health care services, particularly if pharmaceutical products are used in combination with diagnostics or/and treatment involves combining several pharmaceutical products. (Jonsson et al., 2016)

Market entry agreements based on outcomes have strong demands in terms of data collection and its interpretation, making it difficult to work in every case.

Market entry agreements may address one or both of two issues: a) uncertainty about the effectiveness of the new pharmaceutical product, and b) lower prices demand by payers of health care, without jeopardizing other markets through the links of international reference pricing.

More elaborated payment structures, like two-part tariffs, is mentioned in Jonsson et al. (2016) "A two-part tariff, including price volume agreements and different prices for different uses is common in many markets characterized by large investments (for instance, transport, energy and telecoms) and could potentially improve the situation".

A potential avenue in the development of a new framework to payment models for high cost innovative medicines is to move from buying pills to buying services. It also changes

[7] Those Partnered Development Programs are legally regulated under "Asset Transfer Agreements" (2013).

the role of pharmaceutical companies from sellers of a product to partners in the provision of services. There are challenges in this avenue. A major one is the commissioning of the service and what is required to do it – expertise and strategy to the service commissioned, as detailed in EXPH (2016c).

New payment models that move from paying pills to paying services will have a concern and explicit recognition of the role of patient compliance.

3.4.2. Innovation procurement initiatives

One may to increase the set of instruments available is to consider different ways to stimulate innovation besides the "promise" of prices after the innovation is obtained.

Possibilities are the creation of partnerships for neglected diseases, with examples coming from tropical diseases.

Development of early relationship between regulators and pharmaceutical companies may also help to guide R&D efforts, though a careful analysis of advantages and drawbacks needs to be carried out. Whenever neglected areas can be detected and be consensual on the opportunity to have innovation, using available instruments (soft ones, as joint horizon scanning discussions, or hard, as price or reward commitments) can be improve innovation value. In such approach, R&D and product market competition should not curtail open research by companies, as breakthroughs may occur in unplanned ways.

A more active role for health systems to commission innovation may be considered as well, although given the global nature of pharmaceutical markets, it needs to be carefully crafted (so that one country does not subsidize the R&D that benefits all others). Other ways than patents to stimulate innovation other than prices can be considered. One possibility for new modes of innovation is provided the Triple Helix concept (Ranfo and Etzkowitz, 2013), which requires the active involvement in a partnership of universities, industry and government. An example the Triple Helix model of innovation is the development of radiotherapy innovations by the Karolinska university hospital in Sweden, together with other university hospitals, several private companies and government support.

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3.4.3. The incentive role of prices and of the payment model

Secret price discounts are a form of price competition, and also a way to price discriminate across countries. The widespread use of external (international) price referencing makes secret price discounts a way to escape its consequences. The country receiving the price discount has the incentive to agree with it, as the benefit to the other countries from lower prices induced by the reference price mechanism is not internalized. More importantly is that in the absence of the secrecy, no country would benefit from a discount. This may allow some countries to have products available compared to a policy of equal prices in countries where the product is sold. In the case of new pharmaceutical products, competition can occur only across therapeutic substitution possibilities during the life of the patent.

A major issue to be explicitly recognized is that exercise of market power (meaning that prices are well above a benchmark of "fair return" on investment, including R&D investment) is present and it is a result of the current institutional framework. Some relevant proposals will not solve the issue. As mentioned in the European Parliament's Report (p. 10) "value-based pricing of medicines can be misused as profit-maximisation economic strategy, leading to the setting of prices that are disproportionate to the cost structure." The EU competition legislation can have more role here, although the intervention against products under patent protection is delicate. It is probably more adequate to address at a more fundamental level the institutional aspects that allow for high prices to be set in the first place. In particular, price determination mechanisms need to be addressed explicitly.

For example, it should be avoided that principles expressed as "price and reimbursement levels of medicines should correspond with an acceptable value for money from a societal perspective" (Annemans and Pani, 2017, p.2) translate into the maximum acceptable price through the prevailing institutional arrangements. Value-based pricing does not mean that providing price signals (economic incentives) to true therapeutic added value equates to prices allowing companies to capture all possible surplus.

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The incentive signal provided by higher prices for products that bring more value added cannot be taken to mean that excessive prices are acceptable and that unchecked exercise of market power can be done by companies, especially in a context where price elasticity of demand is severely reduced by health insurance protection mechanisms (either public or private).

Different instruments are used for different, sometimes conflicting, purposes. Some of the instruments attempt to bypass implications of other instruments. A main example, as mentioned above, is the use of secret price agreements between companies and payers to avoid international price referencing by other countries' health systems.

When the concern is about the value added of the innovation, outcome-based payments provide the right incentives, as the price linked to outcomes helps to separate high value drugs from low value drugs whenever companies have netter knowledge than payers of care. Also, paying more for higher value drugs provides an incentive for investment in such drugs compared with lower price drugs. The target left behind in this case will likely be affordability, and consequently access to the new pharmaceutical discoveries. When the issue of concern is affordability and high prices that hurt access to the new product, reinforcing the bargaining power of payers or forcing further competition among pharmaceutical companies is likely to improve this target. On the other hand, lower prices will mean less gain from conducting R&D, which will mean over time less innovation. Health benefits will be smaller under low prices. A balance between competing targets has to be achieved.

3.4.4. Searching for a new institutional design

3.4.4.1.Prices set by explicit negotiation

Any payment model involves an explicit or implicit allocation of power to set prices, even if a rule is defined. In a free private market, companies name prices and consumers decide to buy or not the product. The power to set the price is with the firm. It is limited by consumers' decisions. Under a rule that says that a product is accepted to coverage by a health care payer as long as it meets a threshold for (incremental) cost-effectiveness, the power to set prices is with the company and the "demand" decision is

basically and "all or nothing" decision. Thus, the power of the firm to set prices is capped by the threshold limit but essentially free below the threshold. By providing arguments and evidence of more benefits (more value from the product) companies can relax the constraint on prices exerted by the threshold implicitly or explicitly used by the health care payer.

Under cost-plus price regulation, the power to set the price is assigned to the health care payer (or regulator) though companies indirectly regain power to set prices by inflating costs (and in the context of R&D, more costs does not necessarily lead to the more valued innovations being sought, resulting in too many costs for too little innovation).

International (external) reference pricing rules give the power to set prices to governments (health care payers) through the definition of a basket of countries for reference. Multinational pharmaceutical companies can indirectly influence the price through their cross-country pricing strategies (including MEAs that keep the effective prices in each market secret).

Thus, the balance of power in price determination results from institutional rules and from agents (companies, governments, specialized bodies, etc.) decisions and adjustment to institutional setting. Future payment models will also define, implicitly or explicitly, a balance in power to determine prices.

Most prices of new pharmaceutical products are in fact negotiated with healthcare payers. Thus, innovative payment models must be cast in the context of negotiations of price. In particular, knowledge and information that provides further bargaining power to payers should be collected. This means obtaining better and reliable information on outcomes, and their value, resulting the use of new pharmaceutical products. Since bargaining is about division of value generated, it is also necessary to know, at least to the bargaining sides, the costs of obtaining and producing the new product. The difference between value and costs is divided between the two sides by the price set. Accepting that prices can be up to the point a certain pre-specified threshold set by the institutional payer corresponds to lend all bargaining power to the companies in the negotiation up to that highest price that meets that threshold. And higher prices are

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obtained, almost automatically in that case, by demonstrating higher benefits to patients. Thus, without surprise, the "race of information" to show higher benefits has dominated the discussion about value-based health care. Recognizing that a negotiation should take place means that cost-effectiveness thresholds should not be determining prices.

A similar position was recently expressed by the WHO (2017), in which a rebalancing of negotiating power is called for. Still, the examples reported in WHO (2017) are in the current institutional setting. Other ways to change the terms of negotiation should be sought. Knowledge of how value created is divided between the different parties will play a role in negotiations. The use of mandatory licensing (with royalties for patent use being determined by judicial decision) is another way to leverage negotiation power to payers. It does not mean that mandatory licensing will be used widely. It is in the interest of both sides (payers and manufacturers) to find a mutually convenient price. The possibility of mandatory licensing merely avoids that failure of negotiations over price results in the market not being served. Thus, in the great majority of cases, one can expect prices to be set by agreement. The use of mandatory licensing works as a way to rebalance bargaining power towards payers of health care (Scherer and Watal, 2002).

The use of negotiation procedures is not without risks to health care payers. An important risk is the political economy risk of Governments (or public entities) not being capable of saying "no". Thus, an important element of strengthening the bargaining position of the public sector as health care payer is to align Government (or public entities) and public opinion positions.

3.4.4.2.Real world data

If prices are set unrelated to underlying R&D costs, it is far from clear that lowering R&D costs by agreeing on the use of "real world data" (RWD) to fast track products to the market will provide for lower prices. In the discussion about RWD, its ownership is an important aspect. And IT-infrastructure as prerequisite needs to be thoroughly addressed (who makes the investment, how is it paid for, etc.)

Transparency of choice of RWD data to be collected (outcomes), of processing (independent data management) and of reporting of outcomes creates challenges.

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RWD use in this area seems to get quite some attention. Transparency and independence of interests of RWD data collections could be the shared principles, SOPs on how to proceed need to be set.

This area justifies getting more insight into the several aspects mentioned above before carefully evaluating the potential of RWD.

3.4.4.3.Patent laws

There is an initiative (within WHO) of analysing legal models of change of protection by patent-laws, proposing to extinguish the protection once twice the amount of realized investments in R&D were earned.

This sort of proposal needs to incorporate the adjustment by market players because companies will just spend to increase the costs that will keep their protection longer. This is a variant of cost-plus regulation of prices, which leads to inflation of costs. It will require validation of R&D costs, which will be quite difficult to do in a global market. Still, as discussed below, the role of patent laws should be rethought.

For pharmaceutical products, where negotiations about prices of new products are common, patent laws tilt bargaining power in favour of pharmaceutical companies. Patent protection means that when negotiations health care payers and pharmaceutical companies fail, the new product is not accessible to payments under the health care system. Current international rules on intellectual property rights (in particular, the TRIPS agreement), on the other hand, provide a route to introduce new products under the call for public health interest. It involves a risk of costly litigation. Still, this possibility of invoking the public health interest shifts bargaining power away from pharmaceutical companies. The existence of this possibility may lead to lower prices for new products, obtained by agreement (and not by litigation).

Patents are often discussed on their role as a mechanism to provide appropriation of gains from innovation in a decentralized way in the economy. Patents, with their feature of providing protection against rivals, can also be used in companies' strategies to protect markets from entry at later stages by asking patent extensions and/or creation of linked patents.

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The patent system fosters decentralized innovation efforts. But it is important to acknowledge that regulatory frameworks for innovation in the health sector make patents expensive to obtain, and small and medium firms are largely cut off from access to patent and bring to the market their own innovations. It has become increasingly common to for small and medium firms developing pharmaceutical innovations to have a strategy of being bought by large companies with the resources and knowledge required to bring new products to the market.

3.4.5. International cooperation

3.4.5.1.Platforms for stakeholders dialogue

International cooperation, at different horizontal levels, is highly desirable. Countries can benefit from sharing experiences of different innovative payment models and from developing a common framework on issues as transparent price setting, on RWD-frameworks and reporting, among others. It is likely that one-size-fits-all solution cannot be found. Still a common set of principles should exist. Countries hosting large pharmaceutical companies are also affected by the common challenges and can benefit from international coordination.

Synergies can be developed between the payers, HTA bodies and regulators in the EU in terms of shared intentions: sustainable and resilient healthcare systems.

Pharmaceutical companies set R&D efforts having in mind the global market, and as such dialogue platforms may form a global view about more fruitful directions for new research, as valued by health systems/payers.

Some of bodies or organizations where contacts take place should involve high-level representatives from pharmaceutical companies. A dialogue about problems and solutions, and future directions of policy measures and R&D efforts can benefit all.

Box 3

International collaboration

In 2010 the European Medicines Agency (EMA) initiated – in collaboration with EUnetHTA JA2 – a pilot project on parallel scientific advice with National HTA agencies that allowed

companies to receive advice from the regulator as well as from the HTA-bodies. The aim was to explore the levels of communalities between EMA and HTA. The analysis was based on 31 parallel procedures (scientific advices). The level of agreement was highest for questions on patient populations (77% agreement, 9% disagreement, 14% partial agreement), while disagreement were more prevalent for questions on comparator (30% disagreement, 25% partial agreement), overall efficacy and safety data necessities (strategic questions and safety database) (23%/ 18%), study design characteristics (randomization, treatment duration, dosing, statistical analysis methods) (21%/ 19%), endpoints (primary efficacy endpoints, PRO and HRQL, secondary endpoints not including PRO, clinical relevance of the effect size (12%/29%) (European Medicines Agency (EMA) 2016; Tafuri, Pagnini et al. 2016). At present limited information is available on content and outcome of Scientific Advice (EMA) and Early Dialogues (EUnetHTA). In the interest of justifying the use of public resources for Scientific Advice and Early Dialogue initiatives it is necessary to understand whether, or not, the objectives were achieved. To avoid unintentional effects of confidential Scientific Advice and Early Dialogue, they should be conducted in the public domain allowing public debate about requirements for drug approval.

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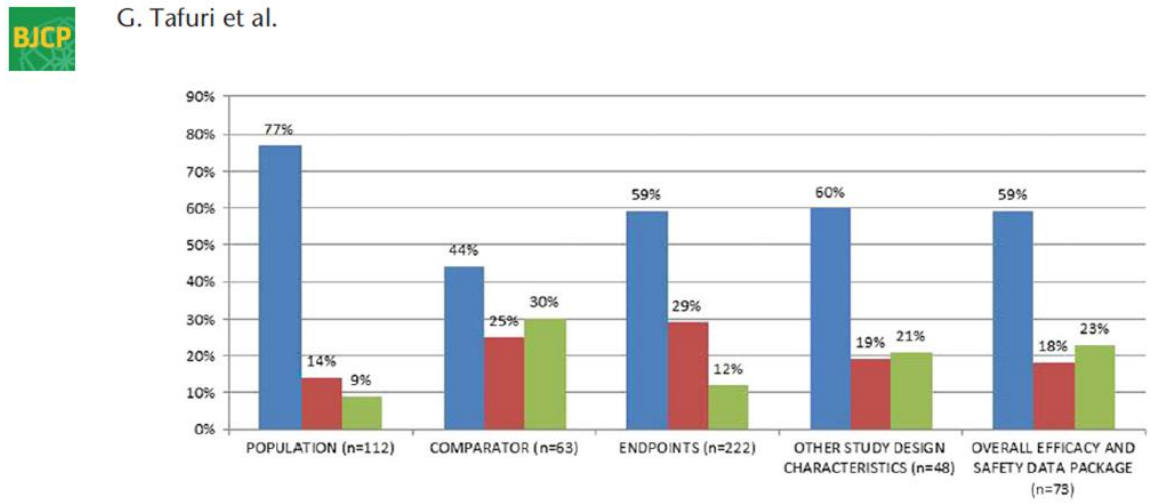
Figure 4: Level of Agreement for Clinical Trial Domains



Source: Tafuri, Pagnini et al. 2016
Note: (blue: full agreement, red: partial agreement, green: disagreement)

3.4.5.2. Structured cooperation

The notion of voluntary structured cooperation between health systems has been advanced as a potentially useful framework to increase access to innovation. It involves creation and operationalization of thematic networks (European reference networks, health technology assessment bodies, building on Joint Action initiatives, etc.). The European Commission's co-funding of EUnetHTA since 2006 has to be emphasized and the EC initiative to strengthen the EU cooperation on HTA after the end of EUnetHTA Joint Action 3 in mid 2020. The general objective of the EUnetHTA is to reduce redundancies in the European HTA production and therefore increase efficient use HTA resources. The development of shared tools facilitates the cross-border HTA collaboration.

One particular case of interest to our discussion is the use of joint procurement initiatives, as a way to improve access to new products. By putting together higher volume, such cooperation may reinforce bargaining power of purchasers. This topic will be taken up in more detail in the next section. Also sharing of information, on what is expected to be available in the near and medium future (known as horizon scanning) and on health technology assessment standards, can provide conditions for Member States to improve access to new products (in terms of decision timing and prices). A potential

hurdle is the different degree of centralization in health care systems management across countries. Still, a common, or at least coordinated, regulatory framework on the evidence required by both drug licensing agencies and health technology assessment bodies.

3.4.6. Public procurement and commissioning

The use of joint procurement auctions cannot address new drugs, but some tools can be useful – joint horizon scanning, joint HTA assessment, joint price negotiation. In this regard, the recent Commission initiative on strengthening the current EU cooperation on HTA including support for joint horizon scanning and joint clinical assessments could be beneficial.[8] The WHO consultation on public procurement practices shows diversity in the methods used.

An important aspect is that price cannot be the single consideration, as ensuring competition and availability of supply is important. Also, having clear and transparent procedures is key to ensure equal knowledge of opportunities, equal treatment and non-discrimination of suppliers. The way to set the tendering procedures needs to consider a) the need to have several suppliers in the market willing to participate, b) production capacity, c) frequency of future tenders, d) type of tender (and how to select the provider or providers, if fractioning the tender is selected). A very aggressive tender procedure in one moment in time may result in monopoly, with a single firm showing in future tenders. This would undermine the benefits from competition that underlies the procurement procedure. Of course, the procurement has to be made at the therapeutic level, in the case of needs satisfied by on-patent drugs.

The WHO (2017) document provides a useful breakdown of different types of strategic collaboration: a) central contracting and purchasing; b) group contracting; c) coordinated informed buying; and, d) informed buying.

Informed buying the less demanding type of collaboration, requiring only information sharing about prices and supplies. Coordinated informed buying requires joint market

[8] More information on this initiative can be found at http://ec.europa.eu/smart-regulation/roadmaps/docs/2016_sante_144_health_technology_assessments_en.pdf.

research, sharing supplier performance information and monitoring prices. Group contracting has already joint price negotiations and joint selection of providers, from which the participating entities will buy. The central contracting implies a single entity defining the tender, representing all participants. Different health systems in Europe make it unlikely to reach the level of central European contracting.

3.4.7. Adaptive pathways

Existing systems for approving new drugs have been criticised as being complex, expensive, and introducing unnecessary delays into the process of bringing new products to market. Critics have called for a "paradigm shift", that would allow some products to be approved on the basis of preliminary data, allowing their benefits and harms to be monitored among those using them using what has been termed "real world data".(1) This approach has been supported by the European Medicines Agency (EMA), using the term "adaptive pathways". This would omit several existing steps in the approval process and expedite the launching of drugs designed to meet "unmet medical needs". The incoming health of the US Food and Drug Administration has also voiced support for a relaxation of the approval process, going well beyond anything suggested elsewhere. However, these ideas have not attracted universal approval,(2) and others have argued that existing mechanisms to expedite approval are already too lax, that regulators have failed even to adhere to these mechanisms, and that this approach has failed to stimulate genuine therapeutic innovation.(3) The following sections, which are based on a recent more extensive analysis,(4) examine some of the key areas of contention.

First, in what conditions would such expedited approaches be used? There are circumstances where a need for special measures is clear, but they are quite exceptional.

A second concern is the extent to which existing data systems are adequate to detect the benefits and harms of new drugs undergoing expedited approval. Previous evaluations have challenged the ability of these systems to detect and confirm signals of adverse effects (6, 7) and a review failed to find credible evidence that they could detect new unsuspected events while the results were rarely reproducible.(8) Thus, the burden of proof lies with those advocating this approach.

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A third concern relates to the attribution of benefits and harms to the new product. The randomised controlled trial is viewed as the gold standard, for good reason. While recognising that it does have limitations, specifically external validity because of the restricted set of subjects included as compared with those who will receive the drug in routine practice,(9) in the absence of randomisation it will be very difficult to determine whether any events (beneficial or adverse) are due to the drug or to other characteristics of the subject.

Fourth, there is sound empirical evidence of the need for existing safeguards and, in some cases, to strengthen them. Approximately half of all new products that complete Phase II studies successfully fail at Phase III.(14) Hence, the use of such expedited approaches could see significant numbers of products brought to market despite being unsafe, ineffective, or both. A particular concern with the existing systems, which could be exacerbated by a simplified regime, is the use of surrogate end points, which although easy to measure often overstate real benefits.(15, 16) A further concern is that premature approval of drugs is a disincentive to speed up the necessary evaluations.

Fifth, there are concerns that, once released onto the market, it will be very difficult to restrict the use of products should evidence of ineffectiveness emerge, with numerous examples of drugs that continue in widespread use despite research questioning their efficacy or safety.(19)

3.4.8. Revisit patent system and find news ways to fund R&D by results

The patent system has been the backbone of the innovation incentives system set by modern economies. It allows for a decentralized model of innovation discovery in all areas of economic activity and some innovations have created their own sectors over time.

Still, Governments' involvement in promoting R&D has also increased over time under a variety of regimes (Government sponsored research grants, tax breaks for R&D expenditure by private entities, subsidization of facilities, sector-specific or technology-specific grants and subsidies, etc.).

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The variety of problems in health-related, and drug-related, R&D advise a review of the role and performance of the current system as the overwhelming dominant way to reward innovation. Different alternative paths have emerged as proposals. Although none of them is likely to completely replace the patent system, the use of alternatives can be a better way to obtain certain types of innovation, on the hand, and to achieve a different division of value created, in the specific context of the health sector.

Given the magnitude and relevance of public funds supporting R&D in health-related issues, the call for a "public return on public investment" has a natural appeal. Additional to the more upfront equity considerations that are usually raised about public funding and private appropriation of R&D benefits, efficiency reasons are advocated by some in favour of different rules.

Possibilities are public funding to be conditioned to non-exclusive or equitable licensing, open data and affordable access to resulting drugs (Health Action International (HAI) 2016). This would allow other companies to build on the knowledge created by public funds, fostering competition in the subsequent R&D stages.

The Consultative Expert Working Group on Research and Development (CEWG) at the WHO strongly recommends a multilateral global R&D convention to promote international coordination of publicly funded R&D results and treat them as public goods (not constrained by IP rights) (Health Action International (HAI) 2016).

It is not straightforward to find alternative ways to fund R&D efforts though in some selected areas, other models to provide R&D incentives, to pay for innovation and to ensure that health system's objectives are met in the best way possible should be tried. This is particularly true when health systems identify clear areas that should be addressed in R&D and Governments, or other entities, direct money towards such areas.

Among the potential alternatives, and deserving a more in-depth analysis of their static and dynamic properties, we include the use of prizes (contests for innovation), the award of multiple-step grants with success conditionality and the build up of amortizing funds.

The creation of international funds, as necessary to set a global prize, has strong coordination costs and it is more appropriate to induce innovation in an area of interest.

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It is hard to envisage how such system would survive under claims of successive innovation by companies, at least until the fund is exhausted, under a decentralized, non-commissioned, innovation process.

An amortizing fund is generally a sinking fund established for the gradual extinction of a future obligation in advance of maturity. The fund, maintained by periodic contributions, eventually discharges a debt or makes a replacement when it becomes necessary. This latter type has the objective of accumulating sufficient money to replace capital assets at the end of their technical/economic lifetimes. Few concrete examples of the second type of amortizing fund exist in today's economic environment which features borrowing money to build revenue-producing assets that then generate the cash flow to pay for the principal plus interest charges.

Other proposals are due to Ridley and Grabowski (2006) (priority review voucher) and Boldrin and Levine (2013) (eliminate the patent or at least reduce its duration and scope).

3.5. Basic principles for new payment models

This section brings together several elements that should be included, according to the specifics of each new product, in new payment models. It is unlikely that a broad-spectrum new model of payment can be elaborated. Thus, no single model of payment can be reported as "the solution" to achieve all intended objectives (financial sustainability of health systems, access of patients to innovation and ensuring conditions for innovation that matters to take place). There are, however, principles that should be observed when health care payers and pharmaceutical companies design and use new payment models.

3.5.1. Greater price and cost transparency

Current price-setting models are inserted into an institutional framework that is benevolent with market power exercise, exacerbated by financial protection systems (health insurance) that reduce the price-sensitivity of demand.

Fully transparent cost-based prices are not an alternative to replace the current system, as they would promote high cost R&D efforts, irrespective of results, as a way to obtain

better prices. This being said, the lack of systematic and reliable knowledge on costs incurred by companies is a feature that facilitates very high prices asked by pharmaceutical companies that commercialize the new products (which may not be the innovator firm). The reporting of cost information to regulatory bodies, even if kept as commercial secrets, will act as an implicit deterrent on very high margins.

On the other hand, competition, when feasible, takes place sometimes by way of "secret" price discounts. Such price competition element should not be discarded, and advises against full posting of all prices. Of course, in a world where full information on efficient costs of doing R&D and producing new products is available and where all decisions by all relevant economic agents can be costless included in complete contracts, prices set according to costs and known to everyone would be optimal. However, economic activities are performed in imperfect settings, in which full price transparency and cost-based prices can easily be sub-optimal.

Still, under the current and foreseeable conditions of pharmaceutical markets, greater price transparency can be beneficial to the performance of the health care sector, including the rate of innovation.

Use of health technology assessment and economic evaluation works as necessary but not sufficient condition. It limits too high prices, but does not advocate lower than threshold prices.

There is a need for more information on costs of manufacturing and about the sharing societal gains.

A possible course of action is that firms submit an estimate of the costs they incurred and its breakdown (R&D, marketing and productions costs) as part of the HTA assessment.

The term “costs” should be reserved for companies’ costs. What health systems/ pay should be termed expenditures or payments, reserving “costs” for R&D, marketing and market development, and production costs. This would make clear to institutional payers and assessment bodies how disproportionate prices are from costs, even if does not make it public (and so known to competitors).

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Box 4: R&D costs and the role of public funding

The recent case of the orphan drug Spinraza (approved in June 2017) shows the need for price transparency. With a price tag of €500.000 in the initial year and €250.000. per annum as maintenance therapy, affordability to health systems is in question. The return of public investment done in the R&D process leading to the discovery should be known. The extensive (several million dollar) NIH research funding has not been disclosed at time of patent filing. The failure to disclose federal funding might lead – according to US-law - to loss of patent rights (https://keionline.org/node/2710). A mapping of the public support that goes into medical R&D should be conducted and the disclosure of all public funds granted for the R&D of each new drug approved should occur.

3.5.2. Changing the rules of protecting innovation

The patent system is out of balance: in the European Union on top of the lengthy protection period, additional market exclusivity, data exclusivity and eventually supplementary protection certificates (SPC) is granted to market authorization holders and delays price-lowering generic competition (Health Action International (HAI) 2016). The practice of "ever-greening" – referring to the multi-fold ways of exploiting the patent law (extending protection) is criticized for offering over-protection and misuse of intellectual property rights (IP) (Health Action International (HAI) 2016).

Thus, exploration in existing flexibilities under the TRIPS (Trade related Aspects of Intellectual Property Rights) agreement is to be seriously considered by health care payers, namely regulatory bodies that approve prices of new drugs. This possibility does not mean that prices will be set by courts under legal challenges invoking TRIPS. The existence of this possibility as a real course of action available influences the prices asked by companies in new products.[9] The potential use of mandatory licensing under the internationally accepted rules should an exception and not the rule.

1. [9] For a related discussion, see Voluntary and Compulsory Licensing: http://apps.who.int/iris/bitstream/10665/204522/1/9789241510295_eng.pdf?ua=1

It is important to recognize both the limitations and the advantages of patent-driven innovations. In particular, decentralized innovation efforts are better served by a patent system, and it is unlikely that innovation in health, and in medicines in particular, can be done without a patent system in place. This being said, it does not mean that all innovation has to be cast in the patent system.

3.5.3. Changing the rules in R&D funding

There is growing consensus that alternative models to finance R&D for actually needed drugs (rather than me-too drugs) might be offered within the EU-research system of Horizon2020 or thereafter and might lead on the long term to more innovative drugs.

The delinkage of R&D from sales is demanded (Health Action International (HAI) 2016) and should be explored. DNDi (drugs for Neglected Disease Partnerships) Development Partnerships can serve as role model (Gerlinger 2017).

Another tool is offering mid-term and end-stage prizes (Health Action International (HAI) 2016). This implies announcing a "prize" for discovery of a drug, which is bought by the entity awarding the prize (international consortium would be the best option here). It then can license it for production and commercialization (eventually making it an immediate generic product).

There are obvious problems of coordination across health systems in order to make it work other, prize-based, forms of R&D funding. Solving those problems will require multilateral negotiations between health care payers.

Other alternatives are also possible, including unbundling phase 3 in development of new products, with trials being performed by independent groups and allowing open access to results.

Other alternative courses of action are discussed in Vandenbroek et al. (2016), including ways of sharing the costs and returns of R&D investment in new products. These options involve a different approach to R&D public funding, with a higher involvement by the public sector in the appropriation of returns from the R&D it funds.

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3.5.4. Changes in Governance

About 29% of new biological products approved by EMA received safety warnings within 10 years on the market (data from 2008 in (Light and Lexchin 2012)).

The small percentage of drugs with clinical important advantages is in contrast with the steady increase of EMA instruments providing access to products ever more early and with less evidence (orphan drug status, conditional approval, adaptive pathways (Davis, Lexchin et al. 2016), Accelerated Development of Appropriate Patient Therapies ADAPT SMART (http://adaptsmart.eu/), etc.)

EMA should be fully funded by public fund rather than by industry generated user fees, in order to end the potential risk of "industry´s capture of the regulator" (Light and Lexchin 2012). This is particularly relevant, as EMA should raise the bars for approvals and top approvals of drugs, reducing the cases of approval with little therapeutic value by a) demand for substantial benefit to patients: Superiority or non-inferior over comparator; b) comparison to active treatments; c) patient relevant clinical outcomes only over surrogate endpoints; d) approvals only with mature data. Fast track approvals should be more scrutinized. It also should be clear that Real World Data and Adaptive Pathways pose risks. There is a distinction to be made on the evidence required for approval to market and for price setting.

The role of EMA should be discussed, in particular policies and strategies aiming at identification of real unmet medical needs, on the one hand, and the trade-offs involved in a shorter time of approval versus ensuring that a sizeable benefit is present. The importance of getting better products quickly to patients that may benefit from them has to be balanced with too-fast approval of pharmaceuticals with marginal benefit and asking high prices (sometimes, using an "orphanisation" strategy to provide evidence of high effectiveness on a very short number of selected type of patients to support a high price to the product).

3.5.5. Develop methodologies to measure the value of pharmaceutical products

One of the key elements in more sophisticated payment models is the ability to accurately measure outcomes and value of new products in a continuous way.

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There are several methodologies being developed to achieve the objective. The important element is that identification of relevant outcomes is made and that measurement can be made in a clear and easy-to-understand way.

3.5.6. Have an assessment of exercise of market power in each price negotiation

High prices may have an important element of exercise of market power. The practice of prices above production costs, made possible by patent protection, rewards innovation. The limits to price increases are set, in other areas, by consumers' decision of not to buy the product. That role of prices is much weaker in health care, as insurance protecting patients from the financial hardship associated with health care needs also withdraws the natural barrier to very high prices set by providers of care, including pharmaceutical companies. There is the need to define the meaning of abusive exercise of market power in pharmaceutical markets with help from competition authorities. This assessment may not be turned public and be considered "commercial secret" but available to network of public payers.

3.5.7. Set better rewards for higher therapeutic added value

Reward better value, but not with rule that allows highest price under cost-effectiveness threshold. New payment models need to be cleverly designed so that the correct signals are sent (higher rewards for better products) but at the same time keeping the pressure for low prices (by mimicking a certain degree of demand sensitivity to price).

3.5.8. Move towards acquisition of service rather than product

The point is to reward successful treatment instead of buying product, which implicitly makes the pharmaceutical company accountable for the quality of its product and result from R&D efforts. It also requires a different sort of relationship between payers and pharmaceutical companies, as buying services is considerably more difficult than procuring and buying products.

3.5.9. Explore non-linear payment systems, including bundling, differentiation across geographies and across indications

The payment model needs to define the conditions under which affordability and access increases under these sophisticated pricing rules. The payment model should mimic

demand price elasticity with price – volume contracts. That is, obtain lower price if more patients are treated. In case of price differentiation, set a (average) price cap over the different markets such that all parties benefit. A simple example is that allowing price differentials across groups of users of the same pharmaceutical product should lead to a decrease in the average price relative to the single-price situation .

3.5.10. Create dialogue platforms

Different platforms for information and dialogue can be set to discuss and prepare future payment models. One platform involves only countries. Another platform involves countries and high-level representatives of pharmaceutical companies. These platforms will share information and knowledge. Horizon scanning and guidance on priorities for research should be in the agenda of these platforms.

New payment models should be accompanied by mechanisms that take pharmaceutical companies as a partner of health systems in promoting innovation and financial sustainability, although recognizing that companies also have shareholders to whom management is accountable.

Decisions taken by public authorities need to be part of a broader policy making process. Such policy would help on the convergence and reconciliation of various policy objectives (safety, innovation, access, affordability etc.).

3.6. Final remarks

The discussion of innovative payment models for high-cost innovative medicines results from the concern about financial sustainability of health systems under the pressure of very high prices asked by companies to introduce newly developed products into the health insurance coverage provided by health systems.

A variety of different pricing models have been proposed, and some introduced in several health systems.

A first point is the existence of several issues that new pricing models intend to address: uncertainty about the true benefits of the new product, the desire to promote quick

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access of beneficial products to patients, reward innovation, promote innovation in neglected therapeutic areas and maintain sustainability of health systems, are among the highest ranking ones.

A second point is that only one type of payment model will not be able to address all these objectives at the same time. Aiming at several objectives at the same is likely to require several instruments, including payment models but not restricting to a single one. Different payment models imply distinct trade-offs across objectives. In particular, managed entry agreements are often designed to deal with uncertainty about true benefits of the new product at the cost of high prices, which may configure situations of abuse of market power. It is important to note that abuse of market power results from the institutional framework defined by countries, and as such requires use of instruments directly aimed at curbing it, as the role of price-sensitive demand is mitigated, or even eliminated, by the existence of insurance protection, public or private, against the financial consequences of health care needs. Removing such protection entails social costs, and different institutional frameworks have to be defined to address the issue of market power. The intuitively attractive idea of pricing according to costs has the drawback of undermining the incentives to obtain innovations with high value in an efficient way to instead promote high-cost incremental innovations to justify prices.

Thus, the policy toolbox has to make use of several payment models, according to the most relevant problem in each case. More than defining a single payment model, it is important to define a set of principles that payment models should follow, and allow flexibility in the design in each case. For example, for neglected therapeutic areas, payment models based on new ways of procuring innovation can be used. Under asymmetric information between companies and health care payers about the true value of new products, the use of health technology assessment provides a way to health systems learn about such value. When uncertainty exists about effectiveness of new products in the overall population, managed entry agreements with a performance component embedded in the payment model and use of real world evidence may be a useful instrument. Whenever high margins over costs are likely to be present,

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strengthening the bargaining power of health systems and using payment models that reduce exercise of market power is desirable.

Thus, the definition of a single payment model for new pharmaceutical products should give way to definition of a set of principles to be followed, and let payment models adjust to the particular conditions of each therapeutic area. These principles were described in detail above.

Pricing of new, innovative, medicines is best seen as a dynamic process starting from early phases of development (R&D costs) and adjusted where relevant and towards the end-life of the product (but such approach needs clear criteria), good use of different tools and continuous cooperation of relevant economic agents.

From the principles outlined, several concrete actions can be defined, including, *inter alia*, (i) relevant authorities within health systems (say, health technology assessment bodies, regulatory agencies deciding on reimbursement, etc.) asking for R&D costs, marketing costs and production costs, even if these are not disclosed to the general public or to other companies; (ii) select one neglected area and launch international prize initiative with patent being retained by the set of countries participating; (iii) check existing payment models used in each country against the principles defined above; (iv) introduce a competition policy review of high prices asked by companies, with cooperation of competition authorities; (v) assess value of new products of uncertain benefit using sound and transparent health technology evaluation methods; and, (vi) strengthen bargaining power of health systems as buyers by using joint negotiation procedures and consider the use of mandatory licensing in extreme cases of public health risks.

Companies that produce truly innovative medicines (of high value and benefit to patients) and are rewarded in a way compatible with financial sustainability of health systems will thrive and grow on the basis of the merits of their innovation.

Four activities have dominated the management of healthcare in the last twenty years – prevention, evidence based decision making, quality improvement and cost reduction.

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All of these are important in value improvement but it is important to remember that although low quality care is of low value, high quality care is not necessarily high value. For example, imaging may be delivered at high quality but be of little or no value to the patients who have had the investigations. In particular, if the higher resolution image does not produce different decisions than previous images, it brings no value. Interventions of unnecessarily high cost are of lower value but even when cost is reduced value is not necessarily increased unless that intervention produces outcomes of relevance to the people treated.

There is now a new management agenda developing, which includes several key points: ensuring that every individual achieves high personal value by providing people with full information about the risks and benefits of the intervention being offered and relating that to the problem that bothers them most and to their values and preferences; shifting resource from budgets where there is evidence from unwarranted variation of overuse of lower value interventions to budgets for populations in which there is evidence of underuse and inequity; creating population-based systems that ensure that those people in the population who will derive most value from a service reach that service, that the service is of high quality with no waste, that there is faster implementation of high value innovation to improve outcome, funded by reduced spending on lower value interventions for that population and that increased rates of higher value intervention within each system are achieved .

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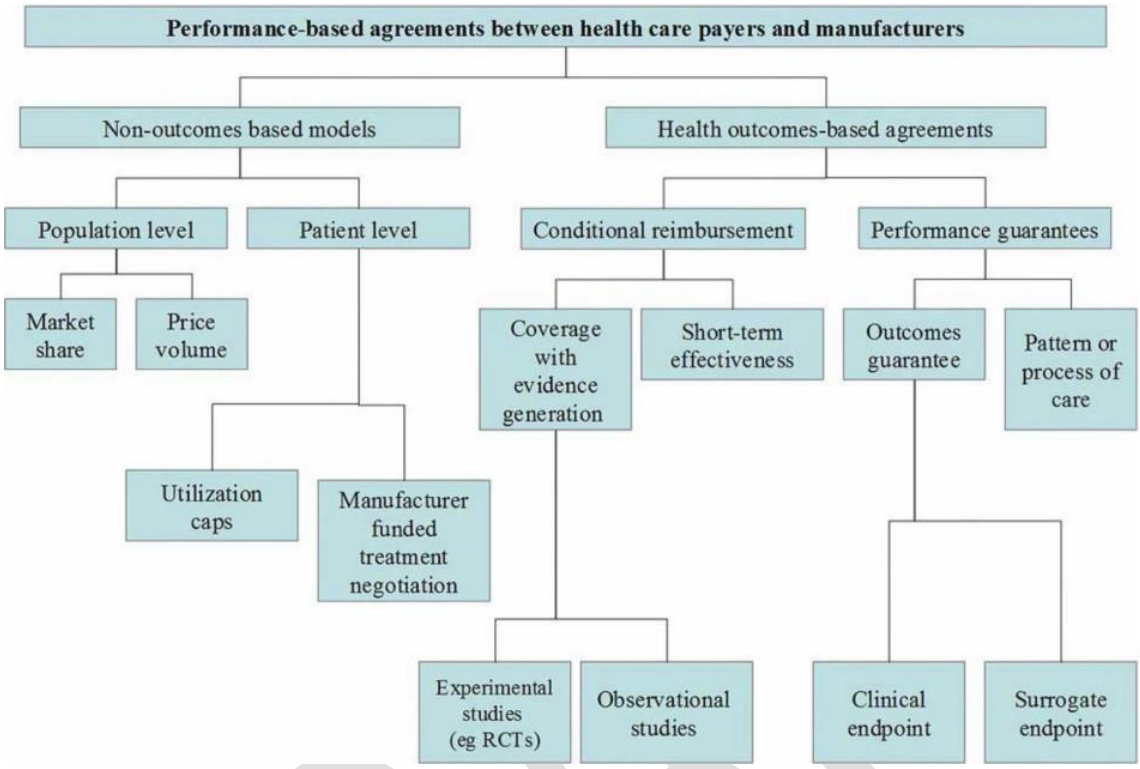
4. APPENDIX

4.1. Alternative taxonomies for MEAs

Figure A1: Taxonomy of Risk Sharing Agreements



Source: Carlson, Sullivan et al. 2010; Espín, Rovira et al. 2011

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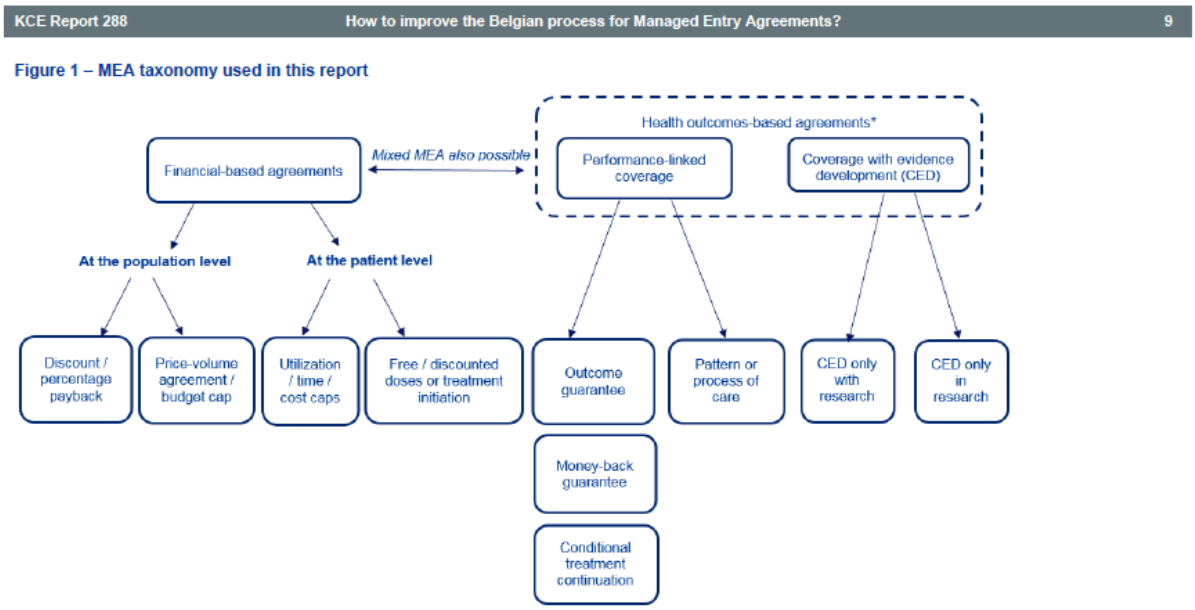
1800 Figura A2: Taxonomy of managed-entry agreements



1801 Source: KCE (2017, p. 9)

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5. MINORITY OPINION

None expressed.

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6. LIST OF ABBREVIATIONS

HTA	Health Technology Assessment
EU	European Union
HIV	human immunodeficiency virus
HIP	Highly innovative product
MEA	Managed Entry Agreement
RWD	Real World Data
TRIPS	Trade-Related Aspects of Intellectual Property Rights
NHI	National Institutes of Health

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