



**A call to  
make valuable  
innovative  
medicines accessible  
in the European  
Union**

Recommendations for a coordinated action to stimulate,  
measure and valorise pharmaceutical innovation

**Background report for the ministerial conference  
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# Introduction

The primary goal of any health care policy should be to maximize the health of the population within the limits of the available resources. This must be done within an ethical framework built on equity and solidarity principles.

In the past decades, health policy makers in the different European Union (EU) Member States have striven to increase the quality of care, control costs, and improve equal access to care for all EU citizens. Yet, in undertaking these efforts, they have been confronted with conflicting objectives. For instance, improving *quality of care* is often associated with higher *costs of care*. Only few new investments in health care lead to net savings, i.e. the initial investment is completely compensated by later (short and/or long term) savings. These are the so-called dominant strategies, which are rare. The vast majority of new technologies will lead to additional health care expenses, even when accounting for the induced savings on a long term basis.

The latter finding is valid for any type of health technology, including innovative medicines. As a result, innovative medicines that come at a price premium compared to current care are considered on the one hand as the main cause of increasing pharmaceutical expenditures, while on the other hand they can contribute to improved quality of care and significant benefits for patients. In other words, innovative medicines play an important role in meeting the health objectives but at the same time exert a continuous pressure on health care budgets (if their cost is higher than that of the standard treatment). Furthermore, to the extent that these medicines are not made equally available to those who need them, the equity and solidarity principles might be endangered, and it is more and more questioned whether the available public budget will remain sufficient to cover all needs.

A main challenge for the EU pharmaceutical policy is to pursue all mentioned objectives at the same time: to increase quality, to improve equal access to new technologies for those patients who need them, to guarantee equity and solidarity, and to control costs.

**It is proposed in this report that stimulating and making equally available innovative medicines that offer a therapeutic benefit and fill unmet medical needs is a necessary condition to achieve the combined objectives . It is also proposed to call these medicines “valuable innovative medicines”.**

Valuable innovative medicines are both **truly innovative** and **valuable**. A drug can be called ‘**truly innovative**’ if and only if it offers **additional** clinical efficacy and/or effectiveness as compared to current care. Relative *efficacy* can be defined as the extent to which an intervention does more good than harm, *under ideal circumstances*, compared to one or more alternative interventions. Relative *effectiveness* is defined as the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided *under the usual circumstances of health care practice*. (<http://ec.europa.eu/pharmaforum/>)

Truly innovative medicines have a potential to lead to key improvements in health outcomes at the individual and the population levels. If, in addition, these medicines fill an unmet medical need, we propose to call them **valuable**. Indeed, even if a drug is more effective than current care but its clinical benefit lies in a field where the medical need is very small, this drug is not really valuable to society or even to the patients. Overall, in the meaning of 'valuable' there is an explicit connotation of need. This may be a medical need, a therapeutic need, or a societal need. According to the High Level Pharmaceutical Forum, valuable innovation should be encouraged, identified and rewarded. (<http://ec.europa.eu/pharmaforum/>)

Finally, when a valuable innovative medicine leads to net savings or induces a reasonable additional cost in an acceptable proportion to the associated health gain, i.e. when it is cost-effective, and when its impact on the health care budget is acceptable, it can be considered value for money and therefore should be largely implemented and made accessible to all in need for it.

A recent study by IMS Health has revealed that uptake to valuable innovative medicines in the EU is characterized by huge differences between Member States and between disease areas. Not only a difference between "above average" and "below average" income is observed, but also within those clusters, market penetrations that are 3 times higher for one country compared to another, are not an exception (IMS Health 2010, data on file). Moreover important delays in market access are observed.

This IMS report suggested that the current call to make valuable innovative medicines accessible in the European Union is timely.

## Objectives

It is proposed that a coordinated EU policy should aim at fostering valuable innovative medicines and making them accessible to all EU citizens who need them. This policy should account for the health care budget limitations at the Member States level and should therefore consider "value for money". It is necessary to create an environment where:

1. The research and development (R&D) of valuable innovative medicines is optimally **stimulated** and facilitated in response to the medical needs of all patients in the EU and the EU's industrial and economic interests.
2. The magnitude of innovation (relative efficacy and relative effectiveness) and its fulfillment of medical, therapeutic or societal needs can be **measured** through logic structures, transparent processes, and reliable and valid criteria.
3. Valuable innovative medicines can also provide value for money in the patient populations and in the way they are used. This should be accomplished through transparent and efficient pricing and reimbursement structures, processes and criteria.

The aim of this draft background report is to provide possible ways forward for a coordinated EU action to meet these three objectives, i.e. to stimulate measure and valorise pharmaceutical innovation, with the ultimate aim to improve the health of the EU population.

Although the importance of basic or fundamental research is fully recognized by the authors of this document, and more public means are needed for academic research in this field, the deliberate choice has been made not to include reflections on this issue, in order not to broaden the discussion beyond tangible objectives.

## Methods

Six main steps were followed in the creation of this draft report.

1. We created an inventory of **existing** structures, processes and criteria related to:
  - the stimulation of the development of innovative medicines,
  - the way the magnitude of innovation (also called “innovativeness”) and medical needs are assessed, and
  - the pricing and reimbursement decisions.
2. We established an overview of the current **legal context** related to pharmaceutical innovation in the EU.
3. Based on desk research and expert/stakeholder interviews, we reviewed international (including Australia, Canada and USA) **initiatives** in the 3 areas as mentioned under (1).
4. We then identified the current challenges related to meeting the three main above-mentioned objectives and we explored various **options** for developing more coherent policies related to the stimulation, measurement, and valorisation of pharmaceutical innovation, with a special focus on efficiency and equal access.
5. Finally, we considered EU policy options for future developments in this area.

The bulk of this report presents the results of the above reflection in three stages. In each of them we describe (a) the current situation, (b) recent activities, and (c) initiatives and challenges. Chapter 1 is related to stimulation of innovative medicines. Chapter 2 is related to measuring the magnitude of innovation (relative efficacy and effectiveness) and the way innovative medicines fill medical, therapeutic and societal needs. Chapter 3 is related to measuring value for money. Finally, in Chapter 4 we propose several ways forward to meet the three main objectives at the EU and Member States levels.

1<sup>st</sup> Part

Stimulating pharmaceutical  
innovation

# Stimulating pharmaceutical innovation

## 1. Why stimulate innovation

Stimulating pharmaceutical innovation is a means to meet the objectives of maximising health within the budgetary limits and to meet the current unmet medical need in the EU population. At the same time, it also aims at promoting high-quality research in the EU and ensuring the competitiveness of the European pharmaceutical industry.

Both objectives should not be opposite to one another, as creating a pharmaceutical innovation that meets an unmet medical need is likely to improve relative competitiveness of the European industry. However, opposite may not be true: a product that improves the competitiveness of the European pharmaceutical industry does not necessarily fill an unmet medical need. Such a situation should preferably be avoided as it would imply the use of resources for activities of research and development (R&D) that could have been spent to serve a larger goal; i.e. the industrial as well as the societal goal.

Thus, linking the improvement in R&D in the EU pharmaceutical industry and the fulfilment of meeting medical needs is crucial. Also the WHO states that ensuring R&D that responds to the needs of populations is crucial, as the contribution that innovation can make will be meaningful only if products are acceptable, affordable and accessible. (Omi, 2007)

But the industry is not “spontaneously” attracted towards unmet medical need and previously unused drug targets: it has been shown that drug discovery programs targeting precedented drug targets (“copycat drugs”) have 10- to 20-fold higher probability of success than those that pursue new drug targets. (Ma and Zimmel, 2002; Silber, 2010)

By clearly defining the areas in health care where there are unmet medical needs, the EU could stimulate the pharmaceutical industry to develop innovative products that are both valuable for the society and at the same time beneficial for their competitive position.

Yet, notwithstanding the medical need one witnesses a number of therapeutic domains in which for many years almost no innovation has taken place, because of a lack of new scientific insights. Creation of new scientific knowledge sometimes depends on serendipity, pure luck or other factors that are difficult to steer. Hence, one cannot rely on a “demand pulled” approach only.

It is encouraging nevertheless that the need to stimulate truly innovative research leading to the fulfilment of unmet medical needs has been expressed in the Strategic Research Agenda (SRA) drafted by EFPIA as a basis for the creation of the Innovative Medicines Initiative (IMI), as discussed in more detail below. The SRA focuses on five disease areas (cancer, brain disorders, inflammatory diseases, diabetes and other metabolic diseases, and infectious diseases) that are considered important themes of unmet need affecting the lives of millions of European citizens. (IMI, 2006)



## 2. Current situation related to stimulating innovation

The EU has undertaken many efforts to try to stimulate innovation, through intellectual property legislation, co-financing of initiatives and the creation of clear rules of conduct in development processes, such as the legislation related to clinical trials in the EU. As is mentioned further in the text the harmonization effort of the conduct of clinical trials should not be presented as a great success story to stimulate innovation.

A key element in promoting innovation has been the elaboration of substantive law on intellectual property applied in the EU. The international Agreement on trade-related aspects of intellectual property (the TRIPS Agreement), approved by the EU and its Member States, contains provisions on the means of enforcing intellectual property rights.

Because the period that elapses between the filing of an application for a patent for a new medicinal product and its marketing authorization (MA) may make the period of effective protection under the patent rules insufficient to cover the investment put into the research, a supplementary protection certificate may be granted according to Regulation (EC) 469/2009. In addition, Directive 2001/83/EC lays down specific rules to protect data relating to pre-clinical tests and clinical trials.

Public authorities of Member States that want to take initiatives in promoting innovation have, however, to take into account article 107 TFEU, stipulating that “save as otherwise provided in the Treaties, any aid granted by a Member State or through State resources in any form whatsoever which distorts or threatens to distort competition by favouring certain undertakings or the production of certain goods shall, in so far as it affects trade between Member States, be incompatible with the internal market.” Article 108 TFEU stipulates that “the Commission shall, in cooperation with Member States, keep under constant review all systems of aid existing in those States.

The recent Innovative Medicines Initiative (IMI) Joint Undertaking has filled an important need. This is a public-private partnership wherein the EU and the pharmaceutical industry have joined forces in order to boost investments in bio-pharmaceutical research and to overcome bottlenecks in the development of innovative medicines (IMI JU Factsheet). Interestingly, the IMI Joint Undertaking states that the research resulting from this initiative will lead to finding better methods for *predicting* efficacy and safety of new medicines. It is indeed crucial to evaluate the potential benefits of a new compound as early as possible.

It can however be asked whether this early assessment should focus exclusively on efficacy and safety, as stated by IMI, or should already involve elements of medical need and relative efficacy and effectiveness. We will come back to this in Chapter 2.

The conduct of clinical trials is the mainstay of the development process of innovative medicines. Current EU rules aim at:

- harmonized procedures for the application and authorization of clinical trials by the National Competent Authority (“NCAs”) and Ethics Committee;
- harmonized provisions on the requirements for a clinical trial, including the rules for protection of the clinical trial participants; and
- harmonized rules on reporting adverse events during the clinical trial.

### 3. Challenges and initiatives related to stimulating innovation

Given the participating nature of stimulating and facilitating innovation and innovative research, several types of governments must play a role: health authorities, industrial policy authorities, and scientific and academic authorities, all of them on the EU and the Member States levels. This requires a huge coordination that should be facilitated.

The OECD goes one step further stating that a key challenge for policy makers towards efficiency in pharmaceutical expenditure is to reconcile static and *dynamic* efficiency objectives, i.e. marrying value for money and the promotion of future innovation in medicine (Docteur and Paris, 2008). This statement suggests that selecting the right valuable innovations today will have an impact on available budgets and expertise for subsequent innovations with a larger incremental benefit. Dynamic efficiency indeed means that one may allow uncertainties in proof of value and inefficiencies today, in order to keep the innovation engine running, and that one can only really judge the innovation decennia later. The OECD statement however also suggests that any initiative to stimulate innovation must already inherently account for the concepts of future truly and valuable innovative medicines.

A crucial and related challenge is therefore to find the balance between health policy objectives and industrial policy objectives at national levels. This balance can undoubtedly affect the regulation of the pharmaceutical industry across the EU.

In the following paragraphs we discuss in more detail specific challenges related to (a) the identification of medical needs (the health policy objective of stimulating innovation), (b) the attractiveness of the clinical trial environment, (c) orphan drugs, (d) personalized medicine, and (e) financial issues.

#### a. Identifying medical needs

The identification of unmet medical needs, their prioritization, and the resulting allocation of resources and efforts is a first example of an area where better coordination is required. If such identification is coordinated and takes place at a supra-national or European level, its impact will be much stronger.

Indeed, the EMA 2015 Roadmap indicates that the first objective is to “Stimulate medicine development in areas of unmet medical needs/neglected and rare diseases [...]” The “Impact and Result Indicators” for this objective will be the “Increase in the number of scientific advice requests for medicines for unmet medical needs/neglected and rare diseases.

This is not an easy task. Each pharmaceutical company has its own way to identify unmet medical needs. Most of the time this identification is based on marketplace analyses. On the other hand, both public and private initiatives have been launched and should be further encouraged to identify “pharmaceutical gaps” by defining the burden of specific diseases (based on epidemiology and morbidity/mortality in specific populations), the current scientific and public health knowledge about existing interventions, and their cost-effectiveness. Examples are the Priority Medicines Project launched by WHO and the Dutch government during its presidency of the EU in 2004 and the SRA of the IMI mentioned above. Another example is seen in the incentive mechanisms for R&D in orphan drugs for rare diseases (see *infra* paragraph c).

The FDA’s Fast Track Program is also designed to facilitate the development and expedite the review of drugs and biologics that are intended to treat serious or life-threatening conditions, and that demonstrate the potential to address unmet medical needs. However, this program has been criticized for its patent commercial orientation. (Cohen, 2004)

In the European legislation, the concept of unmet medical need has been used in Article 11 of Commission Regulation (EC) No. 507/2006 on the conditional marketing authorization for medicinal products. One of the requirements in granting of a conditional marketing authorization is that unmet medical needs will be fulfilled. Paragraph 2 of Article 11 specifies that unmet medical needs mean a condition for which there exists no satisfactory method of diagnosis, prevention or treatment in the Community or, even if such a method exists, that the medicinal product concerned will be of major therapeutic advantage to those affected. In 2006 the European Medicines Agency (EMA) has published a guideline to help pharmaceutical companies demonstrate that their product will fulfil unmet medical needs. (EMA, 2006) In addition, many companies request Scientific Advice to the EMA/CHMP in order to debate unmet medical needs and conditional marketing authorizations for those drugs in their pipeline that they consider most promising.

Recently, EU regulators have suggested that new medicinal products covering areas of high unmet need such as a life-threatening disease for which there is no effective treatment could be granted early marketing authorizations associated with a higher uncertainty about their benefit/risk balance, or, alternatively, early approvals for narrowly defined subgroups within a given disease population (“staggered approval”). (Eichler et al, 2008)

In this report, we propose that, rather than attempting to delineate all possible areas of unmet medical needs, scientific advice strategies should be set up and fine-tuned to discuss with pharmaceutical companies, on a case-by-case basis, the ability of new medicines in development to fulfil specific needs, which could be medical, therapeutic or societal needs. Workshops could also be organized with the relevant stakeholders to make public those areas where the authorities believe there are significant unmet needs. It is noteworthy that innovation can also refer to current medicines in the market, whereby additional insights may lead to better pharmacokinetic performance or – via the identification of biomarkers – to better targeting of patients (*cfr. infra* personalized medicine).

It is thereby crucial that the principles of equity and solidarity remain the key drivers of a demand-oriented process of identification and assessment of Unmet Medical Need.

Well structured patient organizations can play an important role in this detection and identification process, but Europe should take particular care not to neglect the undoubtedly vulnerable small patient groups – with and without orphan diseases – who cannot benefit from efficient means of communication.

## b. Attractiveness of the clinical trial environment

In recent years, there has been a widespread criticism that the Clinical Trials Directive has led to a significant decline of the attractiveness of patient-oriented research and related studies in the EU. This could greatly reduce competitiveness in Europe in the field of clinical research and bear a negative impact on the development of new and innovative treatments and medicinal products. (EC Public consultation paper ENTR/F/2/SF D(2009) 32674).

In fact, it has been shown that, since the directive was edited, there has been in general no decrease in clinical research activity in the EU, but that performing clinical trials, on the other hand, has become considerably more difficult and costly, with an increased and sometimes unnecessary administrative burden. Experience has shown that the requirements of the clinical trial directive are applied very differently by the Member States. Consequently, sponsors have to respond to the various required changes and adapt their protocol in view of diverging assessments by the Member States. In some cases, sponsors have been unable to pursue the envisaged clinical trial in one or more Member States. Smaller companies are even hurt more by this situation.

Any sponsor intending to start a clinical trial based on a single protocol has to wait not only for approval by several Ethics Committees but also by the NCAs of each of the Member States individually. Since the entry into force of the Clinical Trials Directive, the delay in starting a trial (first patient in) has increased by 90% and is now reaching an average of 152 days. This, in turn, means that patients do not have access to new, innovative treatments, and the costs for the sponsor increase.

It appears that adaptations in the way Member States apply the Clinical Trial Directive may become a necessity in the near future.

Finally, NCAs do not use resources efficiently. The available resources in NCAs are used in multiple assessments of the same information in different Member States.

## c. Additional challenges related to rare diseases

A rare disease is a disease with a very low prevalence. In the EU, rare diseases are defined as life-threatening or chronically debilitating diseases that have a prevalence of 50 per 100,000 individuals or less. There are currently between 5,000 and 7,000 rare diseases. Orphan drugs (i.e. drugs to treat rare diseases) are less likely to be developed by industry because the market is small, and R&D costs are usually too high to make the products profitable. With 60 orphan drugs on the European market by March 2010, only a small part of the treatment needs for rare diseases is covered. Yet, in the light of solidarity, patients with rare diseases should have the same right for treatment and care as those with common diseases.

The EU has identified unmet need in the area of rare diseases by stating that 'patients suffering from a rare condition should be entitled to the same quality of treatment as other patients'. This reflects the observation that orphan medicine reimbursement conforms to the principle of social solidarity in which vulnerable groups receive support; that orphan medicines tend to target life-threatening diseases for which there may be no alternative therapy; and that orphan medicines have a considerable impact on patients' health care expenditures if they would have to incur the medicine costs themselves. In response to this, the European Union has implemented specific policies in 2000 to stimulate innovation in the field of orphan medicines.

At the EU level, discussions on orphan drugs started in the late nineties and led to the adoption of Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999, stating that patients suffering from rare conditions should be entitled to the same quality of treatment as other patients, and that it is therefore necessary to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry.

In the EU, companies with an Orphan Designation (i.e. the award of orphan status to a drug) for a medicinal product benefit from incentives such as:

- protocol assistance (scientific advice during the product development phase);
- direct access to the European Medicines Agency (EMA) Centralized Procedure with respect to registration;
- 10-year marketing exclusivity after Marketing Authorization (MA);
- financial incentives (fee reductions or exemptions, possible assistance with research and development);
- national incentives.

The impact of orphan drug policies is reflected in the rising number of orphan designations and marketing authorizations granted by the EMA, increasing from 270 designations and 22 authorizations end 2005 to 642 designations and over 60 authorizations by March 2010.

Still, it can be questioned why there are only +/- 60 MA granted compared to +/- 600 Orphan Designations, and why MA seems to concentrate on very few diseases (for instance 4 or 5 on pulmonary artery hypertension alone).

With regard to national incentives, art. 9 of Regulation (EC) No 141/2000 requires Member States (MS) to communicate to the Commission detailed information concerning any measure they have enacted to support research into, and the development and availability of, orphan medicinal products or medicinal products that may be designated as such. The European Commission regularly publishes an inventory of measures taken by Member States according to art. 9. Countries such as France, Italy and the Netherlands have implemented domestic policy measures and research incentives for orphan drugs and rare diseases.

In France, there are several incentives to stimulate orphan drug development:

- Research support through national funding programmes: GIS-Rare diseases, Hospital Programme of Clinical Research (Programme Hospitalier de Recherche Clinique);
- During development: Free scientific advice from the French Agency for the Sanitary Security of Health Products;
- Budgetary incentives: tax exemption of the Sickness Insurance and the French Agency for the Sanitary Security of Health Products;
- Innovative orphan drugs may receive an authorization for temporary use (ATU) from the French Agency for the Sanitary Security of Health Products if it is a treatment for a serious or orphan disease; no therapeutic alternative is available; it has a positive risk/benefit and it is for temporary use (see also Chapter 2).

The Italian Medicines Agency has set up a fund of around 45 million Euro a year, half of which is used for the reimbursement of orphan and 'life saving' drugs and the other half is aimed at supporting independent research, drug information programs and pharmacovigilance. At the start of 2009, three calls for proposals (2005-2007) have been concluded and 69 studies have received funding in the area of rare diseases.

In the Netherlands, several policy measures were taken to develop orphan drugs:

- A Steering Committee for Orphan Drugs was established in 2001 to encourage the development of orphan drugs and to strengthen the transfer of information on rare diseases.
- An orphan product developer was appointed in 2006 within the Dutch Organization for Health Research and Development to inform academia and enterprises about the European Regulation on Orphan Medicinal Products.
- The Dutch registration fee for a medicinal product can be waived if the medicinal product is already registered in one or more other EU Member States and the prevalence of the indicated disease is less than 1 in 200,000 inhabitants.
- An Orphan Drug Designation Support Programme was launched in January 2009: Dutch enterprises can apply for a grant to compensate the application costs for the EMEA Orphan Drug Designation.
- In April 2009, the Dutch Orphan Registry Consortium was launched: this is a multidisciplinary group that will use best practices to build a registry framework for inborn errors of metabolism.

To stimulate the R&D for rare diseases, priorities for research on orphan diseases should be defined at European level in order to target public research funds for research and development of orphan drugs. For the high-priority orphan diseases, European registries should be set up as early as possible; preferably before a drug is being developed for the disease. Data on the natural history of the disease and baseline risks are indispensable for describing the epidemiology of the disease and put into context the clinical effectiveness and cost-effectiveness of a treatment (cfr. *infra*). Funding and governance of the registries should be independent. Some types of tax benefits for orphan drugs may possibly also be considered.

Innovative models combining European and national funds could be explored to set up such a system, the beneficiaries being the companies considering the clinical development of an orphan drug, the medicine agencies in assessing efficacy and safety, the national health care insurance funds, and the patients. The latter, represented by patient advocacy groups, should be involved in working out the above suggestions.

#### d. Additional challenges related to stimulating personalized medicine

Within the recent evolution towards genetic testing for predicting risks of disease, identifying carriers, establishing prenatal and clinical diagnosis or prognosis, and predicting treatment outcomes, EU countries have taken different approaches towards steering and facilitating research in this field.

In personalized medicine, by definition the molecular mechanism of disease or drug metabolism is well understood and the drug or the dosing targets this specifically, resulting mainly in a higher proportion of responders to the drug.

The field of personalised medicine based on a broad range of “genomics” technologies (eg pharmacogenomics)... has bloomed in the academic setting. However, whether pharmacogenomics, or personalized medicine based on other biomarkers, will make a significant impact on new drug development within the coming years is still uncertain. This uncertainty derives from several concerns of pharmaceutical companies including ethical issues during clinical trials and post-trial biobanking, reductions in market size and difficulties in developing drug-diagnostics combinations, in particular if the developments are done by two different companies. The latter issue is even more contentious in Europe, where no specific legislation exists regarding these combinations, than in the US, where two separate Centres of the FDA regulate drugs and devices, respectively.

The EU should continue to stimulate R&D in personalized medicine through various initiatives designed to facilitate the recognition of validated biomarkers which can already be “qualified” through specific and parallel EMA- and FDA-based procedures. (EMEA, 2008) In addition, various stakeholders have stressed the need to demonstrate clinical utility of biomarker-based personalized treatments; this reinforces the call for a common assessment of efficacy, relative efficacy and relative effectiveness as discussed below.

#### e. Financial challenges

In 2007, the pharmaceutical industry has invested about € 26 billion in R&D in Europe. By comparison with the North American and Asian regions, Europe is still seen as a less attractive R&D investment location in terms of complexity, market size and incentives for the creation of new innovative biotech companies.

It should be acknowledged that a roadmap towards more coordinated action regarding the stimulation of innovation, in particular in the field of personalized medicine and orphan drugs, will run against budgetary limits: the EU and Member States budgets to undertake this role are limited and choices must be made to spend this money as wisely as possible.

For instance, IMI spends 1 billion Euros of public money per year to achieve its objectives to modernize the development processes of drugs, provide better and more quality jobs for scientists, increase the European expertise and know-how in new technologies and provide stronger competitive advantages for small and medium sized innovative companies. Also better coordination of the national budgets and stimulation of pan-European institutes will increase the performance of European R&D. As an example a European coordinated cancer programme e.g. a European Cancer Institute, would enable such performance to the benefit of patients.



2<sup>nd</sup> Part

Measuring the level  
of innovation

# Measuring the level of innovation

## 1. Why measure the level of innovation

Despite the enormous contribution of medicines to enhancing health, the quality of pharmaceutical innovation varies widely. (NIHCM, 2002) It ranges from breakthrough treatments for life threatening diseases to minor modifications of medicines that have been on the market for some time. Because of this diversity, efforts to understand the value of new medicines need to be supported by an account of pharmaceuticals that distinguishes among levels of innovation. (NIHCM, 2002)

Therefore, once innovative medicines approach the market, a system of measuring the magnitude of innovation, at this point regardless of the economic dimension but accounting for unmet medical need, should be established. Currently, only MA structures, processes and criteria have been harmonized across EU Member States.

## 2. The current situation related to measuring innovation

The EMA centralized approval for new medicinal products requires acceptance in all EU Member States and is mandatory for, e.g., all new biotechnology products and orphan drugs. According to Article 51 of the Council Regulation (EEC) No 2309/93, EMA provides the Member States and the institutions of the Community with the best possible scientific advice on any question relating to the evaluation of the quality, the safety, and the efficacy of medicinal products.

However, the remit of this system does not include the assessment by the EMA of the innovative potential or additional therapeutic value of new medicines. For instance, placebo controlled trials are still often accepted by MA agencies in areas where there are one or several existing therapies. The FDA is known to endorse or even ask for placebo-controlled trials in some circumstances.

In the EU, annex I of Council Directive 2001/83/EC states that in general clinical trials shall be done as “controlled clinical trials if possible, randomized and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control group will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo”.

For recommendation of a MA - in view of the clinical data - it is usually necessary to show:

- In case no established pharmacological treatment is available (scenario 1), that the benefit/risk of the new medicine is positive in the target population of the indication i.e. adequate therapeutic efficacy and acceptable safety profiles.
- in case an established pharmacological treatment is available, two situations may be envisaged:

1. The new product does not compare unfavourably with an established active control in the target population of the indication, with or without a placebo controlled trial in the MA application. Overall the benefits of the new medicine outweigh the risks and a MA can be recommended. Should other clinical trial designs be used, these should be justified on a case-by-case basis and the same considerations should apply (namely that the new medicine does not compare unfavourably with existing medicinal products and/or is superior to placebo if an active comparator is not appropriate).
2. The new product seems to compare unfavourably with an established medicinal product. It may for example be that the new product is shown to be more effective than placebo, but less effective than the active control. In such a case the overall benefit/risk assessment taking into account all aspects of quality, efficacy and safety and the clinical context of use may still be positive, sometimes after introduction of relevant modifications to the product information. In this situation a recommendation of MA will have to be discussed on a case-by case basis. (EMA/119319/04).

One may argue that that in the today's context non-placebo-control is only going to be chosen (by a company designing the trial) if ethical considerations do not permit a placebo-controlled design. This possibly explains why approximately half of the studies presented up to 2005 to the EMA by companies for MA of their product, the efficacy has been measured compared to placebo rather than based on head-to-head trials against usual care or active controls (van Luin et al., 2006).

The assessment of relative efficacy and especially relative effectiveness is currently done by other bodies, like Health Technology Assessment (HTA) bodies and competent authorities deciding on pricing and reimbursement at the national level. Although these bodies look at much more criteria than just the clinical benefit and the medical need (see Chapter 3), they play a key role in the assessment of these criteria in their evaluation of medicines.

HTA has been defined as a multidisciplinary field of policy analysis studying the medical, economic, social, and ethical implication of development, diffusion, and use of health technology (INAHTA, <http://www.inahta.org/HTA/>). Thereby, technology is broadly defined as to include the drugs, devices, medical and surgical procedures used in health care, as well as measures for prevention and rehabilitation of disease, and the organizational and support systems in which health care is provided ([www.inahta.org](http://www.inahta.org)). The medical and social/ethical implications, i.e. assessing the clinical benefit and the medical/therapeutic need, as well as guidance related to best practice (e.g. an innovative drug may be recommended in second line based on an HTA) are a key responsibility of HTA bodies in the assessment of the extent to which an innovative medicine is valuable.

Given the still strong emphasis on placebo comparisons in the MA process, several medicinal products have been approved that may not have had much added clinical benefit. This lack of relative efficacy or relative effectiveness may not necessarily be an issue if the new products are introduced into the market at the same price level as existing medicines, since the new products may have specific characteristics (such as a different interaction profile) that justify their place in the market next to the existing ones. However, if a price premium is claimed for a new medicinal product, the least a decision maker needs to know is whether an added therapeutic benefit is present. (Garattini et al. 2007).

Therefore, terms such as relative efficacy, relative effectiveness and comparative effectiveness are more and more cited and applied in official EC documents and lectures. It is stated that different bodies who are involved within the EU in the assessment of the added therapeutic benefit of medicines (EMA, HTA bodies, NCAs, ...) should cooperate better in order to avoid double and unnecessary efforts in the assessments of efficacy, relative efficacy and relative effectiveness. Within the EUnetHTA Joint Action, a specific work package is devoted to the assessment of the relative effectiveness of pharmaceuticals. The aim of the work package is to develop principles, methodological guidance as well as functional online tools and policies for relative effectiveness assessment. Areas where methodological guidance is needed are being identified. These efforts should eventually lead to a reduction in the duplication of assessments by the NCAs of different Member states.

Yet, different issues and challenges emerge together with these new insights.

### 3. Challenges and initiatives related to measuring the level of innovation

#### a. Defining relative efficacy and relative effectiveness

In the introduction of this report we defined relative efficacy as the extent to which an intervention does more good than harm, under ideal circumstances, compared to one or more alternative interventions; and relative effectiveness as the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice. <http://ec.europa.eu/pharmaforum/>

Note the importance of the term “relative” in this definition. It means “in relation to” and has to be seen as opposed to “absolute” (in the sense of not in relation to something else).

Although not explicitly stated, relative effectiveness seems to be at a higher level than relative efficacy. This is not new. For instance, the Agency for Healthcare Research and Quality (AHRQ, 2007) in the US states that a number of factors may limit the generalisability of results from efficacy studies. Patients are often carefully selected, excluding patients who are sicker or older and those who have trouble adhering to treatment. Racial and ethnic minorities may also be underrepresented. Efficacy studies also often use regimens and follow-up protocols that maximize benefits and limit harms but may be impractical in usual practice. Effectiveness studies, which are conducted in practice-based settings, use less stringent eligibility criteria and assess longer-term health outcomes. They are intended to provide results that are more applicable to “average” patients.

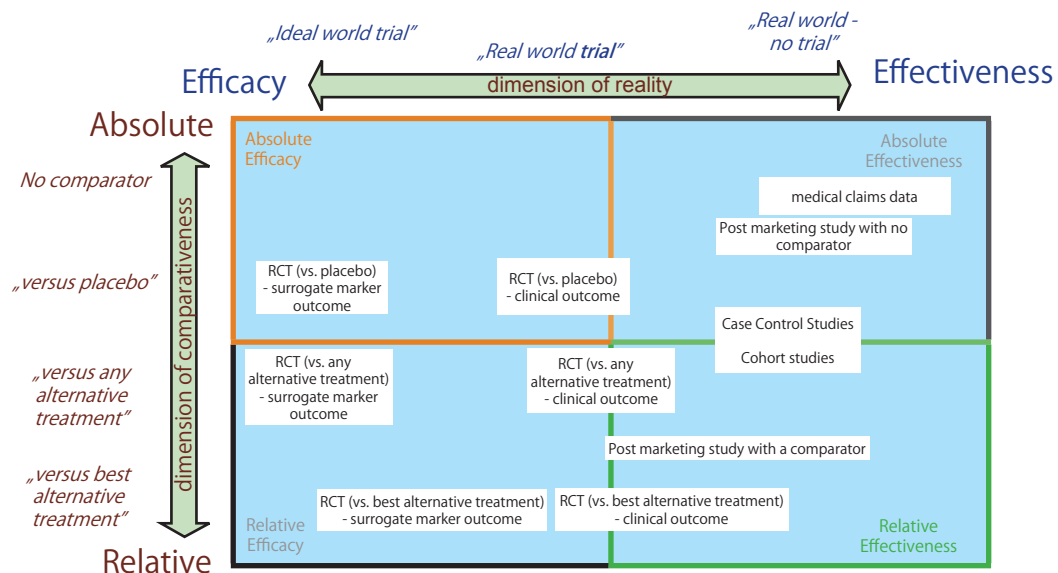
The above definitions of efficacy and effectiveness were provided by the High Level Pharmaceutical forum, an initiative from the European Commission that started in 2005. However, based on interviews, the pharmaceutical forum identified some issues with understanding and interpretation of these definitions among the EU Member States.

- First, there seems to be no clear consensus as to whether clinical trials yield efficacy or effectiveness information. All data on drugs yield information that is somewhere on an efficacy/effectiveness spectrum (see Figure 1). As a general rule, conventional clinical trials tend to run on the efficacy side of the spectrum. The term “effectiveness” entails some confusion: while some interviewees use it to describe what is actually happening in real life (to a certain extent, this leads to a theoretical concept), others use it exclusively to describe clinical trials that are oriented as far as possible to the effectiveness side of the spectrum. This, in their opinion, gives the best estimate of what happens in real life. Unfortunately, there is no consensus on these divergent views among Member States.
- When evidence is created in clinical trials, a new drug can either be compared to a placebo (this is non-relative efficacy), to any drug (a suboptimal situation) or to the best possible alternative drug (this is the optimal situation). However, different Member States may have different views on what is the “best alternative therapy”.

There is also some misunderstanding of the term “relative” versus “absolute”. This is due to the well known epidemiological logic that expressing benefits in absolute terms (for example, a treatment prevents one event for every 100 treated patients, i.e. the Number Needed to Treat = 100,) is more meaningful than presenting results in relative terms (for example, a treatment reduces events by 50%). It should be clearly stated that the term “relative” in “relative effectiveness” does not refer to “results in relative terms” but to “in relation to a comparator”.

To solve this misinterpretation, one should consider these concepts on continuous scales as shown in Figure 1. Hence, a randomized trial that has a rather pragmatic (naturalistic) design and looks at hard endpoints such as avoided major vascular events or mortality can also be called an effectiveness trial. If the trial compares the new drug to current treatment(s), then it reports relative effectiveness.

Figure 1: Absolute and relative efficacy and effectiveness (Pharmaceutical Forum)



A term that has been introduced in the USA some years ago is “comparative effectiveness”. According to the US Senate (2009), the term comparative effectiveness research (CER) means research evaluating and comparing health outcomes and the clinical effectiveness, risks and benefits of 2 or more medical treatments or services (note these include medicines as well). Title VIII of the American Recovery and Reinvestment Act of 2009 authorized the expenditure of \$1.1 billion to conduct research comparing “clinical outcomes, effectiveness, and appropriateness of items, services, and procedures that are used to prevent, diagnose, or treat diseases, disorders, and other health conditions.”

CER is thus said to be used to better understand the effectiveness, risk and benefits of medical interventions and strategies for managing diseases. CER investigations are originally applied to improve individuals’ health care outcomes by providing evidence that informs how doctors and patients should make health-related decisions. But their role on a higher level, i.e. for policy decisions, is growing.

Just like evidence-based medicine, a fully formulated CER topic consists of a set of questions, denoted “key questions”, that specify the patient populations, interventions, comparators, outcome measures of interest, timing, and settings (PICOTS) to be addressed.

Hence, CER does not seem to add something really new to the debate, as it does not seem to differ a lot from the principles of evidence based medicine nor from relative effectiveness.

Note that some – mainly US – authors criticize the fact that the definition of CER does not involve an economic aspect. Weinstein and Skinner (2010) state that such reviews should explicitly account for medical need and include cost-effectiveness and budget impact considerations. These authors are entirely right in that societal decisions should consider to what extent innovative medicines are valuable and whether they are value for money (see also further). But then the term should not remain “comparative effectiveness”, since those words do not cover these additional criteria sufficiently.

## b. Choice of comparator

When “more or better relative effectiveness data” are demanded, the “relative” nature should ideally refer to trials that have the best possible alternative treatment as a comparator. This means that ideally, a comparison with placebo would only be acceptable when it can be motivated why a comparison with an active comparator was not possible (for instance, when the new drug is an add-on drug, it is acceptable that the comparator group receives current treatment plus placebo).

If this is not the case, and one still needs to know how the innovative medicine compares to the current best alternative, indirect comparisons can be made either through value judgment or by modelling. Although a lot of progress has been made regarding the quality of these indirect comparisons, many methodological issues remain. That might explain why such comparisons are not preferred by many Member States, and guidelines are needed with this regard.

## c. Availability of effectiveness data

At the time of a primary reimbursement decision there are often no effectiveness data available, beyond what can be assumed from phase III clinical trials (i.e. based on a clinical trial one can never achieve the right part of Figure 1 above).

Efficacy-oriented clinical trials leave residual but important uncertainties about performance in real life clinical practice, as this performance can differ greatly from that established in a controlled experimental setting. There remain uncertainties about who will be treated, adherence to the therapy, impact on long-term individual and population outcomes, dosages, etc. Findings of efficacy-oriented trials are incomplete and systematic biases exist, due to the choice of the comparator, selection of patients, duration of the trial and choice of intermediate endpoints, as opposed to ‘hard’ morbidity or mortality endpoints.

Very often, data available in most or all Member States are limited to efficacy data. Since it is believed that in the absence of effectiveness data, efficacy data are the best approximation of effectiveness, data that have already been assessed for marketing authorization are re-assessed by local decision makers on market access, whereby EMA assessments are questioned again at the local level. In addition, because of different reimbursement application times, the number of studies or the volume of efficacy data available may vary between Member States. Ideally the data made available to the local decision makers should include all of the clinical study data used to obtain marketing authorisation. Unfortunately however, often only the subset of publicly available studies or endpoints is made available to the local decision makers, and it has been shown that the results in this subset of studies or endpoints tend to be more favourable for the product to be reimbursed. (McGauran et al, 2010)

In general, information on effectiveness is based either on effectiveness data alone or on a combination of efficacy data and some form of extrapolation of these data. (High level Pharmaceutical Forum) Modelling exercises are often used to bridge from efficacy to effectiveness, but this leads to uncertainty about the potential effectiveness of medicines.

Today, not all Member States accept modelling techniques. This is probably due to bad experiences whereby non-validated, poorly reliable or opaque models have been applied in submissions. It should be recognized, however, that due to better implementation of methodological guidelines, the quality of health economic models has improved over time (see for instance Wolowacz et al, 2008). Moreover, since health economic expertise improves at the level of the HTA bodies and competent bodies, a better distinction can be made between high and low quality submissions. This forces the industry to improve the validity and reliability of the submitted material.

A second trend to overcome the limited availability of effectiveness data is a so-called two-stage decision – or conditional reimbursement –, whereby an initial decision based on modelling techniques, is taken, followed by a second decision later on (for instance after one or more years, depending on the nature of the disease), when more effectiveness information based on post-marketing research is available. However, these post-marketing evaluations are also confounded with several issues, such as selection bias, confounding factors, etc... (cfr. infra).

In any event, it is clear that better clinical trials (large pragmatic trials/effectiveness trials) will yield data that are more oriented to the effectiveness side of the spectrum. This is highly desirable for the benefit of all stakeholders. Increased attention to these aspects will impose a paradigm shift whereby development of a medicinal product should not be for the sake of authorization only but also for reimbursement and market access.

#### d. Roles in assessing clinical benefit

It is not clear today who should assess the relative efficacy and effectiveness of new medicines and how this should be done. Currently, this task is largely the responsibility of national pricing and reimbursement authorities, often supported by health technology assessment (HTA) bodies. HTA obviously differs from relative effectiveness assessment. While costs, ethical and social aspects are commonly excluded from relative effectiveness studies, their inclusion is frequently required in HTA (Drummond et al, 2008). HTA is used to address more and distinct questions, from different perspectives, and motivated by different needs. (Drummond et al, 2008). Of course, relative efficacy and relative effectiveness are a cornerstone of any HTA, and it is not surprising that HTA bodies currently play a significant (probably the most significant) role in the assessment of relative effectiveness.

As a result, to date HTA and relative effectiveness studies are mostly national prerogatives. This leads to a situation whereby Regulators and HTA bodies, although both aiming at the availability of medicines which make a contribution to public health, are currently applying different approaches. Despite the identified differences in approaches and requirements, there are also areas of possible interaction such as the drafting of clinical guidelines, scientific advice, benefit/risk evaluation, risk management plans. Calls have been made for a closer interaction and collaboration between both parties. The assessment of relative efficacy and effectiveness, and the way it is organized should be better coordinated and aligned in order to avoid duplication of efforts and deal with the identified challenges. Although different European networking initiatives have been launched at the level of competent authorities (e.g. the initiative of the Slovenian Presidency) and HTA agencies (cfr. EU-netHTA – see further), increased coordination is needed.



In this light, the High Level Pharmaceutical Forum agreed in October 2008 on a set of recommendations including that EMA and Member States should continue their efforts to consider how the EMA public assessment reports (EPAR) can further contribute to relative effectiveness assessments. Indeed, HTA bodies should be able to access the results of all endpoints of the clinical trials as available to the regulatory agencies, including data obtained after the initial submission. In practice this may be achieved by an extended and regularly updated EPAR, which could also contain meta-analyses based on all data (in contrast to meta-analyses in “systematic” reviews based on publicly available data only).

The EMA stated, in their text entitled *“the EMA road map to 2015. The agency’s contribution to science, medicines, health”*, that there is no reason why the EMA and the HTA bodies should take a different approach to the assessment of net health benefit (benefits minus risks) since the ultimate objective should be to achieve integrated medicine development satisfying the various needs”.

According to the EMA, 3 major initiatives can be undertaken to make further progress in this field:

- First of all, the Agency should improve as an information provider. HTA bodies rely heavily on the EPARs and the Agency will increase its level of transparency on the outcome of the scientific review process as summarized in the EPARs, including the rationale for the decision/opinion, whereby more emphasis should also be put on the quantitative aspects of the benefit/risk assessment. This refers to the abovementioned statement from the Pharmaceutical Forum (2008)
- The Agency will also strive for a harmonization of data requirements (e.g. in the context of the drafting of clinical guidelines, the participation of HTA bodies as observers in scientific advice meetings) as well as methodological aspects.
- Finally, there is a need to engage with HTA bodies from early medicine development (to avoid as much as possible the appearance of two different medicine development programmes) throughout the medicinal product’s lifecycle. Maintaining the dialogue with HTA bodies especially in the post-authorization phase is very important in view of the vast amount of data which are obtained through post-authorization collection. Ways to address the needs of both Regulators and HTA bodies during this important stage of intensified patient exposure should be explored.

The aim of a recent conference organized by the Swedish presidency and a following pilot project is to find ways of cooperating systematically across Europe on the collection and sharing of data on the relative effectiveness of drugs. Examples for this common assessment project which are of particular interest include biologic agents for chronic inflammatory diseases, cancer drugs, and orphan medicinal products (see further) where divergent assessment methods and different assessment outcomes may exist between Member States because of poor or uncertain evidence of effectiveness.

### e. Specific challenges for orphan drugs

Of particular interest in the Swedish initiative is the special attention for rare diseases. Indeed, the challenges in assessing the relative effectiveness for orphan drugs are even more pronounced. In the context of rare diseases, it may prove difficult to recruit a sufficient number of patients and medical centres in clinical trials. Given that these diseases are rare, few medical centres have sufficient long-term experience with affected patients to be able to describe the natural history of the diseases. Furthermore, in many rare disease areas, there is a lack of knowledge on disease processes, on the influence of genetics, on prevalence figures, and on how to conduct clinical trials.

To address such issues, the EMA has issued guidelines that relate to clinical trials in small populations. It could also be recommended to modify the review process for rare disease therapies by allowing greater use of surrogate outcome measures and efficacy rather than effectiveness data for orphan drugs if clinical data are incomplete, and by imposing at the same time a commitment from industry to continue research.

Also in the case of orphan drugs, the EMA checks the quality, safety and efficacy when considering an application for MA, but not their relative effectiveness, i.e. the improvement as compared with existing approaches. Hence, most positive decisions taken by the CHMP to grant market access are based on 'benefit of the doubt'. For orphan drugs, there is even more seldom proof of relative effectiveness at the moment of MA. This clinical benefit is mostly assessed at the level of Member States as part of reimbursement procedures.

HTA agencies could play a role in the design of patient registries to ensure that the data collected can be used to help appreciate the effectiveness and cost-effectiveness obtained for orphan drugs. These registry data from all Member States should be integrated on the European level and be available for analysis for the different Member States. As said, a pilot project related to coordinated assessment of relative effectiveness is envisaged in the Swedish initiative, but questions remain about who should be responsible for this pilot project, how long it should last, and how to finance it.

### f. Measuring medical need

A related point of attention when assessing the magnitude of innovation is the medical need. We defined a valuable innovative medicine as one offering an added therapeutic value and filling a medical need. The latter is however difficult to define. It is associated with the severity of the condition as well as with ethical and social considerations. The importance to find solutions for the patients facing unmet medical need cannot be ignored. This may include very early access to promising new products in severe or life-threatening diseases where no satisfactory alternative treatment exists, but also the development of solutions for those patients suffering from the same type of serious diseases but treated with off-label products as supported by the scientific literature.

In this light it is again interesting to observe that countries such as Belgium, France, Italy, the Netherlands and the United Kingdom have introduced specific legislation governing compassionate use of orphan and other medicines. For instance, in Belgium, specific regulations for programmes of compassionate use exists for medicines that have not yet gained MA. There is in Belgium also a local medical need programme for patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by current care.

It should be noted that there is a distinction between “compassionate use” (programmes for use of a drug which has not yet received a marketing authorization) which is a European initiative and which has been translated in MS laws; and “medical need programmes” (programmes for use of a drug which has a marketing authorization but for e.g. an indication which is not approved) which is not an European initiative but a national initiative.

Currently there is no attempt to evaluate compassionate use programs and the assessment of medical need is not explicitly considered at the EU level and is rather a responsibility of the Member States. It could be argued that a pan-European assessment of or at least reflection on medical need could provide better insights into existing inequalities and therefore help setting priorities for Research and Development and influence the assessment of and access to innovation. Moreover the initiatives regarding compassionate and off-label use seem to be lacking coordination as well. An integrated overview would be useful in this regard.

### g. Challenges related to the assessment of clinical benefit of personalized medicine

In addition to the above issues, with regard to the emerging field of personalized medicine it is today not clear at all who are the decision-making institutions, reimbursement agencies and individual decision-makers responsible for genetic testing technologies used in the targeting of treatments, screening and/or diagnosis of disease. There is wide variation in the approaches taken to evaluate genetic tests and the individual and/or institutions involved in reimbursement decisions. There is an urgent need to identify and describe current decision-making processes across Europe.

A recent summary article contends that measuring real-world clinical effectiveness, ensuring regulatory transparency and optimizing payer coverage are the three main ingredients for translating pharmacogenomics into clinical practice. (Frueh, 2010)

An ongoing research project – called HIScreenDiag – funded under the EU Framework VII programme aims at developing a common set of procedures and criteria for the evaluation of health investments related to screening and diagnosis of disease across Europe, with a special focus on genetic testing technologies. HIScreenDiag is a collaboration between six publicly funded research centres: Helmholtz Centre Munich (Germany); Institute of Prospective Technology Studies (Seville, Spain) and the Universities of La Rioja (Spain), Gent (Belgium), Groningen (Netherlands) and Manchester (United Kingdom). The project is co-ordinated by Ghent University, Belgium.

It seems appropriate to distinguish between the pre- and post-market situation. Indeed, in case of a post-marketing situation the introduction of biomarkers that would result in a more targeted use of the drugs will only succeed if significant safety issues exist that could be avoided by the extra testing. As the initiative for all other changes to the product label remains with the marketing authorization holder company there is little incentive for a company to go this route. Perhaps re-evaluations some years after the initial introduction in the market could provide a way forward (cfr. Infra). In case of a pre-market situation, one should further stimulate collaboration between agencies, even consider to do own research (as at FDA), or to collaborate with diagnostic companies on this matter.



## 3<sup>rd</sup> Part

Valorising and creating  
access to innovative  
medicines

# Valorising and creating access to innovative medicines

## 1. Why assess value for money of innovative medicines

If investing in health is to be considered an investment by society of human and financial resources, aiming for a return expressed in health outcome - a higher health status for individual patients and for the society as a whole - it is self-evident that this society should monitor with particular scrutiny the return or cost-effectiveness of its investment. Therefore, once a new medicine can be considered as truly innovative, i.e. showing an added therapeutic value and filling a medical need, the next question is whether it is worthwhile to spend public money to cover the cost of this medicine. Explicit decisions must be made about funding a new medicine, mostly by large third-party payers (especially social health insurance institutions or national health services or bodies representing them), taking into account a legitimate return on investment for the pharmaceutical company, transparent prices and value for money. These decision-makers are involved with allocating substantial health care budgets and use more and more standardized methods of systematically assessing and appraising such medicines. Besides relative effectiveness, as discussed above, other criteria such as cost-effectiveness, budget impact, and again medical/therapeutic needs, and social and ethical considerations, play a role in these decisions.

The importance of cost-effectiveness analysis is critical in a society with substantial health expenditure. On one hand, the EU is spending an ever-increasing share of its GDP on health, while on the other hand Europe loses over 500 million working days every year due to work-related health problems (European Commission). As Commissioner Byrne said in July 2004, "each Euro better spent could make a net saving both for individual well-being and for economic competitiveness". With such a heavy disease burden, improving returns on health investments must become a priority. In a 2003 OECD report, Jacobzone stated that health care policies should be based more on cost-effectiveness assessments and applying appropriate incentives for effective and cost-effective care. (OECD, 2003) A more fundamental question to be asked is whether more money should be spend on health and health care versus other societal sectors such as education, environment, traffic safety, ... We do however not explore this question in this document.

A health economic evaluation is defined as *a comparative analysis of both the costs and the health effects of two or more alternative health interventions.* (Drummond 2008)

The important elements in the definition are, on the one hand, the comparison of alternatives and on the other hand, the two dimensions of costs and health effects.

In most cases new interventions in health care will give rise both to higher costs and also to more effectiveness in comparison with the therapies already available. An economic evaluation makes it possible to examine whether the money that would be invested in a new intervention for a particular condition would actually be used efficiently. This is done by means of comparisons with the current therapy. Note that in this context 'current therapy' may also be the 'do nothing' option.

In exceptional cases the cost of the intervention is entirely recovered by savings resulting from avoided disease, complications, or side effects. These are known as net saving interventions.

In most cases there will still be net costs related to a new technology or treatment in health care. If a new treatment is more expensive than the current treatment (in terms of acquisition cost) and again less other costs are induced to some extent (due to less failure of therapy, or less adverse events) than if the current treatment were followed, then part of the investment will be recovered. However, if these savings are not sufficient to compensate for the initial investment, then there will still be a net cost. This net cost can be balanced with the net health effects, often expressed in quality adjusted life years (QALYs) and the ratio, the so called ICER (incremental cost effectiveness ratio) between both can be assessed. The lower the ratio, the more cost-effective a drug can be called. (Annemans, 2008)

It is indeed necessary to translate health outcomes into standardized measures that make comparisons between different therapies possible. While subject to criticism, the use of QALYs, DALYs, Willingness to Pay Index or HUI (Health Utility Index) enable comparisons to be made between the therapeutic benefits of different medicines in a standardized way and thus to find a meaningful measure of the value of an innovation for society.

Health economic evaluations are increasingly used to support policies on reimbursement and pricing, as well as to evaluate and advise on use in clinical practice. Regarding the latter, value for money is also related to the correct and optimal use of innovative medicines. Inappropriate practices and variations in use are still present such that the most effective and cost-effective medicines are not always employed in the patients they should be administered to. (Sorenson et al, WHO, 2008). Moreover, some pharmaceutical therapies may have become obsolete throughout time but may nevertheless continue to be used.

In this regard, the process of evaluating new technologies should go hand in hand with the search for current practices where there is room for disinvestment, in order to free up budgets for valuable innovation.

A main problem with this regard is that there are no readily available methods on how to adequately assess sub-optimal or inappropriate use of medicines.

In addition to the evaluation of costs and effects, a budget impact analysis must also be part of the value for money assessment. Mauskopf et al (2007) state that Budget impact analysis (BIA) is an essential part of a comprehensive economic assessment of a health-care technology and is increasingly required, along with cost-effectiveness analysis (CEA), before formulary approval or reimbursement. The purpose of a BIA is to estimate the financial consequences of adoption and diffusion of a new health-care intervention within a specific health-care setting or system context given inevitable resource constraints. In particular, a BIA predicts how a change in the mix of drugs and other therapies used to treat a particular health condition will impact the trajectory of spending on that condition. It is thereby important to look not only at pharmaceutical costs but also at other domains within health care. Whereas cost-effectiveness informs decision makers about efficiency, budget impact analysis informs them about affordability.

Cohen et al (2008), however, argue that the economic and equity rationale for carrying out budget impact analyses is broader than just the affordability question. It relates to the opportunity cost, or benefits forgone, of reimbursing a particular product, measured in terms of utility or equitable distribution, by using resources in one way rather than another. In other words, decision makers have to explicitly ask the question what the consequences are of not being able to spend the budget that would be allocated to a given medicine to an alternative investment in healthcare. Obviously, as is the case with cost-effectiveness, the budget impact will to a large extent be influenced by the type of patients and the modalities in which a drug is used, both affecting the target population size.

## 2. Current situation related to the value for money assessment of innovative medicines

In deciding whether or not to reimburse the cost of (innovative) medicinal products, Member States must take into account the principles laid down in Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems.

The explicit assessment of cost-effectiveness and budgetary impact is however not mandatory on the EU level, and it is the responsibility of the MS to implement these criteria or not.

Internationally, the first countries implementing such assessments were Australia and Canada in the early '90s of the previous century. Interestingly, a recent review compared the results of assessments conducted by the National Institute for Health and Clinical Excellence (NICE) in the UK with those of the Australian PBAC and the Canadian CDR. It was observed that NICE recommended 87.4% (174/199) of submissions for listing (= coverage by the NHS) compared with a listing rate of only 49.6% (60/121) and 54.3% (153/282) for the CDR and PBAC, respectively. (Clement et al, 2009) According to the authors, the data suggest that the 3 agencies make recommendations that are consistent with evidence on effectiveness and cost-effectiveness but that other factors (medical need, ethical considerations, budget impact) are often important.

It was concluded that "comparative effectiveness and cost-effectiveness, along with other relevant factors, can be used by national agencies to support drug decision making". However, the results of the evaluation process in different countries are influenced by the context, agency processes, ability to engage in price negotiation, and perhaps differences in social values.

It is clear that such conclusions are also valid within the EU, where the context, agency processes, ability to engage in price negotiation, and social values differ among countries.

The role of Health technology assessment (HTA) in this process of pricing and reimbursement is becoming crucial, since HTA by definition takes all the required criteria for decision making into consideration and looks moreover at best practices with technologies. The HTA-methodology might therefore benefit Member States in the implementation of an objective, verifiable and transparent decision-making process.

But also here many challenges do remain in place.



### 3. Challenges and initiatives related to the value for money assessment of innovative medicines

#### a. Different structures, processes and criteria

The role of HTA in decision making strongly differs between Member States. Sorenson et al. (2007) explain that divergent structures, processes and roles may hinder the efficiency of the decision-making process and lead to unnecessary duplication of efforts and resource use.

On the structural level, some countries have different institutions involved in HTA, with overlapping responsibilities and tasks and a lack of coordinated recommendations; others have no HTA facilities and are required to always rely on foreign evaluations, which may not always come to conclusions that are relevant to their local situation.

On the process level, the applied methodologies are different as well (for instance some HTA agencies or competent bodies consider non-published data as relevant while others may not), limiting the comparability and transferability across countries. Also, lack of transparency, accountability and stakeholder involvement is often cited as a common flaw of the current systems. Finally, any process should foresee that recommendations need to be reviewed on a regular basis in order to account for the evolving practice in any given disease area.

With regard to the applied criteria, most assessments take a variety of criteria into consideration, including the already discussed relative effectiveness, cost-effectiveness, budget impact and medical/therapeutic need. Some countries also explicitly include the public health impact, and equity considerations. Some apply a societal perspective (also taking into account productivity related costs) while others apply a more restricted health care perspective. Few countries apply a formal threshold for willingness to pay for one unit of extra health, and even the – according to many academics – golden standard unit itself (the QALY) is challenged by several Member States. (Cleemput et al. 2008)

It is remarkable that some countries (UK, Netherlands, Sweden, and – to a lesser extent - Belgium) explicitly prefer the incremental cost per QALY as a parameter for cost-effectiveness, while others (Germany, France) favor disease related outcomes. Table 1 provides an overview of applied criteria in the valorization of innovative medicines.

It is crucial that HTA bodies, competent authorities and the EMA work closer together with transparent assignment of roles and responsibilities in order to avoid duplication of efforts on the one hand or lack of adequate data for decision making on the other hand.

The creation of the European Network for HTA EUnetHTA has made a significant contribution to the coordination of HTA in the EU. A dialogue is currently taking place between the HTA agencies and EMA, as part of the activities of the EUnetHTA Joint Action, in order to try to align the agencies' activities and roles with those of the EMA and the competent authorities. It is therefore necessary to explore how the EMA's scientific evaluation and recommendations on the benefit/risk balance of medicinal products could further contribute to the cost/ effectiveness assessment performed by Health Technology Assessment (HTA) bodies within the EU. On this point, Mr. Thomas Lönngrén informed that the EMA will continue exploring the optimal collaboration between EMEA and HTA bodies. It was noted that this activity was recommended by the High Level Pharmaceutical Forum. (EMEA/91746/2009).

Table 1: Applied criteria for HTA in selected EU countries (Sorenson et al, 2008)

Criteria	AT	BE	CH	DE	FI	FR	NL	NO	SE	UK
Therapeutic benefit	x	x	x	x	x	x	x	x	x	x
Patient benefit	x	x	x	x	x	x	x	x	x	x
Cost-effectiveness	x	x			x		x	x	x	x
Budget impact		x			x	x	x	x		x
Innovative characteristics	x					x	x			x
Availability of therapeutic alternatives	x	x					x		x	x
Equity considerations		x				x		x	x	x
Public health impact						x				
R&D					x					

## b. Applying principles of HTA

The organization of HTA and the settings in which HTA agencies operate vary considerably across countries. Moreover, there are significant differences in the practical application of HTA. Differences in health care systems and in the organization of HTA probably explain a large part of the variance in international HTA. On the other hand, differences in how HTA is perceived, understood or used in various parts of the world may have an important impact on the way it is performed and used. Hence different applications of HTA may exist even in settings where there are no substantial differences in the health care system or in the organization of HTA.

Collaboration on HTA between Member States requires standardization in the structure, transparency, and handling of information in any HTA. Steps towards defining some standards at the international level have been done by INAHTA (by use of a checklist) and previous European Projects (EUR-ASSESS, ECHTA/ECAHI). More recently, EUnetHTA was established, as a response to the expressed need by the European Commission and EU Member States for a sustainable European Network for HTA. (Kristensen et al. 2009).

The HTA Core Model developed within the EUnetHTA project built on this earlier work.(Lampe et al. 2009) The HTA Core Model specifies the questions that should be asked and answered within an HTA and defines and standardizes the structure of an HTA report. To support European collaboration some elements are prioritized over others. They are defined as “core elements”. A core element is an assessment element that is considered to be both important for every HTA and transferable to other jurisdictions. A Core HTA is an actual assessment that has been conducted using the HTA Core Model and has considered all core elements of all 9 HTA domains (Health problem and current use of the technology (implementation level); Description and technical characteristics of technology; Safety; Clinical effectiveness; Costs, economic evaluation; Ethical analysis; Organizational aspects; Social aspects; and Legal aspects.). Through the wide scope, focus on core elements and the summary chapter, a Core HTA gives an overview of a technology that is likely to be useful in the European context. A Core HTA can be used as a basis for producing local HTA reports that take into account local circumstances (e.g. epidemiology, organization, resources, values).

Drummond et al (2008) listed 15 principles of HTA that could be used as a good starting point for aligning the approach of HTA bodies and even for a system of accreditation of HTA bodies. While corresponding partially with the core elements of EUnetHTA, the authors add some important elements related to the process of conducting HTA's, such as:

- The goal and scope of the HTA should be explicit and relevant to its use
- HTA should be an unbiased and transparent exercise
- HTA should include all technologies relevant to the decision to be made
- A clear system for setting priorities for HTA should exist
- Those conducting HTAs should actively engage all key stakeholder groups.
- Those undertaking HTAs should actively seek all available data
- HTA findings need to be communicated appropriately to different decision makers and stakeholders
- The link between HTA findings and decision making processes needs to be transparent and clearly defined.

It is clear today that the variability in complying with these principles is apparent, and ways forward to align the HTA bodies with this regard are to be established as well. Thereby, it should be recognized again that unless HTA agencies have access to all endpoints of all trials (including those not published, but available to the medicines agencies) their reports will remain to be biased (see second bullet point above).

### c. Uncertainty and performance based agreements

A crucial element in value for money assessment is how to deal with the already described uncertainty about effectiveness but also uncertainty about costs and budgetary impact and about the applied modelling exercises.

Although the earlier mentioned study by Clement et al 2009 showed that most of the uncertainty is found around clinical effectiveness, typically resulting from inadequate study design or the use of inappropriate comparators and non-validated surrogate end points, we did not elaborate on the issue in the chapter on measuring the level of innovation, because there are direct economic consequences of such uncertainty.

Indeed, facing rising expectations from patients and health care providers together with uncertainty on both cost and effectiveness, payers are forced to study new methods and techniques for clinical and financial risk management and cost/sustainability when allocating resources to promising innovative pharmaceuticals.

Thereby, additional appraisal is to be made as to whether the benefit of more information and more evidence is greater than the cost of delaying the decision until this evidence is available. Decisions made under uncertainty - and therefore risks - could result in the reimbursement of pharmaceuticals that are subsequently shown to be clinically or cost ineffective (the 'type I error' of inappropriate credulity). On the other hand, reimbursement and thus access may be denied for valuable innovations that later prove to present value for money (the 'type II error' of erroneous scepticism). In both cases, there are opportunity costs in terms of healthcare expenditures and health benefits associated with these inappropriate decisions.

A possible way forward to deal with this uncertainty is the application of risk sharing agreements, or more broadly "performance based agreements" (Carlson et al, 2009).

In general, Performance Based agreements could be defined as formal agreements between a payer and a manufacturer where the price level and/or revenue received is related to the (future) performance of the product in either a research or in a real life situation, in order to remain within predefined limits in terms of cost-effectiveness. They are in a sense hybrids of ex ante and ex post value-based pricing approaches.

In these agreements, the eventual effectiveness and costs will drive formal actions oriented to conditional reimbursement, such as companies paying themselves in case of treatment failure or paying back part of the reimbursed money in case of worse than expected cost-effectiveness.

It is clear that the crucial requirement for Performance Based Agreements to be effective is that it has to be possible – or made possible – to measure performance and to make reasonable good assessments of the value in 'real life'. Measuring performance means objective measuring outcomes on scientifically validated clinical end-points as well as patient reported outcome (PROMs), since from a patients' point of view, 'better health' means improvement in length and quality of life. It involves not only mortality and morbidity data but also the patients' well-being before and after treatment.

Such constructs are also in the interest of the industry, since companies, engaging in Performance Based Agreements can benefit from new information becoming available on non clinical positive attributes, such as compliance, impact on quality of life, comfort for health workers, and potential cost-savings. Moreover, predictability (and relative stability) of a 'fair' list price, reflecting the true value of the product and capturing a reasonable share of the consumer surplus created, can be appealing and an incentive to further invest in innovative research. Flexible discount and rebate schemes can also provide means to meet with the willingness to pay/invest of the purchaser, without touching the global price – and the impact on revenue due to benchmarking pharmaceutical prices across several countries ('external reference pricing'). At the same time, 'deadweight loss', (financial) losses caused by a possible negative decision on coverage if no settlement could be found, can be minimized. (Claxton, 2008).

Performance Based Agreements can be a valuable asset to Compassionate Use and Medical Need Programs as useful tools to provide access for patients and health care providers to promising innovative pharmaceutical therapies in domains where an Unmet Medical Need is identified, without compromising the delicate equilibrium between cost and effectiveness, while at the same time enhancing transparency in decision making.

Over the last two decades, quite a number of these Performance Based Agreements have been put into place. Relative simple 'No Cure, no pay' and 'Money Back Guarantee'-schemes have been established, such as those for finasteride (US) in benign prostatic hyperplasia, for vardenafil (Denmark) in erectile dysfunction, for valsartan (US and Denmark) in blood pressure treatment, and for bortezomib (UK) in multiple myeloma (NICE, 2007), alongside with more sophisticated schemes as the UK Risk Sharing Scheme for Multiple Sclerosis (price adjustment to ensure an agreed threshold value for the cost-effectiveness ratio) (Sudlow and Counsell, 2003), a US 'inversed' discount scheme (greater discount in case of greater performance) for sitagliptin (+ metformin) in type 2 diabetes and US coverage of disease-related sequelae in case of non-performance for risendronate in the treatment of osteoporosis.

It is noteworthy that the National Institute for Health and Clinical Excellence in England and Wales has examined scenarios in which a (orphan) drug provides value to the National Health Service by proposing such risk-sharing arrangements.

A key component in this is the commitment to ongoing evaluation through, for example, patient registries designed to collect the necessary data to follow up and evaluate uncertainties surrounding the longer-term effectiveness and cost-effectiveness. The use of patient registries would support the decision-making process, inform clinical practice, and could provide information about long-term adverse events.

However, patient registries have their limitations. A patient registry may be biased if the patient aetiology and disease severity change over time. Also, patient registries tend to collect data on a specific drug used in the treatment of a disease, but not on alternative treatments, thus providing partial information to calculate the cost-effectiveness of the drug relative to an alternative treatment. Furthermore, new treatment strategies may become available during the period covered by the registry. Therefore, patient registries need to be set up in a flexible way to collect sufficient data and to account for the evolution in patient population and treatment strategies over their lifetime. There is a real added value for cooperation at EU level that could lead to better access to medicines for patients, and many efforts have been done over the past years by the EMA, the HTA community and by country initiatives (such as Sweden and Slovenia).

Although there is some experience with this type of Agreements, it is probably too early to make a relevant full assessment. If however there are reasonable grounds to believe that a new pharmaceutical could offer significant benefits that could answer to an unmet medical need, but uncertainty remains about the clinical or cost-effectiveness, and this uncertainty can be overcome through evidence that can be generated in an appropriate time frame, it is clear that Performance Based Agreements can be worthwhile.

The Pharmaceutical Forum underlines that approaches of risk-sharing or conditional pricing are welcomed by patients as they provide an opportunity for early access. They offer an early reward for companies while they give funding authorities the certainty of control over the spending and at the same time collect valuable experience about how the innovative medicine works in real life settings.

But, according to the Pharmaceutical Forum, today such agreements often take place rather at the end of a sometimes long negotiation between a pharmaceutical company and a decision maker and are considered as a kind of last resort. If such agreements would be proposed earlier they could avoid important delays and enable faster data collection on clinical experience and therapeutic value in controlled settings while the patient still had access.

Then again, early access to new pharmaceutical technologies means early exposure, including the risks involved in using technologies that are not fully evaluated, for instance on long-term safety. This may cause the patient to miss-out on optimal treatment for a period of time, or worse, expose these patients to a treatment with possible adverse and harmful effects. That is why early access is especially useful for severe diseases where there is an unmet medical need (no alternative exists).

More possible disadvantages occur. For instances, for establishing and negotiating sophisticated scheme-details, data collection and analysis, complex monitoring and review must be feasible and will generate an extra burden and possible additional costs. In fact this might even delay market access. Prices of new pharmaceuticals might rise in anticipation of later performance-based adjustments. Therapies that prove not to be clinically or cost-effective for the whole target population might be difficult to withdraw if there is proof or even only a perception of benefit for some individual patients. Investments might be canalized by companies towards risk-free research. Granting conditional reimbursement could also jeopardize incentives for manufacturers to further invest in additional data collection by optimal evaluative study design and study conduct. Furthermore, the clinical community may regard this experimental research unethical and patients could be reluctant to participate in those trials.

Making the balance between possible advantages and disadvantages, we believe that, if designed sufficiently flexible and dynamic to cope with evolving medical evidence and if rewarding for innovators in a fair, value-based way, these controlled frameworks can create a win-win situation for both society and company and be an incentive for indispensable continued investment in innovation. Especially for diseases with currently no treatment options such a new thinking and more flexible approaches are needed. (Pharmaceutical forum)

A final remark relates to the involved costs in such agreements and additional data collection. Value-of-information analysis (VOI) can be used to estimate the expected relevance and benefit of additional evidence gathered in a routine care environment (within a performance based agreement) and to eliminate, or at least quantify the decision uncertainty that remains. (Claxton and Sculpher, 2006) Perhaps, exchange between member states about such agreements could help to improve their efficient application. Especially in the field of rare diseases, cross-border assessment of effectiveness in the light of such agreements may be useful (cfr. infra).

#### d. Affordability, access and solidarity

In the EU, the use of generic and biosimilar medicines have contributed to the accessibility of adequate medical treatments for European citizens.

However, when it comes to new innovative drugs, these should as well be accessible to all those in need.

Innovative medicines are generally launched in markets where the companies can get a high price for them and then launched in other markets later. These later markets decide the price by looking at prices in other countries, so there is little price difference, which makes it difficult for low income countries to have affordable access to medicines. (E. Docteur, OECD)

In addition, methods for assessing budget impact are way behind the methodological advance in cost-effectiveness studies. This has led to sometimes unrealistic budget impact estimates that are not confirmed once the drug is in the market. There is an urgent need for better guidelines for budget impact analyses and for making these mandatory.

Keeping in mind the requisites on equity and (international) solidarity, a crucial challenge within the EU context is to make valuable innovations accessible to all EU citizens, which requires solidarity within Member States and solidarity between Member States. Ideally, valuable innovative drugs should be launched in all markets and available there at an affordable price.

With regard to within country solidarity, it is important to understand that estimates of the ICER do not account for distributive aspects (poor/rich; young/old; rare diseases, ...) The utilitarian vision on health investment and making choices in health care goes against the principle that everyone has the right to the same quality of health care. Perhaps the societal willingness to pay for QALYs or the QALYs themselves should be weighted for factors such as severity of disease.

Reflection is needed on a country level about the elements based on which such solidarity and weighing can be achieved, and all stakeholders need to be involved. A good example is given by the citizens council reports in the UK.

But reflection is also needed at the EU level, related to between Member State solidarity. In principle all Europeans have the right to the same quality of health care and it is not acceptable that in case of a severe condition inhabitants of country X have access to new treatment whereas inhabitants of country Y do not. Obviously, due to differences in health systems and priorities, a solution for this problem will be very difficult to achieve.

It should perhaps be explored whether a system of price differentiation can be applied in function of GDP per capita in order to enable such access.

Although these kind of pricing systems reflect in a sense the principles of solidarity and equity, as countries with more resources would carry part of the financial burden of more vulnerable countries, reflection on implementation is needed. Such systems would require substantial coordination and cooperation between Member States on issues that are now the sole and undisputed competence of individual Member States.

The establishment of a systematic price differentiation scheme would call for the determination of some sort of European 'base' price, reflecting the value and the value for money of medicines on a European level. Whether or not the determination of such a European value and value for money is feasible needs careful consideration. 'Value' - this has been explored earlier in this document - will largely depend on Unmet Medical Need, hence on priorities, which on themselves can be substantially disproportionate between vulnerable countries and countries with more financial power.

A European 'average' value, with a European 'average' price, reflecting a European 'average' value for money would therefore not necessarily reflect the true value or the true value for money for individual countries. It remains to be examined if adjustments or price-differentiation, merely on GDP, will suffice, and should they not, which other criteria could be considered..

At the same time, as these schemes could in a way be considered as formal or formalized external reference pricing schemes, they could limit room for individual countries to negotiate (for instance compensation mechanisms or value/performance based agreements) on prices of the concerned pharmaceuticals.

It should also be examined how these differential pricing systems – can be structured in a way that is, compatible with the actual European position and regulation on the internal market, more specifically on free traffic of goods, the freedom to provide services and the freedom of establishment. Free parallel import and export for instance, should not be hampered or hinder itself the efficiency and sustainability of such structures. As a minimum, systems should be put in place that guarantee that those medicines offered on the local market effectively reach local patients.

A way forward could be to consider innovative pharmaceutical drugs as a social insurance service, hence not requiring the rules of the EU internal market.

### e. Additional challenges for orphan drugs

For orphan drugs, additional challenges again occur. Indeed, given their high price for an often modest health benefit, orphan drugs are often unlikely to be cost-effective, at least if the cost-effectiveness of an intervention is judged based on its cost per quality-adjusted life year gained, and this cost per QALY is compared to a fixed threshold value. If decisions are primarily based on cost-effectiveness considerations, orphan drugs will tend to fail these criteria.

Possibly, additional criteria that are not included in the traditional cost per QALY measure (the seriousness of the health condition; the availability of other therapies to treat the disease; and the cost to the patient if the drug is not reimbursed,...) can even be more relevant to inform decisions on orphan drugs. These criteria are indeed particularly relevant to orphan drugs, which tend to target serious health conditions, make up the single strategy to treat a disease, and have a huge impact on patients' health care expenditures if they would have to pay for the drugs themselves.

The question arises as to how these various considerations can be aggregated. In contrast with medicines for non-orphan diseases, how can the often poor cost-effectiveness ratio, weak clinical data, small health benefit, high cost and absence of an alternative therapy for orphan drugs be taken into account in a payer's decision to cover such a medicine? It could be argued that the cost-effectiveness threshold value should be higher for medicines to which society attaches a high social value. Orphan drugs may attract a high social value, although future research will have to elicit social values ascribed to various health technologies.



These considerations can be illustrated with two cases. Despite an unfavourable cost-effectiveness ratio, the National Institute for Health and Clinical Excellence in England and Wales approved imatinib for the treatment of chronic myeloid leukaemia in the absence of any effective alternative therapy (except for bone marrow transplantation) and on equity grounds. A second example relates to enzyme replacement therapy for Fabry's disease. A health technology assessment stated that, although the incremental cost-effectiveness ratio of enzyme replacement therapy is at least six times higher than the threshold of the National Institute for Health and Clinical Excellence, clinicians and manufacturers argue that the National Health Service has no option but to provide this therapy because Fabry's disease is an orphan disease.

The new agreed EU principle that "Member States, stakeholders and the Commission should strengthen their efforts to ensure access to orphan medicines in all EU Member States", led to EU Exchange of Knowledge on the Scientific Assessment of the Clinical Added Value of Orphan Medicines, specific pricing & reimbursement mechanisms and an early dialogue on research & development, as well as an increased awareness on rare/orphan diseases. (pharmaceutical forum)

Still it is felt that EU policy makers should share more intensively their considerations and criteria when deciding on adopting (reimbursing) orphan drugs and more efforts should be made to coordinate processes and criteria. In 2010, the European Commission issued a call for tender concerning "the creation of a mechanism for the exchange of knowledge between Member States and European authorities on the scientific assessment of the clinical added value for orphan medicines" (EAHC/2010/Health/05). The underlying purpose is to facilitate timely and effective access to orphan medicines by those affected by a rare condition by increasing collaboration at the European level.

#### f. Additional challenges for personalized medicine

A special challenge exists in the assessment of medicinal products whose use is or can be dependent on the result of genetic tests. Often the decision makers dealing with the value for money of such tests (if clear decisions are made at all) are different from those dealing with pharmaceutical drugs, and the criteria applied are different as well, leading to additional problems of lack of coordination. The same principles of cost-effective use and budget impact should also apply to such genetic tests, and the decision making for tests and associated drugs must be aligned.



4<sup>th</sup> Part

Recommended ways forward

# Recommended ways forward

The previous chapters have listed several challenges related to coordinated action to stimulate, measure and valorise innovative medicines. Better and more coordinated structures, processes and criteria need to be set up if we want innovation and solidarity to go hand in hand.

In the following sections we will provide recommendations for future coordinated action in this regard.

## 1. Stimulating, steering and facilitating innovation

Stimulating, steering and facilitating innovation and innovative research is a pro-active policy role. The aim is to create a sustainable R&D environment whereby the likelihood that valuable pharmaceutical innovation reaches the market place is maximized. To this aim, a novel EU policy should:

- identify the medical fields where innovative research is required (and hence should receive priority),
- assess the potential of success of innovative concepts and facilitate R&D in these directions, including the stimulation of public initiatives,
- steer R&D of these concepts towards a proof of concept,
- learn from past experiences, especially failures in innovation, with a goal to improving new approaches,
- co-finance such R&D, and
- facilitate research by avoiding barriers for efficient clinical research programmes.

Regarding the latter, the assessment of multi-country trials could be done by only one of the Member States concerned, hereinafter referred to as reference Member State; the reference Member State would draw up the assessment of the clinical trial. (Pharma Forum, 2008) The other Member States concerned would be consulted and could assist in this assessment, for example by providing additional expertise with regard to certain products or product categories. The assessment of the reference Member State would be applicable for the clinical trial in all Member States concerned. In case of disagreement by another Member State, a clear decision making procedure would have to be established. As an alternative, a centralised approval system for pan-European Trials could be introduced.

In addition one should envisage a new “quality label” indicating that a compound has the potential for early access. However, it should again be emphasized that ‘success’, already at this stage, should be interpreted as “leading to improvements in health outcomes” and “filling in unmet medical needs”. It also needs to become clear which body, based on which criteria, can grant such a label for early access.

## 2. Measuring the level of innovation

As said before, the aim of a coordinated EU health policy should be to recognize true innovation as well as the size/magnitude of that innovation, and both the EU market authorization process and the local HTA bodies and competent authorities should play a role in this regard.

Obviously, a distinction must still be made between data needed for obtaining MA and data needed for appraising the innovativeness and value of a new drug. Criteria for MA remain quality, safety and efficacy as it is today, while elements such as need, relative effectiveness and value for money must play a decision in pricing and reimbursement decision.

With regard to the latter, the EMA needs to engage with HTA bodies from early medicine development throughout the medicinal product's lifecycle in order to provide input in the assessment of relative effectiveness and medical need. Other elements of HTA, such as the majority of the social and ethical aspects, and all the economic aspects, would remain within the local responsibilities of HTA bodies and Member States.

With regard to the assessment of relative effectiveness, it is more and more understood that what has been assessed and decided at one step should not be reopened for evaluation at a following step, unless new evidence has emerged in the meantime.

One may therefore argue that the assessment of relative effectiveness and medical need could be based on an *integrated* approach, with focus on well defined roles and responsibilities, while the assessment of value for money rather requires a coordinated approach, with focus on exchange of information.

One of the problems here is that some Member States are still reluctant to accept models for bridging from efficacy to effectiveness. Improved validation efforts by those who develop models are required. Improved methodology and high quality guidelines that are approved by all stakeholders would enhance the quality and thus usefulness of these modelling studies (Pharmaceutical Forum). Indeed, unless the source code and all input of models are made public (or very well documented and validated) so that everyone can reproduce it (or not), cost-effectiveness models are not a fully transparent exercise.

According to the Pharmaceutical Forum, all Member States, irrespective of whether they accept modelling or not, would benefit from effectiveness-oriented clinical trials. However, it must always be discussed whether effectiveness trials – with their inherent lack in internal validity – can reasonably be expected in the drug development programme. While prolonging observation times might come at too high a price (longer waiting time for new drugs), using the right comparator, relevant outcome measures and realistic inclusion criteria is something that would lead to better decisions. If studies were to be designed along these lines they would yield data that are more effectiveness than efficacy-oriented. If this goal is to be achieved, it needs to be made mandatory for companies. But the Pharmaceutical Forum acknowledges that this is probably not very realistic. One way to improve the quality of data for decisions on relative effectiveness is for the competent authorities and other players to give (coordinated) advice to companies during the development process.

### 3. Assessing value for money of innovation

From the previous chapter it becomes clear that we are currently still far away from optimal assessment of value for money in the EU. The reason why this is so difficult to achieve is probably because pricing and reimbursement decisions need to find agreement between three types of very different expectations (Pharma Forum):

- The patients' need to access to the best health solutions available, at an affordable cost, that is, affordable from the patients' point of view.
- Manufacturers' expectations for a reward for their long and risky investment in R&D.
- The funding authorities' need to optimally use their limited resources. They need to invest national budgets in cost effective health solutions. (<http://ec.europa.eu/pharmaforum/>)

An important difference between valorising and measuring innovation is that valorising involves a local appraisal of the value for money, the budget impact and the local medical need that can be filled with new medicines. Indeed, local priorities and national health care policy environments should be reflected in the processes and criteria used for assessing value for money and ultimately for reimbursement decisions. Hence, in contrast to the systems associated with measuring the level of innovation, the systems used to valorise new medicines should continue to rely heavily on local decision power.

On the other hand, as mentioned before, a pan-European, coordinated or even integrated assessment of both relative effectiveness and medical need at the EU level (including general ethical and social considerations) should be envisaged in order to feed part of the data needed for the local decisions in an efficient way. This could be the task of EMA, HTA and competent bodies together.

Local assessment of medical need, supplementary ethical and social aspects, cost-effectiveness, and budget impact should then remain the responsibility of the Member States, although cross-border exchange of methods, information and decisions would be highly valuable. Note that local assessments may be based on core international cost-effectiveness and budget impact models that are adapted to the local setting.

According to this scheme, similar outcomes of relative effectiveness assessments will nevertheless allow different Member States to come to different reimbursement decisions based on either differences in value judgment or budgetary evaluations, or on any other reason for that matter, such as differences in the objectives and priorities of the different national healthcare systems.

The Pharma Forum correctly states that this momentum on pricing and reimbursement is to be maintained with further cooperation and exchange of experiences at EU level. The Commission, in cooperation with relevant stakeholders, is to undertake a first review of progress on pricing and reimbursement within the next 2 years.

Future discussions between Member States should strive at defining and triggering such a dual system with an integrated approach for relative effectiveness and EU medical need assessment and a coordinated/exchange based approach for value for money assessment.

The following scheme illustrates the desired shift compared to the current situation.

Assessment criteria for innovative medicines	Current		Future	
	Centralized	Local	Integrated	Local with exchange
	EMA	HTA and competent bodies	Joint Initiative for Medicines (JIM)	HTA bodies and competent bodies
Efficacy	√	√	√	
Safety	√	√	√	
Relative efficacy	√	√	√	
Relative effectiveness		√	√	
EU medical need			√	√
Local medical need		√	√	√
Ethical and social aspects		√	√	√
Cost-effectiveness		√		√
Budget impact		√		√
Organizational aspects		√		√

“Joint Initiative for Medicines” points to a joint initiative between EMA, HTA bodies and competent bodies.

## 4. In conclusion

In this report, we have tried to provide an overview of the current challenges related to stimulating, measuring and valorising pharmaceutical innovation.

Although some progress has recently been made to improve access to valuable innovative pharmaceuticals, there is still a huge need to improve structures, processes and applied criteria.

Both the productivity of R&D investment as well as society's ability to deliver innovative medicines to all patients who are in need of them must be improved.

Several suggestions have been put forward, and we summarize the most important here:

- A more coordinated system for prioritization in pharmaceutical research could increase the likelihood of valuable innovations being developed and provide better answers to unmet health needs. Unnecessary delays and increases in the cost of research and development should be avoided.
- With regard to measuring the magnitude of innovation there should be a continuous update of the European Public Assessment Report (EPAR) and the risk management plan (RMP) to make it a dynamic and permanently relevant document. Also, European co-operation in Health Technology Assessment (HTA) of medicines should further be encouraged. In order to optimize the quality and the pertinence of HTA, Member States should have full access to all relevant data and information, available with the Authorities responsible for Marketing Authorization (as EMA).
- Moreover, common methodologies for the integrated assessment of relative effectiveness should further be developed and appropriate implementation mechanisms be examined. There should be a clear principle of governance to avoid unnecessary duplication of work and efforts.
- Especially where limited patient populations are concerned, an efficient cross-border exchange of clinical data, information and knowledge for orphan drugs should be achieved between Member States.
- An update is needed of the existing European legal framework in relation to the transparency of the procedures and criteria for pricing and reimbursement. This update could moreover take into account new mechanisms of conditional (or "only in research") reimbursement, performance based agreements, as well as specific procedures for early access.
- Valuable innovative medicines should be brought within reach of all concerned patients in the different Member States. Taking into account the differences in the level of wealth and resources, efficient mechanisms for international and intra-national solidarity should be examined.
- An inventory and an evaluation of the mechanisms and regulation on Compassionate Use, before actual marketing authorization, should be made. Also, "Off label use" of medicines in Unmet Medical Need situations calls for more clarity on a European level.
- Finally, with regard to an efficient management of expenditures (in terms of affordability and sustainability), initiatives promoting the good and justified use of innovative medicines in daily practice are required.

We recognise that the current document only provides a high-level overview. Some of the proposed initiatives will deserve more detailed plans in order to be impactful on the future access of medicines to all patients who are in need of them throughout the EU.



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