Priority Medicines for Europe and the World 2013 Update

Background Paper 8 - New approaches to promoting innovation

BP 8.1 - Public private partnerships

BP 8.2 - Regulatory structures to support pharmaceutical innovation

BP 8.3 - Pricing and reimbursement policies: Impacts on innovation

BP 8.4 - Real-life data and learning from practice to advance innovation

BP 8.5 - Patient and citizen involvement
Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper
Written by Elizabeth Ziemba, JD, MPH

Background Paper 8.1
Public Private Partnerships

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# Table of contents

Acknowledgements ........................................................................................................... 3

1. Introduction .................................................................................................................. 4

2. Rationale for setting up PPPs ....................................................................................... 6

   2.1 Increasing scale at critical stages of drug development ........................................ 6

   2.2 Sharing risk through public funding ...................................................................... 7

   2.3 Agenda setting ........................................................................................................ 9

   2.4 Focusing R&D activities ....................................................................................... 9

   2.5 Optimizing use of available knowledge and resources ........................................10

   2.6 Foster a more competitive private sector to promote economic growth ...............11

   2.7 Address topics that require a neutral/multi-stakeholder environment ....................11

3. The place for different types of PPPs in the R&D process ............................................ 12

   3.1 Research partnerships focusing primarily on early stage R&D ......................... 12

   3.2 Product development ............................................................................................ 13

   3.3 Concept development and overall systems strategy .............................................. 13

4. Challenges for PPPs ..................................................................................................... 15

   4.1 Timelines and sustainability ................................................................................... 15

   4.2 The role of Small and Medium Enterprises (SME)s and large companies .......... 15

   4.3 Consortium leadership and project management .................................................. 15

   4.4 The role of the central entity ................................................................................. 16

   4.5 Intellectual Property (IP) structure and management ........................................... 17

5. Performance measurement ............................................................................................ 18

   5.1 Stages .................................................................................................................... 19

   5.2 Domain for measurement of valued ..................................................................... 20

6. Conclusions and recommendations for future research ............................................. 21

References .......................................................................................................................... 21
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1. Introduction

Public-private partnerships were mentioned in the 2004 Report as a promising solution for addressing challenges in pharmaceutical innovation. Since 2004 considerable progress has occurred in the development of the public-private partnerships (PPP, for definition: see below) in particular in the product development partnerships (PDP). The current challenges in drug development require the mobilization of significant resources from a wide variety of stakeholders, PPPs can help facilitate this process and capitalize on the benefits of new approaches such as ‘open innovation’. The number of PPPs is increasing rapidly. For example, in Europe the number of disclosed public-private partnerships increased from 151 in 2011 to 243 in 2012. In addition, in the Horizon 2020 draft regulation the importance for the future of public-private partnerships is also emphasised: “A greater impact should also be achieved by combining Horizon 2020 and private sector funds within public-private partnerships in key areas where research and innovation could contribute to Europe’s wider competitiveness goals and help tackle societal challenges.”

A public-private partnership, in its broadest definition, is any form of intended collaboration between public and private parties. The WHO defines a public-private partnership for health as a: “wide variety of ventures involving a diversity of arrangements, varying with regard to participants, legal status, governance, management, policy-setting prerogatives, contributions and operational roles. They range from small, single-product collaborations with industry to large entities hosted in United Nations agencies or private not-for-profit organizations.” In the European Union a public-private partnership is defined as: “a partnership where private sector partners, the Union and, where appropriate, other partners, commit to jointly support the development and implementation of a research and innovation programme or activities”. A definition for a public-private partnership for health that the authors of this background paper prefer, and which combines elements of both the WHO and EU definitions, is: any informal or formal arrangement between one or more public sector entities and one or more private sector entities created in order to achieve a public health objective or to produce a health-related product or service for the public good. In a PPP, the partners share certain risks and may exchange intellectual property, financial, in-kind, and/or human resources in any mutually agreed proportion.

Traditionally, most research and product development was carried out in the private sector, including pharmaceutical and biotechnology companies. Recently, a broadly felt understanding has developed that the traditional way in which pharmaceutical R&D is organized does not adequately address current medical needs and public health challenges, output of medicines has remained constant despite increasing investments. At the same time, demographic and societal trends will lead to increasing health care needs and a growing disease burden for conditions for which limited or no treatment options are available which creates a demand for new medicines developed in a different way.

Additionally, some research and development priorities are not met by pharmaceutical and biotechnology companies because the potential number of patients using a new drug would be limited or there is no economically viable market, or accessing the market is too complex to warrant investment. This is especially the case for neglected tropical diseases, but is
becoming the case for traditional European therapeutic areas such as Gram-negative bacterial infection and psychiatric disease.

Governments and other public actors have an important stake in resolving this double ‘innovation crisis’. In addition to the imperative to address public health needs, a thriving pharmaceutical sector is an important economic asset: it creates a significant number of (knowledge intensive) jobs and is a source of high economical, added value. For these reasons, governments can use public funds as a leverage to align research activities to healthcare needs and to attract private investments. Financial support from government increases the likelihood that private firms will cooperate with public research organizations. The increased ‘knowledge flow’ between the various partners that is potentially one of the results of collaboration that is essential for economic growth.

Public-private partnerships have been mentioned as a ‘disruptive strategy’ to remove bottlenecks in pharmaceutical R&D and as an important element in the road forward to maximize the impact of biomedical research. External partnering and internal capabilities are traditionally considered as complementary rather than substitutes for one another. In a more collaborative innovation model, companies look outside their boundaries for ideas, IP and partnering opportunities. In this way, the cost of developing innovations internally is reduced, and the balance between cost and revenues is improved.

PPPs can be seen as part of the movement towards open innovation models: “a paradigm that assumes that firms can and should use external ideas as well as internal ideas, and internal and external paths to market, as the firms look to advance their technology.” The rise of the open innovation model has been heralded as one of the most important developments in the research-based pharmaceutical and biomedical industry of the past decade. Additionally, PPPs can also play an important role in undertaking drug development for neglected tropical diseases.

This background paper will discuss the more important developments since the 2004 Priority Medicines Report and highlight priorities for future research. The paper consists of six sections. The first section is this introduction. Section 2 focuses on the main arguments for setting up PPPs. Section 3 describes the different types of PPPs. Section 4 highlights some of the main current challenges for PPPs. Section 5 discusses main challenges we see for the future: proper measurement of the performance of PPPs. Section 6 closes this paper and provides some general conclusions and research recommendations.

Below we will use as examples European PPPs that focus on pre-competitive research (such as the Innovative Medicines Initiative [IMI] at the EU level and Top Institute Pharma in The Netherlands), and PPPs that focus on the development of products for neglected tropical diseases (such as the Medicines for Malaria Venture [MMV] and the Drugs for Neglected Diseases Initiative [DNDi]). These two groups of PPPs are described in more detail in Section 3 of this paper. In practice both type of organizations undertake (pre-)clinical and late-stage development.
2. **Rationale for setting up PPPs**

There are several important other reasons for setting up PPPs (both with a pre-competitive and a product development focus). These include: increasing scale, sharing risk, focusing research and development priorities, optimizing use of available knowledge resources, fostering a more competitive private sector to promote economic growth and addressing topics that require a neutral/multi-stakeholder environment.

2.1 **Increasing scale at critical stages of drug development**

Pooling of resources can help to address issues that cannot be addressed by a single entity. For example, because the knowledge or expertise that is needed to answer a question is not available in a single company or institute, or the scale of the activities required is too large. Additionally, PPPs can also help to reduce the amount of duplication and facilitate knowledge transfer.

Attrition rates in drug development are high, especially for drugs in early clinical development (phase I/II). For example, only 11% of drugs that enter Phase II and 66% of drugs that enter phase III will reach the market.\(^{17}\) This is the case both for diseases prevalent in high-income countries, and for diseases in low- and middle-income countries. Therefore, apart from initiatives that aim to resolve the attrition rates in clinical development, there is a need to have a sufficient number of high quality candidates entering the pipeline. Public-private partnerships can play an important role in this respect by leveraging resources and creating synergies.

A recent example is the European Lead Factory PPP project that was launched in 2013 through the Innovative Medicines Initiative (IMI).\(^{18}\) A key tool in the earlier stages of drug development is a technique called High Throughput Screening (HTS), in which compounds are screened against potential targets for pharmacological activity. For modern high throughput screening advanced machines are needed that are generally only available within pharmaceutical companies. The same holds for large compound libraries. As a result of this, drug targets developed within academia are rarely screened against large compound libraries. This lack of scale may have hampered drug development. This PPP consortium has set up a large screening centre in which a selection of 500,000 compounds, including high-quality industrial compounds, can be screened annually against promising targets through 48 HTS screens. This project is an important project to watch as such large scale public-private collaboration on HTS has not been seen before in Europe at such a scale. One of the key challenges of the consortium will likely be to assure that such a large consortium can operate as a whole and challenges surrounding IP and its utilization can be tackled.

Moreover, the experience gained with screening consortia such as these can also help to further strengthen R&D in neglected diseases, where current screening, lead identification, and optimization programs are significantly below what is required to yield a registered drug.\(^{19}\) The lack of availability of high-quality compound libraries and the resources and expertise to support the prioritization and analysis of any hits is a well-known problem in this field and is being addressed.\(^{20}\) For example, in the area of neglected diseases DNDi has set up a screening consortium in collaboration with Institut Pasteur Korea with the aim to
identify novel compounds, using libraries from various companies with over 350,000 compounds, for Chagas, visceral leishmaniasis and human African trypanomiasis.\textsuperscript{21}

Also, in 2009-2010, MMV and its academic and industry partners screened six million compounds from some of the world’s major compound libraries (GSK, Novartis Institute of Tropical Diseases, St Jude Children’s Research hospital, Rutgers University), yielding more than 25,000 new chemical starting points. Data from this screening exercise has been placed in the public domain to expedite the discovery and development of future antimalarials. In addition, 400 of the most promising compounds with the broadest cross section of structural diversity comprise MMV’s Malaria Box, that has been sent free of charge to over 150 researchers across the world in a bid to catalyse malaria and neglected disease drug discovery and research.\textsuperscript{22}

### 2.2 Sharing risk through public funding

By sharing risks, for example by government involvement, projects can be made interesting for parties for which, without a subsidy or support, would be unwilling to get involved (for example, repurposing of existing drugs).\textsuperscript{23}

An important aspect of the sharing of risk is the pooling of resources. For example, in the Dutch Technological Top Institute (TTI) model resource sharing is done through a 50% government, 25% public partner (e.g., academia) and 25% private sector (large companies and SMEs) contribution.\textsuperscript{24} When projects move further along the development pipeline, and trust in the ability of the consortium and the partners to deliver, project risk can be deemed to be lower, and the government contribution can be reduced. This may be less relevant for PDPs for neglected diseases.

In the IMI model the European Commission contributes 50% of the funding to a project (cash) and 50% is provided by EFPIA members (mostly in kind).\textsuperscript{25} Public partners that participate in a project can receive EC funding at a 75% funding rate of direct eligible costs (comparable to the EU Seventh Framework Programme). In addition, there is a possibility to claim for actual indirect costs.

For the development for neglected diseases, next to government and companies are private sector donations, from organizations such as the Bill & Melinda Gates Foundation and the Wellcome Trust. The international funding landscape is well-captured by the Global Funding of Innovation for Neglected Diseases survey (G-FINDER) which has been created by Policy Cures.\textsuperscript{26} G-FINDER is currently the primary source for historical multi-year, specified data on funding for research on neglected diseases. One of the important developments since the previous Priority Medicines Report is the sustainability of PDP funding for neglected diseases. The most recent neglected diseases research and development five year review\textsuperscript{27} shows that of the total funding in the form of grants of about 2 billion US dollars (2011) 20.8% goes to PDPs. Product development partnerships received 451.5 million US dollars in 2011. Four PDPs received somewhat over half of all PDP funding: Program for Appropriate Technology in Health (PATH), Medicines for Malaria Venture (MMV), International AIDS Vaccine Initiative (IAVI) and Aeras. On the donor side, funding sources also quite concentrated, four organisations (the Gates Foundation, UK DFID, USAID
and Dutch DGIS) have provided over three quarters of the funding during the period 2007-2011.
PDP funding peaked in 2008 with 580 million US dollars. The decrease since then has been caused by ‘rational’ cuts (e.g. on completion of clinical trials), artefacts (disbursement of funds for multi-year periods) but also a freeze or decrease on the side of some funders. Some of these cuts came from the Gates Foundation, but the most striking shift has been the reduction in funding from aid agencies and the increase in funding from science & technology agencies such as NIH and the European Commission. Overall, the G-FINDER report characterises the funding situation for PPPs as “steady overall but with significant changes in funding sources.”

2.3 Agenda setting

By defining a strategic research agenda, in consultation with stakeholders, resources can be focused on questions of particular public health interest. These research agendas form the basis for the implementation in calls for proposals.

For defining this research agenda, several approaches can be taken. They can be focused on an explicit priority health care need approach. This approach was taken with the TI Pharma program in the Netherlands, which based its research program on the 2004 Priority Medicines Report from authored by the World Health Organization. Based on this report, a portfolio was built bottom-up which also included a number of projects with a focus on neglected tropical diseases.

The IMI has formulated a Strategic Research Agenda adopted by the IMI Governing Board (representing the European Commission and EFPIA) and which is based on extensive consultations with stakeholders and forms the basis of calls for proposal that are used to build the portfolio. In the IMI set-up EFPIA members have a strong role in the identification of research topics. The rationale behind this is that in this way IMI can assure that the research agenda efficiently addresses gaps in drug development.

In general, project selection in PPPs takes a number of steps that are comparable for most PPPs. Five steps can be discerned:\(^{28}\)

1. definition of the research topics (e.g. through a Strategic Research Agenda);
2. launch of a call for proposals;
3. submission of expression of interest/short proposal by applicants.
4. invitations to write full proposal based on peer review
5. final grant agreement and start of consortium.

Within this general set-up there are numerous differences. For example, while in some PPPs a full ‘consortium’ applies, in other set-ups this is not the case. For example, in IMI the expression of interest is submitted by the public partners and full consortium formation, and writing of a full proposal, takes place later with a broader involvement of partners in this process.

2.4 Focusing R&D activities

One of the important advantages of working through PPPs is the possibility to focus resources on potential ‘winners’ and act as a focal point for efforts. MMV has played an important role in this respect when it comes to the selection and progression of candidate
update on 2004 background paper, bp 8.1 public private partnership

products for malaria. mmv handles a full portfolio of malaria drugs at different stages of development and has played a key role in funding promising projects and bringing them forward to overcome critical hurdles in development.\(^{29}\)

another striking example from outside of the therapeutic medicine field, is the rtS,S/AS01 vaccine for malaria, which has been developed through a long-standing public-private partnership launched in 2001 between GlaxoSmithKline (GSK), Program for Appropriate Technology in Health (PATH), Malaria Vaccine Initiative (MVI), and the Bill and Melinda Gates Foundation (the Gates Foundation). PATH MVI then co-finances the development with grants from the Gates Foundation, contributes to technical and management decision-making, and supports infrastructure development at the clinical trial sites.\(^{30}\) The aim of the collaboration is to achieve the licensing of rtS,S/AS01 and to enable its use, particularly in infants and young children. Published figures suggest that MVI has contributed more than US$ 200 million in funding from the Gates Foundation to the development of rtS,S. GSK has made an investment, according to self-reported data, of more than US$ 300 million to date and expects to contribute at least another US$ 200 million to complete the project. This would include costs for FDA approval, but excludes potential post-marketing studies.

2.5 Optimizing use of available knowledge and resources

To make progress in many areas, data or expertise that resides with different parties has to be brought together. Also, PPPs can be used to create a research infrastructure for future work (networks, biobanks, research databases, etc.).

This can be done through the creation of certain standards for research. An example from the Alzheimer field is the Critical Path Coalition Against Major Diseases (CAMD) that, together with the Clinical Data Interchange Standard Consortium (CDISC), created a standard for collecting, storing and interchanging Alzheimer clinical trial data. Up until now, seven companies have remapped and shared existing clinical trial datasets to facilitate Alzheimer Disease research. The database currently includes de-identified control arm data of about 6500 patients from 24 clinical studies in Alzheimer disease and Mild Cognitive Impairment.\(^{31}\)

research on the performance of PDPs for neglected diseases showed that industry working alone and public groups working alone performed more poorly, in general, than public–private collaborations.\(^{32}\) Metrics that were used in this analysis include health outcomes for target country patients, level of innovation, speed of development and cost-efficiency. On all these measures PPPs performed very well. Although the data used is already several years old (2005), we believe that the findings are still valid. As one reviewer of this background paper commented: “there is a first analysis in the same report showing that Europe’s Poverty-related and Neglected Diseases (PRND) R&D investment has contributed to the creation of technologies that not only save lives and money in the developing world, but have also generated significant value within Europe. Between 2007 and 2010, for every euro that Member States and the EC gave to PRND R&D, approximately 66 euro cents were reinvested back into Europe, going to researchers and product developers working in European laboratories, universities and companies to unravel the science of PRNDs and develop new products to combat them.”

8.1-10
2.6 Foster a more competitive private sector to promote economic growth

Governments that support PPP research can also aim to support new R&D activities within their region or country. In this way, PPPs both aim to address medical need, and generate new economic activity. From a different perspective, this is also an important goal of many of the PPPs in the neglected diseases field.

While this dual goal of addressing medical needs and generating economic activity is often a stated aim of public support for PPPs, this is an area in which additional research is still needed to quantify these benefits. One of the reasons for the lack of information is that PPPs are relatively new in the biomedical sector. However, there are best practice examples from other industry sectors that illustrate these considerations. Imec in Belgium is such an example. It was set up as a partnership to address the increased R&D costs in the microelectronics and semiconductor industry. With imec running for more than 25 years its success can be directly measured by the multiplier on the public investment made: started in 1984 with more than 90% subsidy, it reached a multiplier of more than five in income generated from contract research on its subsidy of €53 million in 2009. The stamina of the Belgium government continuing its investment in imec is now paying off, but it took 12 years before the subsidy part was lower than 50%. In addition, the long time horizon has allowed imec to identify the ‘true winners’ and to set up fruitful cross-disciplinary projects.33,34

Additionally PPPs can help to improve R&D capacities in low- and middle income countries. This was one of the rationales behind the African Network for Drugs and Diagnostics Innovation (ANDI). The mission of ANDI is to “To promote and sustain African-led health product innovation to address African public health needs through efficient use of local knowledge, assembly of research networks, and building of capacity to support economic development.”35 One of the activities that are undertaken to support this mission is the formation, coordination and funding of partnerships with public and private players. The rationale behind ANDI is that significant R&D capacity exists in Africa, but that consolidation and coordination is needed and that research agendas should closely align with African health problems. Moreover, collaboration within Africa is lacking as most partnerships that do exist are with organizations in Europe and the United States.36,37 Assessing the impact of initiatives such as this seem valuable.

2.7 Address topics that require a neutral/multi-stakeholder environment

To make progress on some issues, a ‘neutral’ environment has to be created. A partly publically-funded consortium can be a tool for such a structure. An example could be topics in the regulatory arena and in which regulatory authorities (should) play a role, but input from industry is also needed.

Recently, the IMI has launched a call that focuses on the use of real-life data in drug development.38 The main output of this proposed project is a set of decision frameworks and tools to assist regulators, HTA bodies and decision makers in industry to make a better assessments about the relative effectiveness of new medicines. This could also contribute to a more efficient design of clinical trials thus reducing patient burden, costs and development times. This is a topic that addresses the need for innovation in the regulatory and HTA/reimbursement field (See Chapter 8.2 and 8.3). Future projects may also focus on this.
area, for example, when it comes to piloting new developments in the field of the regulation of medicines, such as adaptive licensing.

Such ‘systems innovation’ projects, seem promising and should be further monitored and expanded. One of the main challenges in these projects is to strike a balance between public bodies as ‘participants’ in partnerships, without the risk of ‘binding’ themselves too much for future policy decisions and allowing sufficient room to manoeuvre. One could also envision that these types of projects will have a broader scope and also could involve global players (e.g. from the United States, European Union, Japan and emerging countries). One of the challenges for the future of PPPs is to identify which type of project is best suited for inclusion in a programme.

3. The place for different types of PPPs in the R&D process

In general two different types of PPPs in the life sciences can be identified based on their focus on different parts of the medicines development pipeline, though in practice the two types often stray across what are artificial boundaries. Additionally, both of these PPPs often take on projects that focus on concept development and overall systems strategy.

3.1 Research partnerships focusing primarily on early stage R&D

These initiatives support early stage innovation or create technology platforms in high priority disease areas. Examples of this type are the Top Institute Pharma in the Netherlands which was launched in 2006 with a total funding of € 260 million and which has used the 2004 Priority Medicines Report as the foundation for its research programme; and the Innovative Medicines Initiative, which was launched in 2008 with a total funding of € 2 billion, at the EU level. Both these examples are discussed in more below.

Often these initiatives focus on so-called ‘pre-competitive’ collaboration. Pre-competitive research can be defined as “science participated in collaboratively by those who ordinarily are commercial competitors.”

Pre-competitive research can take different shapes. For example it can mean preclinical development, phase I or IIa trials or working on new concepts such as developing new enabling technologies such as RNA interference (RNAi) and identifying biomarkers to aid in predicting patient benefit and risks.

A trend can be observed in which PPPs such as IMI are moving beyond this traditional ‘narrow’ definition of pre-competitive research. First, PPPs have also moved into projects aimed at proof-of-concept for the action of lead compounds and even late phase pre-registration trials in areas of high societal need. An example is the New Drugs for Bad Bugs (ND4BB) initiative by IMI. Part of this initiative is COMBACTE (Combatting Antimicrobial Resistance in Europe) a project with a total budget of €194 million which includes designing and implementing efficient clinical trials for novel antibiotics. The COMBACTE project focuses on addressing the barriers to clinical development. Two key outcomes of the project will be a European clinical trial network and a pan-European laboratory network, which will deliver epidemiological information and data from microbial surveillance work to guide the
selection of clinical trial sites. COMBACTE aims to generate innovative trial designs to facilitate the registration of novel antibacterial agents. It will also design and validate tests to support the diagnosis of patients, identify the most appropriate treatments, and monitor the patient’s response. As such, if COMBACTE is successful, it could play a pivotal role in addressing both the issue of growing antimicrobial resistance as well as the dearth of new antibiotics.

Public-private partnerships such as IMI are a relatively new model for collaboration in the development of medicines. Many of such partnerships face a challenge in that funding timelines are often short and it can take a long time (5-10 years or more) to see the impact that such research partnerships can have on the development of drugs or diagnostics that reach patients. Reconciling this tension between short term funding and long term scientific commitments will be necessary for these partnerships to fulfil their great potential.

3.2 Product development

Product development partnerships focus activities on concrete medicinal products, in many cases to treat diseases of low- and middle-income countries. These partnerships operate in a different environment. The term pre-competitive does not seem to fit these types of partnerships as there is limited competition without outside support.

Examples in this area are the Medicines for Malaria Venture (MMV), the Foundation for Innovative New Diagnostics (FIND) and the Drugs for Neglected Diseases initiative (DNDi).42, 43, 44 Partnerships focusing on malaria, tuberculosis other neglected tropical diseases as well as diagnostics for neglected diseases have had considerable success since the 2004 Priority Medicines Report. While the previous report indicated challenges for these partnerships with respect to the sustainability of funding, the present outlook for many of these PDPs is that, if they deliver on their targets, access to funding should be expected, notwithstanding the impact of the financial crisis.

3.3 Concept development and overall systems strategy

Both types of PPPs can also play an important role in overall discussions and contribute to systems reform. Many broader issues in pricing, market authorization or sustainable models for innovation can only be addressed in projects that involve all stakeholders. These kind of projects could potentially have a broader scope and also involve global players (e.g. the EU, Japan, the United States and emerging market economies). Examples are the Escher Project from TI Pharma and the seventh call for proposals from IMI which called for a project on incorporating real-life clinical data into drug development.38, 45 Such ‘systems innovation’ projects, appear promising and should be further monitored and expanded.

There are several additional forms of public-private collaboration, such as public supply partnerships. For example, the Supply Chain Management System managed by the Partnership for Supply Chain Management which focuses on providing a reliable, cost-effective and secure supply of products for HIV/AIDS programmes from PEPFAR.46 These partnerships are not discussed here as they fall outside of the scope of this Report.
4. Challenges for PPPs

Within PPPs, irrespective of their overall goal, several challenges can be identified. These are more prominent for PPPs in early stage R&D as we have more limited experience in this area.

4.1 Timelines and sustainability

PPPs generally receive tranches of funding for a three to five year period. Given the long timelines in drug development, this amount of time may be insufficient to achieve the development of new compounds and targets: true value may only be demonstrated after more than 10 years. For PDPs the situation is different in that most funding comes from foundations and development agencies which all have shorter funding cycles than ministries of science & technology and the EC, which usually funds for longer periods.

At the moment, for government funded PPPs, funding cycles are often linked to regular funding cycles for policy programs, in general for a four or five year time period. In the life sciences, this is generally too short a timeframe to make a valid assessment about the success or not of a PPP programme. TI Pharma can serve as an example, although the Dutch government heavily invested in this PPP programme with initial funding of €130 million (2006), follow-up funding in 2010 was of a far smaller scale (€6 million). This means that a program of the scale that was set-up in 2006 cannot be continued, and creates the risk that the potential value that was created through this collaboration (also for projects in the area of neglected diseases) will be lost.

4.2 The role of Small and Medium Enterprises (SME)s and large companies

Properly engaging SMEs is especially important to achieve economic targets (e.g., nurturing new companies, job creation). This aspect of economic development is important to the EU and many other countries.

For IMI, in the project resulting from the first five IMI calls, SMEs accounted for 14.8% of all participants, and received 22.1% of the financial contribution. However, one of the recommendations from a recent report from an independent expert panel on IMI was that ways to strengthen SME involvement should be explored. This also means that the opportunities for non-EFPIA companies to participate in ‘IMI2’ should be opened up.

4.3 Consortium leadership and project management

Managing partnerships requires a different set of competences and skills than managing regular research projects. Capacity building for this skillset is of critical importance for any PPP to be successful.

Additionally, successful public-private partnerships also create a situation where persons working on the project should be aware of differences in culture and expectations with the different partners involved. For example, academic researchers may be used to more freedom in defining goals and adjusting projects, while in companies this is more strictly
controlled and regulated. Working in these two different cultures also requires specific skills from project and programme managers involved in PPPs. Therefore, creating ‘awareness’ of these cultural differences and giving participants the opportunity to learn the skills required to be successful in such a setting, e.g. through a dedicated education and training program, should be part of a PPP support programme.

4.4 The role of the central entity

A central entity or ‘office’ plays a key role in any PPP. Most PPPs work as ‘virtual organizations’ with activities being outsourced to academic or private sector partners. The role of the PPP organization is to play a role as a neutral entity, trusted third party or honest broker. The main responsibility of the central entity is the proper functioning of the individual public-private projects managed by the programme. As such, the central entity needs to balance the interests of academia, companies (both large companies and SMEs) and public funders in order to achieve a successful outcome of the project. Through its activities, the central entity bears a large responsibility for the success of the programme. The central entity needs to be able to assure that the project selection process is of sufficient quality and that the right projects are selected. Additionally, the central entity should be sufficiently empowered to monitor progress and to intervene where necessary.

Moreover, the central office requires strong leadership that has an excellent network in the field and is able to allow the PPP programme to be attuned to developments in the field. This allows the PPP to build a portfolio of products and requires designing tailored portfolio management strategies. Good examples of these strategies can be found in many of the PDPs for neglected tropical diseases.

As an example, the Drugs for Neglected Diseases initiative aims to establish a R&D portfolio that covers the discovery process, from early-stage discovery to clinical development and distribution for kinetoplastid diseases such as human African trypanosomiasis, leishmaniasis, Chagas and diseases such as malaria, paediatric HIV and helminth infections. DNDi divides its portfolio into five categories and hereby creates a portfolio with a long, medium and short-term approach: (i) new drug candidates identified through screening and lead optimization efforts, (ii) new molecules with an existing data package (“low-hanging fruits”), (iii) new indications for existing medicines, (iv) new formulations and combinations of existing drugs, and (v) existing drugs for target diseases (e.g., extensions of registration, completion of dossier). In addition to a number of screening projects for all kinetoplastids disease, DNDi has nine projects in a pre-clinical stage, 11 projects in clinical development and six projects at an implementation stage.

MMV has built a comparable portfolio in the field of malaria. In Q1 2013 the MMV portfolio contained about 37 projects at the research stage (lead generation & optimization) stage, 9 projects at the translational stage (preclinical, Phase I, Phase IIa) and 12 projects at the development stage (Phase IIb/III, Registration, Phase IV) stages. For the purpose of building and managing this pipeline, which consists of projects with multiple public and private stakeholders, both DNDi and MMV have built up significant capacity and experience ‘in house’. For an in depth discussion of malaria and development of new therapeutic products in that field, please consult Background Paper 6.10.
4.5 Intellectual Property (IP) structure and management

The goal of many PPPs is to generate innovative insights into diseases and their diagnosis or treatment. How intellectual property is handled in the consortium is of key importance and provides an important reason for partners to participate or not. In the classical drug development model the monetization of IP is one of the core incentives for medicines development. Within a PPP, some form of mutually beneficial arrangement has to be made that creates the right incentives, and lack of disincentives, for partnerships.

Although it is outside the scope of this paper, and the expertise of the author, to give an in-depth analysis of the various aspects of intellectual property rights in the context of research partnerships, some general observations can be made.

Before the start of any consortium, clear agreement about how IP (both background and foreground) is treated in the consortium must be established. Some PPPs favour a more clearly defined approach in which strict ground rules exist that apply to all consortia, others take a more case-by-case approach. For example, IMI favours the latter approach. A second issue is: who in the consortium will be the ‘owners’ of any foreground IP that is generated. These could, for example, be the participants who generated the foreground IP (with access rights to other consortium members for work within the context of the consortium), or IP could be jointly owned by the consortium. In the latter case, the central entity in a PPP sometimes is also co-owner of the foreground IP. For example, in the TI Pharma model, TI Pharma itself would have a 10% stake in any IP generated, the rationale behind this is that in such a way, TI Pharma is a full partner in the negotiations about the IP and has a role in seeing to it that IP was used in a manner supportive of the original goals of the consortium.

For partnerships that focus on products for neglected diseases, the main aim is that any products are available and affordable to patients in all endemic countries. This is clearly outlined in the IP policies of, for example, DNDi and MMV. Both MMV and DNDi take a pragmatic approach to IP policies, and assess on an individual basis what best suits the needs to achieve the goal of the partnership. In the words of MMV: “MMV has found that flexible, results-oriented approaches to dealing with IPR best serve their use as a tool to form and manage collaborations that can further MMV’s public health mission.”

DNDi, from 10 years of experience have identified a ‘gold standard’ of licensing terms to ensure equitable and affordable access to patients, which can be summarized as follows:

- perpetual royalty-free non-exclusive sub-licensable licenses in the specific disease areas determined in the contract;
- worldwide research and manufacturing rights;
- commitment to make the final product available at cost, plus a minimal margin, in all endemic countries, regardless of income level;
- non-exclusive licensing agreements.

The way in which IP is treated in different PPPs is still a field that would benefit from research investments to identify the range of practices and what types of IP arrangements work best for which objectives. For example, IP rules may play an important role for SMEs, as they are often active in a limited number of therapeutic areas and/or technologies. Safeguarding their IP position is, therefore, of key importance to the sustainability of the
company and the IP set-up will play an important role in their decision-making about participating in a PPP.

5. **Performance measurement**

To assess whether public-private partnerships succeed in their approach of collaboration and achieving their targets from the perspective of the funders, measurement of the activities of PPPs is essential. Especially from the perspective of public stakeholders, it is critical to justify the use of public funds. This need for agreed key performance indicators is also reflected in article 19(e) of the draft Regulation for the establishment of Horizon 2020.\(^3\) For PDPs, products produced and patients treated are ‘hard’ outcome measures but these would not apply to PPPs focusing on early stage R&D. However, methods by which the added value of a PPP in pharmaceutical sciences can be measured, is still a relatively unexplored terrain. At this moment, value measurement protocols of PPPs, in particular for early R&D, often use measures that are used for traditional evaluations of research, such as citation scores.\(^55\) Although such measures are important, for a full evaluation of the performance of PPPs a more holistic approach is needed.

A key challenge for partnerships is to measure what the real added value of the partnership. This is important from the perspective of the efficient and responsible allocation of their different resources.\(^56,57\) Pardoe et al. provide three ‘core principles’ that should ensure that a scoring method is valuable and relevant for a R&D partnership. These principles are also applicable to PPPs:\(^56\)

1. Enable meaningful comparison of partnerships: partnerships can focus on all stages of R&D, therefore, comparing cost-per-deliverable should be done with caution;
2. Apply weighting profiles to highlight important factors: some elements are more important than others. Each element must be weighted according to its individual importance to the partnership;
3. Recognise that the value a partnership delivers often changes over time: recently started partnerships may not yet be able to deliver full results, while more can be expected from partnerships that start later;

Denee et al. introduced a framework for measuring the value of PPPs in the pharmaceutical sector, taking into consideration the complexities of the operating environment. This has been published elsewhere in abbreviated form.\(^57\) The key table from this paper is depicted below in Table 8.1.1 and explanatory remarks will follow in the text.
Table 8.1.1: Measurement of key indicators for PPPs

<table>
<thead>
<tr>
<th>Input</th>
<th>Process</th>
<th>Output</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Networks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Network coverage in number</td>
<td>Exchange of information between partners (meetings, intranet use, etc)</td>
<td>Percentage of projects continued after PPP funding</td>
<td>Number and size of new partnerships inspired by PPP</td>
</tr>
<tr>
<td>and diversity of partners</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Knowledge</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formal knowledge sharing, e.g. background IP in consortia</td>
<td>Knowledge sharing through personnel exchange and number of consortium meetings</td>
<td>Number and citation score for joint publications</td>
<td>Number of products in clinical development based on (partial) knowledge generated in PPP</td>
</tr>
<tr>
<td><strong>Human capital</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of experts involved, based on citation impact</td>
<td>Percentage of researchers trained via PPP specific courses</td>
<td>Percentage of completed PhD's and post-doctoral positions</td>
<td>Percentage of trained researchers working in (R&amp;D) positions in the sector</td>
</tr>
<tr>
<td><strong>Financials &amp; operations</strong></td>
<td>Total research funding available in partnership</td>
<td>Percentage use of intranet on regular basis by researchers &amp; staff</td>
<td>Percentage of milestones achieved in consortia</td>
</tr>
</tbody>
</table>


5.1 Stages

Performance of PPPs can be measured at different stages. In general, we identify four stages for indicators: input, process, output and outcome.

An input indicator can be defined as “the human, financial, and physical resources received to support programs, activities, and services.”58 The input indicators should measure the ability of the PPPs to bring together the people, funds and knowledge to create the network for public-private collaboration. Measurement of input is most useful at partnership level, covering all projects. This can include quantitative (e.g. funding) and qualitative measures (e.g. types of stakeholders involved).

A process indicator can be defined as “the means or method used to deliver programs, activities, and services.”58 Process indicators should measure how the different parties in the partnership work together. These indicators should be used to monitor the R&D progress at the individual project level. In addition to measuring operational aspects, one also wants to measure in more detail how knowledge and resources are shared in the partnership.

An output Indicator is defined as an indicator that reflects “the quantity of products or services actually produced”.58 Output indicators express the results of projects in the short term. Measurement of output should be closely related to the input, and should also be undertaken at partnership level. Furthermore, the focus should be on the actual use of knowledge created in a PPP and not just the ‘production’ of knowledge. Thus, merely
counting the number of scientific publications or patents is insufficient, it is what is being done with the publications that matters (e.g., by looking at citations).

An outcome indicator is defined as an indicator that reflects “the quality of the benefit for or impact on stakeholders of programs, activities, and services.”\textsuperscript{57} Outcome indicators show the eventual social and economic impact of the PPP, and thus provide useful information when measured at program level. Preferably, all outcome indicators are translated into clear measures of value, e.g. costs saved and QALY gained. However, it is very difficult to link an ultimate outcome directly to the work of a PPP, especially when you have to take into account the pre-competitive nature of the research. Consequently, most outcome indicators can therefore only be shown and measured by case examples and expert analysis.

5.2 Domain for measurement of valued
The four domains for creating value encompass the incentives for collaborating in a PPP. Although the exact definitions may vary, and therefore also the indicators, we believe that the domains identified below have a certain level of generalizability.

Networks – A main driver for stakeholders to participate in a PPP is the network created by the bundling of parties in the partnerships. The public private platform serves as a bridge between the various stakeholders.

Knowledge & expertise - Access to new techniques and proprietary knowledge to tackle biomedical problems is another important driver for collaboration.\textsuperscript{59,60} Output measurements for PPPs often focus on this domain.

Human capital - Next to formalized knowledge in the form of, e.g., Intellectual Property (IP), tacit knowledge or “know-how” is very important.\textsuperscript{61} Therefore attracting the right people to make a success of the project is crucial. In addition, the training of a new generation of biomedical researchers is critical to transfer and disseminate knowledge, and often an important driver for participation, for example by industry.

Finance & operations - The eventual economic benefits which should arise from partnerships are an important driver to participate. This could be realised by joint risk sharing and, of course, the ultimate outcome of the research: a new product or a process innovation. The financial contribution of governments can also form an important driver to participate in public private partnerships as it creates a multiplier. However, one of the main research challenges is that these multipliers are often hard to quantify in a robust manner.
6. Conclusions and recommendations for future research

As has been said earlier, PPPs in early stage R&D are a relatively new development. Although there is some experience with this model for collaboration, we are in the early stages and still have a lot to learn.

For PDPs that focus on neglected diseases, the situation developed positively since the last Priority Medicines Report. Concerns about their sustainability have been overcome. Although the funding situation is stable, with some reductions in funding in recent years, the overall picture is positive.

We believe that in terms of research recommendations, some general recommendations can be made that are relevant for both types of PPPs discussed in this background paper.

For future research, our key recommendation is that we need to learn more about what constitutes successful models for PPP collaboration. At this moment little is known about what constitutes proper measures for assessing successful public private collaboration. This is an area in which industry, governments and academia have to invest, in particular by the sharing of information and experience. Knowledge about what are the most useful structural, process, output or outcome indicators of successful partnerships would be beneficial for all partners involved.

When we know more about what constitutes a successful partnership, apart from better prioritisation, this will also allow us to make realistic assessments of what can be achieved with the resources invested (goals/objectives). At this moment, it is unclear what can actually be achieved within the funding timeframe of a typical PPP programme. Also, it can help us to identify which projects are most suited for PPPs.

As is also discussed in Chapter 8.5, the involvement of patients and citizens is a topic of specific interest. How stakeholders such as patients can be involved in PPPs is another topic for future research. Furthermore, the optimal ways for involvement of SMEs in agenda setting, and in the actual research work also warrants further investigation.

Public-private partnerships are playing an increasingly important role in pharmaceutical R&D. When the previous Priority Medicines Report was published they were still in their early stages. At this moment, we have about one decade of additional experience. However, we are still in the early stages of this innovation model and we have much to learn about how we can unlock the full potential of PPPs and how they can optimally serve public health needs.

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Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper

Background Paper 8.2
Regulatory structures
to support pharmaceutical innovation

Towards a marketing authorization system that better supports pharmaceutical innovation and addresses priority health care needs;
Recent developments and research priorities

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Preface .......................................................................................................................... 3

1. Developments in the overall marketing authorization system ..................................... 7
   1.1 Adaptive approaches to marketing authorization ..................................................... 8
   1.2 Key policy priorities from regulatory agencies ....................................................... 9

2. Developments in key components of the system .......................................................... 10
   2.1 Evidence generation and requirements .................................................................. 10
   2.2 Benefit-Risk assessment ....................................................................................... 14
       2.2.1 Initiatives to improve benefit-risk assessment ................................................ 14
       2.2.2 Quantitative instruments for benefit-risk assessment ...................................... 15
       2.2.3 Opportunities of quantitative benefit-risk assessment instruments .................. 16
       2.2.4 Challenges for implementation ...................................................................... 16
   2.3 Scientific Dialogue ............................................................................................... 17
       2.3.1 Types of interaction between pharmaceutical companies and regulatory authorities .... 18

3. Development in specific regulations ........................................................................ 22
   3.1 Specific disease categories: rare diseases, neglected diseases and unmet medical needs .... 22
       3.1.1 Regulatory incentives for rare diseases .............................................................. 22
       3.1.2 Neglected tropical diseases and collaboration with the World Health Organization .... 24
       3.1.3 Diseases with unmet medical needs .................................................................. 25
       3.1.4 Antimicrobials ............................................................................................... 26
       3.1.5 Specific patient groups: paediatrics, elderly and women .................................... 27
       3.1.6 Paediatrics ..................................................................................................... 27
       3.1.7 Elderly ............................................................................................................ 29
       3.1.8 Women .......................................................................................................... 29
   3.2 Specific products: advanced therapy medicinal products ......................................... 30
       3.2.1 The ATMP regulation: scope and objectives .................................................... 30

4. Developments in the context of the regulatory system ................................................. 32
   4.1 Collaboration with Health Technology Assessment bodies ..................................... 32
   4.2 Globalization of regulatory requirements and decision-making ............................. 34
   4.3 Patient involvement in regulatory decision-making ............................................... 35
   4.4 Integration with devices and diagnostics ............................................................... 35

5. Conclusions and research priorities ......................................................................... 37

Reference ..................................................................................................................... 41
Preface

In this Background Paper to the 2013 Priority Medicines Report we describe developments in the system for marketing authorization of new medicines related to pharmaceutical innovation and meeting priority health care needs. In order to support the development of innovative medicines, and to properly address health care needs we propose research priorities for the regulatory system in the coming years. We consider relevant developments at four levels: (1) the overall system of marketing authorization; (2) key components of the system; (3) specific regulations within the system; and (4) broader developments surrounding the system.

The previous Priority Medicines Report was published nine years ago and mentioned a number of issues in the regulatory field, including: innovation in trial design/evidence generation, better communications between stakeholders, the role of patients and the importance of phase IV studies and post-marketing surveillance (see Box 8.2.1).

Box 8.2.1: From the 2004 Priority Medicines Report

“All authors agreed that every aspect of the regulatory process should be re-examined and that the evidence base for regulatory practices should be critically analysed using modern methodologies. In particular, this includes preclinical regulatory ‘rituals’. For clinical research, there is a suggestion from Rawlins that alternatives to randomized controlled trials should be investigated. Under some circumstances, he suggests, historical controls could be utilized and alternative analytical statistical techniques using Bayesian statistics could be used to analyse data. A key recommendation of all the authors is the need to improve communication between industry, physicians and regulators in the regulatory process. What is particularly striking about the EMEA, Rawlins and FDA papers are two significant omissions. Apart from the industry paper, none of the three regulatory papers mention any role for patients in the regulatory process. They are referred to as beneficiaries of the process but never as contributors to the decision-making. This is surprising as patients have been very influential in the rapid authorisation of AIDS medicines and in the orphan drug movement. It is not clear how patients could be most effectively involved in promoting innovation and removing barriers but this is clearly an area for research. The second striking omission is the absence of any discussion of post-marketing surveillance as a critical component of the overall process. The FDA diagram of the stages of the medicine development process omits Phase IV from its description of all of the steps in medicine development (see Figure 8.3.1 in Background Chapter 8.3).”

Work has been done in the past decade on the topics highlighted in the 2004 Report, shown above. Various regulatory authorities now accept the changing role of patients and that they should be involved in the regulatory process. However, more information is needed about what patients can add at the different stages of decision making (see Chapter 8.5 and the related Background Paper). With regard to post-marketing activities, the strengthening of the pharmacovigilance legislation and discussion about adaptive licensing are important drivers.

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*This background paper is partly based on the discussion paper ‘Towards appropriate levels of evidence, a regulatory science perspective on adaptive approaches to marketing authorization’ written in the context of a workshop on 6-7 December in Amsterdam, organized by the Dutch Escher Project. See also: www.escher-projects.org*
for an increasing role for post-marketing studies. While 10 years ago it was not uncommon for important policy documents to exclude the post-marketing phase, today this is rarely seen, and the role of post-marketing (safety) surveillance is well entrenched.

The current background paper will revisit all of the topics from the 2004 report and will also describe completely new developments in the regulatory system. We will start out by providing a brief overview of developments in the overall marketing authorization system, such as ‘adaptive licensing’ (Section 1). Following this, we will describe three key components of the regulatory system (Section 2): evidence generation and requirements, decision making about the benefit and risk balance, and the dialogue between regulators and applicants. Next, we discuss regulations introduced for certain disease areas, patient populations or products (Section 3). In Section 4 we will address broader developments surrounding the system for marketing authorization, such as the interaction between health technology assessment bodies and regulatory agencies, and the integration of medicines, diagnostics and devices. In each of these sections we propose research priorities and in the final section (Section 5) we provide a number of general conclusions on research agendas for the regulatory system.

Although this paper takes the EU regulatory system as a starting point, the discussions here are relevant for developments at a global level. We will mention other regulatory arenas, such as the United States of America, where relevant, or where examples are illustrative.

Figure 8.3.1 – Overview of the sections in this background paper
In this background paper to the 2013 Priority Medicines Report we aim to identify research priorities for the coming years concerning the regulatory system for marketing approval of medicines. Research priorities identified in this paper can help to shape a regulatory environment that is beneficial for pharmaceutical innovation and that addresses priority health needs.

Section 1 gives a brief overview of developments that aim to improve the whole system of marketing authorization, amongst others proposals for adaptive approaches towards marketing authorization. These adaptive approaches propose to replace the single transition from non-approval to approval with a series of approval stages with iterative phases of evidence gathering and regulatory evaluation.

In Section 2 we describe developments in three key components of the regulatory system: evidence generation and requirements, decision-making, and the scientific dialogue. A key challenge for the regulatory system is how to improve efficiency and quality of evidence generation in order to support the development of innovative and needed medicines. Several new methods, such as introducing innovative design features in clinical trials (e.g. adaptive study designs) and the development of surrogate endpoints have been developed that could optimize evidence generation. Piloting and validating these instruments should be a research priority. Research should also focus on assessing the added value, possibly including cost-effectiveness considerations, of existing regulatory requirements and guidelines in order to support a more flexible approach to evidence requirements.

To facilitate the marketing authorization of pharmaceutical innovations, regulatory benefit-risk assessments should be consistent, transparent and predictable for applicants. Several (quantitative) frameworks have been developed that aim to structure, standardize and simplify benefit-risk assessments. Case studies of these (quantitative) benefit-risk instruments are needed to explore the opportunities and limitations for further implementation.

A timelier and more continuous scientific dialogue between companies and regulators could help to implement a more case by case approach to regulatory requirements for evidence, which could support the development of innovative and needed medicines. However, the current practice of scientific advice revolves around getting reassurance of ongoing development plans in the later stages and on interpretation of guidelines. Research priorities would be to identify opportunities and challenges for a more prospective discussion on development plans and whether more binding agreements about clinical study programs are desirable. The initiatives for joint advice with regulatory bodies such as the U.S. Food and Drug Administration and Health Technology Assessment bodies should be evaluated and further explored.

In Section 3 we discuss regulatory initiatives that aim to stimulate pharmaceutical innovation and better address medical needs by focusing on certain disease areas (e.g. orphan and neglected diseases), specific populations (e.g. paediatrics and the elderly), and special products (e.g. advanced therapy medicinal products). These initiatives vary from scientific guidance by specific guidelines, to free scientific advice, commercial incentives such as market exclusivity and special marketing approval pathways. The need for new incentives and the performance of current incentives has to date, not been assessed in a
systematic way. We have collected the scientific evidence that is currently available and recommend conducting such systematic assessments.

In **Section 4** we address several major developments in the context of the regulatory process for marketing authorization, such as the interaction between regulatory agencies and Health Technology Assessment bodies and the role of Notified Bodies, responsible for evaluating devices. Research efforts could focus on making better predictions about relative effectiveness during drug development, at marketing authorization and afterwards. Studying differences in marketing approval decisions between leading regulatory authorities and the practical implications of these differences is also needed. An evaluation of the regulatory procedures for combined devices and medicinal products can indicate whether these are in need of further harmonization.

In **Section 5** we present four overarching messages for the approach of regulatory studies, based on the discussion of current developments and possible research priorities in this paper: (1) continue to test and explore new methods using (pilot) studies; (2) clearly identify expectations and key performance indicators for new regulations and set up prospective studies; (3) set up constructive collaborations and dialogues with key actors and (4) invest in sharing and analysis of regulatory documents. Combining these approaches can strengthen future research agendas that aim to help the regulatory system support the development of innovative and needed medicines.
1. Developments in the overall marketing authorization system

Over the years, an extensive regulatory system has been constructed that covers virtually all aspects of drug development, from early stage pre-clinical development to phase III trials and post-marketing studies. This system has to take into consideration the protection of public health, while at the same time ensuring that patients have timely access to new medicines that address medical needs. Overall, the system has been successful in ensuring that many valuable medicines with a positive benefit-risk profile have reached the market. However, there are also important challenges that this system has to meet in order to ensure a continuous flow of innovative, safe, effective and good quality medicines most needed by society. For example, public trust in the system is frequently challenged by the controversies over timely access to new medicines, medicine withdrawals, and post-approval modifications to labels. Furthermore, the price of innovation is on the rise. Figure 8.2.2 shows that the number of new active substances approved by the European Medicines Agency (EMA), U.S. Food and Drug Administration and Japanese Pharmaceutical and Medical Devices Agency (PMDA) has been relatively stable from 2002 to 2011. However, in the same period research and development expenditures have increased substantially, meaning that the investments per medicine that is brought to the market has also increased.

Figure 8.2.2: Number of New Active Substances approved by major regulatory agencies by approval year in the EU (EMA), USA (FDA) and Japan (PMDA)

An even more important issue is whether the medicines that have been developed are the ones that are most needed by society. In general, portfolio decisions of pharmaceutical companies and research and development strategies are driven by: market opportunity (competitive landscape, reimbursement environment), exploitable scientific knowledge (new targets) and developmental challenges (barriers and the investment of time and resources). The regulatory system plays an important role in the developmental challenges for...
pharmaceutical innovation: amongst others, it sets the thresholds for market approval and steers the development process through its interactions with companies. In order to function optimally the regulatory system has to find the right balance in three key areas:

1. Cautiousness: It can be overly or insufficiently cautious (for example, by not granting marketing approval for a medicine with a favourable benefit-risk profile that could have addressed an unmet medical need, or by allowing unsafe or ineffective medicines on the market). This is especially relevant in the context of a society that is increasingly risk averse, and in which regulatory authorities have to make clear to the general public the rationale for their decisions.

2. Incentive structure: It can lack incentives for pharmaceutical innovation, or can provide incentives for innovations that do not address public health needs.

3. Comprehensiveness: It can add undue regulatory burden through redundant regulation or have regulatory gaps.

1.1 Adaptive approaches to marketing authorization

To find the proper balance in these areas and find ways to accelerate the flow of innovative and important medicines, in the last decade, several ‘adaptive’ approaches to marketing authorization have been proposed by key opinion leaders in the EU and the United States (e.g. staggered approval, managed entry, adaptive approval, progressive authorization, and adaptive licensing).

These adaptive approaches are all based on the premise that knowledge about medicines is not binary but continues to evolve over time (Figure 8.2.3). They propose to replace the single transition from non-approval to approval with a series of approval stages with iterative phases of evidence gathering and regulatory evaluation. Adaptive approaches aim to facilitate early access by approving medicines early, with acknowledged uncertainty about the favourable and unfavourable effects. The appropriate level of uncertainty can be decided on a case by case basis depending on considerations about the therapeutic area, medical need and willingness of stakeholders to accept more uncertainty.

Figure 8.2.3: Transition from existing pathways to a comprehensive vision of adaptive approaches to marketing authorization.

Note: Current regulatory pathways (left hand side) consist of various approaches to balance the moment of market authorization with a certain level of knowledge about the product. Adaptive pathways (right hand side) approach this in a more dynamic manner and allow for more tailoring in the level of knowledge of a product required at marketing authorization.
Adaptive approaches, which incorporate elements of existing pathways, should be seen as a holistic vision of a possible future regulatory system, but incorporate also many elements of existing pathways. For example, in the European Union this includes the regulations/guidelines for Conditional\textsuperscript{8} and Exceptional Marketing Authorization,\textsuperscript{9} the introduction of Risk Management Plans and the recent pharmacovigilance legislation\textsuperscript{10}. In the United States this includes the Accelerated Approval pathway\textsuperscript{11} and the recent proposal for regulations concerning Special Medical Use.\textsuperscript{12}

Although adaptive approaches are attractive options, they also have to confront several challenges. For example, when medicines are initially approved for a restricted population, based on specific evidence for this subpopulation, appropriately defining, targeting and learning from this population during the initial phases after approval to avoid safety issues would require systematic restrictions on prescribing, monitoring of utilization, and interventions to ensure appropriate drug use, including patient adherence. These steps would need to be strong enough to influence the behaviour of patients, physicians, pharmacists, HTA bodies, and reimbursement authorities and to provide sufficient information for policy makers.\textsuperscript{13} In an adaptive approach, a medicine’s regulatory status (authorization and indication) are likely to change over time. This will have implications for pricing and reimbursement decisions, especially when value-based pricing is fully implemented.

Furthermore, ensuring the appropriate conduct of post-marketing studies could be challenging.\textsuperscript{14} Having proper evidence of favourable and unfavourable effects later in the life cycle of a medicine is crucial for being able to allow more uncertainty early in the life cycle. An additional critical issue here is what the regulatory action will be in the event promised studies are not (adequately) performed: restriction of the label could affect patient groups currently taking the medicine and taking no action would undermine the foundation of such an adaptive system. The introduction of the new pharmacovigilance legislation in 2012 may offer the conditions needed for the conduct of additional studies after initial approval.\textsuperscript{15} Over recent years, numerous studies have been conducted on different elements of the regulatory system such as evidence generation for initial marketing approval and the benefit-risk assessment. Adaptive licensing is a strong focus of the NEW Drug Development ParaDIGmS (‘NEWDIGS’) program which studies more flexible, adaptive regulatory models and is launching a series of demonstration and research activities in this field.\textsuperscript{16} In addition, various new trial designs and analysis techniques are being piloted. Meanwhile, other initiatives such as\textsuperscript{17} CASMI\textsuperscript{18} and The Escher Project\textsuperscript{19} have created networks for analysis of regulatory practices and information sharing in Europe. However, a number of topics remain to be studied in detail.

1.2 Key policy priorities from regulatory agencies

The issues described above are reflected in the strategic priorities from various regulatory agencies.\textsuperscript{20,21,22} Table 8.2.1 gives an overview of nine general strategic priorities that were identified by the authors in key policy documents from the FDA and EMA but that can also be found in strategy documents from national authorities.

These strategic priorities tackle the challenges in stimulating innovation and addressing public health needs from a policy perspective. The research topics that are proposed in this
background paper aim to fuel an evidence driven discussion on how these strategic priorities could best be supported and implemented.

Table 8.2.1: Key priorities identified in strategy documents/activities from leading regulatory agencies.

<table>
<thead>
<tr>
<th>Strategic priorities</th>
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<tbody>
<tr>
<td>- Address medical needs and align basic methods to estimate an unmet medical need during drug development</td>
</tr>
<tr>
<td>- Facilitate the development of new methods for drug development and approval</td>
</tr>
<tr>
<td>- Ensure an efficient regulatory approval process</td>
</tr>
<tr>
<td>- Improve the quality of information for regulatory decision making about medicines</td>
</tr>
<tr>
<td>- Improve the quality of the regulatory decision making process for medicines</td>
</tr>
<tr>
<td>- Make regulatory decisions about medicines more transparent</td>
</tr>
<tr>
<td>- Align standards for marketing authorization and Health Technology Assessments</td>
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<tr>
<td>- Stimulate responsible use of medicines</td>
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<tr>
<td>- Strengthen post approval safety monitoring of medicines</td>
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Sources: 20, 21, 22

2. Developments in key components of the system

In this section we discuss three components of the regulatory system for marketing authorization that impact pharmaceutical innovation and the addressing of health needs via a wide number of new products or applications; evidence generation and requirements, decision making about the benefit-risk balance, and the dialogue between regulators and applicants. We describe how these components have evolved in recent years and suggest research priorities.

2.1 Evidence generation and requirements

The amount of evidence about medicines is the result of two major forces: (1) the supply of evidence by companies through development plans, ‘evidence generation’; and (2) the demand for evidence by regulators through regulations and other requirements, ‘evidence requirements’. One of the challenges for the regulatory system is to find an appropriate balance between the need for (more) rapid and affordable access to new medicines and the need to ensure comprehensive evidence on benefits and risks needed for an approval decision. This balance has shifted in the last decades towards an increase in evidence requirements for efficacy and safety and more evidence generation for marketing approval decisions. The regulatory system has therefore been criticized by some as overly cautious in the pre-marketing phase, hampering pharmaceutical innovation. This development indicates a need to critically evaluate evidence generation over the whole lifecycle in order to achieve a more sustainable situation, which is also an important tenet of adaptive approaches to marketing authorization, as described in the first section of this paper. In this
section we identify opportunities from recent research to optimize evidence generation and requirements and provide research priorities for the future.

Evaluating the evidence on efficacy and safety of a medicinal product and evaluating the uncertainties surrounding this evidence is at the core of the regulatory assessment and should be based on scientific methods. An assessment of the internal and external validity of the data (preclinical and clinical data, including statistical uncertainties) that is provided by companies constitutes the key input for aggregated information on a product’s multiple favourable and unfavourable effects and quality. Subsequently, the (clinical) relevance of available information on favourable and unfavourable effects is evaluated and combined into an overall picture of the product’s quality and ‘benefit-risk balance’.

Re-evaluating the added value of studies for medicinal products in various phases of drug development could help optimize data generation. Although different types of studies are required for marketing authorization, regulators often do not make explicit how important a study is for the body of knowledge about a product. Obviously, refraining from conducting studies that contribute little to the body of knowledge could help to reduce upfront data generation. However, this requires insight in the added value of different types of studies at the particular point in time of the development process at which the decision is made to conduct them. For example, recent publications show that appropriate preclinical and early Phase I and II studies contribute significantly to reducing attrition rates and successful marketing authorization. On the other hand, data from animal (toxicology) studies are sometimes of limited value to detect safety issues. Deciding to refrain from conducting studies with limited added value to the assessment of efficacy and detection of safety issues will lead to more uncertainties about a medicinal product’s value. However, in order to stimulate pharmaceutical innovation, besides deciding how much uncertainty is appropriate, a major challenge will also lie in deciding which studies to forego at which moment during development or how these studies can be redesigned.

For the purpose of redesigning studies, many novel methods for trial design and statistical analysis have been introduced that could serve as ways to optimize efficiency of confirmative evidence generation. However, an important point to consider in accepting new methods is that they involve a trade-off between statistical precision and validity and thereby introduce another type of uncertainty: decreased validity. In the words of the CHMP: adaptive designs could render ‘confirmatory’ trials to be considered merely ‘exploratory’.

The internal validity of current clinical trials is ensured by a number of design features, including randomization, blinding (of allocation, patients, treating physicians and measurements), and a thorough follow-up of all patients. Although it is possible to give up some of these design features, this can be problematic for three reasons: (1) it can lead to systematic error (of unknown source) and render results simply untrue; (2) it is unlikely to shorten or reduce the size of studies and therefore does not help early access to the market; (3) it is unethical to enrol research subjects in less rigorous studies because it can mean that their efforts will not contribute to the body of knowledge about a medicine. Nevertheless, a currently used route that sacrifices internal validity is to conduct single-arm and observational studies instead of trials. This has been the basis for the conditional marketing authorization for some cancer and orphan medicines. Still, even for orphan medicines,
randomized controlled trials are preferred by regulators and are in fact supplied in almost 60% of the dossiers.\textsuperscript{27}

Besides the general design features of trials, the use of alternative outcome measures, so-called “surrogate outcome measures”, is also a way to optimize evidence generation. Although surrogate outcome measures can turn out to be inadequate predictors of clinical effects, they hold promise to shorten development timelines, especially for diseases with long-term outcomes.\textsuperscript{38,39} The validation of surrogate outcome measures seems to be high on the research agenda of both EU and USA public-private partnerships\textsuperscript{40,41} and should continue to be so in future. However, the next step is to introduce validated outcomes in regulatory practice. This will require effort from scientists, companies and regulators.

Reconsidering external validity also seems a promising avenue to optimize evidence generation. This line of thinking can be seen in a recent concept guideline by the EMA on ‘extrapolation’. Extrapolation can be done between: population subsets, diseases, animal-to-humans, healthy volunteers to patients, and between medicines, within and between classes.\textsuperscript{42} Studies on extrapolation within and between medicines have shown that this could be a valuable way to reduce uncertainty, without requiring additional data generation. A study that focused on medicines from the same class during marketing approval found that adverse drug reactions of first in class medicines were not always included in the Summaries of Product Characteristics of second in class medicines.\textsuperscript{43} Another study showed that for HIV medicines safety issues were taken into account in the approval process of other medicines in the same class.\textsuperscript{44} Improving this kind of learning could help to achieve a proper level of knowledge about a product while requiring less data to be collected preapproval.

A complementary way to achieve an ‘appropriate’ level of evidence in an efficient manner could be to use guidelines more flexibly and decide more on a case by case basis whether guideline adherence is needed for a specific medicinal product or group of medicinal products. However, a more flexible approach to evidence requirements needs to be supported by having (better) insight in the effects of existing requirements and guidelines. This is also in line with the 2002 WHO report ‘Effective Drug Regulation’ which states that “ideally, an assessment of drug regulation should begin by studying regulatory outcomes to judge overall performance”. The report concluded that “outcomes are often not readily measurable”.\textsuperscript{45} However, regulatory science has made progress in this respect by providing insight into the effects of evidence requirements.\textsuperscript{46,47} Recent studies show that promising instruments exist to adjust regulatory requirements, also for the case-by-case evaluations of the need for evidence as proposed by adaptive approaches to marketing authorization.\textsuperscript{48,49}

The EMA acknowledges the value of evaluating the need for an ‘impact assessment’ for new guidelines.\textsuperscript{50} However, currently this impact assessment results in a standard formula which does not describe a comprehensive assessment of pros and cons and the resulting ‘go/no go’ decision for the development or application of a guideline. A possible solution for this is to involve companies, academia and patients more intensively in the early stages of guideline development, which is in line with recent EMA thinking.\textsuperscript{51} We would suggest that this activity is strengthened, and is combined with a comprehensive assessment of the effects of evidence requirements in regulatory practice.

One element of optimizing evidence generation that is not prominent in regulatory thinking is the costs of evidence requirements. Hardly any evidence regarding the cost-effectiveness
of regulatory requirements exists. Recent studies show that systematically evaluating the cost–effectiveness of regulatory requirements is feasible. An example is the cost-effectiveness study of guideline ICH E14 requiring QT/QTc studies for particular products which shows that this requirement in its current form is not cost-effective. Such evaluations could become part of a comprehensive impact assessment of regulatory requirements and could support a more flexible approach to evidence requirements.

As described above, both evidence generation and evidence requirements could be optimized and tailored in order to achieve a more efficient development process towards marketing authorization. When the 2004 Report was published, the traditional randomized controlled trial was still seen as the gold standard for measuring efficacy. In 2013, this is increasingly being challenged, based on the need to move from efficacy based on limited clinical trials to real-world effectiveness, with broadening of indications, repurposing of medicines and demands for comparative effectiveness. According to recent proposals for adaptive approaches to marketing authorization, medicines could be initially approved with more uncertainty about efficacy and safety, but only if this is adequately supported by continuous evidence generation throughout the lifecycle of medicines. Currently, the conduct of Phase IV activities and studies to monitor and explore (un)known risks is controlled by EU risk management requirements in the 2012 pharmacovigilance legislation. Post-marketing evidence on efficacy, effectiveness and safety can for example be generated by Phase IV randomized clinical trials in therapeutic settings, but observational studies can also play a major role. So far experience with observational studies has mainly been gained with safety studies to detect and monitor adverse effects of medicines. In line with the proposals for adaptive approaches to marketing authorization, observational studies could also contribute to reducing uncertainty about efficacy. Observational data gathering can be conducted within existing infrastructures such as electronic medical records, but might also require additional investments (see the Background Paper Chapter 8.4). Furthermore, improvements in health information technology will be needed to facilitate proper information exchange between parties.

Research priorities evidence generation & requirements

To improve efficiency and quality of evidence generation in drug development for initial marketing authorisation, research should focus on:

- Assessing the added value of existing regulatory requirements and guidelines to support a more flexible approach to evidence requirements;
- Making cost-effectiveness evaluations part of a comprehensive impact assessment of regulatory requirements;
- Piloting and validating promising instruments aimed at efficiency in drug development (e.g. surrogate outcome measures and adaptive study designs).
- Further developing methodology for post-marketing observational safety studies (e.g. linking datasets and signal detection), in particular relevant in a flexible/adaptive approach of requirements for initial marketing approval.
- Developing effectiveness studies to reduce uncertainty around efficacy and to compare the effects of medicines in real life settings.
In the next section we focus on another important component of the regulatory process: the benefit-risk assessment by authorities. We describe a number of initiatives that intend to make this crucial step more transparent and consistent.

2.2 Benefit-Risk assessment

The assessment of benefits and risks of new medicinal products is a central element of the evaluation of a marketing authorization application by regulatory authorities. Additionally, benefit-risk assessments play an important role in companies’ development strategies, in reimbursement decisions by health technology assessment bodies and in decision making by research ethics committees. Regulatory benefit-risk assessments should be as consistent and transparent as is reasonably possible, to increase predictability of the approval recommendations for applicants and facilitate marketing authorization of innovative medicines, and to allow for clear communication with applicants and the public about the rationale behind decisions. In recent years, improving consistency and transparency of the decision-making process by regulatory agencies is also seen as an opportunity by the EMA, which has led to a number of initiatives that will be discussed here. Although we focus on benefit risk assessment in the context of decision-making about marketing authorization by EU regulators, much of our discussion is relevant to other decision makers and for other geographical areas.

Benefit-risk assessments consist of three ingredients: (1) data about the favourable and unfavourable effects of a product; (2) uncertainties about these effects; and (3) judgements about the clinical relevance of effects based on data and accompanying uncertainties. In addition, a properly conducted benefit risk assessment should have two important qualities:

1. It should be a rational process of combining objective elements (data and uncertainties) with subjective elements (clinical judgement, trust), leading to consistent decisions;
2. It should be a transparent process, making it communicable and accountable.

Although the elements identified above provide a clear structure, in ‘real-world’ practice, benefit-risk assessment is a complex, multi-person process that requires the evaluation of a large volume of data (up to 10Gb, when the required digital storage space is used as a measure) on multiple effects and transformation into an overall balance, usually resulting in a ‘yes/no’ decision. In general, discussions and evaluations of a qualitative nature guide this transformation by regulatory agencies and most companies.

2.2.1 Initiatives to improve benefit-risk assessment

To help increase consistency and transparency of benefit-risk assessments, many organizations, including companies and regulators, have developed frameworks to structure, standardize and simplify benefit-risk assessments. Examples are the Unified Methodologies for Benefit-Risk Assessment (UMBRA) initiative of the Centre for Innovation in Regulatory Science (CIRS), the IMI PROTECT work package on benefit-risk integration and representation and EMA’s Benefit Risk Methodology Project. We will discuss some of these initiatives in more detail.
The EMA Benefit Risk Methodology Project aims to improve the transparency, consistency and communicability of marketing approval decisions of medicines by developing instruments and processes for balancing multiple benefits and risks\(^\text{66}\) that can aid benefit-risk assessment by regulators. So far, the project has resulted in an improved conceptualization of ‘benefit’ and ‘risk’, replacing these words with four separate items: 1) favourable effects; 2) uncertainties about the favourable effects; 3) unfavourable effects; and 4) uncertainties about the unfavourable effects. The CHMP has incorporated this conceptualization in relevant guidance documents for assessment reports. Furthermore, the project has endorsed a descriptive (‘PrOACT-URL’) framework for systematically evaluating the benefit-risk profile and has proposed an ‘Effects Table’ for displaying a product’s relevant effects and uncertainties.\(^\text{69}\) The PrOACT-URL framework consists of the following steps: Problem formulation, Alternatives (options), Objectives and criteria, Consequences, Trade-offs, Uncertainty, Risk attitude, and Linked Decisions. Both PrOACT-URL framework and Effects Table are descriptive tools to structure the benefit-risk evaluation.

### 2.2.2 Quantitative instruments for benefit-risk assessment

However, many of the recent initiatives to achieve more consistent and transparent decision making involve not only descriptive tools, but also ‘quantitative’ instruments \(^\text{56,67}\). Although currently no regulatory authority uses them, various authors and organizations (including the EMA\(^\text{70}\)), endorse these ‘quantitative’ instruments.\(^\text{71,72,73,74,75,76}\)

To support benefit-risk assessment quantitative instruments distinguish three steps in decision making: (1) decompose problematic situations into its constituent pieces; (2) make assessments about these pieces; and (3) recompose the pieces to a whole. The first step is descriptive (e.g. PrOACT-URL framework and Effects Table), but step 2 and 3 are ‘quantified’; in step 2, input elements (effects, uncertainties and value judgments) are translated into numbers or ranks on a common scale; step 3 consists of a formal model with an algorithm for integrating different input elements into a single output.\(^\text{77}\)

A commonly discussed quantitative instrument, also within the EMA, is the Multi-Criteria Decision Analysis (MCDA) instrument. Within the context of regulatory benefit risk assessment, MCDA can incorporate in a logical, coherent model, different forms of data, multiple objectives, uncertainties, and value judgements. This covers all elements of regulatory benefit risk decision making.\(^\text{77}\) An additional feature of MCDA (and many other quantitative instruments) is that it can visualize how different elements contribute to the overall benefit-risk balance, comparing one product to another.

The EMA field-tested an MCDA approach with medicines that were under review at the CHMP. At five member state agencies, a one-day, facilitated ‘decision conference’ was organized using the EMA’s PrOACT-URL framework in order to construct on-the-spot a benefit-risk model of the medicines and their comparators. Field-tests showed that a quantitative approach was feasible within the context of regulatory benefit-risk assessment of a product. Assessors especially appreciated the feedback the quantitative model gave them on the impact of uncertainty in the data and of differences of opinion about clinical relevance. Limitations of the software instruments utilized were that the instruments had limited capabilities to incorporate statistical uncertainty, an essential element of benefit risk assessment. Furthermore, building up the model through input of data and relevant criteria
with measurement scales was time consuming.\textsuperscript{78} There are currently software tools under development that aim to address these limitations.\textsuperscript{79}

Although the EMA considered the field-tests a success, recent EMA proposals for implementation of benefit-risk tools focus on purely descriptive tools such as the Effects Table.\textsuperscript{80} Currently, case studies are conducted within the PROACT-URL framework to explore opportunities for implementation in regulatory practice.\textsuperscript{81}

### 2.2.3 Opportunities of quantitative benefit-risk assessment instruments

Because quantitative instruments force decision makers to explicate and systematise judgements about benefits, risks and their uncertainties, and because they allow an exploration of any discrepancies between personal intuitions and computer results, quantitative instruments can increase consistency of decision making between different medicinal products, and of repeated decisions about the same (type of) product. In particular, quantitative instruments could help to (re)align judgements about clinical relevance between regulators which could contribute to consistent decision making. Furthermore, explicating these judgements about clinical relevance could help regulators to better communicate the rationale of benefit risk decisions to companies and the public and so strengthen trust in the regulatory system.

Furthermore, during the process of medicine development, regulators could use quantitative instruments to simulate scenarios and thereby explore how changes in value judgements or (uncertainty about) data could affect the overall benefit risk balance. This would allow regulators and companies to have a constructive and prospective discussion on what evidence is needed for marketing authorization. In addition, such scenario analyses could help to get insight into how robust decisions are in relation to different perspectives about clinical relevance (e.g. by patients or prescribers) and how (new) real world data would affect the balance. Having insight in the robustness of decisions could strengthen the confidence of regulators for approving medicines on the basis of adjusted evidence requirements in areas of high medical need. In collaboration with the European Network for Health Technology Assessment (EUnetHTA) the EMA is currently looking into how the information on benefits and risks of medicines in European public assessment reports (EPARs) could better contribute to assessments by HTA bodies.\textsuperscript{82} Quantitative instruments may further support this process.

### 2.2.4 Challenges for implementation

Introducing quantitative instruments as a tool to support scientific judgements might be challenging by requiring additional skills, supporting staff and time investment. Decision conferences are time intensive, although on the other hand a standardization of models used, an intensified preparation and using models to facilitate communication could save time.

It may also be possible to decide on a case-by-case basis how much quantitative modelling is needed. A first step here would be to study the time investments involved. It should also be taken into consideration that although quantitative instruments can incorporate statistical uncertainties about effects, these models can currently not account for other forms of ‘uncertainty’ such as different levels of validity: regulators need to assess the quality of studies before adding these into a model. Another challenge for implementation is finding
the best mode of visualization of model results. Finally, explicating value judgements through quantitative instruments and use this to communicate the rationale of benefit risk decisions to the public can pose challenges because the regulator’s value judgements might be different from those of patients. The recent EMA initiatives to increase patient involvement in regulatory decision-making may address this challenge.

In the next section we will discuss a third key element in the regulatory process: the interaction between regulatory authorities and companies in the form of a scientific dialogue.

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Research priorities for benefit-risk assessment

All in all, further field tests and study of both descriptive and quantitative models is needed to guide further implementation. To further advance the methodology of benefit-risk assessment, research priorities should focus on:

- Conducting case studies of quantitative benefit-risk instruments to explore opportunities and limitations for further implementation in practice.
- Conducting simulations of assessments of previously (dis)approved marketing authorisations, to gain insight into how robust approval decisions are in relation to different perspectives about clinical relevance (e.g. by regulators, patients or prescribers).
- Improving methods for visualization of results of quantitative benefit-risk assessments to communicate the rationale of benefit risk decisions to companies and the public.
- Exploring how quantitative benefit-risk instruments could contribute to providing information on benefits and risks of medicines to assessments by Health Technology Assessment bodies.
- Developing methods for how prescribers and patients can better be involved in regulatory decision-making and how their preferences can be taken into account in models.

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2.3 Scientific Dialogue

A constructive (scientific) dialogue between pharmaceutical companies and regulatory agencies can facilitate pharmaceutical innovation for several reasons, these include:

- The application of emerging science and technologies for drug discovery and development (e.g. proteomics, nanotechnology, synthetic biology, new statistical methods, quality by design etc.) have increased the needs of interaction and knowledge transfer;
- New regulatory tools prompted by changes in legislation and updates in requirements (e.g. regulation for paediatric medicines, advanced therapies medicinal products, pharmacovigilance and risk management) have increased the need of interaction between companies and regulatory authorities to streamline the development process;
- A scientific dialogue may enable a more flexible approach to regulatory requirements (e.g. in scientific guidelines) when it is discussed what requirements are actually relevant for a particular medicine in order to ensure a proper assessment of quality, safety and efficacy.
In this section we discuss opportunities to expand the scientific dialogue and explore how future research could help in this respect.

### 2.3.1 Types of interaction between pharmaceutical companies and regulatory authorities

An issue that was highlighted in the 2004 Report was the need for communication between stakeholders. An overview of recent discussions shows that this field has progressed considerably in recent years. For example, there is now widespread interest in how regulators and industry can further improve communication and most productively engage in an early dialogue in the drug development process and in how changes in regulations impact on product development.

Interaction between regulatory authorities and pharmaceutical companies about medicines can concern regulatory issues (interpretation of legislation), administrative issues (how to submit an application) and scientific issues. This latter kind of interaction concerns what data needs to be generated in order to demonstrate the quality, safety and efficacy of a medicine. Interaction on scientific issues can be of a more general nature such as takes place during workshops, information days, or guideline consultation procedures organized by regulatory agencies to discuss new methods, study designs and draft guidelines. However, scientific interaction can also focus on a particular medicine. This kind of interaction takes place in all phases of a medicine’s lifecycle: during initial drug development, during the marketing authorization procedure, and in the post-marketing phase (Figure 8.2.4 depicts the medicine-specific interaction between the European Medicines Agency and pharmaceutical companies).

**Figure 8.2.4:** The figure shows that scientific advice can be requested during all phases of drug development, including the post-marketing phase

Most of the scientific interactions between applicants and the EMA on a medicine, such as pre-submission meetings, CHMP list of questions and clarification meetings (see Figure 8.2.4),
concern how additional information and justification can be provided in the dossier. These types of interaction all concern interpretation of available evidence about a medicine, not evidence generation. However, in the scientific advice procedure the EMA can interact with companies about development plans before data are generated. The scientific advice procedure thus provides companies the opportunity to tailor evidence generation to regulatory requirements, which is highly relevant for successful marketing authorization.

In 2006, the scientific advice procedure of the EMA has been reformed to enable companies to discuss a broader set of issues concerning development plans with regulators. Figure 8.2.5 shows how the number of scientific advice procedures has increased over the last decade: in 2011 76% of marketing authorization applications included scientific advice.

Figure 8.2.5: Number of scientific advice procedures (by CHMP) per year for the period 2001-2011

Below, we discuss the following aspects of scientific advice in more detail (a) the objectives of scientific advice, (b) the timing, (c) its (legal) status, and (d) stakeholder involvement, and discuss opportunities for improvement.

a. Objectives of scientific advice

In principle, issues related to all phases of medicine development can be discussed in the scientific advice procedure, e.g. quality (manufacturing, chemical, pharmaceutical and biological testing), preclinical (toxicological and pharmacological tests) or clinical issues (early and confirmatory clinical studies pre- and post-approval), as well as opportunities for conditional or exceptional approval. The EMA emphasizes that scientific advice aims to discuss development plans prospectively and is not meant to pre-evaluate study results related to a marketing authorization application. However, a recent study showed that companies request scientific advice primarily to get assurance that on-going development
plans are in compliance with regulatory requirements and guidelines and that scientific advice was used to a lesser extent to discuss development plans in cases where guidelines provided insufficient detail.\textsuperscript{92} This current practice of scientific advice is not fully in line with the EMA’s aim that scientific advice can help to set up a development plan. Also, this practice is not suitable for the implementation of adaptive approaches to marketing authorization which require a constructive dialogue about how much and what kind of evidence is required for a particular medicine.

\textbf{b. Timing of scientific advice}

The EMA does not specify timelines for scientific advice but companies can seek scientific advice as many times as necessary and in all phases of the product lifecycle: either during the initial development of the medicine or during the post-marketing phase, e.g. related to risk management plans.\textsuperscript{91} Since 2006 companies can also ask for follow-up advice when they have additional questions and post-marketing advice on risk management plans has been reinforced too. According to the EMA Roadmap to 2015, scientific advice should be further expanded towards \textit{continuous} scientific support during the development of a medicine with an \textit{earlier} appointment and involvement of (co-)rapporteurs, in order to augment the interaction between regulators and sponsors during the development of medicines.\textsuperscript{93}

However, a recent study of scientific advice questions indicates that current scientific advice is neither provided at an early stage nor in a continuous fashion.\textsuperscript{94} An analysis of the Dutch and European scientific advice procedures showed that most questions were asked about the later stages of the pre-authorization phase, e.g. discussion on the interpretation of phase III guidelines when phase III studies were already ongoing.\textsuperscript{94}

\textbf{c. (Legal) status of scientific advice}

Scientific advice in Europe is not legally binding, neither for companies nor for authorities with regard to a future marketing authorization application.\textsuperscript{95} However, although companies are not obliged to follow scientific advice, compliance with scientific advice is associated with a higher rate of successful marketing authorization.\textsuperscript{96} Furthermore, companies have to justify deviations from scientific advice to the CHMP when applying for marketing authorization, for example when the company has decided to use a different study design than recommended during scientific advice. Similarly, the CHMP has to explain during the review of a marketing authorization application why it deviates from previous advice.\textsuperscript{97}

Although scientific advice is currently not binding in Europe, there could be good reasons to give advice a more formal status and come to some sort of agreement on development plans in an early stage. If regulators would want to evaluate the need for generating evidence on a product more on a case by case basis (for scientific reasons or reasons related to addressing medical need, for example in the context of an adaptive approach), and would thereby allow companies to deviate from guidelines, companies should feel confident that the evidence generated during the course of development will still be considered acceptable at time of marketing authorization application.

Otherwise, companies would be inclined to ‘play safe’ and comply with all available guidelines, also those guidelines that companies consider a waste of time because of limited added value or the availability of better alternatives. Naturally, there should be some process to adjust the agreements made, based on scientific developments, but in a recent interview
study Dutch small and medium enterprises indeed stressed the usefulness of making agreements with regulators about the clinical development plan.\footnote{Error! Bookmark not defined.}

In contrast to the EMA, the FDA does allow for formal agreement on plans for phase III studies in their ‘Special Protocol Assessment’ procedure.\footnote{98} In this procedure regulators and the applicant agree explicitly on the design, execution, and analyses in proposed study protocols \textit{(i.e.,} carcinogenicity protocols, stability protocols, and phase III protocols for clinical trials that will form the primary basis of an efficacy claim\textit{)}. The FDA states that “\textit{it will not later alter its perspective on the issues of design, execution, or analyses unless public health concerns unrecognized at the time of protocol assessment under this process are evident.}”

Further research could identify opportunities and challenges for other regulatory agencies to offer such a procedure to applicants in specific circumstances.

d. Stakeholders involved in scientific advice

The parties involved in current scientific advice procedures are companies and the EMA Scientific Advice Working Party (SAWP).\footnote{99} To strengthen the discussion, external stakeholders such as the FDA, but also health technology assessment bodies, patients and in particular cases the World Health Organization could be involved in the scientific dialogue.\footnote{100} Below we discuss several examples of on-going experiments in this respect.

The FDA and EMA have set up a ‘parallel scientific advice’ procedure which was revised in 2009. Parallel scientific advice provides a mechanism to exchange views on scientific issues during the development phase of new medicinal products \textit{(i.e.,} new human drugs and biologics) between the EMA and FDA regulators. The expected advantages from this interaction are intensified interactions between these two agencies and sponsors, especially in the beginning of the lifecycle of a new product, a better understanding of the basis of regulatory decisions, and the opportunity to optimize product development, \textit{e.g.} by avoiding unnecessary replication of testing or use of diverse testing methodologies. Parallel scientific advice focuses primarily on important breakthrough drugs and on major safety issues that are considered important by both agencies.\footnote{101} In 2011 eight requests for parallel scientific advice were submitted.

A second example of expanding the number of stakeholders involved in scientific advice is the EMA’s aim to increase the number of scientific advice procedures for medicines for unmet medical needs, neglected diseases and rare diseases.\footnote{102} According to a 2011 update, scientific advice with involvement of WHO experts has been reinforced.\footnote{103}

Finally, the EMA and EUnetHTA have begun to explore how scientific advice could be harmonized with advice given by HTA bodies, and aim to establish what evidence both parties need.\footnote{103,104} Since 2010, 17 procedures of joint scientific advice have been initiated for various therapeutic areas. In a recent joint meeting of the EMA and EUnetHTA, it was established that joint scientific advice in an early stage \textit{(e.g.} the phase of non-clinical proof of concept studies\textit{)} is most beneficial for companies in order to learn what would be needed in terms of general study designs. In a later stage, when exploratory clinical data are available, more precise responses could be given related to the choice of endpoints, duration, comparators, size of the trial and the statistical plan.\footnote{105}
3. Development in specific regulations

For certain specific disease categories, patient populations or type of products, regulatory incentives have been introduced at the European level to stimulate pharmaceutical innovation in areas that address public health needs (see Table 8.2.1). In this section, we describe various regulatory incentives for these topics and identify avenues for future research.

3.1. Specific disease categories: rare diseases, neglected diseases and unmet medical needs

Specific disease categories discussed here are those diseases for which market conditions lead to a lack of incentives for developing medicines due to the low numbers of patients (e.g. rare diseases) and/or insufficient purchasing power (e.g. tropical neglected diseases). Additionally, the development of medicines for life threatening diseases with no alternative treatments available is also a specific group for which incentives have been introduced. Moreover, particular disease areas of high medical need are recognized, such as infectious diseases and the related need for the development of new antibiotics.\textsuperscript{106}

3.1.1 Regulatory incentives for rare diseases

Rare diseases are defined as life-threatening or chronically debilitating conditions that affect no more than five in 10 000 people in the EU. In general, for these conditions the cost of developing a medicinal product would not be recovered by the expected revenues because of the low number of patients. In the United States, the first Orphan Drug Act was introduced in 1983 and in 2000 the Orphan Regulation was introduced in the EU, which offers incentives for the development of medicinal products for rare diseases such as fee reductions, 10 years of market exclusivity and free protocol assistance for products with an orphan designation.\textsuperscript{107} The total estimated number of rare diseases lies between 6 000 and 8 000.\textsuperscript{108} From 2000-2010, more than 850 orphan designations were granted to medicines under development from the
1235 requests submitted to the European Medicines Agency by the end of 2010. In total, 63 orphan medicinal products have been approved for the market.

Initiation of orphan drug development and successful marketing authorization seemed to focus on certain disease areas. Uncommon cancers represent the highest number of orphan designations and marketing authorizations in the EU and the United States. Uncommon or rare cancers are often subtypes from more common cancers that have been stratified into molecular subsets. Research into these specific molecular subsets has led to valuable results for targeted agents, which can also be extrapolated to common cancers. Using the orphan definition in this way can create a ‘perverse incentive’ for developers to carve up the market of a medicine for a relatively common disease into components that fall within the orphan medicine category, this may be an ‘adverse effects’ of the orphan regulation. For example, relatively high volumes of use of expensive orphan drugs, leads to a rise in healthcare costs.

In contrast to the rare cancers, for certain other types of rare diseases, such as neurodegenerative diseases, orphan designations are far less frequently requested. Analyses of orphan designations demonstrated that prevalence and scientific output of the disease were determinants for an orphan designation request. For example, rare cancers could benefit from the amount of global research conducted and scientific output in the oncology field. A recent study on exceptionally rare metabolic diseases confirmed the role of prevalence for orphan designation applications and identified that publicly available scientific output of preclinical proof of concept of a drug target was most relevant for an orphan designation application.

Among the incentives for orphan drug development, financial incentives such as market exclusivity are generally perceived as most attractive to initiate drug development and request an orphan designation. Market exclusivity provides protection for an orphan medicinal product that has been authorized for a particular indication from similar products in the same indication. Market exclusivity can be challenged in case of lack of supply, proven clinical superiority of a different medicine or an agreement to share the market with the original sponsor. The likelihood of having such a follow-up marketing application of an orphan drug was also associated with disease prevalence, disease class and disease specific scientific output. In addition turnover of the first orphan medicinal product and age of onset of the disease were driving follow-up marketing applications. Apparently disease scientific output is a relevant driver for initiation of development of medicinal products for rare diseases for which no therapy exists as well as for innovations with clinical superiority over existing therapies. Fundamental research on the pathophysiology of the disease and potential new drug targets is needed for those diseases for which no medicine development initiatives have been undertaken.

The numbers of orphan designations are high compared to the number of marketing authorization applications and approvals. Critics state that orphan medicinal products that are approved, are based on submitted clinical studies with low quality of study designs including: insufficient sample sizes, inadequate outcome measures and follow-up. A study of all orphan medicinal products evaluated by the CHMP since 2000 demonstrated the relevance of the clinical development plan e.g. study design and choice of endpoint for marketing approval. Moreover, a study with FDA data also identified the clinical trial design to be associated with non-approval, which implies that regulators consider a robust study design relevant for marketing approval. A recent analysis that compared marketing
approval review of orphan and non-orphan medicinal products demonstrated that regulatory standards for orphans were just as high as for non-orphan medicinal products.\textsuperscript{121} Lower quality of study designs e.g. single arm studies were only allowed under the scope of conditional or exceptional approval, when alternative therapies were lacking. Apart from design characteristics of submitted studies, the level of experience of the company and dialogue with FDA regulators were also associated with marketing approval. In the EU protocol assistance (the special form of scientific advice available for companies developing designated OMPs for rare diseases) was received in 48\% of OMPs that were submitted for marketing approval by 2010.

Overall, many consider the orphan regulations in the EU and the United States a success,\textsuperscript{122} but improvements are still needed to stimulate (appropriate) clinical development of medicines for rare diseases. For example, for the numerous diseases for which orphan designations exist, but clinical development is a major challenge, how protocol assistance can be of optimal use should be further investigated.

3.1.2 Neglected tropical diseases and collaboration with the World Health Organization

(See also Chapter 6.9)

Another field of attention with regard to gaps in medicine development are neglected tropical diseases. The EMA works with the WHO on medicinal products intended for markets outside the EU on quality matters, and international non-proprietary names. Article 58 of Regulation (EC) No 726/2004 allows the EMA’s CHMP to give opinions, in cooperation with the WHO, on medicinal products for human use that are intended exclusively for markets outside of EU to prevent or treat diseases of major public health interest. So far, six products have been evaluated by the EMA, mainly antiretroviral medicinal products for the treatment of human-immunodeficiency-virus (HIV-1)-infected patients, acute, uncomplicated malaria infection and diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and \textit{Haemophilus influenzae} type b conjugate vaccines.\textsuperscript{123} Article 58 will in itself not act as a regulatory incentive for the development of medicines for neglected tropical diseases. Non-regulatory initiatives such as Product Development Partnerships have been a critical driver of the considerable increase in drug development for neglected diseases in the EU.\textsuperscript{124} In contrast to the EMA, in 2007 FDA did introduce incentives for drug development for neglected diseases by awarding ‘Priority Review Vouchers’ to any company obtaining marketing approval for a medicine that prevents or treats a neglected disease.\textsuperscript{125} These vouchers can subsequently be used to accelerate approval of another medicine for a condition prevalent in wealthier countries that would not have normally qualified for priority review. This financial incentive for a company is considerable, as use of the voucher can take months off the standard FDA evaluation time, leading to earlier marketing authorization. These Priority Review Vouchers were criticized for being inefficient because the incentive is not directly linked with the innovation: the value of the voucher depends on the successful development of a potential ‘blockbuster’ for the United States market. Such a subsequent drug development initiative obviously is not certain.\textsuperscript{126} For example, Novartis received a Priority Review Voucher for its anti-malarial drug Coartem\textsuperscript{®} (an oral combination of artemether and lumefantrine). The company had used its voucher to obtain priority review for Ilaris\textsuperscript{®} (canakinumab), a humanized antibody for gouty arthritis in
Despite the criticism, the initiation of such a regulatory incentive is, in itself, commendable. However, it can be questioned whether a similar regulatory incentive could be introduced in the EU since introducing a similar incentive at EMA, besides FDA, may offer limited additional advantage to large pharmaceutical companies. Moreover, since SMEs play an important role in drug development for neglected diseases, alternative measures could be introduced aiming at small companies. Kesselheim argued that, in contrast to large companies, small companies’ initiation of drug development for neglected diseases was driven by commercial reasons. The introduction of fee reductions for protocol assistance, as is the case for orphan medicinal products, may therefore not mean a crucial improvement in the initiatives for neglected disease drug development by large companies, although it may be relevant for small companies.

3.1.3 Diseases with unmet medical needs

EMA, but also other regulatory agencies worldwide, have acknowledged the need to stimulate pharmaceutical innovation for medicines for areas of high medical need. The ‘conditional approval’ pathway is the key incentive in this area. In the EU, medicinal products fall under the scope of ‘unmet medical needs’ if they are aimed at the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, as well as medicinal products to be used in emergency situations, in response to public health threats and medicinal products designated as orphan medicinal products. In case of conditional approval, marketing authorization is granted based on a smaller package of clinical data, with follow-up obligations to submit additional clinical efficacy and safety evidence of the product. For some products, such as certain orphan medicinal products for extremely rare diseases, it will usually never be possible to assemble a full dossier. These products may be approved under an ‘exceptional approval’ scheme, without further post-approval obligations.

Since the initiation in 2006, 18 medicinal products have been conditionally approved. Moreover, 26 products for human use were approved under exceptional circumstances, of which the majority were orphan medicinal products or influenza vaccines. Out of all the orphan medicinal products that have been authorized until 2010, 38% of the marketing authorizations were granted ‘under exceptional circumstances’ and 6% were given ‘conditional approval’. Considering the low numbers, it can be questioned how much of an incentive conditional approval actually is. It may be questioned whether conditional approval was proposed by either the EMA or the applicant and for what reasons in order to increase the number of conditional approval requests.

A limited number of scientific studies exist that evaluate the EU conditional marketing authorization. A recent study investigated whether exceptional circumstances or conditional approval pathways for marketing authorization led to more safety issues, measured by the frequency and timing of Direct Healthcare Professional Communications (DHPCs). The
study included 289 new medicinal products approved in Europe between 1999 and 2009 and found that conditionally and exceptionally approved drugs were not associated with an increase in the risk of serious safety issues emerging after marketing approval. In addition, conditional rather than exceptional approval was found to be associated with shorter clinical development timelines than other innovative drugs, whereas review timelines were about the same, leading to earlier patient access to new drugs.

These results show that the use of conditional approval pathways can be supported with properly designed studies. One major area in which research is still needed is on post-approval marketing authorization studies after conditional approval. Experience of the FDA accelerated approval procedure demonstrated post-approval commitments take long or are not fulfilled. These studies can result in specific challenges. For example, patients may be less willing to participate in randomized clinical trials when the drug is available in standard care or companies are reluctant to fulfill post-marketing obligations. The recently introduced EU pharmacovigilance legislation aims to strengthen the conduct of post-marketing studies. The effects of this legislation should be closely monitored and evaluated, not only from the perspective of whether it delivers the data that is promised, but also whether the resources that are required for data collection and interpretation warrant the additional knowledge that is gained and whether efficiently used (see Chapter 8.4 on observational studies).

### 3.1.4 Antimicrobials

(See Chapter 6.1)

One particular group of medicines that has been recognized as a high priority area, already in the previous Priority Medicines Report, are the antibiotics for the treatment of infectious diseases. In a 2009 report, the EMA concludes that a particular lack exists of medicinal products under development with new targets or mechanisms of action against multidrug resistant Gram-negative bacteria. Unfavourable market conditions for new antibiotic agents play an important role in the availability of new products. Governments, and regulatory agencies have responded to this high medical need with the launch of various joint initiatives to address the lack of development of antibiotics and the misuse of antimicrobials in human and veterinary medicine, leading to resistance issues. Examples are the governmental work performed within the context of the Trans-Atlantic Task Force on Antimicrobial Resistance (TATFAR), to which the EMA contributes, as well as to activities jointly undertaken by the EMA and other EU agencies such as the European Centre for Disease Prevention and Control (ECDC).

On the regulatory side, strategies to improve the pipeline of new antibacterial medicines in the EU have been limited to the provision of guidance documents. In 2012, the EMA released a guideline on how to optimize research and development of pathogen-specific antibacterial drugs, in particular for small numbers of patients. In addition to adhering to the guideline, companies are recommended to consult the addenda to guidelines with further explanations as well as to request scientific advice. No specific regulatory incentives exist to stimulate the development of antibiotics. In contrast, the FDA incorporated incentives to address the long-recognized shortfall in new antibiotics to combat resistant bacteria. The Generating Antibiotic Incentives Now (GAIN) Act Regulation in Prescription Drug User Fee Act (PDUFA) V, which came into effect at the start of October 2012, provides an additional five...
years of market exclusivity to ‘qualified infectious disease products’, as well as automatic priority review. In addition, specific guidance will be introduced for pathogen-specific antibacterial drug development as provided by EMA.

European research activities for antibacterial medicines are a newly launched public private partnership (PPP) that is part of the Innovative Medicines Initiative (IMI): the ‘Drugs4BadBugs’ consortium, which brings together several pharmaceutical and biotechnology companies and academia to focus on targeting resistant bacteria that cause serious infections and boost the pipeline\textsuperscript{146}, and ReAct, an independent global network, which plays a role in advocating and supporting concerted action on antibiotic resistance.\textsuperscript{147} For more information about this topic consult the background paper to Chapter 6.1.

Thus, from the many projects that have been initiated, it becomes clear that awareness of the need for antimicrobial development is high and that collaboration between academics, companies, and regulators is deemed necessary to collect the knowledge, investments and experience to bring new antimicrobials to the market. In the coming years monitoring of whether these activities yield the results required and identifying which incentives are most effective (also including access and reimbursement issues) to help fill the gap in new antimicrobials is warranted.

### 3.1.5 Specific patient groups: paediatrics, elderly and women

In Chapter 7 of the Priority Medicines Report (cross-cutting themes) various groups of particular interest and importance from a pharmacotherapeutic gap perspective are highlighted: children, elderly and women (see Background Papers 7.1, 7.3 and 7.2, respectively). The development of medicinal products for these specific patient groups are discussed below from a regulatory perspective.

#### 3.1.6 Paediatrics

(See Background Paper 7.1)

Since 2007, the Paediatric Regulation is in force in the EU to improve the health of children by: (i) facilitating the development and availability of medicines for children from birth to less than 18 years, (ii) ensuring that medicines for use in children are of high quality, ethically researched, and authorized appropriately, and (iii) improving the availability of information on the use of medicines for children. In addition, the Paediatric Regulation should prevent children from participating in unnecessary trials, or prevent delaying the authorization of medicinal products for use in adults.\textsuperscript{148}

To help realize this, the European Network of Paediatric Research at the EMA (ENPREMA) has been established in 2010, coordinated by the WHO. This network aims to provide expertise and access to infrastructure for companies to conduct studies in children, define consistent and transparent quality standards, harmonize clinical trial procedures, and define strategies for resolving major challenges.\textsuperscript{149}

The Paediatric Committee (PDCO) at the EMA is primarily responsible for the assessment and agreement of Paediatric Investigational Plans (PIPs) and waivers. The PIP describes the studies and measures proposed to generate the data for paediatric use of medicine. In
principle, a PIP is mandatory for new applications. However, in some cases, studies can be deferred until after studies in adults have been conducted, this to ensure that studies in children are only done when it is safe and ethical. Nevertheless, in case of deferrals, the PIP will still include details of the paediatric studies and their timelines. For those diseases that do not affect children, a PIP is not required and it will be waived.150

At the time of a marketing authorization application, compliance with the PIP will be checked and is needed for a company to receive specific rewards. Once authorization is obtained in all Member States and study results are included in the product information, the medicine is eligible for six months of supplementary protection certificate (SPC) extension. Medicines developed specifically for paediatric use not covered by an SPC or eligible for an SPC, can benefit from a ‘paediatric use marketing authorization’, with a 10-year period of data/market protection.151 For orphan-designated medicinal products, the 10-year period of market exclusivity will be extended to 12 years.152

From 2007-2010, the PDCO has agreed on more than 400 PIPs, granted 176 product-specific waivers, and adopted several class waivers. Deferrals have been granted for 91% of new products, and for 64% of the already authorised products, which means that the paediatric development may be completed after the adult development.153 By the end of 2011, 29 PIPs were completed in compliance with the PDCO decisions. The plans resulted in 24 new paediatric indications and seven new pharmaceutical forms appropriate for children. Data from five completed PIPs provided important information which did not support the use in children and which has been included in the product information of these medicines. Between 2008 and 2012, 10 out of 113 new active substances were centrally authorised and received a paediatric indication. The EMA granted the first paediatric use marketing authorization to Buccolam® (midazolam, oromucosal solution) which was specifically licensed for infants, toddlers, children and adolescents to treat severe convulsions and epileptic seizures.154

According to the EMA, the paediatric regulation has stimulated high-quality research and has produced valuable clinical trial data for the industry, has resulted in an increase in the number of applications to develop paediatric treatments, new paediatric formulations and important labelling changes, including paediatric dosing recommendations.155,156 However, the fact that only one paediatric use marketing authorization has been requested and granted means that the paediatric regulation may not be an effective incentive. Although it takes time to conduct studies with off-patent medicines in children, the period of five years that has passed since the introduction should be sufficient and one would have expected a higher number of PUMA requests. Limitations to license off-patent medicines for paediatric indications, may be because of financial prospects: it was suggested that the target population for a PUMA is too small, that national reimbursement rules may not offer rewards to cover research costs for off patent medicines and that investment sources for paediatric research among generic companies may be lacking.157

Regarding the paediatric regulation in general, critics emphasize the system fails to stimulate research in areas of unmet medical need, and instead has resulted in companies adding paediatric information to medicines developed for adults in lower priority areas.158 Additionally, a survey of companies of the European Federation of Pharmaceutical Industries and Associations (EFPIA) indicated that the paediatric regulations are overly bureaucratic and have led to delays in marketing authorization. The survey indicated that
paediatric development and trials are more expensive per subject than adult development. In addition, according to some, the system failed to focus global research on areas of high medical need, but rather focuses resources on adding paediatric information to medicines licensed for adults in low priority areas.\textsuperscript{159}

Apparently, a discrepancy exists between the evaluation of the Paediatric regulation by regulators, companies and other stakeholders (e.g. medical researchers). Considering the lack of interest for the paediatric use marketing authorization incentive, other forms of incentives to generate paediatric data in off-patent medicines may need to be considered. It may prove more sustainable to create incentives to also collect and analyse the existing knowledge on off-label use of medicines using real life data (see Chapter 8.4) in children, and disseminate the information among health practitioners.\textsuperscript{157} For future research different types of incentives are of particular interest.

3.1.7 Elderly

(See Chapter 5 and Background Paper 7.3)

Medicinal products for the elderly are an important topic on the agenda of policymakers. In Europe, the median age is high compared to other regions, and the elderly population will grow rapidly in the next decades.\textsuperscript{160} Off-label use of medicines occurs frequently in elderly patients, for example the use of antipsychotics in nursing homes.\textsuperscript{161} Additionally, co-morbidity and polypharmacy are a major topic in this population. To take the needs of elderly patients into account, the EMA introduced the ‘EMA geriatric medicines strategy’ in 2011 to ensure that the needs of the elderly are considered in the development and evaluation of new medicines and in the post-authorization follow-up of already approved medicines. Additionally, it is suggested to improve the availability of information on the responsible use of medicines for the elderly to support better informed prescribing.\textsuperscript{162}

To achieve both objectives the EMA wants to ensure that medicinal products are developed in accordance with current guidelines, particularly guideline E7 of the International Conference on Harmonisation. The EMA has identified gaps in regulatory and scientific knowledge and wants to address these by drafting guidelines and the provision of scientific advice. In addition, an experts’ pool has been established to make full use of the experts available within the EMA.\textsuperscript{162} Currently, the conduct of clinical trials in the elderly is not an obligation and no specific incentives exist for this. Whether the EMA strategy focus on specific scientific and regulatory guidance will be sufficient for development of geriatric medicines in elderly should be evaluated.

3.1.8 Women

(See Chapter and Background Paper 7.2)

There may be a need to explicitly include women in clinical studies as, for example, metabolism rates may differ and some drugs have adverse effects that women are known to be more susceptible to than men, including cardiac effects like QT interval prolongation.\textsuperscript{163}

The inclusion of women in studies is addressed in guidelines for clinical trials in variable ways. On the one hand, the International Conference on Harmonisation of (ICH) guidelines
only briefly mentions women in more general clinical trial guidelines. On the other hand, both the USA and Canada have for many years had well-respected policies and guidelines on inclusion of women in clinical trials.\textsuperscript{164,165,166}

To explore the need for introducing specific guidelines for the inclusion of women in clinical trials, the EMA has undertaken a review of pivotal marketing application trials for evidence of gender bias. The review involved marketing applications filed between 2000 and 2003, involving 84 products and 240 pivotal clinical trials, to assess whether the percentage of females in trial populations is comparable to the target population. In addition, ten randomly selected products were examined to assess whether the sponsor performed subgroup analyses by sex. The review demonstrated that in general women were adequately represented in pivotal trial populations, well reflecting the gender prevalence of the disease or condition in the target population. In assessing deviations, the difficulty in determining accurate estimates of disease prevalence in target populations and the variation in relative disease prevalence in the sexes with age should be considered; for example, the delayed onset of heart disease in women as compared to men. While women appear to be participating in all phases of study development, participation is lower in early (phase 1 to 1/2) studies.\textsuperscript{167}

According to the review, ICH guidelines do address gender, in particular guidelines M4E and E3, which require adequate demographic (including gender) characterization, analysis and assessment of the patient population. Guidelines express the need to explore possible demographic (including gender) differences in dose-response (E4, M4E) and define certain safety precautions (E8, M3). The results of reviews and experience argue against the need for a separate ICH guidelines on women as a specific population in clinical trials.\textsuperscript{167}

3.2 Specific products: advanced therapy medicinal products

3.2.1 The ATMP regulation: scope and objectives

The regulatory system stimulates pharmaceutical product innovation by means of advanced therapy medicinal products. The EU regulation on advanced therapy medicinal products (ATMPs) (“Regulation (EC) No 1394/2007”) was adopted in 2007 and came into force on 30 December 2008. The regulation defines an ATMP as a product intended for gene therapy; a product intended for (somatic) cell therapy or tissue engineered products (TEPs).\textsuperscript{168} Before the regulation came into force, gene therapy and cell therapy products were considered as medicinal products. However, TEPs, were not covered by EU legislation. TEPs were excluded from the scope of the medical devices legislation and did not fall within the scope of medicinal products legislation leaving them unregulated. To fill this legal gap, new legislation was designed. Originally a specific regulation on TEPs was proposed, but the proposal was withdrawn and TEPs were included in the ATMP Regulation.

The ATMP Regulation was designed to ensure the free movement of advanced therapy medicines within the EU, to facilitate their access to the EU market, and to foster the competitiveness of European pharmaceutical companies in the field, while guaranteeing the highest level of health protection for patients. The regulation aims to (i) authorise existing ATMPs and to (ii) boost the development and of new ATMPs. Therefore, ATMP legislation describes how these medicinal products are authorized, supervised and monitored to ensure that they are safe and effective and provides incentives to encourage research and development.
development in the area of advanced therapies. The incentives consist of a (partial) waiver of authorization fees and fees for scientific advice and protocol assistance, support by the SME office, introduction of certification of parts of the authorization dossier, etcetera (see Table 8.2.1). A relatively new procedure is the certification of ATMPs developed by SMEs that provides an evaluation of the submitted quality and (when available) non-clinical studies performed by the applicant SME during their ATMPs development.\textsuperscript{169}

At the EMA, a new scientific committee, the Committee for Advanced Therapies (CAT) was established, which recommends on the classification of advanced therapy medicines and contributes towards giving scientific advice. Moreover, the CAT conducts the scientific assessment of advanced-therapy medicines and prepares a draft opinion on the quality, safety and efficacy of an advanced-therapy medicine for the CHMP.

Until December 2010, 39 ATMP classifications have been awarded and the final conclusions have been published on the EMA website. In 2011, twelve requests for scientific recommendations on advanced-therapy classification were submitted and an equal number of scientific recommendations were adopted. However, this number of new requests for classification may be lower than expected at the start of the implementation of the ATMP Regulation, as most ATMPs are put under the national 'hospital exemption' scheme. One certification has been finalised on the quality package of an ATMP.\textsuperscript{169}

Additionally, the expectations of the Regulation to authorise existing ATMPs and to boost the development of new ATMPs are not reflected in the results so far. Since 30 December 2008, only eight applications for a marketing authorization for an ATMP have been submitted to the EMA. In these applications no ATMP that was already on the market was present. At this moment only two ATMPs have been authorised: one cell therapy product (ChondroCelect\textsuperscript{170}) and one product for gene therapy (Glybera\textsuperscript{171}).

The question is why the expectations were not met. The development of TEPs, cell therapy and gene therapy often takes place in an academic environment, usually as spinoffs of fundamental research done in university hospitals. For these types of organizations, the clinical development process as required for medicinal products regulated by the EMA may be too ambitious. Even with the support offered to the possible applicants for an ATMP marketing authorization, the level of regulatory experience and the necessary means to complete such a process are unavailable.

In terms of future studies, these could find out why existing products do not follow the ATMP- marketing authorization procedure. New ATMPs that received a certification could be followed to identify bottlenecks in bringing those innovative products to the market.

It is fair to conclude that the Regulation has not been able to promote innovation in light of the number of available authorised ATMPs. However, the regulation has provided clarity on which regulatory pathway has to be followed and ‘gaps’ in EU legislation have been patched.
4. Developments in the context of the regulatory system

Not only the regulatory system has changed since the last Priority Medicines Report, the world around this system probably has changed even more. In this section we describe four topics in more detail that we believe are of special interest for a future research agenda aimed at stimulating pharmaceutical innovation and for developments in the regulatory system. First, HTA bodies have been through important changes, and streamlining the interaction between marketing authorization and HTA is on many agendas. Second, regulation of medicines has also seen important developments in the area of the ‘globalization’ of regulation. Third, increasing interest in products that can be viewed as a combination of a medicines and a medical device has fuelled the discussion about the extent to which the regulation of medical devices may be aligned with medicines. Fourth, the past decade has also seen a changing perspective on the role of the patient. Also through experiences with medicines such as natalizumab (Tysabri®) and bevacuzimab (Avastin®), the patient is seen more and more as a relevant actor in the decision-making process about the marketing authorization of medicines.

4.1 Collaboration with Health Technology Assessment bodies

For companies a marketing authorization is but the first step in bringing a new medicine to patients. Especially in the European setting, marketing authorization is followed by a set of research priorities for specific disease areas, patients or products:

To optimize the regulatory system in stimulating pharmaceutical innovation, research should focus on:

- Re-evaluating the components of regulation to support development of orphan medicinal products, in particular incentives for fundamental research on the pathophysiology and drug candidates for those rare diseases for which no development initiatives have been undertaken.
- Exploring new opportunities for regulatory incentives for drug development for neglected diseases, e.g. fee reductions for scientific advice for SMEs.
- Further evaluating the conditional approval procedure: To what extent is conditional approval an incentive for pharmaceutical industry? And closely monitoring the follow-up of conditionally approved products and evaluating whether post-approval commitments are fulfilled and how frequent the benefit-risk balance remains positive.
- Identifying whether/which regulatory tools are most effective to fill the gap in new antimicrobials development.
- Studying forms of incentive to generate paediatric data in off-patent medicines in the right indications.
- Exploring the need for regulatory requirements or incentives for the conduct of clinical studies in elderly
- Studying why the ATMP-marketing authorisation procedure is not followed for existing products and identifying bottlenecks in bringing new and certified ATMPs to the market.

Research Priorities for Regulations for specific disease areas, patients or products

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- Further evaluating the conditional approval procedure: To what extent is conditional approval an incentive for pharmaceutical industry? And closely monitoring the follow-up of conditionally approved products and evaluating whether post-approval commitments are fulfilled and how frequent the benefit-risk balance remains positive.
- Identifying whether/which regulatory tools are most effective to fill the gap in new antimicrobials development.
- Studying forms of incentive to generate paediatric data in off-patent medicines in the right indications.
- Exploring the need for regulatory requirements or incentives for the conduct of clinical studies in elderly
- Studying why the ATMP-marketing authorisation procedure is not followed for existing products and identifying bottlenecks in bringing new and certified ATMPs to the market.
Update on 2004 Background Paper, BP 8.2 Regulatory Practices

reimbursement decisions at the national level. In these reimbursement decisions, several aspects are considered: whether the medicine should be considered as eligible for reimbursement and how much of the price the public payer should cover. These reimbursement decisions are of prime importance to companies, as they are critical for the commercial fate of a new product. For more information about relevant developments in the pricing and reimbursement arena, we refer to the Background Paper Chapter 8.2.

Health Technology Assessment (HTA) is commonly used to inform reimbursement decisions. HTA is a multidisciplinary process in which medical, social, economic, and ethical issues related to the use of a health technology are assessed in a systematic, transparent, unbiased, and robust manner. HTA focuses on the incremental value of new medical technologies such as medicines, and tries to assess this in the context of a real world setting.

At the moment of marketing authorization, a medicine is accompanied by an extensive data package that provides information about the safety and efficacy of the medicine in a clinical trial setting. This data package is shaped by the requirements of regulatory bodies such as the EMA and FDA.

Within the evidentiary needs of HTA bodies the Relative Effectiveness (RE) of a new medicine is of special importance and constitutes an important input for potential cost-effectiveness assessments. Relative Effectiveness has been defined by the High Level Pharmaceutical Forum 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.”

The ‘real world’ setting of medicines use cannot be compared to the clinical trial setting. This means that making an assessment of how effective a new medicines truly is compared to other health care interventions, or doing nothing, can be hard to tell if only based on the data that is used for regulatory approval. This is described as the ‘efficacy’ – ‘effectiveness’ gap and remains one of the key challenges in medicine development, regulation and use. This means that the evidence generated based on these regulatory requirements is often not ideally suited to meet the needs of Health Technology Assessment (HTA) bodies who start from the evidence available at registration but have to make an assessment about the medical, social, ethical, and economic implications of a new therapy.

At the moment, several initiatives are on-going between the EMA and the HTA bodies collaborating in EUnetHTA Joint Action. The topics for collaboration between the EMA and EUnetHTA include:

- Scientific advice: the EMA and EUnetHTA have begun to explore how scientific advice could be harmonized with advice given by HTA bodies, and to establish the evidence that both groups need (see Section 5).

- European Public Assessment Report (EPAR): a joint activity to discuss how the EPAR can provide the best contribution to the assessment of relative effectiveness by HTA bodies in Member States.

Alignment of requests for evidence by marketing authorization agencies and health technology assessment bodies is a major topic in strategy documents from various regulatory authorities. Without some form of alignment, HTA bodies may decide that proper information is lacking for granting reimbursement of new medicines. For example, it could lead to the situation that medicines would be granted early access to the market for a specific
patient population but without the necessary reimbursement and user access. Moreover, alignment of the requests to conduct post-marketing studies could contribute significantly to a well-functioning regulatory system.

For research agendas, investing in tools to better assess RE during drug development, at the marketing authorization stage and afterwards is of key importance. In general, two routes can be identified for generating evidence on RE in a ‘real world’ setting: observational studies and (pragmatic) controlled trials. When the aim is to generate evidence on the RE of new therapies, observational research can pose limitations for valid interpretation (e.g. due unquantifiable or unrecorded confounders). Pragmatic trials aim to evaluate long-term effects in real world populations of interventions that are directly relevant to clinical care. The design of better pre-launch (pragmatic) trials can therefore provide decision makers with more confidence about the RE of a new medicine based on existing data. Issues of pragmatic trials are non-adherence among patients, loss to follow-up and the need for large sample sizes. Generalizability and validity of pragmatic study results need to be balanced carefully. Furthermore, the implementation and integration of different state-of-the-art mathematical, epidemiological, statistical analytic and decision-making techniques to employ comparative effectiveness can also positively impact current regulatory, therapeutic and reimbursement strategies.

4.2 Globalization of regulatory requirements and decision-making

The majority of new medicines are approved in at least two of the three leading regulatory authorities the FDA, the Japanese Pharmaceutical and Medical Devices Area (PMDA) and EMA. Thus, they increasingly have to meet requirements of multiple regulatory authorities. To restrict the costs of R&D and to minimize the delay in making safe and efficacious innovative treatments available to patients, harmonization of regulatory requirements is valuable. Regulatory agencies and pharmaceutical companies worldwide have responded to the need for harmonization of regulatory guidelines about twenty years ago, by establishing the International Conference of Harmonization (ICH). The ICH has yielded harmonized guidelines on quality, safety, efficacy and multi-disciplinary issues.

For the future, it is of utmost importance for the European pharmaceutical industry to have the ICH reach beyond the original triad and into the emerging markets. An example of regulatory harmonization of emerging markets with those of advanced countries is the East Asia Harmonization which includes China, Korea and Japan.

EMA now has bilateral confidentiality arrangements with the U.S. FDA, Health Canada, the Japanese Pharmaceutical and Medical Devices Agency (PMDA)/Ministry of Health Labour, the Welfare and the Australian Therapeutic Goods Administration and Swissmedic. Interactions with these regulatory authorities continue to intensify, with increasing exchanges of information on product-related activities, but also the development of new cluster activities, in particular with the FDA. An example of such an activity with FDA is the opportunity for parallel scientific advice to applicants on request. However, although scientific information is exchanged between the two agencies, the advice towards the pharmaceutical company is not harmonized, an independent advice is given to the applicant by both agencies. Furthermore, despite harmonized guidelines and parallel scientific advice differences in marketing approval decisions occur based on the same application dossier, as was demonstrated in an analysis of FDA and EMA approval decisions on anticancer drugs. For the many applicants that aim to market their medicine worldwide,
this may seem unneeded delay of the licensing of their product. It would be worth further studying to what extent differences in marketing authorizations occur and what would be the practical implications of these differences.

### 4.3  Patient involvement in regulatory decision-making

Regulatory agencies, including EMA, have recognized the need to involve patients in the scientific dialogue around marketing approval of medicines, and have introduced varying instruments to respond to this need. The EMA established the Human Scientific Committees’ Working Party with Patients’ and Consumers’ Organisations (PCWP), which consists of a large network of patient organisations that represent and provide recommendations on patients’ interests. The PCWP also coordinates patient participation in scientific advisory group meetings, committees and conferences and workshops of EMA. Patient representatives are involved in scientific discussions by taking part in scientific committees such as the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO) and the Committee for Advanced Therapies (CAT). The U.S. FDA also organizes public hearings to involve patients’ perspectives on marketing approval of medicines. The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA has recently started with public hearings on urgent safety concerns. Experiences with these public hearings should be evaluated and may lead to more broadly applied public hearings by the EMA in the future. Patient involvement will in particular be relevant in adaptive approaches to help define acceptable levels of risk and uncertainty. The exact role of patients and their contributions to the scientific discussion around marketing approval is still something that needs to be assessed in more detail (for a broader discussion of the topic of patient involvement we wish to refer readers to Background Paper Chapter 8.5).

### 4.4  Integration with devices and diagnostics

Some pharmaceutical innovations combine a medicine and a device, drug-eluting coronary stents are a well-known example of this. In order to effectively allow such products to the market regulatory harmonized requirements for medicinal products and devices are needed and introduced. In the EU, device approval is overseen by a governmental body called a Competent Authority. These Competent Authorities are designated by the Member States. In some EU countries these Competent Authorities could also be the drug regulatory agency, such as the Medicines and Healthcare Products Regulatory Agency in the United Kingdom. In addition, Notified Bodies are appointed that are responsible for pre-market evaluation of medical devices and monitor all aspects of the evaluation from manufacturing process to post-market surveillance.

According to the European regulation, medical devices are categorized into four classes (I, IIa, IIb and III) on the basis of increasing risks associated with their intended use (e.g. class I devices are wheelchairs and adhesive bandages, class III are implantable prosthetic joints, drug-eluting stents and artificial heart valves). The Medical Devices Directive and its corresponding Guidelines state that in the case of (active) implantable devices and devices of class III, evidence of the clinical performance and safety of a medical device is provided by means of clinical data. Clinical data submitted can come from clinical trials, from scientific publications or through a documented clinical evaluation of an equivalent medical device. Once a device is reviewed and deemed acceptable, it receives the CE marking.
In case that a medical device contains a drug substance, both the device regulation and the drug regulation apply. According to the medical device legislation, the Notified Body has to consult one of the competent bodies of the Member States or the EMA with regards to the quality, safety and usefulness of the medicinal substance incorporated as integral part of the device.

An example of a combination of medical substance and a medical device is, as already mentioned, the drug-eluting (medicinal substance-eluting) coronary stent (DES). The EMA has made a specific guideline to assist applicants and Notified Bodies in the consultation procedure to the competent bodies of the Member States or the EMA regarding the assessment of usefulness and safety applied to a medicinal substance. The level of clinical evidence required depends on whether the active substance of the combination is known to the Competent Authority as a medicinal product or in the setting of a DES.

It has been said that specific requirements for premarketing clinical studies of devices are sometimes unclear, and details of trials are typically not made available to the public. Although clinical data are required for high-risk devices, guidelines for the nature of these studies are not binding on manufacturers or Notified Bodies. Opportunities are explored to consolidate and streamline consultation and interactions with notified bodies for medical devices for the evaluation of combined ATMPs. Procedural advice on the evaluation of combined products and the consultation of Notified Bodies was adopted and published in February 2011. The procedure provides details of possible scenarios and timelines for interaction between the CAT and Notified Bodies in order to establish timely and effective interactions for companies developing an ATMP combined with a medical device. Such interaction should enable the CAT to perform an adequate benefit-risk assessment and to adopt a draft opinion for the combined ATMP. Evaluation of this procedure should indicate whether such a procedure is sufficient to harmonize both regulations.

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**Research priorities in the context of the regulatory system**

To improve efficiency of bringing innovative medicines to patients by further collaboration with external parties, research should focus on:

- Making better predictions about relative effectiveness during drug development, at marketing authorization and afterwards.
- Further studying to what extent differences in marketing approval decisions occur between leading regulatory authorities and what would be the practical implications of these differences.
- Exploring the role of patients and their contributions to the discussion of efficacy and safety evidence needed for marketing authorisation.
- Evaluating regulatory procedures for combined devices and medicinal products should indicate whether these are sufficiently harmonized to facilitate such product innovations.
5. Conclusions and research priorities

The 2013 ‘Priority Medicines for Europe and the World’ Update has been initiated to determine the priority needs for pharmaceutical innovation and to formulate a research agenda towards 2020. In this chapter we have discussed developments in the marketing authorization system in relation to pharmaceutical innovation and addressing priority health care needs at four levels: (1) the overall system of marketing authorization; (2) key components of the system; (3) specific regulations within the system; and (4) broader developments surrounding the system. At each of these levels we have identified research priorities, which are highlighted at the end of each corresponding section. However, in addition to these individual research priorities, we believe that there are four key messages for the methodology of future research agendas:

1. Continue to develop and pilot new methods for evidence generation and benefit-risk assessment

In the last few years the regulatory system has been subject to various proposals for renewal. To actually decide about supplementing elements of the regulatory system in practice, such as introducing changes regarding evidence requirements or allowing innovative methods such as new biomarkers and study designs, proposals should be substantiated by multiple, thorough and robust studies.

Additional research is needed on promising instruments (such as the use of surrogate outcome measures and adaptive study designs) to optimize regulatory requirements for initial marketing approval. In addition, the increased use of post-marketing observational studies for effectiveness and safety should be explored. In line with the adaptive licensing proposals, effectiveness studies would also be needed to make better assessments for the (future) real-world effectiveness of medicines under development based on trial efficacy. Improving this kind of learning could help to achieve an adequate level of (safety and efficacy) knowledge while requiring less data to be collected before the medicines are approved.

For example, the various collaborative initiatives proposed in order to develop structured benefit-risk assessments, based on qualitative and quantitative instruments, could help to increase the consistency and transparency of benefit-risk assessments and thereby the predictability of the marketing authorization procedure. However, introducing quantitative instruments for benefit-risk assessment requires substantial changes in a regulator’s way of decision-making and in the way companies’ prepare submission documents. At present, little evidence exists on how quantitative instruments affect the quality of regulatory decision-making or public health. Additional field studies should identify practical limitations and test optimal ways of data visualization. In addition, field studies of quantitative benefit-risk instruments could gain insight into uncertainties in benefit-risk assessments and demonstrate how robust decisions are in relation to different perspectives about clinical relevance (e.g. by patients or prescribers) and how (new) real-world data would affect the balance. Recently, pilot studies have been initiated and collaborations have been established to further implement current concepts.
2. Clearly identify expectations and key performance indicators for new regulations and set up prospective studies

Measuring the success of regulatory policies is often difficult. In order to evaluate and improve existing regulations and to base new incentives on best practices, expectations should be made explicit and performance indicators should be defined and reported on.

European Union regulatory incentives for pharmaceutical innovation for specific disease areas, specific populations and specific products have demonstrated that introducing regulation does not always take into account all factors involved in successfully bringing a medicine to the market. In case of orphan regulation, the market exclusivity incentive has, without doubt yielded an enormous increase in the number of potential drug candidates for rare diseases. However, some instruments, such as free protocol assistance, may not be a key driver for generating more innovative medicines. Other incentives, such as the significant investments by governments in research into rare diseases, may play a far more important role. The paediatric regulation could be looked at in a similar manner. Future research could establish which incentives provide added value from a societal perspective and help to achieve public health goals. The research climate for rare diseases apparently needs additional or different incentives to increase the number of successful marketing authorization applications.

The regulation of conditional approval offers an opportunity to bring medicines to the market for life threatening diseases for which no alternatives exist. However, the numbers of applications for conditional marketing authorization procedures are limited. In addition, the follow-up of post-marketing commitments seems problematic in some cases. The 2012 EU pharmacovigilance legislation will enforce post-marketing obligations and complement the conditional approval regulation. For the newly established pharmacovigilance guideline EMA regulators explicitly defined measures of impact such as change of behaviour in prescribing, dispensing and consumption and outcomes such as mortality, morbidity and quality of life. For this purpose, the effective use of Electronic Health Record (EHR) databases and real-life data is of critical importance (see also Chapter 8.4). Formulating expectations by qualitative and quantitative performance indicators, and monitoring them through carefully designed studies, could enforce timely adjustments in regulations and provide evidence for new policies.

3. Set up constructive collaborations and dialogues with key actors

Many actors are involved in the marketing authorization of medicines. Collaboration and dialogue between all these parties is essential for an effective regulatory process and should be supported at multiple levels. Creating such dialogues and collaborations is not easy. Often, it is not part of the tradition of the parties involved. As a result, different actors speak different languages.

First, both regulators and pharmaceutical companies could be stimulated to have a dialogue in a very early stage of drug development (e.g. in the preclinical phase or during Phase I), especially for those products using innovative approaches for development. Ways to optimally structure these interactions should be studied. For example, scientific advice could improve the success rate of the marketing authorization procedure, provided that it is given early and frequently to discuss the relevance of evidence before studies are initiated. New
formats for scientific advice, and the interaction between applicants and regulators in practice should be studied in order to focus scientific advice on what evidence is actually needed and feasible.

Second, involving Health Technology Assessment and Pricing and Reimbursement bodies in such a scientific dialogue is important in order to harmonize requirements and post-marketing obligations. Close collaboration with HTA bodies could create faster patient access to innovative medicines. The EMA and EUnetHTA have begun to explore how scientific advice could be harmonized with advice given by HTA bodies, and to establish what evidence both groups need. These activities should be continued and could be fuelled by input from regulatory science (e.g. new tools for benefit-risk assessment).

Third, involving patients and prescribers could help to better adjust benefit-risk assessments to their preferences and risk perceptions. Although networks of patients have been established e.g. in the EMA Patients and Consumers Working Party, there is need to determine how patients can most effectively contribute to decision making. At present, little is known about how to best involve patients in decision making nor at what stage they can contribute effectively (see Chapter 8.5).

4. Invest in sharing and analysis of regulatory documents

In order to support evidence-based improvements of the regulatory system and to test and explore new methods for drug development and regulatory decision making, close collaboration is needed between regulatory agencies and academia, as well as input from companies. For the purpose of regulatory science, regulatory databases should also be examined to learn from previous marketing authorization procedures and to evaluate tools and regulations as discussed in this paper. Regulatory review documents could be examined to learn from previous marketing authorization procedures and to evaluate tools and regulations as discussed in this paper. The EMA publishes the European Assessment Reports of both approved and withdrawn or non-approved products on its website. Although this offers the opportunity to evaluate previous marketing authorization procedures to some extent, certain informative documents that could add to the learning process, such as the objections made during the marketing authorization procedure also offer insight in regulator’s priorities and perspectives. These should become available for the purpose of regulatory science. More detailed data on outcome measures and confidence intervals are also needed in order to validate quantitative benefit-risk instruments. A positive development in this respect is the ‘Ask EMA’ project which was introduced in 2010 and answers requests for publication of regulatory documents, resulting in a release of over 1 000 000 pages in 2011. The project will consider more proactive publication of documents in the next phase.

Furthermore, the EMA has committed to publish clinical-trial data and enable access to full data sets by interested parties to enable the independent re-analysis of the evidence generated for marketing authorization. As a first step, in 2011 the EMA launched the clinical trial register, which has been welcomed by patient and consumer organisations as an important step in increasing transparency about medical research. However, a number of practical and policy issues need to be addressed before complex data sets can be made public. The EMA does not consider clinical trial data to be commercially confidential, but is concerned that the publication of raw datasets may lead to breaches of patient
confidentiality. Besides, re-analysis by third parties may not be free of conflicts of interest nor lead to high quality analyses, e.g. information may be distorted by competitors through the use of biased selection criteria for data or inappropriate statistical analysis methods. To address these issues, several policies need to be developed such as standards for the protection of patient confidentiality, standards for good analysis practice and rules of engagement for sharing raw data from clinical trials to ensure scientific valid analyses of data across clinical trials.203

Another important area of research is the comparison between different medicines for a therapeutic indication (relative effectiveness). Therefore, recent IMI initiatives in this area should be supported and expanded, as they bring together academia, regulators, and industry to develop new models for defining drug development strategies and regulatory frameworks. Projects such as these can help to reconcile data requirements needs from authorities with efficient drug development programs.

In conclusion, the many changes introduced since 2004 demonstrate that regulators in Europe and elsewhere understand their responsibilities with regard to supporting pharmaceutical innovation and addressing priority health care needs. This progress has created challenges and controversies, but regulators have shown a clear role in stimulating innovation. Regulators have a range of tools at their disposal that can help increase the efficiency of drug development and stimulate the development of needed medicines. However, which of these tools are most effective and at what cost to society is not always evident. The research priorities described in this paper hopefully contribute to setting an agenda for the study of regulatory tools and practices that can help find better ways to address public health needs and to assure that patients have access to safe and effective medicines. Regulations play a critical role in balancing people’s expectations for new medicines to address unmet medical needs against the need to ensure that medicines are efficacious and have a positive benefit-risk ratio. For regulators and companies to adapt to a changing world, research on the regulatory process is needed.

Regulatory science has not been a research priority, but many forms of drug innovation need to be supported by research in regulatory science in order to be able to move forward in the most effective way.
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Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper
By David Henry, Danielle Lang and Suzanne Hill

Background Paper 8.3
Pricing and Reimbursement Policies:
Impacts on Innovation

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# Table of contents

Acknowledgements ...................................................................................................................... 4

1. Introduction .......................................................................................................................... 5

2. The (added) value of innovation.......................................................................................... 6
   2.1 Innovation and value ........................................................................................................... 6
       2.1.1 Pharmaceutical R&D ............................................................................................. 6
       2.1.2 Innovative medicines ............................................................................................. 7
   2.2 Decision-making in reimbursement ............................................................................... 8
       2.2.1 Reimbursement of medicines ............................................................................... 8
       2.2.2 HTA and economic evaluation .............................................................................. 9
   2.3 HTA and decision-making in the reimbursement of medicines: challenges ...................... 11
       2.3.1 Willingness to pay .................................................................................................. 11
       2.3.2 Moving towards the use of economic evaluations in reimbursement ..................... 12
       2.3.3 Methodology development .................................................................................. 13
       2.3.4 Limited budgets ................................................................................................... 16
       2.3.5 Decision-making and the public debate ................................................................... 17
       2.3.6 Delays in access ..................................................................................................... 18
       2.3.7 Stratified medicine and medical devices ............................................................... 19
   2.4 Reimbursement outside Europe ....................................................................................... 21
       2.4.1 High-income countries: Australia, Canada, New Zealand ....................................... 21
       2.4.2 Low- and middle-income countries ....................................................................... 21

3. Managing price and volume ................................................................................................. 22
   3.1 Pricing policies and their effects ...................................................................................... 23
       3.1.1 Pricing policies ........................................................................................................ 23
       3.1.2 External price referencing ....................................................................................... 23
       3.1.3 Value-based pricing ............................................................................................... 27
       3.1.4 Priority setting using value-based pricing .............................................................. 29
       3.1.5 Differential pricing ................................................................................................. 30
       3.1.6 Volume control and incentives for prescribing/dispensing .................................... 32
   3.2 New trends in pricing and reimbursement ....................................................................... 34
       3.2.1 Use of managed-entry agreements in Europe ......................................................... 34
       3.2.2 The role of the hospital setting and interface management .................................... 35
       3.2.3 New funding mechanisms ..................................................................................... 38
       3.2.4 Generic promotion as pharmaceutical policy option .............................................. 40
       3.2.5 Tendering ................................................................................................................ 41
   3.3 Current and future challenges for pricing and reimbursement ......................................... 42
       3.3.1 Orphan medicines ................................................................................................... 42
       3.3.2 Discounts and rebates ............................................................................................ 43
   3.4 Managing price and volume outside Europe ...................................................................... 45

4. Networks and infrastructure ................................................................................................. 47
   4.1 Collaborations on the European level ............................................................................. 47
       4.1.1 European processes regarding pricing and reimbursement .................................... 47
       4.1.2 Networks of competent authorities for pricing and reimbursement ....................... 47
       4.1.3 Cooperation on relative effectiveness .................................................................... 48
Update on 2004 Background Paper, BP 8.3 Pricing and Reimbursement Policies

4.1.4 Medicines price databases................................................................. 49
4.2 Infrastructures outside Europe............................................................. 50
  4.2.1 High-income countries .................................................................. 50
  4.2.2 Low- and middle-income countries ................................................ 50

5. Conclusions.................................................................................................. 51

References........................................................................................................ 54

Annexes............................................................................................................ 67
  Annex 8.3.1: High level initiatives by the European Commission ............... 67
  Annex 8.3.2: Price data of selected medicines (in Euros) .......................... 73

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1. Introduction

In recent years, many industrialized countries have been confronted with rising healthcare expenditures. As increases in healthcare expenditures commonly exceed a country’s economic growth, governments have turned to various policies aimed at controlling both healthcare and pharmaceutical expenditure.\textsuperscript{1,2} During the last decade, European countries - particularly those countries hit by the global financial crisis - have implemented a range of cost-containment measures in the pharmaceutical sector.\textsuperscript{1,3} Governments have both an obligation to improve public health (through facilitating access to needed therapies for its citizens), a need to control healthcare expenditures - as a substantial part of healthcare expenditures are financed publicly – and commonly seek to reward pharmaceutical innovation. These goals are potentially conflicting and therefore, policy decisions may well require trade-offs across competing policy objectives.\textsuperscript{2}

The current focus on cost containment measures has given rise to concerns regarding the sustainability of pharmaceutical innovation. Pharmaceutical companies earn back investments in pharmaceutical R\&D through profits generated by the prices of a minority of products that make it from the discovery phase onto the market, as new medicines entering the market will experience a period of market exclusivity due to patent protection. If pharmaceutical prices are not sufficient to (i) earn back investments and (ii) generate resources that can be reinvested in the development of new medicines, price controls and stringent reimbursement regulations have the potential to negatively impact pharmaceutical innovation\textsuperscript{1,2,4,5,6} as for the manufacturer of an innovative medicine, coverage and reimbursement are the key to economic success that is essential for sustaining its R\&D.\textsuperscript{7}

In the context of Priority Medicines, therefore, appropriate policies and incentives for R\&D – that are partly generated by pricing and reimbursement policies – are an important instrument to address pharmacotherapeutic gaps. The objective of this background paper is to discuss current pricing and reimbursement policies that may be able to align conflicting policy objectives – cost containment, access to medicines, rewarding innovation – and to identify priorities for research based on this discussion. Different sources have been used, including scientific publications, grey literature, interviews with experts, and policy documents for writing this paper.

The 2004 Priority Medicines Report included a background paper on the “Approach to the Valuation and Pricing of Future Medicines” which particularly looked for approaches for low- and middle-income countries and proposed differential pricing as a possible way forward. The focus of this background paper is broader, as the impact of current pricing and reimbursement practices in Europe on pharmaceutical innovation will be discussed. In this report, new developments are presented with regard to value assessments, pricing and reimbursement policies, processes and initiatives, and evidence about existing practices on whether they are able to enhance innovation will be assessed. The focus of this background paper will be on Europe. However, developments in the “rest of the world”, both other high-income and middle- and low-income countries will be considered as well.

This background paper discusses three main themes: the first part of this paper discusses how value and innovation are determined in the context of European countries, and analyses how system and policy features could contribute to aligning different policy objectives. The
second theme of this paper addresses how price and volume are managed in European countries. In the third part of this paper the different networks and infrastructures in Europe are discussed, including the way in which they could contribute to enhancing innovation. In the conclusion of this paper, a number of research priorities are identified that could enhance our knowledge of pricing and reimbursement policies and the way they could impact innovation.

The paper contains a number of annexes that show price data of selected medicines and give an overview of high level initiatives by the European Commission.

2. The (added) value of innovation

This section of the background paper starts with a brief assessment of how innovation and value are currently assessed in European pricing and reimbursement systems. In order to develop ways in which the (added) value of innovative medicines is rewarded, while simultaneously adhering to goals of access and sustainability of publicly funded healthcare systems, it needs to be determined how and what type of innovation should be rewarded. Subsequently, the reimbursement of medicines in Europe is discussed, with a focus on Health Technology Assessment (HTA) and economic evaluations as they are increasingly being used in reimbursement decision-making. This report discusses both how decision-making about the reimbursement of medicines currently is performed by countries, as well as how systems could be improved to achieve policy goals. HTA and economic evaluation are considered important tools because of their ability to govern efficient use of resources while rewarding pharmaceutical innovation. However, unlocking the value of these tools requires that several conditions to be met, these are discussed in this section. Finally, a number of topics related to the reimbursement of medicines are discussed, such as delays in access, orphan medicines, limited budgets, and stratified medicines, that all pose a challenge to current reimbursement systems in European countries. Although pricing of medicines and reimbursement of medicines are closely interlinked in decision-making, specific pricing policies are discussed separately in the next section on managing price and volume.

2.1 Innovation and value

2.1.1 Pharmaceutical R&D

Regardless of major scientific advances in pharmaceutical research over the last 60 years, a decline in pharmaceutical R&D efficiency has been observed while the costs of R&D have risen exponentially. This phenomenon has been referred to as Eroom’s Law: the number of new medicines approved by the FDA in the United States per billion US dollars spent on R&D has halved every nine years. Even though Eroom’s law refers to the United States market, empirical evidence suggests that there are no significant differences between European and United States R&D productivity. Therefore, this so-called ‘productivity crisis’ might have relevant impacts on the European pharmaceutical market as well. In short, this means that although the number of medicines entering the market is not increasing, they are becoming more costly to develop. It has been estimated that the costs of bringing a single
medicine to the market have increased from €149 million in 1975 to €868 million in 2000. Although the methods for such calculations have been criticized the costs of developing and bringing medicines to the market have increased. The high level of uncertainty of the R&D process is a main reason for high R&D costs: only a very low percentage of all molecules that enter the discovery phase will eventually reach the market, and out of all pharmaceuticals that do reach the market, only a minority will subsequently recover the investment costs. (See the Background Paper 3 for a more in-depth discussion on drug development). Therefore, it is generally accepted that the price a medicine that is covered by public payers should reflect a sufficient compensation for R&D investment, in order to provide companies with an incentive to continue the development of innovative medicines. What exactly constitutes ‘sufficient compensation’ for R&D, and whether each country should contribute equally to R&D (see Section 3.1.5 on differential pricing), is heavily debated.

### 2.1.2. Innovative medicines

Medicines that reach the market can be classified in many different ways: by patent status (patented medicine or generic medicine), indication (high volume indications, orphan indication, or stratified medicine), or by molecular structure (first-in-class or me-too). Different policies might be needed for different types of medicines, and policy aims might vary for different types of medicines as well. Throughout this background paper, the effects and challenges of policies according to the type of medicine will be distinguished, and the following classification of medicines has been used: first, it is recognized that patented medicines require different pricing and reimbursement policies than off-patent medicines (generics). Generic medicines are discussed separately in this section. For patented medicines, medicines with added therapeutic value and medicines without added therapeutic value are distinguished between. ‘Added therapeutic value’ is defined below. Furthermore, it is recognized that policy makers tailor policies to deal with high volume medicines and low volume (but high cost) medicines (orphan medicines and stratified medicines). The ‘ideal’ reimbursement policy, therefore, is one that sufficiently rewards innovation while securing value for money for the healthcare system and ensuring equitable and timely access to medicines.

A common definition of what constitutes an ‘innovative medicine’ is currently lacking. Furthermore, countries use different definitions of the type of innovation that is considered worthy of rewarding. From a public health perspective, however, the level of innovativeness of a medicine is primarily defined by the benefits the medicine generates for patients. These benefits can be in the therapeutic or clinical domain, the quality of life domain, but also in the socio-economic domain. Examples of benefits in the socio-economic domain include a medicine that would prevent (expensive) hospital admissions or that would enable patients to work.

An OECD study assessed the innovative value (as defined by either a new chemical structure, a therapeutic improvement, or both) of all new chemical entities (NCEs) launched during 1972-2002. They found that 10% of all NCEs launched during this period were considered a ‘radical innovation’, which was defined as a new chemical structure combined with a therapeutic improvement. Most medicines that reach the market therefore do not result in a dramatic therapeutic improvement over existing treatments and would be considered ‘incremental innovations’. Notwithstanding, a first-in-class medicine is not
always the best-in-class medicine\textsuperscript{15} and it is difficult to predict, before the end of large confirmatory trials at the end of clinical development, whether a medicine actually generates a substantial therapeutic improvement or not. Furthermore, the value of a medicine can change over time and could both decrease (once more medicines are approved for the same indication), or increase over time. A pricing and reimbursement system that is not adapted to deal with different types of medicines therefore may not result in the optimal stimulation of innovative R&D.\textsuperscript{15}

Once a medicine’s period of market exclusivity ends, generic competitors will be able to enter the market, which may result in fierce price competition. Although the role of policies regarding generics are not aimed at rewarding innovation (and they are discussed in Section III in more detail), generics are relevant in the context of rewarding innovation through pricing and reimbursement as a combination efficient generics policies could offer the (public) pharmaceutical bill a substantial savings potential – which would free up resources that could be allocated to financing new and expensive medicines. A high generic penetration and low generic prices should be the aim of efficient generics policies.

### Innovation and value: research priorities

- Study the different definitions of innovation and how they play a role in the reimbursement process. A shared understanding of value – in the context of reimbursement systems for medicines – is currently lacking. Definitions of value and innovation that are currently used by countries should be assessed, in order to provide a clear picture of innovation and value of medicines in the reimbursement systems of European countries.
- Assess to what extent reimbursement systems of European countries explicitly offer rewards for innovation, and whether this is subsequently reflected in decision making.

#### 2.2 Decision-making in reimbursement

##### 2.2.1 Reimbursement of medicines

Governments generally consider the following questions in determining whether or not to make healthcare technologies available: does it work, does it add value to society, it is a reasonable cost to the public, and is it the best way to deliver the service? In decision-making processes regarding the reimbursement of medicines, it needs to be established whether a medicine should be considered as eligible for reimbursement. Subsequently, if the medicine is indeed classified as ‘reimbursable’, it needs to be assessed how much of the price the public payer should (or is able to) cover. The process of setting a price (pricing) and deciding on the level of coverage by public payers (reimbursement) therefore are strongly interlinked. The assessment process usually includes criteria such as efficacy, effectiveness, safety, ease of use, and added therapeutic value, beside cost-effectiveness.\textsuperscript{16}

It has been argued that national reimbursement systems should adhere to ‘accountability for reasonableness’, which means that four conditions need to be met\textsuperscript{17}: (i) decisions need to be publicly accessible, (ii) the rationale for coverage decisions should reflect acceptable and relevant principles (reasonable), (iii) there is a procedure for challenging and disputing decisions, and (iv) there is regulation to ensure these conditions are met. These terms are
incorporated in the EU Transparency Directive\textsuperscript{18} as well. Designing a pharmaceutical pricing and reimbursement policy is a competence of EU Member States, although they have to comply with the EU Transparency Directive (e.g. time-lines, justification of reason for their decision).

Several European countries share the implicit of explicit health policy objectives of sustainability, equity, and quality of care, but the way in which these are handled can differ substantially between countries.\textsuperscript{16} Furthermore, most countries also have additional non-health objectives - such as rewarding innovation and investments in R&D - although systems are not very clear about the actual role of such objectives.\textsuperscript{16} European countries use a variety of policies for reimbursement decisions. All countries have either a positive or negative list that specifies which medicines are publicly covered (positive list) or are excluded from public coverage (negative list). A number of countries use internal price referencing to determine the maximum reimbursable price for a group of new medicines that have therapeutic alternatives. Furthermore, several countries use Health Technology Assessment (HTA) to determine whether a medicine should be reimbursed or not.\textsuperscript{1,19} Although HTA can be used for all new medicines entering the market, many countries use HTA procedures for a subset of medicines only, where medicines are commonly differentiated according to the existence of therapeutic alternatives or whether they have added therapeutic value.

Pricing and reimbursement policies also include external price referencing (international price benchmarking); internal reference pricing; decision making based on Health Technology Assessment (HTA) and economic evaluations; value-based pricing; caps and copayments; taxes; price-volume agreements; fixed margins in distribution channels; and tendering. The impact of these policies on the price of medicines, the availability of and access to medicines, and pharmaceutical expenditure vary.

\subsection*{2.2.2 HTA and economic evaluation}

European countries that currently use HTA in reimbursement decision-making are Belgium, Denmark, Sweden, the Netherlands, Finland, the United Kingdom, Ireland, Portugal, Norway, Estonia, Latvia, Lithuania, Germany, Hungary and Poland, and several other countries are planning the implementation of HTA as a reimbursement tool as well.\textsuperscript{1} HTA is a generic term, and each country applies HTA in its own way. Notwithstanding, the European Network for HTA (EUnetHTA) defines HTA as a multidisciplinary process in which medical, social, economic, and ethical issues related to the use of a health technology are assessed in a systematic, transparent, unbiased, and robust manner.\textsuperscript{20,21} Often, an economic evaluation is part of HTA, but HTA incorporates more factors in decision making than only economic factors. It is therefore important to note that ‘decision-making using HTA’ does not necessarily involve the use of economic evaluations, as the foundation of HTA is scientific evidence of patient outcomes from health interventions\textsuperscript{22}, meaning that the relative efficacy or effectiveness of a medicine is the central element of the assessment. Often, however, HTA includes some financial or budget evaluation, albeit not always a full economic evaluation.
Box 8.3.1: Measuring costs and effects in economic evaluations

Costs

The costs that are included in an economic evaluation depend on the perspective that is taken – usually, either a healthcare perspective or a societal perspective. With a healthcare perspective, all costs related to healthcare consumption (i.e. direct costs) are taken into account. This means that not just the costs of the pharmaceutical are included in the analysis, but also the costs of, for example, hospital stay. If a new medicine prevents patients from being admitted to the hospital as compared to an existing treatment, this could result in lower total costs of the new treatment, even if the new treatment would be priced higher than the existing treatment. When a societal perspective is taken, not only costs of healthcare consumption are included in the assessment but indirect costs are taken into account as well. Indirect costs comprise of costs that fall outside the scope of healthcare but are caused by the disease and include travel costs (to healthcare providers), productivity costs (not being able to work) and the costs of informal caregivers (who dedicate their time to caring for the patient). The societal perspective considers the costs of disease to society (lost productivity, informal care costs) as well as healthcare-related costs, whereas the healthcare perspective does not consider indirect costs. The perspective taken in an economic evaluation usually is guided by who is performing the analysis: to a health insurer, the healthcare perspective might be more informative for decision-making than to a government agency that does need to take societal costs into account.

Health effects

Health effects in an economic evaluation can be measured in different ways (life years gained, hospital admissions avoided, deaths prevented) but a commonly used health effect measure is the quality-adjusted life year (QALY). A QALY combines the length of life lived with the health-related quality of life in which life is lived – where 1 represents perfect health and 0 represents death. One QALY therefore can be interpreted as one year of life lived in perfect health. The QALY is a generic health measure as it can be used to assess the impact on a patient’s health, regardless of the treatment or the patient’s disease. Therefore, assessing the value of a medicine for any given indication can be determined using the same measure, making it a practical and widely applicable measure of health.

An economic evaluation is an assessment of the relative merit or value of health services, in which two main questions are asked: first, is this health procedure, service, or program worth doing compared with other things that could be done with the same resources, and second, is there satisfaction that the health care resources (required to make the procedure, service, or program available to those who could benefit from it) should be spent in this way rather than in some other way? An economic evaluation therefore always involves a comparative analysis of alternative courses of action. There are four types of economic evaluation: cost-minimization analysis, in which the costs of two or more treatments are assessed (when the effectiveness of two treatments is assumed to be equal), cost-effectiveness analysis, in which both health effects as costs of two or more treatments are assessed, cost-utility analysis, in which both health effects and costs of two or more treatments are assessed and in which the health effects are expressed as quality-adjusted life years (QALYs) (see box
8.3.1), and cost-benefit analysis, in which both health effects and costs are expressed in monetary terms – where the health effects are expressed in the willingness to pay to achieve those health effects. The term cost-effectiveness analysis is commonly also used for studies that are in fact a cost-utility analysis. Pharmacoeconomics is a term that is used for the economic comparison of two or more medicines, which is usually done through an economic evaluation.

In a cost-effectiveness analysis, the costs (C) and health effects (E) of a new treatment are compared against the costs and health effects of an existing treatment. Consequently, the incremental costs and effects are expressed in an incremental cost-effectiveness ratio (ICER) that is calculated by the following formula: ICER = ΔC/ΔE. An ICER therefore expresses the amount of resources that will be required to gain one unit of health (which is one QALY in a cost-utility analysis), if the existing treatment would be replaced by the new treatment.

2.3 HTA and decision-making in the reimbursement of medicines: challenges

2.3.1 Willingness to pay

When methods and procedures for the assessment of the value of medicines, such as the use of economic evaluations, are properly and consistently applied in decision-making, this is likely to result in a more efficient allocation of resources. In such a system, only medicines that offer value for money to society will be reimbursed, however ‘value’ would be defined by society. When the cost-effectiveness of medicines is considered, this implies that only medicines that are priced at or below the maximum that society will be willing to pay for the added value will be reimbursed. In such a case, the system would result in static efficiency which means that the allocation of resources is efficient (i.e. cost-effective). However, there is no guarantee that such a system will result in dynamic efficiency as well. Dynamic efficiency means that the system also creates sufficient rewards for future innovation, and can only be achieved if medicines are priced such that they sufficiently reward innovation, offering both returns on past investments as well as providing the resources and incentives for future investments. It has been noted by others that in the context of creating incentives for the development of priority medicines, a more dynamic perspective on cost-effectiveness may actually help to stimulate R&D as it would create the financial incentives for indications where therapeutic gaps exist. Therefore, even though the use of economic evaluations in reimbursement decisions would be a required step towards aligning policy goals of cost-containment, access to medicines, and rewarding innovation, the use of economic evaluations in itself does not guarantee that long-term effects of rewarding innovation are reached as well. In order to achieve dynamic efficiency, systems need to ensure that the rewards that are offered through financing of medicines are sufficient. A major component of dynamic efficiency therefore is the maximum willingness to pay for added value.

Several countries assess the added value of medicines through determining the incremental cost-effectiveness of a medicine, as measured by the incremental costs per QALY. Once the incremental costs per QALY gained of a medicine are assessed, it needs to be determined whether or not the incremental costs per QALY gained offer value for money to society (appraisal). Most countries that use economic evaluations in decision-making do not use explicit thresholds for the maximum costs per incremental QALY gained they are willing to pay, with a notable exception being the United Kingdom. However, even in countries where
no explicit thresholds are used, willingness to pay is implicit through historical reimbursement and coverage decisions. These signals are an important consideration in a firm’s R&D portfolio management strategy as a company can integrate a willingness to pay threshold in its net-present value (NPV) calculations during product development. Furthermore, both thresholds that are either too low or too high will result in economic inefficiencies and can reduce societal welfare. Therefore, a country’s willingness to pay is one of the most relevant for a payer who wants to reward innovation through financing the added value of medicines.

The lack of a reimbursement threshold could weaken decision-making based on economic evaluations as without a threshold, the decision maker itself cannot know against which scale the cost-effectiveness of a pharmaceutical should be measured. Yet the only European country that so far has made explicit statements about their willingness to pay per QALY is the United Kingdom, in which a range of £20,000 - £30,000 per QALY gained is used. Many have claimed that the United Kingdom is an exception in its explicit statement about its thresholds due to the nature of its healthcare system, which is financed through taxes and has regional budget holders which make the actual budget impact of new treatments much more visible. Although this may play a role, it does not mean that other national payers do not need a willingness to pay threshold. Still, payers in most countries remain reluctant to be more explicit about maximum thresholds. This comes at a risk, however, as it may increase prices: when a payer determines whether a medicine’s incremental cost-effectiveness ratio is acceptable or not acceptable on a case-by-case basis, companies may ask for whatever price they think the market will bear.

However, there are understandable reasons for policy makers’ reluctance about setting explicit willingness to pay thresholds. Setting explicit thresholds would invoke public debate regarding societal willingness to pay and could be criticized for decision-making based on ‘numbers alone’ (although other considerations still can play a role even when an explicit threshold is set, the so-called ‘soft’ threshold). Furthermore, for policy makers, not setting an explicit threshold allows for arbitrariness, flexibility, and ad-hoc considerations. It has been argued that, in spite of policy makers’ reluctance to set explicit thresholds, a move towards more explicit thresholds can be expected in the future based on the ‘law of unintended consequences’: decision making based on cost-effectiveness evidence will enable retrospective analysis of these decisions, which could provide stakeholders with the opportunity to assess the (in)consistency of the decision-making process. Even though setting explicit thresholds is a politically sensitive issue, not doing so comes at a risk – including a lower transparency and a lower consistency, and therefore predictability, of the decision-making process.

2.3.2 Moving towards the use of economic evaluations in reimbursement

When a country is planning to implement the use of economic evaluations and cost-effectiveness evidence in reimbursement decision-making, this will require technical capacities that take time to develop. Furthermore, small countries that lack the means and/or market size to effectively implement such policies may find it challenging to implement extensive reimbursement policies and procedures. For such countries, collaborative efforts with other (small) countries could help in this matter. International collaborations and networks are discussed in Section IV of the background paper. When a
country is seeking an efficient allocation of resources, all new medicines entering the market would have to be assessed for their cost-effectiveness (as is the case in the Swedish system). In practice, however, it is expensive and time-consuming to assess every new medicine. In most countries, therefore it is only required to submit cost-effectiveness evidence for a subset of medicines, and medicines for which a cost-effectiveness analysis needs to be performed are usually high cost medicines or medicines claiming added therapeutic value. Although Sweden requires an economic evaluation for every medicine seeking reimbursement, the option is available to only provide comparative cost data (i.e. a cost minimization analysis) when the medicine is not better in improving health outcomes than comparators, in response to this particular issue.\textsuperscript{29} (see also Box 8.3.2). Other countries could consider such options as well.

### HTA, reimbursement of medicines, willingness to pay: Research priorities

- Assess to what extent reimbursement systems throughout Europe are consistent in their willingness to pay for innovation, and what the reasons for discrepancies are.
- Study why decision-makers do or do not use explicit thresholds.
- It should be studied whether there are possibilities for joint efforts between countries for areas of unmet medical needs for setting thresholds for willingness to pay.

#### 2.3.3 Methodology development

HTA has expanded enormously since its conception 35 years ago – in terms of its analytical techniques as well as its importance in priority setting and decision making.\textsuperscript{22} As more and more European countries move towards the use of HTA and economic evaluation in coverage decisions, policy makers are faced with a number of challenges. Countries do not always have the resources to perform an HTA assessment, which means that policy makers frequently will have to rely on studies that have been performed in other settings.\textsuperscript{30} The data requirements for economic evaluation differ between countries as many payers have their own guidelines for economic evaluations.\textsuperscript{31} Given the lack of available, local data, it is important that methods used are comparable and that results are reported in such a way that the generalizability and transferability of a study’s results can be assessed.\textsuperscript{30}

#### Box 8.3.2: Reimbursement in Sweden

Sweden’s current reimbursement system was introduced in October 2002. Reimbursement and pricing processes are completely integrated in Sweden and the national competent authority (the Dental and Pharmaceutical Benefits Board (TLV)) will communicate a joint reimbursement and pricing decision. The eligibility criteria for reimbursement, as laid down in the Act on Pharmaceutical Benefits, can be summarized mainly by three principles:

- **The human value principle** underlines the respect for equality of all human beings and the integrity of every individual. Therefore it is not allowed to discriminate against people because of sex, race, age, or other characteristics when making reimbursement decisions.
- **The need and solidarity principle** states that those in greatest need have priority in the
reimbursement of medicines. People with more severe diseases therefore are prioritized over people with less severe conditions. According to TLV, one example of how the need and solidarity principle has been put into practice was TLV’s decision to withdraw the reimbursement for the H2 antagonists within its review of medicines against diseases caused by stomach acid. TLV concluded that H2 antagonists could be a cost-effective choice for some milder symptoms like heartburn, but that these diseases result in such small losses in quality of life that the treatment should not be reimbursed by society. Instead, the patients should bear the full cost of using these pharmaceuticals. In this case the need and solidarity principle took precedence over the cost-effectiveness principle.

The cost-effectiveness principle states that the cost for using a medicine should be reasonable from a medical, humanitarian, and social-economic perspective. This means that Sweden uses a societal perspective, in which both direct and indirect costs are included in the analysis. Benefits that are considered are two-fold: effects on health, e.g. a longer life expectancy or a higher health-related quality of life and cost savings are both considered.

A pharmaceutical company is required to demonstrate the cost-effectiveness of a new (originator) medicine by submitting a pharmacoeconomic analysis to TLV. Guidelines state that the analysis should be performed from a societal perspective, the treatment in question should be compared with the most appropriate alternative treatment in Sweden, the analysis should include the whole patient population to which the reimbursement application refers, all relevant costs associated with treatment and illness should be identified, quantified and evaluated, and the time-frame for the study shall cover the period when the main health-effects and costs arise. Furthermore, a cost-effectiveness analysis, with quality-adjusted life years (QALYs) as outcome measure is recommended and for treatments that mostly affect survival, both QALYs and life years gained should be shown. If surrogate end-points are used, the account should also include modeling from these end-points to illustrate the effects on morbidity and mortality, i.e. QALYs gained. If it is difficult to use QALYs (e.g. with severe pain for a short time in connection with treatment), then a cost-benefit analysis with willingness to pay may be used as a measure of effect. Finally, if there is supporting evidence that the medicine in question has the same health effects as the best comparable treatment, a cost comparison may suffice.

In conclusion, the Swedish system is a valued-based pricing system, in which the added value is assessed for all new medicines and where higher prices are granted to medicines that demonstrate higher added value – where added value can consist of both increased health effects or costs savings – either within the healthcare sector as well or cost savings to society.


Economic evaluations are considered generalizable when the results can be applied to another setting (e.g. another country) without any needed adjustment, whereas an economic evaluation is transferable if its results can be adapted to apply to another setting. A wide variety of factors can influence the generalizability and transferability of study results, but the main factors are the baseline risk, the treatment effect, health utilities, resource use, and unit costs. An assessment of 27 different sets of guidelines for cost-effectiveness studies...
found that in general, estimates of treatment effect are considered more transferable whereas
economic factors are less often considered transferable. Interestingly, it was found that
countries with limited financial and human resources for conducting separate local studies
were more flexible with regard to generalizability of economic evaluations. Furthermore, it
was found that despite the existence of guidelines, considerable variation in applied
methods continues to exist, even between studies conducted for the same jurisdiction.

Even though economic evaluations are not directly generalizable, measures can be taken to
improve the transferability of economic evaluations from one setting to another. Such
measures could greatly increase the value from the investment in economic evaluations and
could especially benefit small countries that lack the resources to conduct economic
evaluations. In order to improve the transferability of economic evaluations, it is
recommended that study sites are selected such that the sites are representative of the
jurisdiction for which economic data are collected, patients are selected such that they reflect
normal a clinical caseload, the comparator that is ‘current practice’ is included in the study,
data should be collected to enable an analysis from different cost perspectives, resource data
apart from cost data should be collected, and health-related quality of life should be
measured to enable for inserting region-specific valuations for health states.

The EUnetHTA is currently working on the development of tools for international HTA –
and it is planned that joint assessments will be carried out in a pilot phase. EUnetHTA
however, does not consider costs – it is developing tools to deliver core HTA reports
concerning the relative effectiveness assessment (REA) of pharmaceuticals. However, a
substantial part of European countries use cost-effectiveness as a criterion in coverage
decisions. Even though each EU country has its own institutions for coverage decisions,
there is much to be gained from a commitment to basic principles and processes and from
sharing experiences and expertise regarding costs, as well as effectiveness. Sharing
evidence tables of efficacy data used in the reimbursement assessment process of new
medicines, as well as joint guideline development, could substantially improve the efficiency
of reimbursement assessments in European countries.

Although there seems to be consensus on the low transferability of cost data, the increasing
use of economic evaluations in decision making regarding reimbursement across Europe will
most likely result in policy makers to be confronted with situations in which less than ideal
evidence is available for decision making. Furthermore, if consensus could be reached on
methods for both measuring and presenting data in economic evaluations such as
compliance to the recommendations made by Drummond, Manca and Sculpher (2005), this
could improve the ease and consistency of co-ordinating submissions for reimbursement in
different European countries from the company’s point-of-view. Smaller countries could
benefit especially from increasing the methods for transferability of economic evaluations as
it would make submitting a dossier in these countries easier for the company. Even though
there is substantial variation in the way that and the extent to which HTA and economic
evaluations are applied in different European countries, their methods still have many
similarities. Therefore, even though pricing and reimbursement decision making remains a
national competence, there is a lot to win from a commitment to basic concepts and
principles, and from sharing experiences, explicitly as well in the measurement and
transferability of cost data, to those countries that require such data for decision making.
Methodology development: research priorities

- Support networks for cooperation and knowledge sharing among countries using HTA
- Study the transferability of economic evaluations between European countries
- Extend the activities and cooperation on relative effectiveness on relative efficacy

Box 8.3.3: European Network for Health Technology Assessment (EUnetHTA)

Starting with the EUnetHTA project (2006-2008), the overall strategic objective of the EUnetHTA network was to connect public HTA agencies, research institutions and health ministries, enabling an effective exchange of information and support to policy decisions by Member States. The strategic objectives included to reduce overlap and duplication of efforts and hence promote more effective use of resources; to increase HTA input into decision-making in Member States and the EU and hence to increase the impact of HTA; to strengthen the link between HTA and health care policy making in the EU and its Member States; and to support countries with limited experience with HTA.

In order to continue the work initiated during the EUnetHTA Project 2006-2008, the self-funded EUnetHTA Collaboration was launched in November 2008 and ran for one year. From 2010 to 2012 the first EUnetHTA Joint Action 1 (JA1) on Health Technology Assessment (HTA) took place. A Joint Action is a cooperation between government authorities (in this case HTA agencies) and researchers and HTA institutions, institutional producers of HTA and assessments of pharmaceuticals across Europe and is co-funded by the European Commission. The overarching objective of the EUnetHTA Joint Action 1 (JA1) on Health Technology Assessment (HTA), including work on relative effectiveness of pharmaceuticals, is to put an effective and sustainable HTA collaboration in Europe into practice that brings added value at the European, national and regional level. Under JA 1, approaches were developed on how to integrate Relative Effectiveness Assessments of medicines as a special version of the HTA Core Model. The current EUnetHTA Joint Action 2 (JA2), which is scheduled from 2012 to 2015, aims to strengthen the practical application of tools and approaches to cross-border HTA collaboration. For more information visit www.eunethta.eu

2.3.4 Limited budgets

Tightening financial situations and limited budgets are a reality in many European countries, which may well result in policy makers’ attention focusing primarily on cost-containment rather than rewarding innovation. Cost containment measures have been taken throughout Europe but from 2008 onwards were concentrated in Iceland, the Baltic States, Greece, Spain and Portugal – countries that have been hit hard by the financial crisis in recent years. Measures taken include price reductions, increases in the value added tax, increases in co-payments for pharmaceuticals, policies aimed at increasing generic uptake, and procedural changes, including methodological changes in the external reference price system. In Portugal, as well as other EU countries, the Troika (European Commission, European Central and International Monetary Fund) signed a Memorandum of Understanding with the government that asked for austerity measures targeting several public sectors including pharmaceuticals. Although it is understandable that, given limited budgets, policy makers...
are focusing on cost-containment measures, there is a need to consider the long-term impact on innovation of such measures. As concerns over the long-term impacts on innovation exist,\textsuperscript{1} considerations of long-term impacts should not be ignored in policy making.

Cost-containment measures in response to tightened budgets such as increased private co-payments and delisting of medicines (i.e. excluding products from public reimbursement) result in a shift of financial burden from public payers to private households. This implies the risk that patients forego needed as well as unneeded medication, discontinue treatment, or delay purchasing medicines\textsuperscript{36,37} but also aim at discouraging the unnecessary use of medicines. From 1990 onwards the share of private pharmaceutical expenditure decreased from 39\% to 32\% of total pharmaceutical expenditure in the EU-15 Member States, with decreases in some countries (e.g. Austria, United Kingdom, Denmark, Greece) and increases in other countries (e.g. Sweden, Italy, Portugal).\textsuperscript{38} The decrease of private pharmaceutical expenditure, unless caused by changes in methodology, appears to be an encouraging trend, but data, both regarding pharmaceutical expenditure and utilization, are still missing on recent developments in order to measure the impact of the financial crisis. A WHO analysis, undertaken one year before and two years after the beginning of the recession (2007-2009), concluded that the economic recession has had a mixed effect on pharmaceutical consumption, expenditure and prices. In Europe, consumption of medicines was seen to have decreased in Baltic States and Romania while Ireland, strongly hit by the crisis, did not experience any decline in medicines consumption.\textsuperscript{39} The impact of cost containment measures and the economic recession on the availability, access to and consumption of medicines, as well as potential long-term effects on innovation in European countries needs to be assessed.

### 2.3.5 Decision-making and the public debate

Payers that seek to revise their policies in order to make trade-offs between sustainability of healthcare expenditures and providing access (defined as financial access (affordability) of patients to medicines – in contrast to the word availability that is used to indicate a medicine that is marketed in a country) to medicines may meet societal opposition against such policies. Moreover, decisions to not reimburse medicines – even in light of legitimate concerns over effectiveness or cost-effectiveness - can be met with heavy criticism from stakeholders, including patients, pharmaceutical companies, and physicians. An evaluation of decision-making by the Swedish competent authority found that several stakeholders (patients, prescribers, pharmaceutical companies) actively lobbied during the decision-making process, with frequent debates in the media, with an aim to put pressure on the competent authority.\textsuperscript{40} It has also been noted that in the case of stakeholder responses to decision-making in Sweden, patients might be unwilling to accept that healthcare resources are limited.\textsuperscript{40}

In the Netherlands, a concept report written by the Health Care Insurance Board (CVZ) that advised the Minister of Health to no longer reimburse two orphan medicines as evidence suggested an unfavorable cost-effectiveness (the products were introduced on the market under a coverage with evidence development agreement) was leaked to the media and resulted in a heated debate on ‘putting a monetary value on health’. NICE in the United Kingdom has also frequently been the topic of debate in the media. In the proposal for the United Kingdom’s new value-based pricing system, it is explicitly stated that in the case the pharmaceutical company sets its price higher than would be justified by the value-based
pricing assessment, it ‘would be the company’s responsibility to explain to the public why it was not prepared to offer that drug to the public at an appropriate price.’

Studies that have assessed public opinion on limitations of public health services due to financial constraints suggest that the public’s valuation cost-effectiveness thresholds might be higher than that of policy makers. When countries will implement decision-making processes that seek to increase efficiency in healthcare and pharmaceutical expenditures, this will almost certainly generate public debate about the societal willingness to pay for healthcare - especially if decision-making will incorporates economic criteria. Societal learning and education regarding the rationale and importance of priority setting in healthcare could play an important role in seeking broad societal support for procedures, reimbursement criteria and decisions. Furthermore, it will be paramount to design clear rules, procedures, and processes, in order to limit inconsistencies in decision-making and outcomes of decision-making.

2.3.6 Delays in access

Pricing and reimbursement procedures can result in ‘delays in access’ – meaning that once the medicine is given market authorization, patients have to wait until the medicine is actually available to them. Delays occur, along with other reasons, due to delays in the completion of the pricing and reimbursement process. The EC Transparency Directive requires from Member States a pricing decision within 90 days and sets a 90-day limit on reimbursement decisions and a 180-day limit is required for joint pricing and reimbursement decisions. Authorities for pricing and reimbursement decision making have pointed out that delays in decision making sometimes occur because they have to deal with submitted dossiers that are incomplete or do not contain all information required for informed decision making.

Although pricing and reimbursement procedures play an important role in delays in access, they can be attributed to non-procedural causes as well. In some countries (e.g. Austria), manufacturers can directly supply a new medicine to hospitals without being subject to the pricing and reimbursement administrative processes, thus allowing “free pricing” to the manufacturer, while the medicine can be prescribed and has be to funded by public payers as well. Furthermore, medicines may be be launched later in countries where it would be sold at a low price so as to not negatively impact the price in other countries applying external price referencing. Delays in access to generics are often caused by unresolved legal patent issues. Since generics encourage competition and are seen as an opportunity to achieve savings which could be re-invested in innovation, delays of generic entry has been voiced as a concern by both industry and countries.

The W.A.I.T. (Patients Waiting to Access Innovative Therapies) report published by EFPIA assessed the average time between the EU marketing authorization and “patient access” – the latter being defined as the number of days until completion of post-marketing authorization administrative processes including pricing and reimbursement (but not necessarily the actual launch time). The report found an average time period between 88 and 392 days for a sample of 84 newly reimbursable medicines, centrally authorized by EMA during 2007-2009, in 14 European countries. The hospital sector is not included, however, where faster uptake may occur. The Pharmaceutical Health Information System (PHIS) project collected data for the two time spans between the period of marketing authorization
and pricing/reimbursement decision and between the pricing/reimbursement decision and actual marketing and data was provided by competent authorities for pricing and reimbursement. The study revealed major gaps, particularly regarding evidence on the timeline until actual market launch, and there are some variations between data of the two studies on the same time spam in a country as well. Further research on the actual delays and underlying reasons is needed as a basis to identify possible ways forwards to reduce delays in access.

**Limited budgets, public debate, delays in access: research priorities**

- Study the impact of the economic crisis on co-payments, financial access, utilization and consumption in all European countries.
- Study the impact of the economic crisis on innovation
- Study whether public debate influences decision-making in European countries and whether this interferes with achieving system objectives in countries or not (e.g. study biases in public perception that influence acceptance of coverage decisions)
- Assess what types of educational programs could be helpful in increasing the social support for decision-making using economic evidence.
- Identify the opportunities for patient and citizen (general public) involvement, and in what setting their contribution is of most value and needed. In this context it should be assessed what the general public and patient preferences are regarding rewarding innovation and value of medicines. For a more extensive discussion of patient and citizen involvement there is reference to Background Paper 8.5.
- Assess the extent to which delays in availability and access occurs in European countries.
- Study the causes for delays in availability and access.
- Study the availability of (new) medicines on the EU market.

**2.3.7 Stratified medicine and medical devices**

Personalized medicine has been a ‘buzzword’ in medicine for years, but until now, only few personalized treatments have been widely adopted in the clinic.\(^{47}\) Personalized medicine means that a tailored approach is taken to treatment, and this approach is usually based on the molecular analysis of genes, proteins, and metabolites.\(^{47}\) (see the Background Paper 7.4 on stratified medicines). For medicines, this usually means that a test is used to determine whether the patient will benefit from the treatment or will experience an adverse reaction.\(^{47}\) Therefore, the term ‘stratified medicine’ is more appropriate, as treatments are not fully individualized but groups of patients are stratified according to having a certain characteristic.

Even though the use of diagnostics could result in lower overall costs and increased effectiveness of therapies, payers have been reluctant to invest in stratified medicine. Reasons for such reluctance include the difficulty with enforcing protocols to ensure that doctors will follow through with appropriate care based on test results, and limited control over the total costs of a diagnostic.\(^{47}\) The cost-effectiveness of a diagnostic is driven by two main factors: per patient savings and the likelihood that the test suggests an intervention for a patient.\(^{47}\) Tests that prevent the use of expensive treatments or delay expensive procedures
can be very cost-effective, but diagnostics that save a small amount per patient or the
classification that it identifies has a low prevalence among patients have a lower probability
of being cost-effective.\textsuperscript{47} It has been argued that value-based pricing systems, in which the
price of the diagnostic and medicines are assessed simultaneously, would provide an
incentive for the development of stratified medicine.\textsuperscript{48}

Pharmaceutical companies have been reluctant in the development of stratified medicines
for a variety of reasons, including the complex economic environment they face\textsuperscript{49} and the
importance of market share: a diagnostic that would identify sub-populations could decrease
market share.\textsuperscript{47} Notwithstanding, pricing and reimbursement issues have been identified as
important factors in limiting the incentives for the development of stratified medicines.\textsuperscript{47,48}
Therefore, policies that enable a more viable system for pricing and reimbursement of
stratified medicines are needed. Suggestions that have been made include the alignment of
market authorization and reimbursement decision-making, tailored approaches to physician
incentives to use diagnostics in line with recommendations, and the use of managed-entry
agreements to collect additional clinical value and economic data.\textsuperscript{47} Comprehensive
information on how different policies stimulate or hinder the development of diagnostics
and personalized medicines is currently lacking, and studying best practices might help in
identifying the best approaches to pricing and reimbursement of stratified medicines.

Medical devices are much less strictly regulated than medicines in most countries. Free
pricing is usually applicable to medical devices and costs are, in principle, borne by patients
or – in case of hospital care – by hospitals, since there are limited medical devices
reimbursement mechanisms. Furthermore, medical devices are not commonly or structurally
evaluated for their (cost-)effectiveness. Yet, as some devices are high technology their use is
cost-intensive and could contribute to increases in healthcare expenditures. Medical devices
are important within the concept of stratified medicines (co-dependent technologies) when
the “treatment package” is composed of a medicine for treatment and a medical device for
diagnostic purposes. Substantial differences have been identified between European
countries that have reimbursement systems for combined diagnostic and therapeutics (e.g.
Germany, the United Kingdom and France) whereas for other countries (e.g. the
Netherlands, Finland and Norway), no clear pathways for evaluation and funding of
stratified medicine were identified.\textsuperscript{49}

While pricing and reimbursement procedures are, in principle, limited to medicines,
information about pricing practices and funding with regard to treatment packages
involving medical devices is rare. Most countries apply price control policies for medicines
but have free pricing for the diagnostic. A split in funding exists in several countries:
medicines expenses are funded by the third party payers whereas tests are paid for by the
hospitals, increasing the pressure on hospital budgets. Given the expected increasing
importance of medical devices and diagnostics, as part of personalized medicine, policies
that address reimbursement for such ‘treatment packages’ need to be developed.
Furthermore, it should be assessed what the impact is of the current policies on the
availability of personalized medicine therapies for patients.
Personalized medicines and medical devices: research priorities

- Assess whether reimbursement systems of European countries have produces for medical devices and what the impact of procedures is on availability and access to medical devices.
- Assess how reimbursement frameworks and procedures could be adapted to better cope with the challenge of personalized medicines.
- Explore the need for new mechanisms, procedures and regulation with regard to stratified/personalized medicine (combination of medicine and medical device).
- Explore procedures for a common assessment of a “treatment package” (medicine and medical device).
- Assess whether price control for medical devices used in stratified medicines might be an option.
- Collect and exchange price information on medical devices and explore opportunities for a building a price database for medical devices.

2.4 Reimbursement outside Europe

2.4.1 High-income countries: Australia, Canada, New Zealand

Australia, Canada and New Zealand have a long tradition in pharmacoeconomics and HTA. Australia was the first country to require pharmaceutical companies to produce economic data in support of new pharmaceutical products on its pharmaceutical benefits scheme (PBS). The first set of formal pharmacoeconomic guidelines were published in 1992 which, while acknowledged as a valuable tool, were critically discussed regarding the policy and methodology. Soon after the introduction of the Australian guidelines, Canada and New Zealand followed: the Canadian Agency for Drugs and Technologies in Health (CADTH) and the Pharmaceutical Management Agency (PHARMAC) in New Zealand published pharmacoeconomic guidelines in 1993. This was a few years before European countries were introducing or considering requiring economic studies as a prerequisite in the reimbursement process.

With the introduction of pharmacoeconomic principles and HTA in an increasingly number of high-income countries, there has been a large body of literature, often looking at single countries or a group of European countries, particularly United Kingdom, together with Australia and New Zealand, which addressed several of the issues which are discussed in different sections of this paper related to Europe. A 2003 OECD report on eleven OECD countries (European and non-European high-income countries) stated the benefits of pharmacoeconomic assessments for decision-making while it stressed the difficulties of determining “an optimum amount of pharmacoeconomic assessment – that amount which balances benefits, in terms of improvements in the cost-effectiveness of pharmaceutical consumption, with costs in terms of delays in consumption and discouragement of innovation”.

2.4.2 Low- and middle-income countries

In countries without reimbursement systems in place patients pay for their medicines out of pocket. This is the predominant method of payment in most low and middle-income countries (LMIC). Various countries have attempted to control medicine prices through a
range of policies including setting the maximum retail prices (MRP) by using cost-plus price setting methods, or by limiting markups and margins or by reducing sales taxes. Most surveys of medicine prices and availability have been undertaken using the WHO/HAI methodology. Surveys performed in 36 countries (nearly all LMIC) showed that procurement prices by governments were generally close to international prices. Public sector generic prices were three to 12 times international reference prices while private generic retail prices varied from 8.7 to 21 times the same international reference prices. Originator products were on average 2.6 times the generic prices, which makes it appear that in most LMIC prices of medicines are high in relation to purchasing power and that policy measures have generally not been effective in ensuring availability and affordability.

Some low- and middle-income countries have introduced pharmacoeconomic assessments and HTA, but it is not commonly used. There is a body of literature on the issue of pharmacoeconomics and HTA related to LMIC. An unpublished literature review on pharmacoeconomics and HTA as part of the WHO/HAI “Medicine Prices and Availability” project stated that a great potential for HTA to be adopted in LMIC was stressed in literature while extensive but not insurmountable barriers were identified. Among those barriers it was noted that resources required to implement pharmacoeconomics are significant, including the establishment of a regulatory system, and it was recommended to start early and support capacity building for HTA in LMIC. Further, the review indicated that the use of pharmacoeconomics would require the introduction of new legislation to formalize the process. It was suggested that LMIC should learn from countries where pharmacoeconomics and HTA are well established, while in turn countries advanced in pharmacoeconomics and HTA were asked to share guidance and expertise and be transparent.

A lack of quantitative evidence was identified concerning the impact of pharmacoeconomics and HTA on prices, reimbursement and access to medicines – not only for LMIC, but also for high-income countries with established pharmacoeconomic systems and asked for research performed in comparison with other pricing policies or generic promotion. Since studies could not provide a clear answer regarding the generalizability and transferability of health technology assessment results from high-income countries to LMIC, the applicability of pharmacoeconomic standards across countries and settings would require further research. However, given the difference in the health systems and cost bases, the transferability of HTA evaluation from high-income countries to LMIC can be questioned. Furthermore, the lack of reliable data and the variability of the functioning of many individual health systems in LMIC could undermine the assumptions that would have to be made and lead to at least sub-optimal and at worse damaging outcomes for patients.

3. Managing price and volume

The reimbursement of medicines in Europe was discussed in the previous section, including a number of key developments and challenges for reimbursement systems. The increasing use of HTA and economic evaluations in the assessment and appraisal of medicines is a clear trend in Europe, and could aid countries in aligning potentially competing policy objectives of rewarding innovation, cost containment, and access to medicines. A reimbursement policy based on HTA and economic evaluations alone however, will not be sufficient for resulting
long-term positive effects of rewarding innovation. Several additional conditions need to be met, most importantly in the way prices of medicines are set and in the way price and volume of medicines are controlled, if payers want to be successful in controlling pharmaceutical expenditure while simultaneously seeking ways to stimulate pharmaceutical R&D. The price of medicines is a crucial factor in both the control of pharmaceutical expenditure as well as profits generated from marketed medicines to determine whether returns on investments are sufficient to stimulate future R&D in areas of unmet medical needs and/or future medical needs. In this section, pricing practices are discussed including their effects, and several key developments in pricing policies.

3.1 Pricing policies and their effects

3.1.1 Pricing policies

Setting the price of medicines can either be left to the pharmaceutical industry and/or a stakeholder in the supply chain (free pricing) or can be performed by the state (price control). Usually, in the European Union, price control is applied for “reimbursable medicines”, i.e. those funded, at least partially, by public payers, while free pricing is common for non-reimbursable medicines.\(^{66}\) In case of price control, different methodologies may be applied. A very common pricing policy is benchmarking of prices, which means that either the price of the same medicine in other countries (external price referencing) or - in case of competitor products available - the price of identical/similar medicines in the same country (internal price referencing) are used as a benchmark for the medicine’s price. External price referencing is the predominant pricing policy in Europe (see below). For internal reference pricing, medicines are usually grouped based on the Anatomical Therapeutic Chemical (ATC) codes (different chemical structure but with the same indication). In pharmacoeconomic assessment the price of a pharmaceutical depends on its cost-effectiveness\(^{15}\) (see section on value-based pricing).

3.1.2 External price referencing

External price referencing is defined as “the practice of using the price(s) of a pharmaceutical product in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country”.\(^{67}\)\(^{68}\) In 2013, this practice is used in 24 out of 27 EU Member States\(^{69}\), and it is also continuously gaining relevance worldwide.\(^{62}\) (see also the section on the rest of the world). There are a large number of variations in the way external price referencing is designed and implemented in the European countries (Table 8.3.1). External price referencing does not necessarily target all (new) medicines: In European countries external price referencing is usually applied to on-patent medicines which are considered reimbursable whereas off-patent medicines may be subject to internal price referencing (see the section on generics and on the rest of the world). It should be noted that in some European countries external price referencing is not the sole pricing policy, but the price of the medicine in other countries is one of several criteria in the price setting process (Table 8.3.1).

Evidence on the impact and limitations of external price referencing is scant (even for the European countries though literature is focused on these countries). This was also a finding of a literature review under the WHO/HAI Pharmaceutical Pricing Project.\(^{67}\) Most studies are descriptive, and very few evaluated the impact of the policy. Usually, only the impact on
prices is assessed – within the country applying external price referencing and possible spillover effects to other countries. Håkonsen et al (2009)\textsuperscript{70} looked at medicines prices development from 1994 to 2004 in Norway, which had introduced external price referencing in 2000, and claimed that consistent use of external price referencing and subsequent price revisions led to substantial price reductions on many medicines. Windmeijer et al. (2006)\textsuperscript{71} measured the effects of the implementation of external price referencing in the Netherlands and came to the conclusion that this pricing practice resulted in lower prices. Merkur and Mossialos (2007)\textsuperscript{72} simulated the effect of external price referencing on medicine prices in Cyprus and showed that this would lower prices and contain costs after identifying Cyprus as a high price country for medicines. Filko and Szilagyiova (2009)\textsuperscript{73} stated that due to the policy change of external price referencing in Slovakia in 2009, the proportion of pharmaceutical expenditure as share of total health care spending declined by approximately 25 per cent showed in a study on 14 European countries that for patented medicines, prices are in general lower in cases where the country applied external price referencing compared to countries which did not.\textsuperscript{74} Nevertheless substantial price differences among countries that apply EPR were identified. Stargardt and Schreyögg (2006)\textsuperscript{75} looked into how the composition of the country basket and possible price reductions have an influence on the price level in other countries: A price reduction of €1.00 in Germany was found to reduce maximum reimbursement prices from €0.15 in Austria to €0.36 in Italy.

Despite these indications that the policy may appear to be able to drive prices down, external price referencing has been criticized for several reasons, among those for its potential to discourage innovation and impede patient access.\textsuperscript{27} A major argument against external price referencing is that it neither reflects the willingness-to-pay nor the ability-to-pay of a country, which other concepts such as value-based pricing do. By setting the price of a new medicine based on the price of that same medicine in a number of other countries, a country would only end up with a price that offers both value for money as a reward for innovation if all referenced prices would be value-based. However, the widespread use of external price referencing provides a pharmaceutical company with an incentive to first launch its product in ‘free-pricing’ countries (such as the United Kingdom, Denmark, Germany), where they are likely to obtain high price, and to delay launching the product in low-price markets.\textsuperscript{1,76}

It is often argued that, if all European countries apply external price referencing and they all refer to each other, eventually the price level across Europe will converge.\textsuperscript{1,67,77} Currently, however, price variances across Europe continue to exist (see also the table on price data in the Annex 8.3.2). These price differences are likely the result of different methodologies that are used for external price referencing. For example, not all countries use the same basket of countries that are referenced, and where some countries reference the lowest price in the country basket, others reference the average price.\textsuperscript{77,78} With regard to price convergence, there is no clear picture for Europe: two recent studies, which tested the price convergence in European Union,\textsuperscript{79,80} suggested no substantial reduction in price dispersion within the EU countries. These findings differ from previous results which indicated for price convergence within the European Union for newly launched medicines.\textsuperscript{81}

The referencing across countries is nearly always done to the list prices of medicines. In practice, actual prices in European countries tend to be lower than list prices due to arrangements between industry and payers, whose provisions are usually kept confidential (see section on discounts & rebates). Since countries will continue to refer to the higher list prices indicated in the price data bases instead of the actual discounted prices, they might...
risk overpaying. Further, the implementation of discounts and rebates offered by industry to public payers in order to avoid statutory cuts of list prices is likely to prevent a transfer of possible savings of price cuts in one country to the reference countries. An analysis on the impact of price cuts in Greece and Spain showed that the price reductions were not automatically translated into price decreases in referencing countries as expected, which could either be due to countries not regularly monitoring the medicines prices in the other countries, or the confidential discounts and rebates which were not reflected in the list prices. This also highlights the complexity in applying external price referencing: apart from identifying and obtaining access to relevant data sources, capacity has to be built on understanding the different price types applied and included in the national databases and on identifying the limitations of the data sources (e.g. inclusion of outpatient sector and/or reimbursable medicines only, no discounts and rebates reflected). Furthermore, regular monitoring on the changes in the prices in other countries, including in distribution mark-up regulation, is needed – given that ex-post adaptations of prices are possible. This makes external price referencing both time and resource-intensive.

External price referencing is still a reality in European countries, particularly for pricing new medicines, and it is generally expected to continue to play a role. Notwithstanding this observation, in 2010 a World Bank expert predicted that external reference pricing would soon reach the end of its useful cycle, as when almost all countries reference each other, prices will converge and price differences between countries will diminish. Whether this prediction will turn out to be accurate remains to be seen for now.

Table 8.3.1: Different methodologies applied for external price referencing in EU Member States

<table>
<thead>
<tr>
<th>Country</th>
<th>Relevance of EPR</th>
<th>Scope</th>
<th>Country basket: number of countries included</th>
<th>Calculation of benchmark price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Main policy / criterion</td>
<td>Reimbursable medicines</td>
<td>24</td>
<td>Average of all countries</td>
</tr>
<tr>
<td>Belgium</td>
<td>Supportive information</td>
<td>All medicines</td>
<td>24</td>
<td>Average of all countries</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>Main policy / criterion</td>
<td>Prescription-only medicines</td>
<td>9</td>
<td>Three lowest prices</td>
</tr>
<tr>
<td>Cyprus</td>
<td>Main policy / criterion</td>
<td>Imported medicines</td>
<td>4</td>
<td>Average of all countries</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>Main policy / criterion</td>
<td>All medicines</td>
<td>26</td>
<td>Average of all countries</td>
</tr>
<tr>
<td>Denmark</td>
<td>Not applied</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>Not applied</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estonia</td>
<td>Main policy / criterion</td>
<td>Reimbursable medicines</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Greece</td>
<td>Main policy / criterion</td>
<td>All medicines</td>
<td>22</td>
<td>Three lowest</td>
</tr>
<tr>
<td>Spain</td>
<td>Main policy / criterion</td>
<td>Innovative medicines</td>
<td>Not defined</td>
<td>Not defined</td>
</tr>
<tr>
<td>Finland</td>
<td>Main policy / criterion</td>
<td>Reimbursable medicines</td>
<td>16</td>
<td>Checking prices of reference countries in a specific order</td>
</tr>
<tr>
<td>France</td>
<td>Main policy / criterion</td>
<td>Innovative medicines</td>
<td>4</td>
<td>Prices not higher than</td>
</tr>
<tr>
<td>Country</td>
<td>Main policy / criterion</td>
<td>Reimbursable medicines</td>
<td>Pricing Policy</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
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<td>------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td>Main policy / criterion</td>
<td>Reimbursable medicines</td>
<td>24 Lowest price of the basket</td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>Main policy / criterion</td>
<td>Prescription-only medicines</td>
<td>9 Average of all countries</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>Supportive information</td>
<td>Reimbursable medicines</td>
<td>Not defined Average of all countries</td>
<td></td>
</tr>
<tr>
<td>Lithuania</td>
<td>Main policy / criterion</td>
<td>Reimbursable medicines</td>
<td>4 95% of average in reference countries</td>
<td></td>
</tr>
<tr>
<td>Luxemburg</td>
<td>Main policy / criterion</td>
<td>All medicines</td>
<td>1 Lowest price per basket</td>
<td></td>
</tr>
<tr>
<td>Latvia</td>
<td>Main policy / criterion</td>
<td>Reimbursable medicines</td>
<td>3 Third lowest price, not higher than price in Lithuania and Estonia</td>
<td></td>
</tr>
<tr>
<td>Malta</td>
<td>Main policy / criterion in the private sector</td>
<td>Prescription-only medicines</td>
<td>26 Average of reference countries</td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>Main policy / criterion</td>
<td>Prescription-only medicines</td>
<td>4 Average of reference countries</td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>Main policy / criterion</td>
<td>Prescription-only medicines</td>
<td>9 Average of three lowest countries</td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td>Main policy / criterion</td>
<td>Reimbursable medicines</td>
<td>17 Lowest price per basket</td>
<td></td>
</tr>
<tr>
<td>Portugal</td>
<td>Main policy / criterion</td>
<td>Prescription-only medicines</td>
<td>4 Average of reference countries</td>
<td></td>
</tr>
<tr>
<td>Romania</td>
<td>Main policy / criterion</td>
<td>Reimbursable medicines</td>
<td>12 Lowest price per basket</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>EPR not applied</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slovenia</td>
<td>Main policy / criterion</td>
<td>Reimbursable medicines</td>
<td>3 95% of average of countries</td>
<td></td>
</tr>
<tr>
<td>Slovakia</td>
<td>Main policy / criterion</td>
<td>Reimbursable medicines</td>
<td>26 Average of 6 lowest countries in the basket</td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>EPR not applied</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

External price referencing: research priorities

- To study the effect of external price referencing on innovation, timely access to medicines, and sustainable funding
- Study the impact of external price referencing on incentives for R&D
- Assess whether there is evidence of price convergence following the use of external price referencing
- Explore to what extent EPR can achieve intended effects and to what extent methodology improvement are possible
- Study the impact of confidential discounts and rebates applied in external price referencing
- Explore the role of price information systems and regular price reviews
- Assess spill-over effects of external price referencing on the availability and prices in lower income countries.

3.1.3 Value-based pricing

‘Value-based pricing’ means that the price of a medicine is set according to the value it generates and is an alternative to external price referencing. Value-based pricing is gaining momentum, although there is no widely-accepted definition of value in this context. Sweden, Canada and Australia have already implemented value-based pricing systems and the United Kingdom will implement a new value-based pricing system, set to replace the 50-year old Pharmaceutical Price Regulation Scheme (PPRS) in 2014. The United Kingdom’s value-based pricing system will focus on quality-adjusted life year (QALY) gains in relation to costs, although considerations related to innovation, burden of illness, and rare diseases might be addressed in decision making as well. Sweden abolished external price referencing and introduced a value-based pricing system in 2002 (see Box 8.3.3), which uses priority setting in healthcare on considerations of human dignity, need and solidarity, and cost-effectiveness. Given that value-based pricing is a policy that has not seen widespread uptake as of now, much of the evidence for its ability to align policy objectives remains theoretical at this point, even though inferences based on economic theory and modeling approaches have indicated that value-based pricing could result in both static and dynamic efficiency.

Value-based pricing for medicines means that in price setting for new medicines, prices are set based on the value the medicine offers, usually, as assessed through health technology assessment (HTA) or economic evaluation. However, there is no widely accepted definition as to what types of policies are in fact value-based pricing systems – the OECD very recently assessed the value-based pricing elements of several countries, and concluded that all countries included have a system in place that assesses the added value of pharmaceuticals, but not all countries included (Australia, Belgium, Canada, France, Italy, Norway, the Netherlands, Sweden, and the United Kingdom) have fully integrated pricing and reimbursement decisions. In the United Kingdom (at the time of the study) the price is negotiated through the PPRS and routine HTA of all pharmaceuticals is not performed. Furthermore, the majority of the studied countries in the OECD report use external price referencing for setting prices. A ‘narrow’ definition is applied for value-based pricing as to not confuse the reader, and do not define systems that use HTA to inform reimbursement
decisions but where price setting occurs separately, from systems in which pricing and reimbursement decisions are fully integrated. According to this definition of value-based pricing, only a few countries worldwide use value-based pricing today (in Europe: Sweden, and the United Kingdom from 2014 onwards), whereas most European countries use HTA primarily as part of reimbursement (and not pricing) decisions. This narrow definition is used as systems that have value-based elements in their reimbursement processes (such as the use of economic evaluations to inform decision-making) still can use pricing policies such as external price referencing for setting prices.

When value is determined by the incremental cost-effectiveness of a new medicine in value-based pricing, information on a new medicine’s incremental health gains ($\Delta E$) and incremental costs ($\Delta C$) over an existing treatment options is required to determine the amount of added value of the new medicine. In ‘normal’ cost-effectiveness analysis the ICER is usually expressed as costs per QALY gained. The decision maker subsequently will determine whether the ICER is deemed acceptable or not. An explicit willingness to pay threshold ($k$), however, is required in value-based pricing in order to determine the pharmaceutical’s price. When the decision maker has access to all information on costs and health effects, given the formula $k = \Delta C / \Delta E$, and given that $\Delta C$ is composed of both price (the unknown) and all other costs (defined), determining the value-based price would be a matter of simply solving the formula. Furthermore, given that the total budget impact of a newly introduced medicine consists of both price and volume, value-based pricing enables the decision maker to derive a ‘menu’ of combinations of prices and volumes – given that a number of sub-populations and indications can be identified for the medicine.\(^8\)\(^5\)

One of the main criticisms of value-based pricing is that by using an explicit threshold (also see the discussion on willingness to pay in the previous section), manufacturers will have no incentive to price their product below the threshold.\(^8\)\(^3\) Although this is true, there are several reasons why such a mechanism is actually considered preferable; firstly, as the price of a new medicine will depend on the additional value it generates, it will allow medicines that generate more health gains to capture a larger price, which will create an incentive for the development of products that generate more added value – and will create a disincentive for the development of products for indications that already have (good) treatment options. Secondly, as the market exclusivity for new medicines is limited, there will be positive net benefits in the long run to the healthcare system as the price of a medicine is expected to drop once generic competitors enter the market due to price competition. Therefore, although no net benefits occur short-term, there will be substantial net benefits once the patent expires – given that the medicine has a long life cycle and is not replaced by innovative medicines in the near future.\(^8\)\(^3\),\(^8\)\(^5\)

Another main argument for allowing manufacturers to price at the threshold is that it will result in both static and dynamic efficiency\(^8\)\(^4\),\(^8\)\(^5\),\(^8\)\(^6\) allowing all value to be appropriated by the manufacturer during the patent life of the medicine will provide an incentivized innovation in the long run.\(^8\)\(^5\),\(^8\)\(^6\) A value-based pricing system that is properly and consistently applied could therefore result in allocative efficiency, and could create sufficient incentives to pharmaceutical companies in the long term for the investment in the development of new medicines. Furthermore, value-based pricing would create a clear incentive to companies for the investment in therapeutic areas of unmet medical needs and in therapeutic areas that have no or ineffective treatment options only. Finally, strategic launching behavior and
delays in access could be reduced as the necessity to rely on external price referencing to set prices would disappear in countries that would introduce value-based pricing.

It is recognized, however, that in order to achieve positive long-term effects, certain conditions need to be met: cheaper generics will enter the market after patent expiration, prescribing will switch to the generic versions, and future patented medicines reflect their value compared to the (cheaper) generic versions of the old branded medicine. The rationale of the use of an explicit willingness to pay threshold that allows manufacturers to price a new medicine to the point where the net benefits are zero (i.e. where the incremental cost-effectiveness ratio of the new medicine equals the threshold) is to provide access to new medicines at a price that is socially acceptable, rewarding companies for innovation, while positive net benefits will be achieved for the healthcare system in the long run (i.e. after market exclusivity ends). Furthermore, it has been argued that value-based pricing holds several advantages over currently used pricing systems, as it is expected that a country’s willingness to pay will be based on citizens’ willingness to pay for medical care, which is related to a country’s per capita GDP – meaning that if multiple countries would implement value-based pricing, it would allow for differences in prices according to differences in willingness and ability to pay between countries. However, the existence of parallel trade could substantially hinder the successful implementation of value-based pricing. This issue is covered further in this section.

### 3.1.4 Priority setting using value-based pricing

In order to create financial incentives for priority medicines, payers could consider the advantages of value-based pricing combined with a societal perspective. If a payer would make explicit statements about its willingness to pay threshold for a new treatment indicated for Alzheimer disease, or depression, this would clearly signal to pharmaceutical companies that for these indications, treatments that result in significant therapeutic improvements, significant cost savings, or both, would be rewarded with a premium price. Allowing a pharmaceutical company to capture all benefits during the period of market exclusivity, as has been proposed in the United Kingdom, will create an incentive for the development of priority medicines.

A study that assessed the reimbursement systems of five European countries concluded that all systems included in their analysis were mainly supply-driven, and that a shift towards reimbursement policies that are more pro-active should be considered. Most decision-makers are not explicit about the types of medicines that they would like to be developed and these are not considerations that are usually taken into account; the pharmaceutical industry determines what medicines are and are not developed. Value-based pricing could facilitate a shift as it provides companies with an incentive to develop products that do not only result in health benefits, but that also prevents costs – either related to illness or broader societal costs (when a societal perspective is taken). Payers could make their demand for certain medicines explicit through their willingness to pay for certain indications. The Swedish value-based pricing system, that uses a societal perspective, allows for economic benefits to be captured in the price (see Box 8.3.2). It has been assessed that for Alzheimer disease, direct medical costs account for 10 to 25% of all costs, whereas indirect costs account for 8 to 79% of all costs. A review of economic evaluation of treatments for depression showed that productivity costs (indirect costs) accounted for 60% of total costs in studies that used a societal perspective. There are substantial savings possible therefore in both
therapeutic areas, which means that, if payers would allow such benefits to be captured in the price, incentives could be created for the development of medicines for these conditions. Methods to set value-based prices using economic evaluations should be developed.

### Value-based pricing: research priorities

- Study and evaluate the impact of value based pricing on innovation aligning with other policy goal such as access to medicines and cost-containment
- Explore which prerequisites needs to be met for achieving the intended results
- Accompany and monitor the implementation of this policy when newly introduced (e.g. the United Kingdom)
- Method development for value-based pricing should be supported
- Study how societal preferences regarding rewarding innovation can be reflected through value-based pricing systems such that thresholds reflect societal preferences
- Study barriers to implementing value-based pricing

#### 3.1.5 Differential pricing

Patents and data exclusivity create a temporary monopoly for a company, which means that pricing is not influenced by the presence of competitors. Given the large fixed costs of pharmaceutical R&D, a period of market exclusivity enables a company to charge prices that are higher than they would be in a competitive market and to generate profits that earn back investments and generate funds for future R&D. Although patents result in high prices, a company that seeks to maximize profits would ideally launch a medicine in multiple countries, where national prices depend on the country’s ability to pay. The cost of R&D is a fixed, globally joint cost for a pharmaceutical company. This means that R&D costs do not depend much on the number of countries where the medicine eventually will be launched, or on the number of people that will ultimately use the medicine. Therefore, once a medicine has been launched in several countries, there is no large incremental R&D expense to launch the medicine in additional countries – and the other costs of launching the product in a country are relatively low. The concept of Ramsey optimal pricing states that prices should differ across markets according to the demand elasticity: more price-sensitive users are charged a lower price than users that are less sensitive. In practice, this means that users in lower income countries usually pay a lower price as they are more sensitive to price than high-income users.

When a company charges a different price to different groups of consumers for reasons not related to costs, this is called price discrimination or differential pricing. ‘Differential pricing’ therefore is not so much a pricing policy (such as external price referencing or value-based pricing) but an economic concept. Differential pricing therefore could be pursued simultaneously with value-based pricing. An essential requirement for companies to engage in differential pricing, however, is that markets need to be sufficiently separated.

Differential pricing is limited within the EU market for two main reasons. First, within the European Union, the legal concept of ‘exhaustion’ restricts differential pricing as exhaustion means that once a patented product is marketed, the company no longer has control over the distribution of the product. As the European Union follows the concept of EU-wide
exhaustion, which is tied to the free movement of goods, the parallel trade of medicines throughout the EU is possible. Parallel trade occurs when products are legally imported from another country without the authorization of the manufacturer. Price differentials are the driving forces of parallel trade: when price differences between countries are large enough, it will be profitable for a wholesaler to import medicines from low-price countries. Parallel trade within the EU severely restricts the possibilities for differential pricing, resulting in reduced patient access in poorer countries.

A second main limitation to differential pricing in the Europe is the widespread use of external reference pricing, which is used by almost all European countries to some extent. As a result, pharmaceutical companies will seek a similar list prices across countries that are linked by referencing, ‘first launch’ in markets where less restrictive pricing mechanisms are used, and will have an incentive to either delay the launch of a medicine in low-income countries, or will not launch in these countries at all, especially if the low-price countries are small markets, although it has been suggested that the causes of observed launch delays could be multi-factorial.

The effects of parallel trade and external price referencing are not shared equally between high-income countries, low-income countries, and pharmaceutical companies, but are most likely to result in reduced social welfare in the relatively lower income countries; given linkage of markets through parallel trade and external price referencing, it is against a company’s interest to launch a medicine in a market where the country’s affordability would result in a price low enough to initiate parallel trade to markets with high prices or that would substantially lower prices in other markets through external price referencing. Additionally, in response to parallel trade, pharmaceutical companies are more likely to bargain for a higher price in low-income countries than they would under a regime where parallel trade was not possible. In contrast, for high-income countries the effects of price inter-dependency through parallel trade and external price referencing are more positive, as it will result in lower prices than without the existence of inter-dependencies. Even though throughout Europe price differences are still observed, there may be reason for concern regarding the access to medicines in EU countries with lower income levels – as well as those European countries that have been affected by the economic crisis.

A shift from external reference pricing towards value-based pricing - where prices for new pharmaceuticals would be set based on added value in relation to an explicit threshold - has been proposed to replace external reference pricing policies, in order to allow differential pricing and achieve both static and dynamic efficiency. However, even if all countries in Europe would implement value-based pricing systems, this would not resolve the issue of parallel trading that could still distort the intended effects of any value based pricing policy.

Without a substantial change to the legal EU framework there are only two mechanisms that could allow differential pricing for medicines in Europe. First, within the current systems, European countries could consider revising their basket of reference countries and remove those countries that do not have comparable GDP per capita, as it would reduce the incentives for pharmaceutical companies to not launch, delay launch, or negotiate high prices in the lowest income countries. A second possibility is for lower income countries to agree to a high list price for new medicines, while negotiating confidential discounts and rebates with pharmaceutical companies. Confidential discounts and rebates are currently the only instrument available to achieve differential pricing, and to help assure that citizens
of European countries with lower affordability for medicines will maintain access to medicines, and mechanisms such as confidential discounts and rebates are necessary to achieve separation of markets under external price referencing and parallel trade.89

The previous Priority Medicines Report proposed to explore a value-based pricing system where the threshold for each country would be based on the national income level.94 The authors of the background paper ‘Approach to the valuation and pricing of future medicines’ argued that it was unfair to expect R&D costs to be spread equally across countries of variable wealth, and therefore a country’s threshold or ability to pay should be based on its GDP per capita. Such a system of differential pricing (or ‘equity pricing’) would be an ‘equitable system for true innovation while ensuring access by those who need them’.94 The variations in GDP per capita throughout the EU are substantial: the average EU-27 capita was €25,200 in 2011, but GDP varies from €9,800 in Latvia to €82,100 in Luxembourg. There would need to be a major political commitment from European countries in order implement such a system, and any country that would not participate could ‘free-ride’ by letting other countries reward innovation while setting lower prices.

**Differential pricing: research priorities**

- Evaluate the impact of EPR and parallel trade, in terms of availability of medicines and the affordability of medicines in EU countries.
- Study mechanisms through which differential pricing could be applied to the European market.
- Explore the prerequisites that are needed to support differential pricing.

**3.1.6 Volume control and incentives for prescribing/dispensing**

Historically, payers’ focus has primarily been on controlling pharmaceutical prices. In recent years, however, it has been increasingly acknowledged that pharmaceutical expenditure is not merely determined by price but is mainly driven by volume (see Figure 8.3.1). Pricing policies therefore are one of several variables influencing profitability of investing in pharmaceutical R&D. Policies that influence volume, as well as generic promotion policies influence market exclusivity, enforcement, and therefore could impact incentives for innovation.2

Furthermore, in many cases the incomes of health care providers (in particular pharmacists) are linked to discounts, rebates and dispensing fees. This can have a positive impact, by creating the right incentives for rational use of medicines, but it can also have adverse effects by creating a stimulus for inappropriate use of medicines, or create a threat to the economic sustainability of health care providers (e.g. if incomes are linked to certain margins on products, and these margins are excessively reduced).

A key volume-control policy concerns the monitoring of the prescription behavior and nowadays all EU Member States have some type of prescription monitoring system in place. The Danish electronic monitoring system (Ordiprax, www.ordiprax.dk) is an example of a prescription monitoring system that allows the authorities to assess pharmaceutical consumption at the central, local and the individual physician level. Doctors have access to
the Ordiprax system as well, enabling them to compare their prescription pattern to other physicians in the region. Some European countries supplement prescription monitoring with specific doctor agreements, such as an obligation to prescribe a specific amount or less expensive medicines. Furthermore, several European countries (Czech Republic, Latvia, Slovakia, United Kingdom, some regions in Spain and Sweden) have pharmaceutical budgets for prescribers in place. Budgets can be combined with financial incentives, for example doctors may keep some of the savings to invest into their practice (e.g. “Indicative Drug Target Scheme” in Ireland whose financial incentive had meanwhile been abolished), or could face penalties in case of excess (e.g. Latvia). During the 1990s, more European countries (e.g. Germany, and France) had pharmaceutical budgets in place that yielded expected savings the first year after introduction but lost their effectiveness in subsequent years - as announced sanctions could not be executed resulting in the abolishment of pharmaceutical budgets in these countries. Although France and Italy nowadays do have targets regarding prescribing limits, they are officially not called budgets.

### Volume control: research priorities

- Study the impact of the volume component on pharmaceutical expenditure, innovation and access to medicines
- Explore how policies aimed at controlling volume, including different incentives targeted at various stakeholders, can be designed to ideally not only contain pharmaceutical expenditure, but also encourage a more rational use of medicines
- Study how an “ideal policy mix” addressing both price as well as volume can be designed

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**Figure 8.3.1: Elements of Growth in 2011 – High income countries**

<table>
<thead>
<tr>
<th>Country</th>
<th>Price</th>
<th>Volume</th>
<th>Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>6.5</td>
<td>-1.7</td>
<td>8.5</td>
</tr>
<tr>
<td>Canada</td>
<td>1.2</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Finland</td>
<td>-2.3</td>
<td>1.8</td>
<td>0.5</td>
</tr>
<tr>
<td>France</td>
<td>-2.8</td>
<td>2.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Germany</td>
<td>3.9</td>
<td>-3.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Ireland</td>
<td>2.7</td>
<td>7.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Japan</td>
<td>6.2</td>
<td>-8.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Netherlands</td>
<td>15.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>4.2</td>
<td>4.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Spain</td>
<td>2.7</td>
<td>4.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Switzerland</td>
<td>4.2</td>
<td>-1.8</td>
<td>0.2</td>
</tr>
<tr>
<td>UK</td>
<td>6.1</td>
<td>-2.8</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Source: IMS MIDAS, Dec 2011

Note: Growth refers to full 2011 growth over 2010 in constant US dollars. Price growth reflects growth due to price differences for packs sold in 2011 compared to their prices in 2010. It is measured in constant US dollars at the ex-manufacturer level. Volume growth is often referred to as sales at constant prices at the ex-manufacturer level and refers to growth due to changes in the packages sold by applying 2010 prices to volumes in both 2010 and 2011. It is measured in constant US dollars at the ex-manufacturer level.
3.2 New trends in pricing and reimbursement

3.2.1 Use of managed-entry agreements in Europe

At the time that reimbursement is sought for a new medicine, overall evidence might be insufficient to accurately assess the clinical effectiveness, cost-effectiveness, or budget impact of a new medicine in clinical practice. As more countries start to use HTA in reimbursement decisions, the lack of long-term data available at the time of market introduction, especially for chronic therapies, becomes more problematic. The added value of medicines for chronic diseases is usually driven by projections on long-term health outcomes, which means that extrapolations based on surrogate endpoints in Phase III trials will have to be made. If such evidence is not accepted by payers and most countries do not accept price increases after product launch, this forces companies into a trade-off of launching earlier at a lower price or delaying launch in order to collect the required evidence that might result in a higher or premium price and delayed access for patients. Managed-entry agreements between payers and companies could, at least partially, solve this issue as they enable the decision-maker to grant access to a new medicine under certain restrictions that are either aimed at reducing this uncertainty or transferring the risk associated with the uncertainty to the manufacturer.

Therefore, in recent years agreements between payers and industry intended to manage such uncertainty have gained importance. These different approaches have been summarized under the concept of “managed-entry agreements” (MEA). In managed entry-agreements, a major distinction can be drawn between arrangements based on outcomes (e.g. coverage with evident development (CEP), patient access schemes (PAS), risk-sharing schemes (RSS), conditional reimbursement, outcome guarantee arrangements) and non-outcome based arrangements (e.g. price-volume agreements, utilization caps). Managed-entry agreements allow for a medicine to enter the market subject to certain restrictions of conditions. These conditions are usually related to tracking the actual utilization or performance of the medicine or to tie the level of reimbursement to a defined outcome.

Managed-entry agreements have been introduced in several European countries, particularly in the United Kingdom, Belgium, Italy, Poland, and the Baltic states. A study by Kanavos et al. (unpublished) studied various managed-entry agreements in Europe and found that 75% of all the agreements in the studied countries aimed to address budget impact, either alone (42%) or in combination with cost-effectiveness (16%), use (15%) or both (2%). Two main trends in European countries employing managed-entry agreements seem to emerge: a focus on budget impact, or on cost-effectiveness. Managed-entry agreements in countries such as Italy, Portugal, Lithuania, the Czech Republic, and Belgium primarily focused on budget impact, whereas cost-effectiveness seemed to be the driving force in countries like Sweden, the Netherlands, and the United Kingdom, when deciding to engage in managed-entry agreements. The most commonly found types of managed-entry agreements were price-volume agreements (40%), followed by requirements for data collection (29.4%), and limited access to eligible patients (12.6%). Price-volume agreements are widely used in Italy, Portugal, and Lithuania while data collection is a common requirement in Italy, the Netherlands, the Czech Republic and Sweden. Italy, the Czech Republic and Belgium limit access to eligible patients in an attempt to manage budget impact and use. In terms of therapeutic groups, antineoplastic and immune-modulating agents represented 37.3% of all the managed-entry agreements identified by Kanavos et al., followed by alimentary tract and metabolism (16.5%) and nervous system agents (9.8%). In all EU Member States apart
from Sweden, the greatest proportion of agreement involved antineoplastic and immune-modulating medicines.

Klemp et al. (2011)\textsuperscript{98} provided an overview of advantages and disadvantages of managed-entry agreements to different stakeholders. The main disadvantages included the costs and bureaucracy required for the implementation of agreements to both companies as well as for payers. Furthermore, for the payer it could be costly and time-consuming to manage multiple schemes. An important disadvantage for a payer, furthermore, is the difficulty to withdraw reimbursement or coverage once certain outcomes are not confirmed. It might prove to be quite difficult to withdraw a medicine once it is made available, and doing so would require clear rules and procedures\textsuperscript{98} – as well as public and stakeholder support for such procedures.

It has been argued that managed-entry agreements are essentially a warranty offered by the manufacturer of a medicine – typically for new and expensive medicines.\textsuperscript{100} As the manufacturer can in some circumstances, be in a better position to be confident about the benefits of its product, a managed-entry agreement can be used to offset some of the risk to the payer that cannot be sure about the performance of the medicine in clinical practice.\textsuperscript{100} However, in the case of the performance of a medicine in clinical practice there is much uncertainty that neither the manufacturer nor the payer are able to reduce. It has been argued, therefore, that managed-entry agreements that seek to limit the exposure of a payer by limiting payment to specific subpopulations or at given prices to unexpectedly \textit{valuable} innovations, can limit incentives to invest in the development of costly and high risk indications.\textsuperscript{100} Although for payers, managed-entry agreements are a good method to reduce the risk of undesirable outcomes (i.e. higher volumes or less health benefits than anticipated), payers have to be prepared to allow companies to reap the upside surprise of a medicine that performs better than expected\textsuperscript{100}, as otherwise incentives to develop products for high-risk indications might be limited.

Managed-entry agreements are usually confidential. Therefore, an important incentive to engage in managed-entry agreements, other than market access, would be to limit spillover effects to other markets as a result of parallel trade and external price referencing. This does, however, have implications for transparency (see later discussion on transparency).

\begin{mdframed}[backgroundcolor=white]
\textbf{Managed-entry agreements: research priorities}
\begin{itemize}
  \item Assess the effects of managed-entry agreements, as there is limited evidence on the impact they have on prices, availability, access, and incentives for innovation.
  \item Support the exchange of best practices between countries
  \item Explore the prerequisites for the implementation of managed-entry agreements, and assess for which medicines they appear most appropriate
\end{itemize}
\end{mdframed}

\subsection{The role of the hospital setting and interface management}

Several innovative medicines tend to be used in the hospital setting, frequently for hospital-exclusive use. Until recently the expenditure of medicines in hospitals has not been a priority for policy makers as the expenditure of medicines in hospitals has been fairly constant and
Update on 2004 Background Paper, BP 8.3 Pricing and Reimbursement Policies

relatively low (usually between 5 and 10 per cent of a country’s pharmaceutical budget) over the years. The introduction of expensive new medicines, including orphan medicines, has resulted in disproportional increases of hospital pharmaceutical budgets and raised the attention of policy makers in recent years. Additionally, it is increasingly recognized that pharmaceutical treatments that start in hospitals influence the medication used in the outpatient sector.

Published information about pharmaceutical pricing practices, medicines management and medicines prices in hospitals in European countries was not available until recently since most research about medicines policies has concerned the outpatient sector only, although there was widespread anecdotic knowledge about discounts on medicines prices in the hospital sector. Policy makers tended to have very limited knowledge about the inpatient sector as well, as national competent authorities in European countries are usually responsible for deciding prices and reimbursement coverage of medicines used in for the outpatient sector only. Medicines used in hospitals are usually financed through hospital budgets (and not by the payers for outpatient medicines), and their procurement and listing on the hospital formulary is not the responsibility of the competent authorities but of hospital pharmacists.

Given this lack of knowledge, there has been a call for examining medicines management and prices in the hospital setting. In response the Pharmaceutical Health Information System (PHIS) project surveyed the pricing and procurement practices and funding models for medicines used in hospitals in European countries (see Box 8.3.4 for procurement methods and Table 8.3.2 for new funding mechanisms for high-cost medicines, see the section on new funding mechanisms). Though prices of medicines used in hospitals are usually linked to confidentiality issues, making it difficult to assess actual prices, the PHS study surveyed official hospital list prices and actual prices paid by hospitals in five European countries. The results confirmed the existence of discounts and rebates granted to specific medicines for hospital use. While hospitals appear to have little headroom to negotiate price reductions for medicines to which no therapeutic alternatives are available, high price reductions, including cost-free provision of medicines (if allowed by national legislation), tend to be granted to medicines whose treatment is likely to continue in primary care after discharge of the patient. The results suggest the need to bridge the gap between the outpatient and inpatient sectors both for (innovative) high-cost medicines - since otherwise payers will have an incentive to find arguments why medicinal treatment might be shifted to the other sector - as well as for high volume medicines to which pharmaceutical companies are likely to grant to hospital pharmacists large discounts and rebates, in order to facilitate starting treatment in hospitals.

Given the complex situation and different incentives to stakeholders; policy makers and stakeholders have been urging for an improvement of medicines management at the interface, but knowledge about good practice examples appear to be scant. There appears to be two different approaches to improve the “interface management” (of note: there are different terms to address such initiatives at the interface between primary care and hospitals. Other common terms are seamless care, continuous care, transitional care, transmural care, integrative care. The different notions and terms also confirm that the cooperation mechanisms between hospital and outpatient sector can still be further explored). Firstly, measures might be set at a micro-level of individual hospitals and consist of cooperation with outpatient carers, including interventions at admission and particularly
hospital discharge (e.g. communication of discharge information to general practitioners and community physicians, education and pre-discharge pharmaceutical counselling of patients, community liaison service, home visits by a health visitor shortly after discharge, a follow-up phone call by a pharmacist, computer-based interventions). Secondly, at the system level, the organisation and funding of the pharmaceutical system could be addressed. Such measures would imply legal and organisational changes. Though few European countries have implemented such system-related interface management policies there are some good practice examples such as the joint reimbursement lists and joint Drugs and Therapeutics Committees in the Stockholm County in Sweden and Scotland. Interface management measures addressing the organisation and funding of the system are likely to be supportive to improve access to medicines, since they no longer incentivize individual payers and procurers to pay attention to the sector only for which they are responsible for but decisions taken would automatically impact both sectors.

Box 8.3.4: Procurement practices for medicines used in hospitals in European countries

The PHIS project identified tendering and negotiations as the most important procurement policies in the European hospital setting, whereas procurement by competitive negotiations is rather rare. For example, it is used in Slovakia via what is known as “market evaluation” in which hospital pharmacists always ask three suppliers for a cost estimate.

Many European countries apply a mix of purchasing policies. In some countries tendering is the sole or key policy for procuring medicines. In eight countries (Cyprus, Estonia, Italy, Latvia, Malta, Norway, Sweden and the United Kingdom) all or the majority of medicines used in (public) hospitals are put out to tender. Tendering may be done by the hospitals (individually or by the organization owning the hospitals) or centrally, usually carried out by Ministries of Health, social health insurance institutions or procurement agencies. Well-known examples for the latter case are the national procurement agencies AMGROS and LIS in Denmark and Norway, in charge of procuring all medicines for public hospitals. In Romania and Slovakia tendering is done centrally for some, mostly expensive medicines such as blood factors, while other medicines are procured via direct negotiations between the hospitals and the pharmaceutical companies or wholesalers.

Several countries have established regional procurement committees (e.g. the Regional Therapeutic Committees in Italy or joint municipal authorities for primary healthcare in Finland), which are responsible for purchasing medicines for hospitals. Hospitals may join purchasing groups that procure together and that are formed by hospitals in the same region or under the same management.

There is a trend for more acquisitions to be made by tendering. Several Western European countries reported tendering being used for most acquisitions, while direct negotiations by hospitals with suppliers (e.g. manufacturers or wholesalers) are the key purchasing policy in Austria, Germany and some countries in Central and Eastern Europe.

(Source: Vogler et al. 2010, PHIS Hospital Pharma Report)
3.2.3 New funding mechanisms

Innovative medicines are often high cost medicines and as such, put pressure on healthcare budgets. As a response, payers throughout the EU have sought for new solutions that would ensure financial access to these medicines and as a result have proposed various new funding mechanisms. This section lists a few examples that were implemented in recent years.

Some European countries have implemented joint funding mechanisms for specific high cost medicines that usually provide that outpatient payers (partially) fund the in-hospital use of high-cost medicines (see Table 8.3.2 for some examples from European countries). The rationale for co-sharing of costs by the hospitals in some of the model is that hospitals should be encouraged “to use these medicines in an efficient way”. 107

In 2011, England established a Cancer Drugs Fund, which has injected £200 million of additional funding into England’s NHS each year to fund new cancer medicines not recommended by NICE. Scotland made a new £21 million fund available for orphan medicines that are not recommended by the Scottish Medicines Consortium (SMC) which will become operational during 2014. All regional health authorities for England’s Cancer Drug Fund, together with an expert panel, developed a “priority list” of cancer medicines to be included. Since its inception, a total of 34 medicines have been made available through this fund, and by December 2011 the fund approved treatment for almost 10 000 cancer patients. 113 The effects of England’s Cancer Drug Fund are not clear. It has been argued that the existence of the fund could lead to NICE’s Appraisal Committees being more likely to refuse new cancer medicines, knowing that the fund will provide access for those patients most likely to benefit. Furthermore, the presence of the fund may encourage manufacturers to set the prices of new cancer medicines higher than they otherwise would have as the Cancer Drug Fund does not incentivise lower prices.
### Table 8.3.2: New funding mechanisms across outpatient and hospital sectors

<table>
<thead>
<tr>
<th>Countries</th>
<th>Special funding mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>At the time of the study, in two provinces in Austria (Styria, Carinthia) the main public hospital owner organisations have concluded agreements with the regional sickness funds stating that the expenditure of selected high-cost medicines (e.g. oncoligic medicines) used in hospitals are funded differently. In these provinces will be covered by the sickness fund even if they are dispensed in the inpatient sector.</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>Some medicines for treating particular diseases in hospitals are paid for through the state budget.</td>
</tr>
<tr>
<td>France</td>
<td>A supplementary list, “liste en sus” or “non T2A” medicines, of high-cost medicines excluded from the DRG system (particularly anti-cancer medicines, blood products, orphan medicines and some treatments for rheumatoid arthritis) has been developed. Medicines on this list are reimbursed up to 70 to 100% separately by the social health insurance. Another list of “reassigned medicines” which may be dispensed to outpatients by hospitals is reimbursed by the sickness fund.</td>
</tr>
<tr>
<td>Germany</td>
<td>For high-cost medicines additional reimbursement based on the documentation of their use.</td>
</tr>
<tr>
<td>Hungary</td>
<td>Anti-coagulant factors are centrally procured products.</td>
</tr>
<tr>
<td>Latvia</td>
<td>Certain high-cost medicines may be covered by the state budget.</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Orphan medicines on the orphan medicine list and expensive medicines on the list of high-cost medicines (both lists set up by the Dutch Health Care Authority) are reimbursed by the health social insurance: 100% for orphan medicines, and 80% for expensive medicines, the rest is of the cost is borne by the hospitals.</td>
</tr>
<tr>
<td>Poland</td>
<td>Highly specialised services (e.g. grafting, incl. pharmaceutical treatment) are funded by the state budget.</td>
</tr>
<tr>
<td>Slovenia</td>
<td>High-cost medicines (e.g. infliximab, rituximab, alemtuzumab, docetaxel) are not part of the hospital budget. The Health Committee evaluates on a case per case basis high-cost medicines and prepares the proposal whether to financed for inpatient treatment (i.e. financing of certain indications for a determined number of patients by a certain scheme in a specific hospital e.g. university hospital, specialised hospital). The final decision of financing of high-cost medicines for hospital use is made by agreements between representatives of hospitals, the Health Insurance Institute and the Ministry of Health. On the basis of these annual agreements, the Health Insurance Institute finances the specific high-cost medicine for a specific hospital.</td>
</tr>
<tr>
<td>Slovakia</td>
<td>Some medicines like growth factors or beta-interferons are purchased by sickness funds directly in case medicines are used in special limited centres in hospitals.</td>
</tr>
</tbody>
</table>


The Italian fund for encouraging independent research, established with the Italian Medicines Agency (AIFA) was created in 2005 and is funded by pharmaceutical manufacturers that are required to contribute five per cent of their expenses in promotional activities. Several AIFA activities are funded from this ear-marked money but the major aim of this ad-hoc fund, which consists of about €40 million each year, is “to support clinical
research on drugs in areas of interest for the National Health Service (NHS) and where commercial support is normally insufficient”. Areas in which research is stimulated include patient populations normally excluded by clinical studies such as children, pregnant women, and the elderly. Other main research areas are orphan medicines, head-to-head comparisons, strategies to improve the rational use and pharmacoepidemiological studies. AIFA launches yearly calls for proposals aimed at researchers in the public sector.

Most of these new funding mechanisms have not been evaluated yet, so it is unclear whether such mechanisms reach intended goals, or what unintended consequences of such policies are.

Hospital setting, new funding mechanisms: research priorities

- Assess actual hospital prices in countries.
- Identify and evaluate existing initiatives to improve medicines management at the interface of the primary and hospital sector with regard to their impact on access to medicines, adherence, cost-containment and innovation.
- Explore barriers and opportunities for cooperation at the interface of the primary and hospital sector and develop a “tool box” for a successful implementation of such a new model.
- Evaluate new funding mechanisms, including prize funds, with a focus on their ability to create incentives for R&D in areas of unmet medical needs.
- Identify best practices in new funding mechanisms.

3.2.4 Generic promotion as pharmaceutical policy option

In recent years, European countries have implemented a number of measures to capture the potential value, in terms of cost savings, created by patent expiration leading to the subsequent market entry of generic medicines stimulating their appropriate use. Yet, in many European countries opportunities still exist to either speed up generic entry, increase generic consumption and/or lower the prices of generic medicines, as substantial differences remain in generic entry, uptake and prices, compared, for example, with the United States. Savings could create “headroom for innovation” and partly be used to facilitate uptake of, or rewards for, innovative medicines.

Policies aiming at encouraging generics uptake can be successful in both containing prices and public pharmaceutical expenditure growth. Savings generated by generic promotion policies can free resources that, in return, could be used to finance access to new innovative medicines. Initiatives to promote generics uptake include a range of policy options and in European countries a range of generic policies are applied, although their design and number vary among the countries. Internal price referencing, which consists of pricing a medicine according to the prices of either identical or similar products marketed in a country, is the most frequently applied practice with regard to generics. Countries may opt for setting the price of the generic medicines at a certain percentage below the price of the originator. Sixteen out of 29 European countries (27 EU Member States plus Croatia and Norway) apply this generic price link policy. Since 2005, Norway has used the ‘stepped price model’ (Trinnprismodellen) to incrementally reduce the price of off-patent medicines.
according to predefined rates, depending on sales volumes, with the first reduction occurring after a medicine has lost patent protection. Countries that do not have a generic price link policy but rather relied on competition to reduce generic prices have been found to have larger price differences among generics, compared to countries with generic price policies.

Twenty years ago only Germany, Denmark, the Netherlands and Sweden used internal reference pricing systems. At the beginning of 2013, all EU Member States except Austria, Cyprus, Malta, Luxemburg, Sweden, and the United Kingdom have a system in place in which groups of identical or similar medicines are clustered in order to fix a maximum reimbursement amount (so-called reference price) to be covered by the third party payer. A sufficient number of generics or other alternative medicines on the market in order to build a cluster is required for an internal reference pricing system to function properly. This may explain why in several European countries a reference price system was only introduced during the last 13 years, although strong opposition to the introduction of such a system might delay the implementation as well.

Major demand-side measures to enhance generics uptake include generic substitution and INN prescribing. Generic substitution means that the pharmacist substitutes the prescribed medicine by another, usually less expensive medicine containing the same active ingredient(s). INN substitution concerns physicians prescribing active ingredients instead of brand names. An increasing number of European countries have introduced generics substitution and/or INN prescribing, and in several remaining countries possible introduction has been discussed. In the 27 EU Member States, generics substitution is in place in 20 countries (all but Austria, Bulgaria, Cyprus – private sector, Greece, Ireland, Luxembourg, and the United Kingdom), and INN prescribing is in place in 22 countries. Most European countries have implemented generic substitution and/or INN prescribing on a voluntary basis but in recent years, Lithuania, Slovakia, and Italy changed from indicative to mandatory INN prescribing.

Financial incentives to enhance generics uptake are not very common in the European countries. Italy applies a different mark-up for originator medicines and biosimilars compared to generics as an incentive to pharmacists and in France a pharmacist will receive the same amount of money for dispensing a generic as the original medicine. In the Netherlands, the opportunity for the pharmacist to keep a third of the savings achieved by generic substitution was abolished in 2004.

3.2.5 Tendering

A major change that has occurred since the publication of the previous Priority Medicines Report in 2004 is the introduction of tendering systems in the outpatient sector in several European countries. The best-known example is the Dutch preference pricing policy, but other countries have also introduced tendering-like elements in their pricing and reimbursement practices for medicines in the outpatient sector. Under the Dutch preference price policy, which was introduced in 2005 by five health insurers and has been extended ever since, health insurance companies determine one or a limited number of medicine(s) per cluster consisting of medicines with the same active ingredient, dosage form and strength, as preferred for a fixed time period of usually six months. The preferred medicine is determined through a tendering process, and only the medicine that wins the
tender will be reimbursed. The preference pricing policy was considered as very successful; initial total savings (projected to €355 million annually) exceeded expectations since the preference policy scheme resulted in fierce price competition among generic companies. However, while the saving potential of tendering has been shown in several cases, its long-term effects are still unclear. As there have been reports of short-term absences of some medicines due to logistic shortages, an important drawback of tendering could be the increased risk of shortages.

Generics policies, tendering: research priorities
In the area of new trends in pricing and reimbursement the following have been identified:

- Explore best practices in generics policies, including the design of tendering in order to prevent shortages.
- Study reasons (system, cultural, other) for differences in generic uptake between countries
- Study the impact of tendering with regard to price and expenditure development, accessibility and availability of medicines in the market, and the implication of these developments on innovation
- Explore how generic policies can enhance innovation.

3.3 Current and future challenges for pricing and reimbursement

3.3.1 Orphan medicines
Rare diseases are severe medical conditions that affect a low number of patients. A range of special regulations have been adopted in order to stimulate the development of medicines for rare diseases – called orphan medicines. These regulations have been successful in stimulating the development of orphans, as it is expected that the hundredth orphan medicine will reach market authorization in the EU in the period of 2012 to 2014 and the two-hundredth in 2017. However, given the limited market size for orphan medicines, many orphans fail to meet standards for cost-effectiveness of medicines. A main challenge for policy makers faced with coverage decisions of orphan medicines, concerns the question whether in the allocation of healthcare resources, special considerations (with regard to cost-effectiveness) should be made for patients with rare diseases.

If orphan medicines are reimbursed at much higher incremental cost-effectiveness than would be considered acceptable for medicines indicated for more common diseases, this would be in violation of the equity principle, as it would imply that a patient with a common definition and who would acquire the save health gain is less worthy of receiving treatment and from a utilitarian point-of-view, it would be unethical to invest substantial amounts of resources for the rare conditions as this would not maximize society’s benefits. However, under EU legislation individuals are entitled to a decent minimum of healthcare, which could require that treatment is made available for orphan diseases, but it has been questioned whether orphan disease pose such an imminent threat to a patient’s health to constitute such a rights-based approach. It has been noted, however, that the mere fact that orphan medicines are reimbursed in many countries demonstrates that budget impact,
clinical effectiveness, and/or equity issues are all weighed more than cost-effectiveness in coverage decisions.129

The low budget impact of orphan medicines might contribute to many orphans receiving reimbursement, regardless of high incremental cost-effectiveness ratios. In the Netherlands, for example, the total costs of all outpatient orphan medicines were estimated at €170 million in 2011130 whereas the total costs of all outpatient medicines were estimated at €5.2 billion, which means that the orphan medicines expenditures make up less than 4% of the total pharmaceutical expenditures. However, the total orphan expenditure increased by 12% as compared to 2010, whereas the total pharmaceutical expenditure only increased with 0.2% in 2011.130 Furthermore, it has been estimated that the costs of inpatient orphan medicines totaled about €90 million in 2011.130 Although the contribution of orphan medicines in terms of pharmaceutical expenditures are relatively minor, total expenditure is increasing – and at a higher rate than total pharmaceutical expenditure. Given the expected numbers of orphan medicines reaching the European markets the coming years, attention of policy makers is required concerning the cost-effectiveness of orphan medicines.

Given the especially small markets for orphan medicines, cooperation between countries in collecting data needed to inform reimbursement decisions of orphans might be warranted, especially for smaller countries. As the low number of patients is a barrier to collect sufficient data regarding clinical effectiveness and costs of treatment, cooperation could result in increased efficiency of the reimbursement process of orphan medicines in Europe. Furthermore, countries could assess together, based on the combined market potential, what type of reward for innovation would be appropriate – by doing so, the responsibility for rewarding innovation through prices could be assessed on an international level instead of the national level. Also, see the background paper on orphan medicines.

### 3.3.2 Discounts and rebates

Price reductions can take different forms; they might be discounts (i.e. price reductions granted to specified purchasers under specific conditions prior to purchase) or rebates (i.e. payments made to the purchaser after the transaction has occurred), medicines can be provided cost-free to purchasers, or the strategy of bundling is applied where several products for sale are offered as one combined product.68 Usually, discounts and rebates agreements are kept confidential. Managed-entry agreements, such as price-volume or risk-sharing agreements (see the section on managed-entry agreements) may also be also be considered as forms of discounts and rebates though the presence of such agreements is usually not kept confidential.

The existence of discounts and rebates granted by suppliers has been long known, at least at an anecdotal basis, for the hospital sector. The findings from the EU PHIS project confirmed that some medicines used in hospitals, particularly those with therapeutic alternatives and which are likely to be used for long-treatment after discharge of the patient from hospital, are supplied to hospitals at high discounts and even for free in those European countries where such practices are allowed.107 This practice of granting high discounts on these typically high volume medicines is more likely to occur when the organization of the pharmaceutical system has different payers for the outpatient and inpatient sector. Its effect on shifting of costs, treatments and thus patients among the sectors were discussed in the section on the hospital setting and interface management.
In the outpatient sector, discounts and rebates have been used by stakeholders in the supply chain to compete on prices, particularly on generic medicines. Additionally, discounts and rebates granted to public payers in the outpatient sector have been increasingly playing a role in Europe (see also the sections of other high-income countries). According to a recent survey, in 25 of 31 surveyed European countries discounts and rebates are granted to public payers by pharmaceutical companies, in the outpatient sector in 21 countries, and in the inpatient sector in all 25 countries. The most common discounts and rebates consist of price reductions and refunds linked to sales volume, but in-kind support, price-volume and risk-sharing agreements were identified as well, and in general, a mix of various types of discounts and rebates is common.

It has been argued that discounts and rebates would offer advantages to the various stakeholders as discounts and rebates serve cost-containment purposes for payers (“hidden price cuts”) and they allow pharmaceutical companies to gain market share. Furthermore, the argument has been raised that for countries that have a limited ability to pay and are included in the reference baskets of other countries, confidential discounts and rebates are a tool to increase access to patients, as under full transparency, companies might be less willing to launch a product in their country or might insist on a higher price. Managed-entry agreements allow for the management of uncertainty and offers patients access to new medicines whose effectiveness has not been fully established (see also the section on managed entry agreements).

However, since discounts and rebates are in most cases confidential, this has implications for transparency. Given the widespread use of external price referencing in European countries (see the section on external price referencing) and the fact that discounts and rebates have been increasingly demanded as a kind of “hidden price cuts” instead of real price cuts, it creates a situation in which the surveyed list prices may provide at best only an indication of, but not a reflection of actual prices. As a result, confidential discounts and rebates limit the opportunities for cost savings for countries that use external price referencing (see also the section on external price referencing) and refer to the list prices indicated in the national price databases. There is no evidence as to whether discounts and rebates have any effect on innovation. Furthermore, the belief that confidential agreements might result in better prices has not been confirmed. On the contrary, there is evidence from the hospital sector that all hospitals were offered the same prices under confidential agreements, and the extent of discounts and rebates did not vary among hospitals but was dependent on the existence of therapeutic alternatives.

Orphan medicines, discounts and rebates: research priorities

- Study the societal support for high prices and high incremental cost-effectiveness of orphan medicines.
- Study the ability for a cooperative structure in data collection for cost-effectiveness evidence between countries.
- Assess the extent to which discounts and rebates are used in European countries, and what are the implications for the countries applying the policies and the other countries.
3.4 Managing price and volume outside Europe

High-income countries outside Europe use similar pricing and reimbursement practices to those applied in European countries. New Zealand uses a system of contracts between the public purchaser, the Pharmaceutical Management Agency of New Zealand (PHARMAC), and manufacturers. The contracts include rebates on list prices, tendering for off-patent medicines, and bundle agreements where PHARMAC may list expensive new medicines in return for the manufacturer discounting the price of other products it supplies.\textsuperscript{132,133}

A pricing policy frequently used in several low- and middle-income countries world-wide is cost-plus pricing.\textsuperscript{134} This is the practice of calculating the medicine price based on the production costs, promotional expenses, research & development, administration costs, overheads and profit.\textsuperscript{68} Cost-plus pricing depends on accurate information on material prices and cost data provided by the manufacturers, which is difficult to obtain. There is a lack of evidence supporting the use of cost-plus formulae, as there is a lack of published evidence on the impact of this pricing policy in general.\textsuperscript{134}

Meanwhile, several countries, particularly middle-income countries, have moved to implementing external price referencing. As for high-income countries (see section on external price referencing), there are variances in the design of this pricing practice. In several LMIC external price referencing tends to be applied to both on-patent and off-patent medicines, whereas in high-income countries the latter are usually subject to internal price referencing. Possible effects and limitations of the external price referencing practice were already discussed under the external price referencing section for the European countries, and they are also relevant in this context. Studies on the impact of external price referencing, particularly on prices beyond the national borders, are rare.\textsuperscript{67}

In many low- and middle-income countries, the provision of a usually limited range of medicines in public sector facilities is procured by the state. While eligible patients can access essential medicines in the public sector either free of charge or with a modest co-payment, they have to purchase out-of-pocket medicines in the private sector.\textsuperscript{61,135} World Health Survey data show that about half (41% and 56%) of households in LMIC spend all of their health expenses on medicines.\textsuperscript{136} A major concern for LMIC is to ensure access to essential medicines. It was argued that the effect of price regulation on innovation is probably not a main concern, as these countries do not often have an innovative pharmaceutical industry.\textsuperscript{67} Moreover, the impact of regulation in a single low- or middle-income country on innovation is considered as negligible since innovation is usually led by global market trends.\textsuperscript{2,67} However, the level of medicines prices have an implication on availability since low medicines can reduce the attractiveness of certain countries to manufacturers and importers which might result in important products not being produced and marketed in a particular country or at least, being marketed with substantial delays.\textsuperscript{67}

As an approach to address this challenge of limited availability, differential pricing was proposed. Differential pricing, tiered pricing or Ramsey pricing, means that different prices are applied for different purchasers (see section on differential pricing). For more than a decade it has been discussed as a possible solution, particularly in the international context, as an alternative to high prices when separated high- and low-to-middle-income markets exist for a medicine and when the seller exerts significant power over pricing, such as when there is limited or no competition due to patent protection, data exclusivity, or other market-
entry barriers. In the Priority Medicines Report 2004, such an approach with thresholds (of maximum prices per medicine as determined by economic evaluation) for each country based on the national income level was proposed as a way forward to enhance innovation and provide access to medicines, particularly for middle-income countries. Recently, the MIT Zaragoza center reviewed existing knowledge and expertise and did not find a widespread use of differential pricing. A systematic use of differential pricing has been limited to vaccines, contraceptives, and antiretrovirals (ARVs) mostly in low income countries.

Although differential pricing is not a panacea to ensuring access, it can benefit manufacturers and poor countries without adversely affecting higher income countries. More research is needed in order to understand on how differential pricing can be expanded to include all essential medicines for low- and middle-income countries and how fair, affordable prices should be determined. Moon et al. (2011) examined international drug medicines developments for antiretrovirals, artemisinin combination therapies, drug-resistant tuberculosis medicines, liposomal amphotericin B (for visceral leishmaniasis), and pneumococcal vaccines and found several shortcomings in differential pricing. It was considered as inferior to competition for achieving the lowest sustainable prices; it often involved arbitrary divisions between markets and/or countries leading to very high prices for middle-income markets; and it left a disproportionate amount of decision-making power in the hands of sellers vis-à-vis consumers. Still, the authors argued that in special cases – such as when market volumes are very small or multi-source production capacity is lacking – differential pricing may offer the only practical option to meet short-term needs for access to medicines.

Another issue that needs attention regarding medicine prices in LMIC is different add-ons, including mark-ups, duties, tariffs, and taxes, which increase the end price for the patient considerably. Thanks to the WHO/HAI work on medicine prices, availability, affordability and price components, there is evidence about the existence and amount of these add-ons, which are high compared to European countries. But there is paucity in information about the impact of these add-ons regarding utilization and access to medicines. A major argument against taxes, duties and tariffs is that it is a regressive form of taxation that targets the sick, and there has been a call for eliminating these taxes on essential medicines without adverse revenue or industrial policy impacts. As far as attention to mark-ups and margins are concerned, care must be taken to ensure that incentives to reach rural and hard to reach patients are not reduced thereby exacerbating lack of access to these groups. In LMIC there has been limited experience with value based pricing policies though South Africa has announced their intention to utilize this approach as a part of their price control regimen.

Promotion of the use of quality-assured generic medicines has great potential to reduce medicine prices to consumers in LMIC. Cameron et al using demonstrated that in 17 countries, savings of between 9% and 89% were possible. In practice however, branded generic medicines frequently dominate the market in LMIC and their prices may be set closer to originator than generic prices. Such patterns also occur in high-income countries.
4. Networks and infrastructure

4.1 Collaborations on the European level

In the following, some initiatives, projects and networks will be presented which are examples of collaboration in the field of pharmaceutical pricing and reimbursement among European countries. In addition, cooperation also occurs in the field of market authorization, for instance with the Head of Medicines Agencies but this is not scope of this chapter. A possible bridging between marketing authorization and pricing and reimbursement will be addressed in the sub-section on relative effectiveness cooperations.

4.1.1 European processes regarding pricing and reimbursement

In the year 2000, concerns were raised regarding the competitiveness of the European pharmaceutical industry lagging behind the United States. In response, The European Union established the G10 group - ten selected Member States and stakeholder representatives - who presented recommendations on how to enhance competitiveness and innovation in the pharmaceutical sector in Europe in 2002. To follow up on these recommendations, the High Level Pharmaceutical Forum was set up in 2005 as a three-year process. The Pharmaceutical Forum focused on three main topics: information to patients on diseases and treatment options, pricing and reimbursement policies, and relative effectiveness. For each of these topics a Working Group was set up. The Relative Effectiveness Working Group for example set out core principles on relative effectiveness assessments that could be relevant for developing national systems and would help to encourage of exchange of information, methodologies and experiences between the relevant national authorities.

After the Pharmaceutical Forum, the European Commission followed the recommendation for a continuation of cooperation and sharing of experiences at the EU level the network of Competent Authorities for Pharmaceutical Pricing and Reimbursement (CAPR) was set up, and the Process on Corporate Responsibility in the field of Pharmaceuticals was launched with three independent platforms. The platform “Access to medicines in Europe” was “dedicated to enhance voluntary collaboration among the Member States and relevant stakeholders in order, when appropriate, to find common non-regulatory approaches to enable timely and equitable access to medicines after their marketing authorization” Its six working groups have been addressing orphan medicines, biosimilars, over-the-counter medicines, supply in small markets, managed-entry agreements and prioritization (Priority Medicines Report). The outcomes of the five first working groups of Platform on Access to Medicines in Europe have been finalized and were endorsed by the Steering Group in April 2003. A more in-depth description of the processes at EU level, including key conclusions of policy papers and recommendations, is provided in the Annex 8.3.1.

4.1.2 Networks of competent authorities for pricing and reimbursement

The first European network of competent authorities for pharmaceutical pricing and reimbursement information is the Pharmaceutical Pricing and Reimbursement Information (PPRI) network. This resulted from an EC / DG Health and Consumers co-funded project (2005 to 2008) which collected and analysed pharmaceutical pricing and reimbursement...
information about countries by producing more than 20 country reports, a set of indicators for comparison pharmaceutical systems, a glossary of pharmaceutical terms and a benchmarking report. The technical deliverables such as the country reports or outcomes of internal queries have produced an evidence base as a basis for further research. The participating members of the competent authorities see as the major value of PPRI its contribution to “to improve the exchange of information between the Member States”. For this reason, PPRI has continued after the end of the EC funding as an informal network of public authorities of pharmaceutical pricing and reimbursement borne by the commitment of all participants, with a financial contribution of Austria for the PPRI secretariat. The PPRI network currently involves around 70 institutions (mainly relevant authorities and third party payers) from 40 mainly European countries, as well as European and international institutions (European Commission services, OECD, WHO). Under the Pharmaceutical Health Information System (PHIS) project the PPRI project was extended to hospital pharmacists and experts. In 2007, the CAPR (Competent Authorities for Pricing and Reimbursement of Pharmaceuticals) network was set up. No public information is available on CAPR. According to delegates who are members of both the PPRI and CAPR network, PPRI is considered as a network of technical staff who deal with pricing and reimbursement decision on a daily basis and benefit from the cooperation from the experiences from the other countries, whereas the CAPR network is rather seen as a strategic group. In order to support the CAPR network, the European Medicines Information Network project (EMINet) was launched in December 2008 to provide information, technical expertise and analysis on pharmaceutical pricing and reimbursement policies and related topics such as the distribution or rational use of medicines during 2009 until 2012.

Further networks have been established which also address pricing and reimbursement issues. The “Piperska group” was set up in 2008, as an informal network of European reimbursement authorities and researchers, with the aim of enhancing a more rational use of medicines. Members of the European Social Insurance Platform (ESIP), which is a strategic alliance of over 40 national social insurance organisations across Europe (www.esip.org), form the MEDEV (Medicines Evaluation) group whose members (staff of social insurance taking reimbursement decisions) meet several times a year to share information about assessments of medicines. The value of these networks has been generally acknowledged and the need for the cooperation and exchange of experiences has been expressed in several policy documents. To the authors’ knowledge, the PPRI/PHIS network was the only one being evaluated. The evaluation report highlighted the value of the network as most outstanding achievement. This report quoted an interviewee who said that “the value of the network as a global model remains very attractive”. The network was reported to serve a good practice model, e.g. it was used in the Western Pacific region for sharing public sector procurement information.

4.1.3 Cooperation on relative effectiveness

The most prominent EU network in the field of Relative Effectiveness is the EC-supported European Network for Health Technology Assessment (EUnetHTA). EUnetHTA has seen different phases of organisation and cooperation structure during the last decade (see Box 8.3.3). EUnetHTA was identified as an appropriate candidate for developing scientific recommendations for improvements in relative effectiveness assessment, and it developed the HTA Core Model (http://www.eunethta.eu/hta-core-model). This is a guidance document for producing extensive multi-dimensional assessments of health technologies that are
Further major cooperation in the field of relative effectiveness is the informal cooperation between HAS (France), IQWiQ (Germany) and NICE (United Kingdom) for exchanging experience in the evaluation of medicines, the AGREE cooperation, aiming at improving the quality and effectiveness of clinical practice guidelines by establishing a shared framework for their development, reporting and assessment\textsuperscript{158}, and Guidelines International Network (G-I-N, \url{http://www.g-i-n.net/}) for promoting systematic development of clinical practice guidelines. The ADVANCE-HTA project co-funded by the EC (FP 7) is a consortium of 13 institutional partners lead by LSE Health that aims to advance and strengthen the methodological tools and practices relating to the application and implementation of HTA. In the project, issues such as value for money, concepts of value assessments, methods associated with the assessment of rare diseases and elicitation of preferences are addressed.\textsuperscript{159}

While there has been a call for more studies which support payer’s decision on reimbursement and more exchange of information on relative efficacy\textsuperscript{160,161}, there are no explicit cooperation structures known in Europe. This might be a task for existing networks to address this issue as well as work on bridging between regulatory authorities and payers.

### 4.1.4 Medicines price databases

In Europe, work on building a database which contains medicines prices began in the late 1990s. The initial project, Ecphin, with institutional support from the Commission’s Joint Research Centre, set out to create a database on the basis of voluntary contributions from Member States and built the technical basis. Within the framework of the next project, EudraNet, it was then fed with price data from Member States, however stopped after some time. The European Commission explained that due to the data delivery at different times and by different means, it was difficult to undertake comparisons.\textsuperscript{162}

Based on a decision in the EU Transparency Committee (a consultative committee established based on the EC Transparency Directive), EU Member States agreed in 2005 on sharing medicines prices for a selected range of medicines. The INFOPRICE exercise was done on a bi-annual level. It was stopped at the end of 2012 to avoid redundancy since a European medicines price database (EURIPID) has meanwhile been set up.

This EURIPID medicine price database is currently (2009-2013) established, with the support of an EC grant. It is led by a project consortium of Hungary and Austria and it contains data provided from Member States. In its report as of 25 January 2013 on the proposal for a Directive of the European Parliament and of the Council relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of public health insurance systems, the European Parliament advised the Commission and the Member States to “examine how to continue to co-operate on the functioning of the EURIPID price information database, which provides EU-wide added value in terms of price transparency”.\textsuperscript{163} However, the sustainability of the EURIPID is not yet known.

The EURIPID medicines price database complements existing national price information systems and databases, which are offered either by commercial providers or have been
established by competent authorities for pricing which require price information for external price referencing. Most of the authorities’ price information systems of authorities are for internal use only. One example of a publicly available service is Pharma Price Information (PPI, http://www.goeg.at/en/PPI) of Gesundheit Österreich GmbH (Austrian Health Institute) which, in accordance with the Austrian Social Insurance law, provides price data for 30 countries. The service started as support to the Pricing Committee of the Austrian Federal Ministry of Health but data allocated can be provided to all interested parties in order that no party would be excluded, however without financial burden for Austrian authorities.

In LMIC, tender price and government procurement price data has been available for nearly 30 years in the MSH Drug Price Indicator Guide (Management Sciences for Health International Drug Price Indicator Guide 2011). This guide provides data from 31 LMIC procurement organizations and nine non-profit suppliers. Prices are reduced to a standard price for a common dosage for each dosage form. Such data is used as the International Reference Price (IRP) for the WHO/HAI price and availability surveys.

4.2 Infrastructures outside Europe

4.2.1 High-income countries

During the last fifteen years, the OECD has produced several works on how to promote innovation for medicines while increasing access to medicines. Major studies in this study were Pharmaceutical Policies in OECD Countries: Reconciling Social and Industrial Goals, Survey of Pharmacoeconomic Assessment Activity in Eleven Countries and the current study on value-based pricing. As in Europe, there are groups and networks for sharing information and experiences in other areas as well. One of them is the Vancouver group, with Canada, Australia, New Zealand and some European countries being represented.

4.2.2 Low- and middle-income countries

In 2000, in response to global immunization rates stagnating, the Global Alliance for Vaccines and Immunization (GAVI) was launched to fund vaccines for children in the world’s 70 poorest countries. Since then, GAVI support has resulted in the immunization of millions of children with different vaccines. Based on a WHO resolution, the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG) open to all Member States was established in 2006, with the aim to develop a global strategy and plan of action aimed at securing an enhanced and sustainable basis for needs-driven, essential health research and development relevant to diseases that disproportionately affect LMIC, proposing clear objectives and priorities for research and development, and estimating funding needs in this area. In May 2008, the World Health Assembly adopted the global strategy and the agreed parts of the plan of action on public health, innovation and intellectual property. To this end, the global strategy proposes that WHO should play a strategic and central role in the relationship between public health and innovation and intellectual property within its mandate.

The WHO/HAI Working Group has developed a methodology to assess medicines’ availability and medicines prices which allowed building a database of survey findings and performing valuables analyses. Gaps in the availability were shown for both acute and
chronic conditions in the several LMIC, particularly in the public and private sector. Overall, public and private sector medicines prices were shown to be substantially higher than "would be expected if purchasing and distribution were efficient and mark-ups were reasonable". Some analyses particularly focused on the price differences between originator and generics and showed that countries were overpaying. Given the fact that most LMIC households have to pay out-of-pocket for medicines, high medicines prices were shown to negatively impact affordability, and they have the potential to push large patients groups into poverty.

In 2010, the PAHO published a report investigating the situation on access to high cost medicines in the Americas and proposed strategies to improve the situation.

Since 2008, the Netherlands-based Access to Medicines Foundation has published a biannual ranking of the top 20 research-based pharmaceutical companies based on their policies and performance to increase access in LMICs. Given that generic medicines make up some 80 per cent of the medicines sold in LMICs, a similar ranking for the major generic companies may prove useful.

### Networks and infrastructure: research priorities

- Evaluate and document the value added of research networks and EC initiatives
- Bridge the cooperation between regulatory authorities and pricing and reimbursement institutions
- Share data on relative efficacy (e.g. evidence tables)
- Support databases, information systems and networks for sharing price information

### 5. Conclusions

This background paper started with the notion that one of the major challenges in (inter)national policies regarding the pricing and reimbursement of medicines is how to align the necessity to control healthcare expenditures with creating sufficient incentives for innovations addressing public health needs. In most European countries, a variety of pricing and reimbursement policies have been implemented during the 1990s and 2000s, primarily in response to increasing pharmaceutical expenditures. Such policies included external price referencing, internal reference pricing, and the use of HTA and economic evaluation in reimbursement decisions. Yet, concerns over both the sustainability of healthcare costs, rewarding innovation, and cost containment continue to exist, prompting the question whether current policies are successful in achieving their intended goals.

The coming years therefore require a systematic and careful assessment and evaluation of the different tools and policies available, a refinement of methodologies, and an assessment of the impact on medicine use and pharmaceutical innovation. This will require significant investments and the involvement of stakeholders will be paramount in this process. Furthermore, it may result in the discovery of ‘uncomfortable truths’ and strongly diverging
points of view of stakeholders will need to be accommodated. Simultaneously, the development and implementation of policies that will make for a truly sustainable and innovative European pharmaceutical sector in the long run are immense - for governments, companies, payers and patients – and therefore, an assessment and evaluation of tools and policies available is evidently needed.

We identified three key interlinked strategies that are available to regulators to control costs and reward innovation of medicines: managing price, managing volume, and managing which products will be reimbursed. Historically, policies have mainly focused on managing prices and managing reimbursement. In recent years two developments can be identified; first, it is increasingly being recognized that policies only serving a single policy goal such as cost-containment might not result in favorable long-term effects on innovation, and second, policies that impact all these factors (prices, reimbursement, and volume) might be most efficient in aligning conflicting policy aims. In line with these developments, HTA and value-based pricing have been identified as promising policies, but even though much research has been done in the field of economic evaluations, HTA, and pricing and reimbursement of medicines, a number of knowledge gaps remain. Further research is needed for the analysis of existing practices, for developing practical “tool boxes” and models for new approaches, and for studies that evaluate the introduction of new policies. In addition, this knowledge and (country-specific) experience should be appropriately communicated and disseminated, e.g. via networks for policy-makers.

European countries currently use a range of policy options that aim to control pharmaceutical expenditure, stimulate innovation, and ensure financial access to medicines. External price referencing is the predominant pricing policy in Europe and is increasingly being used outside of Europe as well. Payers are motivated to use external price referencing as a tool to contain prices of new on-patent medicines. Evidence for both intended effects (lower prices), as well as externalities of the policy, is mixed and sometimes contradictory. The impact of external price referencing on price levels throughout Member States, the distortion of the system due to confidential discounts and rebates, the availability of medicines in lower income countries, delays in market launch, and potential long-term effects on incentives to innovate should be studied.

Even though it is unlikely that external price referencing will be replaced completely by other pricing policies in the short-term, the feasibility of implementing alternative pricing strategies and their impacts on incentives for innovation should be studied. Value-based pricing, which is currently used by Sweden and will be implemented in the United Kingdom in 2014, has been argued to enable efficient pricing together with providing long-term incentives for innovation. Evidence at this point, however, remains scarce and mainly theoretical. Evaluation studies of countries that have implemented or are planning to implement value-based pricing therefore are warranted.

There is widespread evidence that list prices throughout Europe do not reflect actual prices and therefore erode the cost-saving potential of external price referencing. External price referencing therefore could benefit from increased transparency of medicines prices particularly tender price information which are not affected by discounts and rebates and the support of initiatives for exchanging price information. Simultaneously, this could be seen as an important reason to consider alternative pricing strategies since the policy does not seem to achieve its intended goals – and other pricing and reimbursement policies, including
value-based pricing, might have the potential to send clear signals to industry on what innovations are expected and valued by payers. Furthermore, this would enable payers to set prices that reflect their own willingness to pay for innovation, instead of having to rely on prices set by other countries and the success of other countries to achieve fair prices.

Many European countries are moving towards the use of HTA and economic evaluations in the reimbursement of medicines. Payers that consistently apply decision-rules in reimbursement based on cost-effectiveness, as well as other determinants, in the assessment and appraisal of medicines could provide an important positive incentive for pharmaceutical innovation. Existing initiatives of cooperation and networks within Europe and beyond improve evidence-based and informed national pricing and reimbursement procedures. Therefore, a continuation and expansion of cooperation and exchange of experience is needed. Research networks include EUnetHTA, CAPR and PPRI with international organizations such as Health Alliance International (HAI), the WHO and the World Bank (especially for networks between the EU and low- and middle-income countries). Existing networks such as EUnetHTA and the PPRI network could also provide a basis for future networks (e.g. by adding a more explicit academic component), and make important contributions to the development of methodology, such as generalizability and transferability of economic evaluations.

Many stakeholders expect an increasing role of EUnetHTA in joint reimbursement assessment, although joint assessment solely considers relative effectiveness of pharmaceuticals. Improvements in the methodology of cost assessment - especially considering the issue of transferability of economic evaluations - are needed. Such improvements could contribute especially to the quality of the data that small countries frequently need to rely on.

Pharmacotherapy at the interface of the outpatient and hospital sectors can be improved. At the moment these sectors operate as separate worlds from a pricing and reimbursement perspective in many countries. Legal and organisational aspects need to be addressed in order to abolish the duality in the system and to remove existing incentives to stakeholders for transferring treatments and patients between the in- and outpatient sector as stakeholders should be incentivized to define the best point of care, including pharmacotherapy, from a therapeutic perspective. Research is needed to explore the possibility of the implementation of policies applicable to both sectors such as joint reimbursement lists and joint therapeutics committees. The introduction of policies to improve interface management should be accompanied by evaluations. Interface issues are of at least equal importance in low- and middle-income countries.

Differential pricing and separation of markets must be possible in Europe to reflect differences in ability to pay for medicines between countries, especially in light of the economic crisis that has severely affected a number of European countries. Policy options that would facilitate differential pricing need to be studied and developed. The development of differential pricing models is currently very challenging due to the complex EU policy environment and the interaction of parallel trade and external price referencing. The extent of the impact of external price referencing and parallel trade, in terms of availability of medicines and the affordability of medicines in EU countries, and the impact of such policy for all stakeholders, should therefore be evaluated.
There is increased recognition for the fact that price is only one determinant of pharmaceutical expenditure and that effective policies should consider volume as well. It can be expected that in the coming years, new and more adaptive policies will be developed for high cost and high volume medicines, with an increasing role for managed-entry agreements and HTA for such medicines. Furthermore, effective generics promotion policies need to be investigated before effective interventions can be implemented, as many countries still could achieve substantial savings through high uptake of generics combined with policies that result in low generic prices, including tendering.

In addition, more adaptive approaches to pricing and reimbursement need to be developed in order to account for the increasing role of HTA and economic evaluations, as well as the expected increase of rare disease medicines and stratified medicines (see Background Paper 6.19 and 7.5). Whereas many countries now determine a medicine’s price at a single point in time (usually at market entry), moving towards adaptive pricing would allow for managed-entry agreements, price-volume agreements, as well as the re-evaluation of prices when new indications are added for a marketed medicine. Particular attention might be required for high-cost medicines and new approaches such as joint procurement of countries and new integrative funding models might be warranted. In particular, research is needed regarding orphan medicines and their high costs, due to the low number of data generally available for informed decision-making. Furthermore, societal support for high prices, equity considerations, and potential cooperative structures in data collection for cost-effectiveness evidence should be investigated.

Pricing and reimbursement policies play a crucial role in stimulating the future development of medicines addressing unmet medical needs through creating appropriate incentives for innovation. Within Europe, pricing and reimbursement decision-making takes place at the national level and there is much variety in policies and practices. Notwithstanding, dialogue and cooperation between countries, institutions, and stakeholders is needed at both the political as well as the technical level in order to facilitate long-term positive impacts on innovation. Formalised cooperation structures between regulators involved in marketing authorization and competent authorization for pharmaceutical pricing and reimbursement could further aid the improvement of the current European policy landscape for pricing and reimbursement.

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Update on 2004 Background Paper, BP 8.3 Pricing and Reimbursement Policies


Annexes

Annex 8.3.1: High level initiatives by the European Commission

G10 Medicines

In 2000, the Pammolli report about competitiveness of medicines from a European perspective was published and raised a discussion about the actual competitiveness of the European Pharmaceutical Industry compared with that of the United States model. A major finding of the report was that the European industry has been losing competitiveness as compared to the USA: “As a whole, Europe is lagging behind in its ability to generate, organise, and sustain innovation processes”. The authors analyzed the development of prices and market shares in the European countries and concluded that national European markets were not competitive enough, particularly in some countries where prices and market shares were found not to vary substantially after patents expire.

In response to this issue, the European Commission, represented by Commissioners Erkki Liikanen and David Byrne, created in 2001 the High Level Group on Innovation and the Provision of Medicines, then called G10 Medicines.

The G10 was charged with exploring different ways of enhancing the pharmaceutical industry’s competitiveness in Europe, without affecting the satisfactory and affordable delivery of healthcare services to the population. Three broad areas of study were taken into account: innovation; provision of medicines to patients; market structure in Europe, competition and regulation.

After one year, in May 2002, the G10 group produced a final report for Commissioner President Prodi, containing fourteen recommendations. Under the heading of “Competition, Regulation, Access and Availability in Markets” major recommendations of the G10 report were:

Recommendation 3: Respecting national competence, Member States should examine the scope for improving time taken between the granting of a marketing authorization and pricing and reimbursement decisions in full consistency with Community legislation. To do this with a view to securing greater uniformity and transparency between markets and rapid access of patients to medicines.

Recommendation 4: [...] Member States - facilitated by the Commission - explore ways of increasing generic penetration in individual markets (including generic prescribing and dispensing). Particular attention should be given to improved market mechanisms in full respect of public health considerations.

Recommendation 6: That the Commission and Member States should secure the principle that a Member State’s authority to regulate prices in the EU should extend only to those medicines purchased by, or reimbursed by, the State. Full competition should be allowed for medicines not reimbursed by State systems or medicines sold into private markets.
Recommendation 7: The Commission should organise a European reflection to explore how Member States can improve ways of sharing information and data requirements to achieve greater certainty and reliability for all stakeholders, even if the decisions they take may differ. The objective is to foster the development of health technology assessment (HTA), including clinical and cost effectiveness, in the Member States and the EU; to improve the value of HTA, to share national experiences and data while recognising that relative evaluation should remain a responsibility of Member States.

High Level Pharmaceutical Forum

In July 2003, the European Commission adopted the Communication "A stronger European-based pharmaceutical industry for the benefit of the patient - a call for action" which outlines the Commission's proposals for advancing the G10 recommendations. A key action within pharmaceutical pricing and reimbursement proposed was to “provide a forum for member states to generate and share information on common relative effectiveness issues in the context of pricing and reimbursement decisions.”

In 2005, the Pharmaceutical Forum was set up as a three-year process. It focused its work on three main topics: information to patients on diseases and treatment options; pricing and reimbursement policies and relative effectiveness; for each of these topics a Working Group was set up. While the G-10 was composed of ten selected private and governmental health stakeholders in Europe, the Pharmaceutical Forum was a much broader process. It involved EU institutions, all EU Member States, industry, health care professionals, patients and insurance funds being represented in the Working Groups.

The Working Group on Pricing and Reimbursement confirmed in its “Guiding principles for good practices implementing a pricing and reimbursement policy” that decisions on cost of healthcare and pharmaceuticals are a national responsibility and it stated that Member States aim to achieve three overall objectives of (1) optimal use of resources to maintain sustainable financing of healthcare, (2) access to medicines for patients and (3) reward for valuable innovation. With regard to the latter, the Working Group agreed on the following principles which should not be understood as binding rules:

- **Set expectations:** It was argued that through its pricing and reimbursement decisions, each Member State tends to grant incentives (e.g. a high price and reimbursement level, or good access to the market) for those new products that it really appreciates as bringing valuable improvements compared to the standard therapy. The importance to reflect what are and will be the desired additional benefits and to allocate resources accordingly was highlighted (additionally a paper on the value of innovative medicines was developed, see below).

- **Recognise innovation:** Companies were asked to be prepared to clearly prove this added value versus existing therapies, and authorities should be prepared to recognise proven incremental benefits that are estimated valuable and reward them appropriately (i.e. with incremental price-premiums or with measures allowing a higher utilisation). Pricing and reimbursement mechanisms, as well as utilisation guidelines, were asked to be in line with this and ensure a scaled recognition and reward. It should thus not be expected that incremental benefits would be rewarded with break-through premiums. Where added value versus existing therapies cannot be proven and recognised, timing of market
entry of a new medicine should be taken into account as well as its effects on competition. Products coming to market soon after the first-in-class originator are the result of a parallel R&D process and should be rewarded in parallel to the first-in-class originator. Products entering the market significantly later should not get a similar reward.

- **Be consistent when giving reward.** Criteria for pricing and reimbursement need to be transparent, as requested by the Transparency Directive, and consistent over time. This gives the right signals to companies on what innovations are expected and valued.

In addition to the “Guiding principles for good practices implementing a pricing and reimbursement policy”, further documents are produced and agreed upon in the Working Group on Pricing and Reimbursement:

- “Ensuring availability to medicines in small national markets in Europe”\(^\text{176}\): to understand economic factors which determine supply and production, and bring forward some potential solutions to ensure availability of supply in small markets.
- “Improving access to orphan medicines for all affected EU citizens”\(^\text{177}\): to identify the main bottlenecks not only related to (1) development, but also to (2) assessment, to (3) pricing and reimbursement practices by companies and by national authorities and to (4) awareness raising, and to bring forward some ideas to ensure timely and equitable access for all EU citizens to orphan medicines.
- “Characterisation of the value of innovative medicines”\(^\text{178}\): a bottom-up exercise, based on discussions and collection of views from the relevant Member State authorities on how to recognise, assess and reward valuable innovative medicines, in order to identify some common ground between individual Member States.
- “From assessing innovative value of pharmaceuticals to pricing and reimbursement decisions”\(^\text{179}\): to clarify how some European Member States use assessments of innovative medicines in their pricing and reimbursement decisions.
- “The Toolbox exercise”\(^\text{28}\): to collect expertise from Member States and stakeholders for six selected practices (internal reference pricing, cost sharing, payback, prescription information, price control, generic substitution).
- “Risk-Sharing practices and Conditional Pricing of pharmaceuticals”\(^\text{180}\): to describe how these describes how these practices are set-up in different Member States.

In parallel to the Working Group of Pricing and Reimbursement, the Working Paper on Relative Effectiveness aimed to support Member States apply relative effectiveness systems in order to allow containment of pharmaceutical costs as well as a fair reward for innovation. In that working group, the following major documents were produced and agreed upon:

- “Core principles on relative effectiveness”\(^\text{181}\) which set out certain general principles of public administration that could be relevant for developing national systems and help to encourage of exchange of information, methodologies and experiences between the relevant national authorities;
- “Availability of data to conduct relative effectiveness assessments”\(^\text{182}\) which provided findings of provides a survey of the current processes on data availability during relative effectiveness assessments at national level; and
- “Development of networking and collaboration”\(^\text{183}\) which identified the most relevant networks and put forward recommendations for networking at the European level on this topic.
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Platform on access to medicines in Europe under the Process on Corporate Responsibility in the field of Pharmaceuticals

Following on the G10 process and of the High Level Pharmaceutical Forum, the Process on Corporate Responsibility in the field of pharmaceuticals was launched in 2010 as voluntary multi-stakeholder process which aimed to find non-regulatory solution to several of the new challenges. The platform on access to medicines in Europe is one of its strands. Aiming at enhancing the collaboration among the Member States and relevant stakeholders in order to find common, non-regulatory approaches to timely and equitable access to medicines after their marketing authorization the Platform on access to medicines in Europe comprises six projects:

- **Mechanism of coordinated access to orphan medicinal products**: developing a concept of a coordinated access to orphan medicines based on the set up of programmes between companies and groups of competent authorities and results of the ongoing project on a mechanism for clinical added value on orphan medicines.¹⁸⁴
- **Capacity building on managed entry agreements for innovative medicines**: to clarify the various approaches to managed entry agreements (also referred to as risk-sharing, outcome-based or performance based agreements) ensuring access to innovative medicines.¹⁸⁵
- **Facilitating supply in small countries**: to clarify the specific non-regulatory bottlenecks for the access of medicines in small markets with all concerned parties with a view to defining possible specific approaches on pricing and reimbursement of medicines in these countries.¹⁸⁶
- **Promoting a good governance for non-prescription medicines**: to identify the necessary elements to ensure informed and adequate uptake of medicines after a change of their classification from being subject to medical prescription to not subject to medical prescription.¹⁸⁷
- **Market access for biosimilars**: to define what the necessary conditions within the pharmaceutical environment are to ensure informed, adequate uptake of biosimilars.¹⁸⁸
- **Priority Medicines Report**: In order to ensure that the European Commission, Member States and relevant stakeholders are closely associated with the revision of the Priority Medicines Report 2013, the European Commission set up the "Prioritisation" working group under the umbrella of DG ENTR’s Process on Corporate Responsibility in the Field of Pharmaceuticals. This working group is mandated to guide the revision process, and will serve as the advisory group to the project, i.e. give guidance as to the general directions of the whole project (including topics to be covered in the revised report).¹⁸⁹

The outcomes of the five first working groups of Platform on Access to Medicines in Europe have been finalized and were endorsed by the Steering Group in April 2003.¹⁹⁰

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Update on 2004 Background Paper, BP 8.3 Pricing and Reimbursement Policies


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Update on 2004 Background Paper, BP 8.3 Pricing and Reimbursement Policies


### Annex 8.3.2: Price data of selected medicines (in Euros)

<table>
<thead>
<tr>
<th>Country</th>
<th>Blood</th>
<th>Alimentary tract and metabolism</th>
<th>Nervous system</th>
<th>Antineoplastic and immunomodulating agents</th>
<th>Anti-infectives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prasugrel 10 mg/tab</td>
<td>Insulin lispro 100 u/ml inj 3ml</td>
<td>Pioglitazone 30 mg/tab</td>
<td>Naratriptan 2.5 mg/tab /c</td>
<td>Galantamine 16 mg/cap MR</td>
</tr>
<tr>
<td>Austria</td>
<td>1.64</td>
<td>5.90</td>
<td>1.35</td>
<td>4.58</td>
<td>1.20</td>
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<td>Belgium</td>
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<td>5.80</td>
<td>1.15</td>
<td>1.48</td>
<td>1.57</td>
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<tr>
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<td>2.22</td>
<td>8.48</td>
<td>1.47</td>
<td>5.07</td>
<td>2.73</td>
</tr>
<tr>
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<td>Greece</td>
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<td>2.68</td>
<td>2.52</td>
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<tr>
<td>Finland</td>
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<td>0.66</td>
<td>4.20</td>
<td>1.40</td>
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<td>5.54</td>
<td>n.a</td>
<td>1.43</td>
<td>0.68</td>
</tr>
<tr>
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<td>6.98</td>
<td>1.78</td>
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<tr>
<td>Italy</td>
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<td>6.35</td>
<td>1.22</td>
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</tr>
<tr>
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<td>6.14</td>
<td>1.29</td>
<td>4.61</td>
<td>2.90</td>
</tr>
<tr>
<td>Portugal</td>
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<td>5.46</td>
<td>0.55</td>
<td>1.49</td>
<td>1.02</td>
</tr>
<tr>
<td>Sweden</td>
<td>1.89</td>
<td>6.58</td>
<td>1.21</td>
<td>4.73</td>
<td>2.92</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1.84</td>
<td>6.15</td>
<td>0.61</td>
<td>4.22</td>
<td>2.59</td>
</tr>
</tbody>
</table>

Ex-factory prices per unit in Euro are indicated as of June 2012.
If alternative medicines were on the market, the prices of alternative medicines were taken.
Source: Pharma Price Information (PPI) service of Gesundheit Österreich GmbH (GÖG) / Austrian Health Institute
Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper

Background Paper 8.4
Real-life data and learning from practice to advance innovation

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## Table of contents

List of abbreviations ........................................................................................................................................... 3

1. Introduction ....................................................................................................................................................... 3

2. Limitations of randomised clinical trials and market authorization process .............................................. 4

3. Examples of EHR databases ............................................................................................................................. 5

4. Stages in the development of EHR databases ................................................................................................. 6

5. Challenges with using EHR databases ............................................................................................................. 6

6. Opportunities for innovation and learning from practice using EHR databases ........................................ 8
   6.1 Prioritize research needs ............................................................................................................................... 8
   6.2 Disease understanding ................................................................................................................................. 10
   6.3 Identifying pharmaceutical gaps ............................................................................................................... 10
   6.4 Safety of medicines .................................................................................................................................... 10
   6.5 Risk prediction ........................................................................................................................................... 11
   6.6 Comparative effectiveness ........................................................................................................................ 11
   6.7 Evaluation of health care policies ............................................................................................................ 12
   6.8 Informing cost-effectiveness analyses ..................................................................................................... 12
   6.9 Other areas of use ..................................................................................................................................... 13

7. Integrating different EHR databases .............................................................................................................. 13

8. Ethical aspects and guidelines ........................................................................................................................ 14

9. EHR databases and learning health care systems ......................................................................................... 15

10. Identified gaps and recommendations for research ..................................................................................... 17

11. Recommendations for policy ......................................................................................................................... 18

References ........................................................................................................................................................... 20
List of abbreviations

EHRs  Electronic Health Records
RCT  Randomised controlled trials

1. Introduction

The costs of pharmaceutical R&D are high, with clinical trials being a major component of these development costs. There is an urgent need to address therapeutic gaps in order to be able to respond to unmet medical needs. To help resolve this problem, there is a need to increase efficiency and to bridge bench and clinical research with real-world practice. Making better use of real-world data can improve the efficiency of the whole medicine development chain: HTA bodies, regulators, clinicians and patients will be able to make better-informed decisions, and companies will be able to design better and more efficient development strategies that provide the appropriate evidence to decision makers.

Additionally, data obtained from health information systems can be used to support priority setting, detect safety problems and assess the real-world effectiveness of medicines. Moreover, policy initiatives such as adaptive licensing, value-based pricing and comparative effectiveness studies are critically dependent on the efficient use of Electronic Health Record (EHR) data. However, the resources available in Europe are fragmented, and good quality data are often only available for limited disease areas or geographic regions.

In the 2004 Priority Medicines Report, the use of electronic health records was highlighted as an area of high importance. It was suggested as “a way of creating post-marketing ‘randomized epidemiology’ studies to better understand comparative effectiveness and cost-effectiveness.” Although progress has been made since then, the potential is still largely unfulfilled.

Real-world data are now more widely available than ever before and offer new opportunities for research and health systems development. Information in the health care system is increasingly processed electronically in many countries across the world. Databases that collate health care information from larger numbers of patients are becoming available for research. The information that is available for research in these databases has been changing over time and the possible contribution of health care databases to pharmaceutical innovation has been evolving.

We will provide examples in this background paper on how these databases can inform priority setting and support pharmaceutical innovation by assisting in, amongst others, the prioritisation of research needs, better disease understanding, safety monitoring, comparative effectiveness research and the evaluation of health care policies. Examples will be given on how these health care databases can help to identify the greatest challenges with pharmaceutical treatments and test their effects in real life.
2. Limitations of randomised clinical trials and market authorization process

New health care interventions (such as medicines and devices) are typically only given authorization for use in routine clinical practice after randomised clinical trials (RCTs) have shown positive benefit-risk ratio. These interventional studies are in general conducted using strict eligibility criteria with many inclusion and exclusion criteria and with close instructions of study patients how to use the medications. RCTs often exclude patients based on age, gender, co-morbidity and geographical location (also see the Background Papers to Chapter 7.1 and Chapter 7.3). In contrast, patients in routine clinical practice are diverse, with varying disease histories and co-medications and they do not always comply with instructions and persist with treatment over time. Medicine use in clinical practice frequently differs widely from the (pre-approval) clinical trial settings. Selective COX-2 inhibitors provide an example of the challenges in generalising evidence from authorization RCTs to routine clinical practice. The main RCTs of rofecoxib and celecoxib that were used to obtain the marketing authorization restricted study eligibility to patients with severe osteoarthritis or rheumatoid arthritis who were expected to use the study drug daily for the duration of the studies (six to nine months).\(^2\)\(^3\) However, an analysis found that the large majority of patients using selective COX-2 inhibitors in routine clinical practice would not have been eligible for these main RCTs as they did not have severe osteoarthritis or rheumatoid arthritis and did not use these medicines every day for a number of months.\(^4\) The results of authorization RCTs are, therefore, not always generalizable to patients in routine clinical practice.\(^5\)

Authorization RCTs typically assess the *efficacy* of a medicine, that is, the effects under ideal circumstances. On the other hand, *effectiveness* concerns the effects of a medicine under routine clinical circumstances.\(^6\) There are various reasons for differences between efficacy and effectiveness. One reason leading to these differences is the adherence of patients to the medication and the recommended dosage instructions. An example is alendronate; in pivotal RCTs for drug approval 89% of study participants were still using the study drug after three years.\(^7\) In real life, however, only about 35% were still using alendronate after three years.\(^8\) Another reason for the discrepancy between efficacy and effectiveness are differences in dosages. The daily dose of COX-2 inhibitors rofecoxib and celecoxib was about one-third in routine clinical practice compared to that in the authorization RCTs.\(^4\) A challenge in the generalizability of evidence from RCTs to real life concerns patients who were not eligible for the RCTs. It has been proposed recently that all patients aged 50 years or older should receive a statin given their cardiovascular risk. However, most of these patients would not been have been eligible for the statin RCTs, as inclusion was restricted to individuals with high cholesterol blood levels and not based on high cardiovascular risk.

The current requirements for drug authorization do also not always provide the answers clinicians’ need, as exemplified by the high levels of off-label prescribing (i.e., prescribing not consistent with the authorization license). A Canadian study evaluated the treatment indications in the electronic health records (EHRs) for 253 347 electronic prescriptions. It found that the prevalence of off-label use was 11.0%; of the off-label prescriptions, 79.0% lacked strong scientific evidence. Off-label use was highest for central nervous system drugs (26.3%), including anticonvulsants (66.6%), antipsychotics (43.8%), and antidepressants (33.4%).\(^9\)
3. Examples of EHR databases

Today, electronic health records (EHRs) are an increasingly important source of information to capture the real-world setting. Electronic Health Records can be defined as a “longitudinal collection of electronic health information about individual patients and populations.” This includes information about diagnosis (e.g. laboratory tests), treatment (e.g. dispensing of medicines) and outcomes of patients (e.g. hospitalization and mortality). For some research purposes, these data can be linked to other non-health datasets (e.g. data about employment or socio-economic information) to generate a comprehensive picture.

Real-life data on medicine use at the patient level first became available during the 1980s when administrative information about medicine use and health system activities was first stored at a significant level. Over recent decades, innovation in information technology (IT) infrastructure and capabilities and methodological refinements have played an important role in the increasing capabilities and potential of using real-life data to answer questions relevant for innovation.

There are currently over 300 EHR databases in 45 countries with different characteristics as recorded by the International Society for Pharmacoeconomics and Outcomes Research. Examples of EHR databases that are being widely used for research include the Clinical Practice Research Datalink (previously named the General Practice Research Database) in the United Kingdom, the Dutch PHARMO Record Linkage System and the national databases in Sweden and Denmark. The Clinical Practice Research Datalink collates the anonymised EHR information for over five million patients currently registered at a participating general practice. This EHR database has been linked individually and anonymously to other electronic health care datasets, including the national registry of hospital admissions in England (Hospital Episode Statistics), the national death certificates (with primary and secondary cause of death) and prospective disease registries, such as the cancer and cardiovascular disease registries. More recently, the Dutch public-private partnership Top Institute Pharma Mondriaan project established an infrastructure for linkage and enrichment of routine health care data in order to enhance research on benefits and risk of medicines. Currently, data from multiple sources such as general practice (one million patients), community pharmacy (11 million patients), hospital pharmacy and laboratory (100 000 patients) can be linked using privacy enhancing technology such as application of trusted third parties. Using this infrastructure the BIOLINK-NL project is currently developing a national infrastructure for linkage of social and medical registries to biobanks which will enormously enhance the possibilities for research on molecular biomarkers of pharmaceutical response (both harmful and beneficial) and the development of personalised treatment. In Denmark and Sweden, each national health care system provides universal coverage to all residents (5.5 million inhabitants in Denmark and 9.2 million inhabitants in Sweden). Health care coverage includes visits to general practitioners, specialists, hospital admissions, and outpatient visits; where pharmaceutical costs are either partially or completely covered. A centralised civil registration system has been in place in each country for many years, allowing for personal identification of each person in the entire population and for the possibility of linkage to all national registries containing civil registration numbers, e.g., patient registry, cancer registry, prescription databases, and registry of causes of death.
4. Stages in the development of EHR databases

Table 8.4.1 outlines a simplified representation of stages in the development of EHR databases in the United Kingdom. Initial use of electronically obtained health care data mostly consisted of aggregate analyses of administrative data such as hospital admission data. When clinicians started to use computers for record keeping, it was realised that these data could be very useful for analyses of individual patient data. Research databases that collated the anonymised EHRs were created. An example is the VAMP research database which eventually changed into the Clinical Practice Research Datalink. The first use of these database consisted of analyses of safety outcomes of medicines. Over time, the richness and completeness of EHR databases has increased. Linkages between different EHR datasets were implemented (an example is the linkage between data from general practitioners and hospitals). Also, more information was shared electronically between different parts of the health care system. An example is the laboratory data; over the last decade, laboratory results have been communicated electronically and then loaded automatically into the EHR. This background paper will describe how EHR databases can be used to advance our knowledge of medicines that are used in routine clinical practices and inform policymaking and facilitate innovation about how and what interventions are being used in clinical practice.

Table 8.4.1: Stages in the development of EHR databases in the United Kingdom

<table>
<thead>
<tr>
<th>Time-period (approximate)</th>
<th>Development of EHR databases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980s onwards</td>
<td>Data collected for administrative purposes (such as hospital admission data and death certificates); mainly used for aggregate analyses</td>
</tr>
<tr>
<td>1990s onwards</td>
<td>Clinicians starting to use computers for record keeping (replacing paper records) and data collated into research database; mainly used for drug safety monitoring</td>
</tr>
<tr>
<td>2000s onwards</td>
<td>Linkages between various EHR databases and administrative data (e.g. claims for payments); mainly used to obtain complementary information or to validate outcomes</td>
</tr>
<tr>
<td>2010s onwards</td>
<td>Enrichment of routinely collected data by prospective data collection within EHR databases (e.g. collection of blood samples for genetic analyses or patient questionnaires)</td>
</tr>
<tr>
<td>2010s onwards</td>
<td>Introduction of randomisation at the point of care using the EHR database to identify potentially eligible patients and for follow-up of major clinical outcomes (i.e., pragmatic and cluster trials); mainly used to evaluate the effects of medicines in routine clinical practice</td>
</tr>
</tbody>
</table>

5. Challenges with using EHR databases

Since the 2004 Priority Medicines Report many initiatives have been taken to move forward the development of EHRs. However, translating the vision presented above into feasible and sustainable models that are applicable independent of country or health care setting is a major challenge.
EHR databases are currently mostly used for non-interventional (observational) studies in which clinicians determine the treatment allocation (rather than randomisation). Confounding is a major concern in observational studies; it means that observed differences between comparison groups are not caused by the exposure of interest but by unevenly distributed risk factors. As an example, observational studies suggested major reductions in the risk of cardiovascular disease by hormone replacement therapy while this was not confirmed in a large randomised RCT. There is evidence that hormone replacement therapy is given preferentially to healthier women. Observational researchers often seem to assume that it is sufficient to enter potential confounders into a statistical model in order to resolve confounding. Advanced statistical techniques (such as propensity score matching) are becoming more popular recently. But statistical techniques suffer from the same limitation that they cannot overcome unquantifiable or poorly recorded confounders. Instrumental variables may potentially control for unobserved confounding, though the strong assumptions underlying this method are often limiting its widespread application. However, the reverse assumption that observational studies are always fatally flawed may also not be correct. The eminent epidemiologist Jan Vandenbroucke has argued that observational studies should be restricted to questions that meet the underlying assumption that exposure allocation is unrelated to the outcome. As an example, people who start smoking do this for reasons unrelated to the risk of lung cancer. Consistent with this, risk estimates for adverse events were found to be similar between randomised RCTs and observational studies. An analysis of beneficial effects of medicines found frequent differences in risk estimates between RCTs and observational studies.

Data quality is of course very important and not all clinical outcomes can be measured accurately solely from the data recorded in the EHRs. Data may be missing and not measured and medical diagnostic information may be coded incorrectly. Furthermore, not all EHR databases will be of sufficient quality for research. Three dimensions of data quality may be fundamental: correctness, completeness and currency. Correctness refers to whether the information in a study is valid. Completeness refers to whether all required information is available or not. Currency relates to the time period between occurrence of an event and date of recording. Historically, the validations of EHR data have focused on the comparison of paper records and electronically recorded data. With the demise of paper records, such validations are increasingly being replaced by comparisons between linked EHR databases. As an example, a recent study compared cancer recording in the records of general practitioners, hospital records, death certificates and cancer registries and found considerable discrepancies in cancer recording between these different data sources. As data in linked databases are recorded for different purposes and using different systems, these comparisons can be challenging. There is a clear research need for developing and adopting systematic, statistically based methods of data quality assessment. Furthermore, the development of common data models and dictionaries could simplify research across different EHR databases.

EHR databases may not contain all the information that is needed for research. Data on prescribing in hospitals or specialist medicines such as biologics are rarely recorded in EHR databases but may be captured in dispensing databases. Anonymous linkages between registries and EHR databases provide opportunities to enrich research data. In addition to lifestyle factors, patient-centred outcomes are often incompletely recorded in EHR databases. But if patients can be approached through the clinician, these data can be obtained. As an
example, an ongoing study collects questionnaire information about employment histories in order to assess the health risks and benefits of extended working life. This study will examine the inter-relation of changes in employment as reported in patient’s questionnaires and changes in health as recorded in the EHR.23

6. Opportunities for innovation and learning from practice using EHR databases

EHRs are emerging technologies with increased adaptation and use in health care. While EHR databases will not provide answers to all questions, there are substantial opportunities in several areas of research that can inform policy decisions. A few examples of these are listed below and in Table 8.4.2.

6.1 Prioritize research needs

An important role of EHR database is to identify and measure research needs. These could include measurement of the level of off label medicines use and adherence to treatment guidelines. An example is a study of over 600,000 children that reviewed paediatric prescription patterns and reported on off-label medicine use in children.25 A study linking an in-patient hospital registry and the EHRs of general practitioners found that clopidogrel treatment initiated in hospital is frequently discontinued in primary care despite the recommendations in treatment guidelines. Discontinuation of clopidogrel was associated with increased risks of mortality and recurrent myocardial infarction.26

A study that utilised pharmacy records assessed the quality of statin treatment and found that only 41% of patients that started with a statin received the first choice (simvastatin) according to the guidelines at that time.24 Research in the variability of health care between clinicians can highlight important levels of uncertainty with the result that patients can be treated differently. An example is the study that found that the prescribing of antibiotics to patients with chronic obstructive pulmonary disease experiencing exacerbations varied substantially (from 29% and 88%).27 This study supports the need for a large scale pragmatic RCT to evaluate the effects of antibiotics in this condition. If antibiotics would be effective in this condition, a large number of patients would be treated sub-optimally. If they are ineffective, antibiotics are being prescribed unnecessarily contributing to antibiotic resistance. A RCT has been started in order to test the feasibility of recruiting patients with COPD exacerbations at the point of care during consultation and then randomising patients to antibiotics or usual care. The EHR databases (using data from general practitioners, hospital admissions and death certificates) will be used to measure hospital admission over three months and long-term incidence of mortality.32
Table 8.4.2: Examples of different areas of research using EHR databases

<table>
<thead>
<tr>
<th>Area of research</th>
<th>Type of research</th>
<th>Example of a study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prioritize research needs</td>
<td>Drug utilisation studies</td>
<td>Cohort study in three European countries using EHR databases to assess drug use in children(^{25})</td>
</tr>
<tr>
<td>Identify failures of interventions in routine clinical practice</td>
<td>Cohort study in three European countries using EHR databases to assess drug use in children(^{25})</td>
<td></td>
</tr>
<tr>
<td>Measure variability in interventions between clinicians</td>
<td>Considerable variability in the chance that a patient with a exacerbation of chronic obstructive pulmonary disease receives an antibiotics, dependent on which clinic is visited(^{27})</td>
<td></td>
</tr>
<tr>
<td>Prioritize research needs</td>
<td>Disease co-morbidity network</td>
<td>Co-occurrence of different disease and prognosis of connected diseases(^{28})</td>
</tr>
<tr>
<td>Identify failures of interventions in routine clinical practice</td>
<td>Uptake and outcomes of pharmaceuticals</td>
<td>Use of bisphosphonates associated with fracture risk reductions after six to 12 months of treatment but only 58% of patients were treated for at least one year.(^8)</td>
</tr>
<tr>
<td>Measure variability in interventions between clinicians</td>
<td>Considerable variability in the chance that a patient with a exacerbation of chronic obstructive pulmonary disease receives an antibiotics, dependent on which clinic is visited(^{27})</td>
<td></td>
</tr>
<tr>
<td>Disease understanding</td>
<td>Disease co-morbidity network</td>
<td>Co-occurrence of different disease and prognosis of connected diseases(^{28})</td>
</tr>
<tr>
<td>Identifying pharmaceutical gaps</td>
<td>Uptake and outcomes of pharmaceuticals</td>
<td>Use of bisphosphonates associated with fracture risk reductions after six to 12 months of treatment but only 58% of patients were treated for at least one year.(^8)</td>
</tr>
<tr>
<td>Safety of medicines</td>
<td>Safety monitoring</td>
<td>Previous studies reported increased risks of cancer with insulins. Study of users of different classes of diabetes medications found substantive biases without evidence for an increased cancer risk(^{29})</td>
</tr>
<tr>
<td>Disease understanding</td>
<td>Monitoring of regulatory actions</td>
<td>Study found that regulatory advice (to prescribe selective COX-2 inhibitors to patients at high risk of gastrointestinal disease but low risk of cardiovascular disease) was not followed(^{30})</td>
</tr>
<tr>
<td>Identifying pharmaceutical gaps</td>
<td>Research on pharmacogenetics and biomarkers</td>
<td>Recruitment within the Clinical Practice Research Datalink of 150 cases with statin myopathy and 500 control statin users</td>
</tr>
<tr>
<td>Comparative effectiveness</td>
<td>Observational studies</td>
<td>Hypertension treatment was relatively as effective in routine clinical practice as in RCTs, but fewer patients needed to be treated in real-life practice compared to RCTs to prevent a stroke(^{31})</td>
</tr>
<tr>
<td>Policy of treatment allocation</td>
<td>Pragmatic RCTs</td>
<td>Recruitment at the point of care randomising patients with high risk of cardiovascular disease between simvastatin and atorvastatin; follow-up for heart attacks using records of general practitioners, hospitals, death certificates and disease registry(^{32})</td>
</tr>
<tr>
<td>Risk prediction and identification of patients at high risk</td>
<td>Risk prediction and identification of patients at high risk</td>
<td>Individual prediction of cardiovascular risk using EHR data. Used for screening to identify patients that should be treated with statins(^{33})</td>
</tr>
<tr>
<td>Cluster trials randomising clinics between different policies</td>
<td>If a patient resenting with symptoms of respiratory tract infection, intervention clinics get an electronic prompt promoting no antibiotic prescribing or delayed antibiotic prescribing instead of immediate prescription. Clinics randomized to control do not get this reminder(^{34})</td>
<td></td>
</tr>
<tr>
<td>Decision-making</td>
<td>Cost-effectiveness modelling</td>
<td>Model based on absolute risks as derived from the EHR database and relative drug effects as derived from RCTs. Study found that cost-effectiveness of selective COX-2 inhibitors was substantially worse compared to models that only used RCT data(^{4})</td>
</tr>
<tr>
<td></td>
<td>Risk-benefit modelling</td>
<td>The benefit of selective COX-2 inhibitors in reducing the frequency of upper GI events may be offset by their cardiovascular harm, particularly in patients with risk factors for cardiovascular disease(^{35})</td>
</tr>
</tbody>
</table>
6.2 Disease understanding

A recent review suggested that in the near future, EHR databases will impact significantly how we discover and develop safe and efficacious medicines. Novel disease relationships could be identified using EHR data. Hidalgo analysed EHRs of over 32 million patients to analyse the relationships between different diseases. They found that a disease that is connected to many other diseases tended to have worse prognosis compared to diseases that were less connected.

6.3 Identifying pharmaceutical gaps

EHR databases are routinely being used to measure the uptake and outcomes of medicines. Persistence (i.e., extent of long-term use) is often evaluated for treatments that need to be taken long-term. As an example, only one in four patients are using bisphosphonates for more than five years, despite the fact that their risk for fracture remains elevated; about 40% of the patients will stop this treatment within one year. Increased risks of osteoporotic and hip/femur fractures were found in patients with low compliance to bisphosphonates. This study highlights the need for innovation in ensuring persistence of use. Bisphosphonates may be effective medicines, as found in RCTs, but their full potential in reducing fractures is not being realised. Together with non-persistence suboptimal response to treatments can also be explained by other factors (e.g. environmental, genetic, clinical) and highlights another pharmaceutical gap; the exploration of the reasons for heterogeneity between individual patients in treatment response.

6.4 Safety of medicines

EHR databases have been used historically mostly for drug safety studies and the first studies were published over 25 years ago. These studies are widely recognised as being important for the detection and monitoring of adverse effects of medicines. A recent example of a safety study is an analysis of the cancer risks of patients initiating different classes of diabetes medicines. This study was conducted because initial studies reported increased risks of cancer with insulins which triggered substantial concern about the safety of these medicines. However, there was no evidence in this study of either beneficial or adverse effects of glucose-lowering agents on cancer risk.

EHR databases can provide information on the possible magnitude of risks of a known side-effect overall and in subgroups of patients. Such information can help to inform whether the side-effect may occur in e.g. one per 100 patients or one per 1 000 patients and whether these risks may be substantially increased in certain patient groups or exposure characteristics (e.g., increased risks following treatment initiation or with long-term treatment). Spontaneous reporting systems of suspected side-effects can not provide such quantitative information as the level of under-reporting and the characteristics of users and size of the population are typically unknown. Of course, these analyses of crude incidence rates may not provide evidence of a causal relationship between increased incidence of adverse outcomes and the medicine, given the possibility of confounding. Such analyses should be viewed as the first step in reviewing whether further more detailed analyses are required. There has been recent controversy in Europe around the risk of deep venous thrombosis due to cyproterone 2 mg in combination with 35 µg of ethinyl estradiol, which was being used for acne and oral contraception. Following a review of ten spontaneous case reports, the
Dutch regulatory authority advised that women should no longer initiate this medicine but should not stop the treatment. Rather than communicating the number of spontaneous reports, it could have been useful to also communicate the possible levels of excess risks shortly after starting treatment and with long-term treatment as measured in EHR databases.

More recently, EHR databases are being used increasingly for pharmacogenetic research. A recent study identified patients who were using statins and developed rhabdomyolysis or highly elevated levels of creatine phosphokinase. The clinician then approached the patients and requested a blood or saliva sample. This system allows for almost “real-time” recruitment of patients who used a medicine of interest and developed a major side-effect, allowing prospective monitoring of both new and older medicines. (See also Chapter 7.4)

### 6.5 Risk prediction

EHR data are now being used to predict long-term risks of disease. An example is the QRISK score that predicts 10-year risk of cardiovascular disease using the routinely collected EHR data. Treatment guidelines in the United Kingdom now advocate that statins are initiated in patients with higher risks of cardiovascular disease as determined by risk scores such as QRISK.

### 6.6 Comparative effectiveness

Comparative effectiveness is the comparison of the beneficial and harmful effects of interventions in real life. This is defined as “the extent to which an intervention does more good than harm compared to one or more alternative interventions for achieving the desired results when provided under the usual circumstances of health care practice.” There is increasing interest in comparative effectiveness as this can inform e.g. reimbursement policies. A recent study from the Cardiovascular Research Network Hypertension Registry to compare the incidence of heart attacks, heart failure and stroke between different types of β-blockers. It found that there were no statistically significant differences in incident cardiovascular events between atenolol and metoprolol tartrate. The authors of this study concluded that large registries may be useful for addressing comparative effectiveness questions that are unlikely to be resolved by RCTs due to e.g. lack of statistical power.

A recent development is to conduct pragmatic RCTs within EHR databases providing an assessment of the comparative effectiveness in a randomised method. Patients are recruited at the point of care, randomised among routinely available interventions and then followed unobtrusively using the electronic health care database. An on-going RCT recruits patients indicated for statin treatment. The EHR database is used to identify patients at high risk of cardiovascular disease. After eligibility review by the clinician and informed consent, patients are then randomised between simvastatin and atorvostatin. Study participants are then followed for persistence to statin treatment and for major clinical outcomes using the EHR data. Myocardial infarctions are measured using the records of the general practitioner and linked data from hospitals, a disease registry and death certificates. The randomisation ensures that baseline differences and confounding is reduced.
6.7 Evaluation of health care policies

Health care policies, such as interventions reducing the rate of antibiotic prescribing, could be evaluated and tested in cluster trials. Entire areas or health service organisational units are randomly allocated to intervention or control groups in cluster trials, with outcomes evaluated for individuals within each cluster. A cluster trial has recently been completed evaluating antibiotic prescribing for respiratory tract infections. Electronic prompts had been developed based on recommended clinical practice guidelines to be activated during consultations for respiratory tract infections in the selected age range. The electronic prompts promoted no antibiotic prescribing or delayed antibiotic prescribing instead of immediate prescription. The prompts specifically incorporated recommendations from the recent guidelines on antibiotic prescribing in respiratory illness. During consultations with patients presenting with symptoms of respiratory tract infection, primary care professionals received electronic prompts reminding them of recommended standards of care in respiratory tract infections. The prompts also provided supporting information and links to evidence that supports the recommendations. The decision on whether to follow the treatment suggestions included in the prompt remained with the clinician. Control practices did not get any electronic prompts. The EHR database was used to measure the rate of antibiotic prescribing in intervention and control practices. Once the results have been analysed, it can be evaluated whether simple flagging procedures could be helpful in reducing antibiotic prescribing or whether more complex interventions will be needed to reduce the over-prescribing of antibiotics.

Another example of policy evaluation concerns an analysis of potential cost savings of substitution of brand by generic medicines and of changing medicines within the same class (i.e., therapeutic substitution). It was shown in an EHR database study that generic and therapeutic substitution would lead to potential annual savings of approximately €87 million in the Netherlands. The therapeutic substitution in this study consisted of switching patients on atorvastatin, fluvastatin or rosuvastatin to either simvastatin or pravastatin. This study concluded that from an economic point of view, society could gain by substituting statin therapy, especially from therapeutic substitution. However, this substitution may not always concern medicines that have equal effects or an equal evidence base on benefits and risks.

6.8 Informing cost-effectiveness analyses

EHR data have been used to provide information for cost-effectiveness and risk-benefit models. One study evaluated the cost-effectiveness of selective COX-2 inhibitors. It used the EHR data to estimate absolute risks for the outcomes of interest and then combined these with RCT evidence on the relative effects of selective COX-2 inhibitors in preventing gastrointestinal bleeding. The study found that cost-effectiveness models that only used RCT data had substantially exaggerated the cost-effectiveness of selective COX-2 inhibitors as the absolute risks of gastrointestinal disease were considerably lower in actual clinical practice. These findings strongly support that the evidence in health technology assessment consider the external validity of the information used rather than depending on data from authorization RCTs.
6.9 Other areas of use

EHR databases could also be used for measuring performance of clinicians and the auditing of their performance. However, it may prudent to separate research and audit activities. Access to EHR records for research purposes is often controlled by the clinicians with researchers dependent on clinicians for data access, validation of the EHR records and recruitment into prospective studies. Furthermore, EHR databases could be linked to registries that prospectively collect information on patients with a certain disease or using specific medicines. EHR databases may also be used to complement and enhance the results of RCTs. Potentially eligible RCT participants may be identified using the EHR databases and RCT participants could be followed long-term for major clinical outcomes. Natural language processing of electronically recorded notes of clinicians may allow better capture of the clinical information in this free text.

7. Integrating different EHR databases

Increasingly there is a need to perform studies on harms and/or benefits of medicines across different EHR systems and across different countries mainly for reasons of the need for a larger sample size. Evaluations of rare adverse events, comparisons of individual products or heterogeneity of drug effect in different subgroups of patient often cannot be done in a single database. The health care systems in most countries consist of multiple health care providers who often use different systems to store data (either paper or electronic). Furthermore, physicians often record data differently and inconsistently (both on paper and electronically). In order to analyse EHR from different countries and sources, various international initiatives using different approaches are currently ongoing. One approach focuses on IT aspects with the aim to develop EHR systems that are interoperable and allow the seamless transfer of data. This approach requires extensive redesigns of the IT systems. An alternative approach is to maintain the EHR data structure as collected by the health professionals but develop common protocols with similar research questions across databases adapting the operational definitions to each individual EHR database. This model is currently used by the Innovative Medicines Initiative PROTECT project. The OMOP initiative in the USA integrates all EHR data into a central research database according to a common data model. The fourth approach to dealing with heterogeneous EHR databases concerns a distributed model in which basic analyses are run on federated datasets followed by central pooling of results. The EU-ADR project uses this approach. Another approach is being followed by the Canadian CNODES initiative. In this initiative common protocols have been developed to study various drug-adverse event associations, but data are analysed locally in each province using multidimensional propensity scores to adjust for confounding and finally pool results through meta-analyses.

Each of these approaches has advantages and disadvantages and in the coming years it will become clearer which approach may be the more successful. The IT redesign is clearly the most ambitious approach with the aim to have EHR systems that provide for systematic diagnoses using decision support systems, have uniform and standardised recording of clinical data and allow for seamless transfer of data between different health care providers. The ideal system for RCTs would be to build the case report form within the EHR so that data that have already been collected previously (in a standardised manner by fully trained
staff) could be imported seamlessly and immediately into it. While this may be ideal for research purposes, the development of large and expensive EHR systems has not unequivocally been successful, with several substantial failures and few successes. At a recent meeting at the USA Institute of Medicine (discussing large simple RCTs with simple recruitment and follow-up procedures), Michael Lauer of the National Institutes of Health advocated a willingness to experiment: emerging technologies should be embedded into existing projects and be allowed to fail often but inexpensively in smaller experiments. A stepwise approach to learning what works could be useful for expanding research with EHR data as long as lessons are captured and shared.

8. Ethical aspects and guidelines

Research access to EHR databases is typically restricted to data that are anonymised and do not contain patient identifiers such as names and addresses. Re-identification is, however, theoretically possible for an individual with an e.g. extremely rare condition or characteristic pattern of prescription dates. Data protection and security is thus of critical importance for researchers that use EHR databases. Staff training and standard procedures but also skills and attitudes of staff are important to treat data with appropriate care. Regular audits by external experts have been found to be very useful as it helps to maintain a culture of continuous improvement. This example from publishing audit findings and overall system of data security should be followed by other EHR databases.

The informed consent requirements for research use have been widely debated. In many countries, anonymised EHR data do not require informed consent of the patients. Some EHR databases use an opt-out system in which patients can refuse their data to be transmitted to the research database. Other EHR databases require an opt-in system in which patients have to provide consent to research use. A recent evaluation of patients approached for informed consent to use their medical records found significant differences between participants and non-participants. The authors of this study concluded that an opt-in system of consent may threaten the validity of results from observational studies. Clinical interventions need to be monitored and evaluated in order to identify opportunities for improvements. Without data, such activities would be impossible and harmful interventions could go unnoticed.

The models of ownership vary greatly between EHR databases. Ownership varies from governments, universities, independent organisations to commercial companies. The requirements for data access for research also vary, ranging from no external access to access after protocol approval. One of the concerns expressed by patients relate to sharing of EHR data with commercial companies. There has been a clear movement towards open access to research which could minimise any effects of conflict of interest. The Royal Society in the United Kingdom recommended an open data culture and, where the data justify it, scientists should make them available in an appropriate data repository. While it would not be appropriate to put all EHR data on-line for open access, an open data culture would support a model in which researchers can access to EHR data following scientific review of the protocol that is done fully independently of the owners of the EHR database. Patients want clear information about the process and implication of using EHR data. Transparency of access requirements would support this.
Registrations of the study prior to the start of the analyses and external access to protocols after completion of the analyses have been advocated strongly for RCTs. Access to research protocols may be even more important with research that uses EHR data: there are now several examples of studies that reached opposite conclusions when the same EHR database was used. One example concerns discrepant results concerning the possible effects of diabetes medication. Two studies recently evaluated this association in the Clinical Practice Research Datalink between diabetes medication and cancer. One study concluded that the use of metformin was associated with a decreased risk of pancreatic cancer in women only, whereas use of sulfonylureas and of insulin was associated with an increased risk of pancreatic cancer. The second study, conducted independently, concluded that there was no evidence of either beneficial or adverse effects of diabetes medication on cancer risk. These two studies varied in the design (case-control versus inception cohort) and in the definition of exposure. One can easily vary results by e.g. excluding certain patient groups or varying the definition of exposure or case definition. Research that use EHR data can be based on strictly a-priori defined criteria or on data dredging and post-hoc changing of study definitions. There are now several examples of studies, within the same EHR database but with different protocols, that reached opposite conclusions. External access to protocols will ensure that deviations from the protocol are transparent and subjected to peer review.

Initiatives have been taken to develop guidelines for the conduct of observational research with EHR databases. An important example is that the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. This is a collaborative scientific network coordinated by the European Medicines Agency and developed in collaboration with European experts in the fields of pharmacoepidemiology and pharmacovigilance. Its goal is to further strengthen the post-authorization monitoring of medicinal products in Europe by facilitating the conduct of multi-centre, independent, post-authorization studies focusing on safety and on benefit-risk, using available expertise and research experience across Europe. For comparative effectiveness studies, guidelines have also been published on the state of the art approaches to frame research questions and report findings for these studies.

9. EHR databases and learning health care systems

A health care system that generates and applies the best evidence for collaborative health care choices of each patient and provider has been defined as a learning health care system. Such a system would continuously test interventions and collect data on the outcomes and then use these results to inform clinical practice. EHR databases are an emerging technology that can help to fulfil this promise. Low-cost and low-risk pragmatic RCTs within EHR databases should be conducted as a matter of routine in order to resolve uncertainties that clinicians face in daily life. Variability in clinical care between clinicians due to incomplete evidence should be addressed by conducting a RCT. Additionally, using EHR databases in an optimal fashion is of high importance for implementing adaptive licensing policies.

A recent analysis by John Ioannidis found that only one of the 24 blockbuster medicines (those with more than one billion US dollars in sales) had been studied in a RCT with more than 10 000 participants. This is an important deficiency because large RCTs are needed to evaluate effects on major clinical outcomes. For example, few of the RCTs with blockbuster
medicines included death as an outcome, so we currently do not know whether these widely used medicines may increase mortality due to side-effects. Five of the blockbuster medicines included in the study by Ioannidis are used long-term to treat patients with mental-health problems but the use by millions of patients is based on RCTs of short-term duration (three to four months) enrolling only a few hundred patients. Simple pragmatic RCTs that use EHR data could address these uncertainties at low cost; patients would be randomised after consent and the EHRs would be used to record death (or other major clinical outcomes) unobtrusively. A standard RCT with 20,000 patients can cost over €350 million, while a simple pragmatic RCT within an EHR database would cost €7 million. As outlined in a recent article about the continuously rising costs for RCTs, “reducing the costs of trials is absolutely crucial for the public good”.

Adaptive licensing of medicines is being considered as a model that allows step-wise authorization of medicines, with iterative phases of data gathering and regulatory evaluation. Initial smaller RCTs are followed by larger ones and authorization approval by the regulatory authorities is re-considered repeatedly with fewer licensing conditions being imposed over time in case of successful studies. This approach allows approval to align more closely with patient needs for timely access to new technologies and for data to inform medical decisions. EHR databases can play a critical role in implementing adaptive licensing in a cost-effective manner. More limited pre-authorization studies could be followed by larger simple RCTs that collect mortality rates and major clinical outcomes through the EHRs, and additional outcomes through study-specific case report forms. Participants in these pragmatic RCTs would be randomised between the novel intervention and the standard of care. The ideal would be that the earlier studies would be done in specialist centres in carefully selected patients but over time a broader spectrum of clinicians and patients would be involved. Similarly, the earlier studies would implement rigid monitoring of trial participants while the later RCTs in the broader populations would mimic the monitoring as would be routine. Such an approach could address the current gap between internal and external validity of RCTs. In order for this approach to work, the current regulatory framework will need to change. The concept of risk proportionality to research governance needs to embraced fully, so that many more clinicians and patients are willing to participate in research. Currently, only a small minority of clinicians and patients participate in research, even when it concerns low risk pragmatic RCTs. In our ongoing simple pragmatic RCT comparing simvastatin and atorvastatin (two widely medicines), less than 10% of the clinicians were willing to participate and complete the numerous paper forms and training in how to prescribe a statin (which they have done already to hundreds of patients). The health care system needs RCT evidence to guide interventions but its practitioners currently seem unwilling to generate it. Adaptive licensing can only be a success if more clinicians and patients participate in simple RCTs with research governance proportional to the risks imposed by a RCT.
10. **Identified gaps and recommendations for research**

EHR databases permit unobtrusive long-term data collection on major clinical outcomes. With increasing computerisation of health care systems, the quality and completeness of EHR data have been increasing over time. These databases provide an opportunity to integrate research and clinical care. But there remain several gaps related to the use of EHR databases for research and policy. To unlock the full value of EHR databases, investment is needed at the European level to create an efficient infrastructure for research and innovation. The development and appropriate use of EHR databases is essential, especially for the success of new policy initiatives such as adaptive licensing and various pricing schemes. Efforts to strengthen the capabilities of Europe in this area and to build on existing infrastructure are of key importance. Furthermore, from a public health perspective, data that are gathered as part of (publicly funded) health care practice should be available to a broad audience, if the data is of appropriate quality. The key activities to be supported are:

**Establishment of a funded European Research Network for the conduct of comparative effectiveness studies**

The United States Agency for Healthcare Research and Quality funds the development of the research infrastructure to identify new and emerging clinical interventions, review and synthesise current medical research, identify gaps between existing medical research and the needs of clinical practice, promote and generate new scientific evidence and analytic tools, train and develop clinical researchers, translate and disseminate research findings to diverse stakeholders and reach out to stakeholders via a citizens forum. In Europe, networks have been established and funded for the review and synthesis of the evidence on the effects of medicines and for the conduct of cost-effectiveness analyses and health technology assessments. However, there is currently no funded infrastructure across Europe to conduct comparative effectiveness studies and generate the evidence that may be needed to inform health technology assessments. Such a network could build on existing strengths and fund the development of the research infrastructure. A European network could strengthen the collaborations within Europe and help to build on the unique strengths in Europe of EHR databases.

**A focus on systematic measurement of data quality**

EHRs are increasingly being used for research and public health purposes. The content of EHR databases varies greatly as information is being collected for different reasons and using different software and coding systems. Also, information in EHR databases can change substantially over time. As an example of temporal changes, the Quality and Outcomes Framework introduced in England in 2004 resulted in a substantive increase of the data recorded in the EHR databases as clinicians were incentivised to record information. The traditional methods of measuring data quality consisted of comparing the paper charts with the electronically recorded information. This model is increasingly less useful as more and more clinics are using paper-less record systems. Given this multitude of EHR databases, their varying content and possibility of changes in recording over time, there is a need to develop and implement statistical models of data quality. The ideal would be to have models that regularly evaluate the quality of the EHR database for the information that is at a minimum required for a certain study.
Development of methods to predict long-term risks in EHR databases

A multitude of advanced statistical models, such as neural networks and artificial intelligence models, are being applied to large datasets including EHR databases. The objective of these analyses is to improve the prediction of risks of adverse outcomes. But the methods of comparing different statistical models in risk prediction are not yet fully developed. The traditional approach of dividing a dataset into a development and testing dataset may be less applicable to very large databases as one would get statistically similar results. Risk prediction models typically use multiple imputations to deal with data that are not recorded or measured. The underlying assumptions of this technique are typically not met in EHR databases as recording of information (and visits to health care system) are determined by the health status of the patient. The further development of risk prediction with EHR databases can support clinicians in identifying patients who require medical review.

Creation of a European resource to make uncertainties in routinely used interventions explicit and to help prioritize new research

The priorities for research on interventions already used in the health care should ideally be determined by clinicians and patients, rather than by the funders. Patients and the public have a right to expect that research funders, researchers and health care professionals are aware of uncertainties about the effects of treatments. In the United Kingdom, a Database of Uncertainties about the Effects of Treatments publishes treatment uncertainties from patients, carers, clinicians, and from research recommendations, covering a wide variety of health problems. Several sources are used to identify uncertainties about the effects of treatments, including the patients’, carers’ and clinicians’ questions about the effects of treatment, research recommendations in reports of systematic reviews and ongoing research. A European resource on treatment uncertainties could help to set priorities for public health funding in Europe.

Addressing these research questions would ensure that progress is made on the structural, technical and legal/ethical aspects and help to unlock the full potential value in EHR databases. The European pharmaceutical industry, regulators, pricing and reimbursement authorities and patients would all benefit from having interoperable, quality-assured EHR databases available and accessible. Such a pan-European resource would be a major competitive advantage for Europe.

11. Recommendations for policy

Introduction of risk proportionality in research governance for low risk RCTs

The pre-amble of the 2012 proposed revision of the Trial Directive acknowledges the negative effects of the current legislation. One of the proposed changes in the European Trial Directive concerns the inclusion of low risk RCTs, which could include simple pragmatic RCTs that use EHR databases. It defines low-risk RCTs to concern “authorised medicinal products, used in accordance with the terms of the marketing authorization or their use is a standard treatment and the additional diagnostic or monitoring procedures do not pose more than minimal
additional risk or burden to the safety of the subjects…”. Unfortunately, this very reasonable definition may not achieve the important need for simplification and risk proportionality in research governance. We must not continue on the current path of ever increasing complexity and costs of RCTs. Risk proportionality is essential in the research governance of RCTs and this should be made explicit in the legislation to facilitate research that aims to improve medical practice.

Data privacy and research use of EHR databases

There is considerable debate about whether (pseudo)anonymised health care data should be made available for research. Recently, the European Parliament’s rapporteur on the Data Protection Regulation published a draft report with potentially significant consequences for research using health data. The rapporteur’s report stated that “processing of sensitive data for historical, statistical and scientific research purposes is not as urgent or compelling as public health or social protection.” The rapporteur’s report proposed 350 amendments to the Data Protection Regulation. It stated that pseudo(anonymised) data could be used without consent, but only in cases of “exceptionally high public interest” such as bioterrorism. Many people have expressed concerns on the potential negative impact of these amendments to the European Data Protection Regulation to delivering high quality, patient-centred health care and conducting effective clinical and public health research, including the European Federation of Pharmaceutical Industries and Associations and the EU Biobanking and Biomolecular Research Infrastructures.

The right of data privacy is indeed very important and high data standards of data protection are essential for any EHR database. The critical question is whether the right of data privacy trumps all other rights and duties or whether a balance is possible between different considerations. There is also the right of patients to receive proper treatments and the duty of the health care system to, for example, monitor treatments for effectiveness and safety and be cost-effective. The discussion around data privacy should also consider these other rights and duties. Furthermore, it should also consider how to minimise the risk of breaches of data privacy with appropriate data security procedures. An opt-out system, in which patients can refuse to have their data used for research and health care evaluations, is one approach in order to achieve a balance between the rights of data privacy and the duties of the health care system to provide effective interventions in a cost-efficient manner. If it would be logistically difficult to implement such an system, (pseudo-)anonymisation and strict security standards should substantially minimise the risk of breaches of data privacy. A survey of over 1 000 adults found that 97% agreed with the statement that the health care system “has a duty to determine the safety and effectiveness of the drugs its doctors prescribe”. This topic, and the merit of the different approaches, is also being discussed in new European legislation.

Transparency in data security standards

Data protection and security standards are of critical importance to EHR databases. Regular audits by external experts and publication of the results could lead to maintain a culture of continuous improvement. EHR databases need to be accountable for the use of the EHR data, including reviews of the data use by licensees of the database.
Transparency in the research use of EHR data

Research use of the EHR database should follow highest scientific and ethical standards. There is considerable controversy whether all observational studies need to be registered and full methods and results published. This approach of full disclosure is being advocated strongly for RCTs.\textsuperscript{69} A recent workshop on the need for registration of observational studies concluded that this would increase and ethical aspects of observational results. This registration should cover the study protocol and any amendments, the \textit{a priori} defined hypotheses and study results.\textsuperscript{70} However, these recommendations have not been not accepted universally. Arguments against the registration of observational studies include the possible bureaucracy of registration, the timing of a research hypothesis (whether before or after data collection) may be irrelevant to its validity, the potential “transparency” of such registered information could easily be clouded by the complexity of assembling the information and that hypothesis-free exploration may yield new hypotheses.\textsuperscript{71} However, the large amount of information in EHR database can allow unscrupulous researchers to cherry-pick the results and publish the findings in the highest impact journals. An analysis of hip fracture risk with statin use found that the range of results varied from highly statistically significant to non-significant associations. The results of this study varied substantially by changing the exposure definitions, the method of age matching and the selection of risk factors in the regression analysis.\textsuperscript{72} While data mining and the generation of hypotheses through careful review of the data are scientifically important, there remains the possibility that unscrupulous researchers present post-hoc data dredging as a scientific exercise. Transparency of use of EHR data and a simple model for registration of research protocols (at the time of publication) should be welcomed as researchers should be accountable for the use of the data. Deviations from a protocol may occur and post-hoc analyses may provide important results but researchers should be able to explain these and be transparent.

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Update on 2004 Background Paper

Background Paper 8.5
Patient and Citizen Involvement

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Update on 2004 Background Paper, BP 8.5 Patient and Citizen Involvement

Table of Contents

1  Introduction .......................................................................................................................................................... 3

2.  Approach ............................................................................................................................................................ 3
  2.1 Literature review: bibliography of patient and citizen involvement in health system decision making .... 3
  2.2 Expert meetings ................................................................................................................................................. 4
  2.3 Survey: Experiences of patient organizations & reimbursement authorities with involvement .......... 4

3.  Drivers for involving patients and citizens priority setting .................................................................................. 5

4.  Terminology: 'patients and citizens'? or ‘the public'? ......................................................................................... 6

5.  Levels of involvement .......................................................................................................................................... 7

6.  Structures for involvement .................................................................................................................................. 10
  6.1 Initial approaches: Surveys and citizens juries ................................................................................................. 10
  6.2 Institutionalized involvement: NICE, EMA and FDA ....................................................................................... 11
  6.3 Toolkits: G-I-N, INVOLVE, The Participatory Methods Toolkit and Value+ Toolkit .................................... 12
  6.4 Process models: Dialogue Model and Priority Setting Partnerships ............................................................ 14
  6.5 Quality criteria checklists: two examples by Viergever and Saunders ......................................................... 14
  6.6 Other examples ................................................................................................................................................ 15

7.  Roles and expertise of patients and citizens in health research & policy ............................................................. 19

8.  Evaluating the impact of patient and citizen involvement .................................................................................. 20
  8.1 Available evidence: what does it say? .................................................................................................................. 20
  8.2 A framework for evaluating patient and citizen involvement ......................................................................... 23

9.  Conclusion and future strategies .......................................................................................................................... 24
  9.1 Validity and representativeness.......................................................................................................................... 24
  9.2 Framework development .................................................................................................................................... 25
  9.3 Evaluate and learn .............................................................................................................................................. 27
  9.4 Empowerment and capacity building ............................................................................................................... 27
  9.5 Dealing with conflict of interest ........................................................................................................................ 29

References .................................................................................................................................................................. 30

Annexes .................................................................................................................................................................... 37
  Annex 8.5.1: Bibliography patient and citizen involvement in health research and policy .................................. 37
  Annex 8.3.2: Meeting report .................................................................................................................................... 55
  Annex 6.8.3: Survey results ...................................................................................................................................... 60
  Annex 8.5.4: Viergever’s Checklist for health research priority setting ................................................................. 67
  Annex 8.5.5: Saunders’ criteria and rating scales ................................................................................................. 69

Appendix .................................................................................................................................................................. 71
1 Introduction

This chapter serves as background document for discussion on the involvement of patients and citizens in priority setting for pharmaceutical innovation. At the time of the development of the WHO Priority Medicines for Europe and the World Report in 2004, patient and citizen participation in priority setting was uncommon and knowledge about and experience with the effects of such participation was limited. Currently, involvement of patients and citizens in health research and policy is supported by legal and regulatory requirements. Moreover, there is a substantial body of literature on the topic and much work has been done to realize patient and citizen involvement. This progress indicates that the need for patient and citizen involvement is widely acknowledged by stakeholders in the pharmaceutical innovation process. However, there is a general lack of overview, which hampers further development of best practices for patient and citizen involvement.

The aim of this background paper is to contribute to meaningful patient and citizen involvement in priority setting for pharmaceutical innovation by providing an overview of the current state of knowledge and opinion, and to propose future strategies to improve involvement. We broadened the scope of the paper beyond priority setting for pharmaceutical innovation to the field of health care policy and research. This choice was motivated by the limited literature on patient and citizen involvement specific to the topic of priority setting for pharmaceutical innovation, combined with the rich experience reported in articles about patient and citizen involvement in connected areas (i.e. research design, marketing authorization decisions).

In this background paper, we first describe the approach undertaken to capture the scientific literature on, and the experience with, patient and citizen involvement in health research and policy (Section 2). Next, we briefly discuss the most important drivers for patient and citizen involvement. Subsequently, we look into the question of the difference between ‘patients’ and ‘citizens’ when involvement is desired (Section 4). We then describe ‘the state of field’ with regard to patient and citizen involvement, in four sections: levels of involvement (Section 5), structures for involvement (Section 6), the roles and expertise of patients and citizens (Section 7), evaluating the impact of involvement (Section 8). We finish the paper with a conclusion and suggestions for future research and evaluation (Section 9).

2. Approach

The status with regard to patient and citizen involvement has been investigated using three sources: a review of the literature, two international expert workshops and a survey among patient organizations and public bodies.

2.1 Literature review: bibliography of patient and citizen involvement in health system decision making

The literature on patient and citizen involvement in priority setting is difficult to capture; there is a lack of a common structure, no common terminology, and much of what is known is published in grey literature. For our purpose, we made a bibliography which had a broad
approach: not only literature on priority setting for pharmaceutical innovation was included, but also literature on patient and citizen involvement in a broader sense, such as in biomedical research, guideline development and health policy decision making. We limited our investigations to the health care research and policy setting (including regulatory decision making). See Annex 8.5.1.

Methods


A second source of literature was the NHS/INVOLVE Evidence library (updated September 2012). This is an electronic database of references (reports and articles) that cover:

- the nature and extent of public involvement in research, for example mapping public involvement;
- the impact of public involvement on research;
- reflections on public involvement in research.

Additionally, a manual search of reference lists of papers and grey literature identified in the searches described above was conducted. Grey literature was also obtained by contact with key experts in the field.

In total, 353 articles were extracted. Titles and abstracts were screened and 94 articles were excluded because the topic of patient and citizen involvement was not discussed. In most cases, these articles focused on assessment of systems of pharmaceutical innovation, without reference to patient and citizen involvement. Another 28 articles were not accessible. The bibliography for this background document contains 231 articles and documents.

2.2 Expert meetings

Two meetings with experts were organized. The first was held on 27 September 2012 in Brussels with the aim was to identify critical issues and strategies to overcome barriers. The second meeting was on 22 February 2013. At this meeting a draft version of this background paper was discussed. Both meetings were hosted by Belgium’s National Institute for Health and Disability Insurance (RIZIV/INAMI). Meeting reports of both meetings are in Annex 8.5.2.

2.3 Survey: Experiences of patient organizations and reimbursement authorities with involvement

Patient organizations (IAPO and EPF members) and members of the Pharmaceutical Pricing and Reimbursement Information (PPRI) network were asked to complete a survey on their experiences with patient involvement in priority setting and other forms of decision-making related to pharmaceutical innovations. We received completed survey forms from 17 patient organizations and nine members of the PPRI network. An overview of the results is presented in Annex 8.5.3.
3. **Drivers for involving patients and citizens priority setting**

A variety of underlying motivations drives the efforts to involve patients and citizens in priority setting for pharmaceutical innovation. A first category is political and stems from the desire to promote democratic ideals of legitimacy, transparency and accountability. In 2000, The Council of Europe declared that the right of the public to be involved in the decision making processes affecting health care is a basic and essential part of any democratic society. This democratic right is echoed in government reports, legislation and in statements from patient and citizen groups. Setting (research) priorities affects the use of limited public resources and research demonstrates that values and ethical considerations play a role in recommendations on, for example, guideline development. Therefore, societal values should be considered and decisions should be informed by input from patients and citizens, since they are affected by the decisions. If patients are involved in deciding about priorities in pharmaceutical research, the legitimacy of the studies conducted is enhanced. Additionally, there is some evidence that the inclusion of multiple perspectives is seen as an important element in priority setting.

These motivations are supported by trends towards the empowerment of vulnerable and marginalized groups. Patients are being encouraged to exercise greater control over their own health care and to become more involved in the development of health services. This may also be inspired by a commitment to the principle of respect for autonomy, which would prohibit health researchers to conduct research ‘on’ people as opposed to ‘with’ them. Recent policy reforms in health services in western countries stress the importance of public involvement. Such involvement is organized in local health councils for example in Australia, Canada and the United Kingdom; public consultation, in the state of Oregon (USA) and the province of Ontario (Canada); and regional health conferences, as found in France and Thailand. The United Kingdom has required increased public involvement in the decision making of most health care organizations, their Research Governance Framework for Health and Social Care (2nd edition, 2005) states: ‘Research [should be] pursued with the active involvement of service users and carers including where appropriate, those from hard to reach groups such as the homeless.’ At the EU regulatory level, the European Medicines Agency identified ‘a need and expectation for public bodies to listen to the views and experiences of patients who are the ones most affected by the regulatory decisions and engaging with these stakeholders gives the Agency and the public more confidence and reassurance in its outcomes’.

A second category of motivations are health-related motivations that stem from the need to better align pharmaceutical innovation with the unmet needs of patients. Pharmaceutical innovations do not always meet the needs of patients effectively. According to the National Institute for Health Research in the United Kingdom, ‘involving patients and members of the public in research can lead to better research, clearer outcomes, and faster uptake of new evidence’. Biases within the health research system may tend to favour certain research and topics over others. This could result for example in a lack of interdisciplinary and integral approaches and little attention paid to recovery of patient function. In addition, important questions may be overlooked because of emphasis on: chronic but not acute conditions; severe but not common health problems; and disease-specific but not crosscutting issues, such as social care, improved surgery, and anaesthesia.
Evidence shows that health professionals’ values of different health states and research priorities differ from those of patients.\textsuperscript{19}\textsuperscript{20} For example, the values physicians assign to stroke as an outcome and to adverse consequences (e.g. gastrointestinal bleeding) of treatment to prevent stroke in patients with atrial fibrillation differ from those of patients.\textsuperscript{21} Patients at high risk for atrial fibrillation placed more value on the avoidance of stroke and less value on the avoidance of bleeding than did physicians who treat patients with atrial fibrillation. Other divergences in priorities for health research between professionals and the public were found in the areas of arthritis, Alzheimer disease, and mental health.\textsuperscript{22} Based on experience with priority setting for Health Technology Assessment, Bastian et al. suggested that the interests of patients and other end users of information at the societal level may even be the opposite of the concerns of policy makers.\textsuperscript{23} Public involvement in decision making processes could be a route to enhance the relevance and quality of health research.

Another argument relevant to health related motivation focuses on the actual contribution patients can make to the decision making process and thus to the rationality of the process and the quality of its direct or long-term outcome. Beresford, for example, argues that, “the shorter the distance between direct experience and interpretation (for example as can be offered by user involvement in research), then the less distorted, inaccurate and damaging resulting knowledge can be.”\textsuperscript{24} Patients not only have a right to engage in discussions on decision making about priorities (the political stance), their input is also needed, because they have a specific, relevant type of knowledge: their ‘experiential knowledge’.\textsuperscript{25} \textsuperscript{26} \textsuperscript{27}

In a third and final category of motivations, patient and citizen involvement can be promoted by arguments of transparency and trust. For example, an analysis of the benefits of patient involvement by the EMA lead the investigators to conclude: “participation of patients in the scientific committees leads to increased transparency and trust in regulatory processes and develops mutual respect between regulators and the community of patients. It is also acknowledged that their contribution enriches the quality of the opinion given by the scientific committees.”\textsuperscript{28}

These motivations provide a strong justification for efforts to further develop patient and citizen involvement in priority setting. A next step is to create an evidence base for meaningful models of involvement. At present, there is a lack of an overview of various initiatives undertaken and several knowledge gaps exist; together these are hampering efforts to evaluate and further develop patient and citizen involvement in priority setting.

4. Terminology: ‘patients and citizens’? or ‘the public’?

In this background paper, we discuss the available knowledge and experience on patient and citizen involvement. A preliminary question is whether patients and citizens need to be viewed as separate groups. In general, patient involvement is distinguished from public (or citizen) involvement.

However in, for example, the United Kingdom, policy guidelines on involvement usually refer to ‘the public’, including: “Patients and potential patients; people who use health and social services; informal carers; parents/guardians; disabled people; members of the public who are potential recipients of health promotion programmes, public health programmes and social service
interventions; and organizations that represent people who use services.” In some cases, the term ‘stakeholder’ is used. Stakeholders are those who have a legitimate stake in an issue, independently of whether these actors have decisional power. Since the group of stakeholders in priority setting for pharmaceutical innovation is much broader than patients and citizens, this term seems less adequate for our purpose.

While there is widespread belief that values for health states differ between patients and the general public, there is a longstanding debate among health economists about the evidence to support this belief. A systematic review of 33 studies found that preferences for hypothetical health states did not differ between patients and the public. Another meta-analysis demonstrated that patient preferences for an actual health state do not differ significantly from population preferences for a hypothetical health state. These findings suggest that patient and population preferences can both be used to set priorities for pharmaceutical innovation. However, Peeters and Stiggelbout claim that patients give higher valuations to health states compared to members of the general public, based on a meta-analysis of studies reporting valuations given by patients and non-patients. Hence, there is evidence for treating patients and citizens as different populations, as well as for the use of one term (‘the public’) for both patients and citizens.

In general it seems that that patients and citizens involvement can be captured by the term ‘involvement of the public’ or ‘public involvement’ in many cases but not all. First, patients and citizens may have competing or contrasting interests in priority setting for pharmaceutical innovation. For example, it is in the general interest of citizens and society to have medicines with a favourable cost-benefit profile. For patients, access to the best available treatment is the primary interest. In setting priorities, these interests will not always converge. Second, there are circumstances that ask for a more specific use of experience. This is the case when involvement is sought with the explicit aim to grasp the experiential knowledge of a patient, or a well-described group of patients or carers. For our recommendations we will use ‘patients’ and ‘citizens’ where appropriate and distinguish between the two terms only when necessary.

In this paper, we give an overview of the literature on patient and citizen involvement. We will follow the terminology used in a study, report or article when we refer to it in this paper.

5. Levels of involvement

Patient and citizen involvement is organized in numerous ways, though these approaches are considered to be not equally meaningful. The ‘participation ladder’ is a conceptual model that can be used to assess different types of patients and citizen involvement in decision-making. Arnstein published the participation ladder to distinguish degrees of citizen control over decisions in 1969. The ‘ladder’ aims to categorise different sorts of participation, ranging from an illusory form of powerless participation to citizen control. Abma et al. adapted the model in 2010 to analyse patient participation initiatives.
Discussing of the model proposed by Arnstein in some more detail could give an overview of the general types of involvement in decision-making. The participation ladder has eight rungs: Manipulation, Therapy, Informing, Consultation, Placation, Partnership, Delegated Power and Citizen Control (see Figure 8.5.1).

The first two levels of involvement are actually forms of non-participation: they are ‘Manipulation’ and ‘Therapy’. Examples of such ‘illusory forms’ of participation are placing people on advisory committees for the express purpose of ‘educating’ them: patients and citizens are subjected to advice and persuasion from the experts who retain their full decision making power.

Tokenism is the label for the next three levels: ‘Informing’, ‘Consultation’ and ‘Placation’. These forms of involvement can be a first step towards genuine participation: they allow patients and citizens to have a voice. However, at the tokenism-level their influence on policy-making can be restricted by practical and financial structures, differing knowledge bases, cultural barriers and personal attitudes. Examples of tokenism-level involvement are providing information to patients, the collection of patients’ and citizens’ views (e.g. through surveys, opinion polls, interviews or focus groups) and inviting patients and citizens in advisory bodies without giving them any decision making power.

Actual patient and citizen decision-making power is achieved in the highest three rungs of the participation ladder: through Partnership, Delegated Power and Patient/Citizen Control.
Partnership enables patients and citizens to negotiate and engage in trade-offs with traditional power holders. Delegated Power implies that citizens and patients obtain the majority of decision making seats. At the top of the ladder is Patient and Citizen Control, which refers to a situation where decision making power is transferred from experts to patients and citizens.

Arnstein described the participation ladder with the aim of separating meaningful involvement of citizens in political decision making from illusory forms of participation. The model has been criticized for its sole emphasis on power. This may close off other relevant considerations such as the existence of different relevant forms of knowledge and expertise. Also, the focus on gaining decision-making power may limit effective responses to the challenge of involving patients and citizens. For example, expecting people to participate in formal election processes to attain a position on a board or committee may exclude members of populations that are both more likely to require health services and, historically, have been less well served. Another limitation is the fact that the question of how effective patient and citizen involvement should be organized, cannot be answered by referring to the participation ladder. Moreover, it should not be concluded that ‘higher’ rungs on the ladder are the best for each situation.

The participation ladder is also used by authors in the field of health policy and research. For example INVOLVE, the national advisory group on public involvement in health research of the United Kingdom’s National Institute for Health Research have presented a condensed ladder of participation with three steps: consultation, collaboration and lay control. Consultation is defined as asking lay people for their views and using those views to inform decision-making. For example, funders of research have held one-off meetings with people to ask them about their priorities for research. Collaboration involves an on-going partnership between researchers and the members of the public, where decisions about the research are shared. For example, members of the public might collaborate with the researchers on developing the research grant application, be members of the study advisory group and collaborate with researchers to disseminate the results of a research project. Lay-controlled or user-controlled research is research that is actively controlled, directed and managed by service users and their service user organizations. Professionals are only involved by invitation. INVOLVE reported several examples of user-controlled research. One example is a project carried out by Thyroid UK, a small registered charity run by people with direct experience of thyroid and related problems with the aim of providing information and resources to promote effective diagnosis and appropriate treatment for people with thyroid disorders in the United Kingdom. The personal experience of some of their members (people with continuing problems despite blood test results that fall within the normal range) prompted this research, a clinical trial to examine and compare the accuracy of two different tests (blood and urine) in relation to people’s symptoms.

Similar categorizations of levels of public involvement have been identified by for example Boote et al. and Steyaert. They were also used in the Value+Toolkit, which was developed in 2010 by patients organisations and the European Commission (EC) to support the exchange of information and experience on good practice relating to patient involvement in EC projects.
6. Structures for involvement

Patient and citizen involvement is a broad subject, covering a wide range of activities, policies, and research. Reviews of ‘service user involvement’ in health and social care research have highlighted a wide range of theoretical approaches and conceptual models, indicating how widespread it has now become. The literature on structures for involvement is comprised of mainly qualitative or case study reflections of patient and citizen involvement, or cross-sectional studies reporting individual or organizational views of involvement, with relatively little critical evaluation. The available information is very often descriptive and very seldom conceptual or evaluative. While involvement of patients and citizens is becoming more frequent as partners in research projects, for example as members of supervision committees, consultation of patients and citizens at the beginning to identify and prioritize areas for research is still rare.

The various approaches that are available to guide priority setting for health research differ on important aspects (role, position in process, responsibility). Consensus on a gold standard or best practice for health research prioritization thus seems difficult to achieve and is, more importantly, disqualified by some as ‘not an appropriate response’.

To grasp the experiences with patient and citizen involvement, we analyzed publications on models and strategies for involvement. Our aim was to provide a structure for the knowledge available. Literature on priority setting for pharmaceutical innovation is limited, and often involves case description. Therefore, our scope was broadened to health policy decision-making and medical research. In this section we describe several approaches: surveys and citizens juries; institutionalized involvement; toolkits; dialogue model and priority setting partnerships; and checklists and criteria. Finally, a list of published examples is added to illustrate the variety and nature of employed strategies.

6.1 Initial approaches: Surveys and citizens juries

In brief, citizens juries bring together members of the public (jurors), and provide a structured discussion of relevant information provided by expert witnesses. Facilitators or moderators are present to guide the process. The end result is a written report authored by the jurors. An example of a health priority setting process with jury input is in Box 8.5.1. In a comprehensive overview of the literature on public participation processes, Abelson et al. report that the National Health Service (NHS) in the United Kingdom started exploring possibilities for a greater role for public views in setting health care priorities in the early 1990s. Mail surveys and interviewer-administered surveys were the initial method of choice, but their ability to generate meaningful insight was limited. This lead to a search for new (deliberative) public involvement methods. In the mid-1990s citizens juries became popular for priority setting processes in the United Kingdom and New Zealand. Several juries have dealt with questions of whom should set priorities and how; others were asked to allocate resources within or between programme areas. There are considerable challenges to the process, and it has become clear that juries are imperfect means of ensuring democracy, representation and influence.
6.2 Institutionalized involvement: NICE, EMA and FDA

The task of giving guidance on which treatments or services should be provided out of public funding by the NHS and which should not, was given to the National Institute for Health and Clinical Excellence (NICE) on its creation by the United Kingdom government in 1998. As such, it has a fair degree of independence. NICE produces guidance in three areas of health: public health, health technologies and clinical practice. NICE has adopted a very comprehensive approach to involving patients and consumers. The activities can be categorized into four broad areas:

(i) Stakeholder consultation

Organizations can register and comment at any stage during the clinical guideline development process from the suggestion of guideline topics, drafting of scopes, development and initial drafting of guidelines, to the second consultation draft.

(ii) Direct input

All NICE committees and working groups are expected to include at least two members who play a crucial role by providing a patient/carer perspective to their discussions and decisions. They may be patients, carers or patient advocates.

(iii) Indirect input

Examples include focus groups with patients, patient written testimonials and video-taped interviews with patients that are presented to a technology appraisal committee.

(iv) Dissemination of NICE guidance to and by patients

All NICE guidance is produced in versions written for patients, carers and the public.

The European Medicines Agency is an agency of the European Union, located in London. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. It has a Working Party with
Patients’ and Consumers’ Organizations (PCWP). It implemented the ‘Framework on the interaction between the Agency and the patients’ and consumers’ organizations’, which has established formal interaction between patients'/consumers’ organizations and the EMA. PCWP members monitor patient participation in the varied activities within the Agency, i.e. the review of information for the general public, participation in scientific advisory group meetings, Committee/Working party consultations, participants in conferences and workshops. One method to involve patients in decision-making is their inclusion on committees. For example, at EMA patients are included as formal members in the Agency’s Scientific Committees, such as the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO) and the Committee for Advanced Therapies (CAT). The tasks of patient members include:

(i) *Participation* in the assessment of applications and in peer reviews.
(ii) *Providing advice* on the identification of external experts.
(iii) *Collaboration* in the preparation of public summaries of opinion.\(^{54,55}\)

The U.S. Food and Drug Administration (FDA) has organized patient participation in advisory committees, a consultation program and public hearings. These are organized under three headings:

(i) *Patient Representative Program*: responsible for providing the FDA and the Advisory Committees the unique perspective of patients and family members directly affected by a serious or life-threatening disease. Patient Representatives are invited to participate in FDA Advisory Committee meetings to discuss medical products for the treatment of serious or life-threatening diseases such as cancer or AIDS. These FDA advisory committees provide independent expert advice and recommendations to the Agency on scientific, technical, and policy matters related to FDA-regulated products.

(ii) *Drug Development Patient Consultant Programme*: incorporates the perspective of patient advocates into the drug development process allowing them an opportunity to participate in the FDA drug review regulatory process.

(iii) *Open Public Hearings*: Every Advisory Committee meeting includes an open public hearing (OPH) session, during which interested persons may present relevant information or views orally or in writing (21 CFR 14.25(a)).\(^{56}\) The FDA may also solicitate the opinion of stakeholders by organizing a public hearing.

### 6.3 Toolkits: G-I-N, INVOLVE, The Participatory Methods Toolkit and Value+ Toolkit

The Guidelines International Network, G-I-N, is a global network, founded in 2002. By 2013 it has grown to comprise 92 guideline organizations, and 127 individual members (implementers, end-users, researchers, students and other stakeholders) representing 48 countries from all continents. G-I-N aims to promote evidence-based guideline development, adaptation, dissemination and implementation. Guideline organizations use a number of different methods to involve patients and the public. In the ‘G-I-N PUBLIC toolkit’ three general involvement strategies are presented. The toolkit provides practical advice on how to implement these methods successfully.\(^{57}\)
(i) **Consultation strategies**: involve the collection of information from patients and the public. This can include methods such as surveys, focus groups, individual interviews, online consultation, the use of primary research on patients’ needs and expectations, or the use of a systematic review of studies on patients’ and the public’s perspective.

(ii) **Participation**: involves the exchange of information between guideline developers and the public. This can be done through participation of patient and public representatives on guideline development groups and other methods.

(iii) **Communication strategies**: involve the communication of information to patients and the public to support their individual health care decisions and choices. This can include the production of plain language versions of clinical practice guidelines or the development of patient decision aids or education material.

The United Kingdom based intermediary organization INVOLVE aims to stimulate and support active participation of the public in NHS, public health and social care research. It is part of the National Institute of Health Research (NIHR). Recently, a collection of briefing notes for researchers was published by INVOLVE. It refers to numerous examples of public involvement in a range of health research activities. These include helping to develop the research question, applying for funding and ethical approval, sitting on advisory groups, carrying out the research and disseminating the research findings. Briefing Note Eight considers the different ways members of the public can get involved in the stages of the research cycle.

The Participatory Methods Toolkit from the King Baudouin Foundation offers an overview of techniques to actively involve ‘the public’ in decision-making processes. The public can be regular citizens, the stakeholders of a particular project or policy, experts and even members of government and private industry. The approach can be applied by various organizations that wish to engage a broad range of perspectives in decision making processes. It is the aim of participatory methods to emphasize the processes of democracy by giving structure and organization to various forms of dialogue. It invites pluralism, diversity, and dissent with the ambition to examine issues from as many angles as possible in order to find the best common solution. The contents of the toolkit comprise a description of thirteen techniques and methods, for example consensus conference, deliberative polling, Delphi methods and expert panels. Moreover, a comparative chart for the 13 participatory methods is given. Finally, in-depth general guidelines and tips for conducting participatory methods are described.

The Value+Toolkit is the result of a project to support the exchange of information and experience on good practice relating to patient involvement in projects co-financed by the EC.

The Value+Toolkit was developed by patient organisations and is divided into chapters covering several topics. Among these are:

(i) **Meaningful Patient Involvement.** This chapter includes the Value+ research findings on the barriers and challenges to patient involvement and good practice in patient involvement.

(ii) **Your Own Organisation and Meaningful Patient Involvement.** In this chapter, basic information which may help patient organisations prepare themselves for taking on an EC-funded project is provided.

(iii) **Resources** contains tools and examples from Value+ and other sources, examples of good practice, a list of websites, the Value+ Literature Review, a list of patient...
organisations that operate at European and national level, information on patient rights specific to individual countries, and national contacts for the European Commission.

The Value+Toolkit has been published with the support of the European Commission, Directorate General for Health and Consumers under the Public Health Programme 2008-2013.

6.4 Process models: Dialogue Model and Priority Setting Partnerships

The Dialogue Model is based on the idea that in order to give patients a real voice in decisions on health research, they need to be involved as partners. In this model, research is not framed by the relevant interests of the scientists but developed in interaction with various stakeholders.

The overall process is a dynamic and cyclic process of activities, in which tentative results are tested and refined in practice in an iterative way. The activities are structured in roughly six phases:
1. **Initiation and preparation**, in which the project team is established, an initial assessment is made of the problems, ideas and wishes of patients and other stakeholders, and a start is made with creating conducive social conditions.
2. **Consultation**: in which various stakeholder groups are consulted separately to develop different lists of issues that are relevant from the perspectives of the different stakeholder groups.
3. **Prioritization**: in which stakeholder groups value the different research topics from their lists and rank them in order of importance, resulting in different tentative research agendas.
4. **Integration**: in which stakeholders exchange information, address conflicts and integrate research agendas through dialogue, resulting in one integral research agenda.
5. **Programming**: in which the integral research agenda is translated into a coherent program or action plan.
6. **Implementation**: in which participants determine and take action, monitor progress and evaluate results.

Priority Setting Partnerships (PSPs) unite patients or carers, or both, with clinicians (or representative groups of patients, carers, or clinicians) to prioritise treatment uncertainties for research using consensus development methods. The James Lind Alliance (JLA) has published a Guidebook to establishing PSPs. The activities of PSPs take place in five phases:
1. **Identification and invitation of potential partners**;
2. **Initial stakeholder meeting**;
3. **Identifying treatment uncertainties**;
4. **Refining questions and uncertainties**; and
5. **Prioritisation**.

6.5 Quality criteria checklists: two examples by Viergever and Saunders

Some authors have described a health research priority setting process to assist researchers and policymakers in effectively targeting research. Taking the heterogeneous nature of research priority setting exercises into account, we present two proposals for a priority setting process that explicitly address involvement of stakeholders.
Update on 2004 Background Paper, BP 8.5 Patient and Citizen Involvement

First, a checklist for health research priority setting developed by Viergever et al. explicitly addresses stakeholder involvement (see Annex 8.5.4). Under the heading of inclusiveness, the checklist demands that it should be decided which stakeholders need to be involved in the research priority setting exercise, why their opinions need to be sought and what role they should play in the process. Among the potential roles that stakeholders can play in the process are: providing opinion, providing evidence and being a part of the group that decides on priorities.

Second, a strategy of using a set of criteria to evaluate research that reflects consumer values is suggested by Saunders et al (Annex 8.5.5). The values held by cancer consumers and the wider community with regard to research were identified and combined in optimal rating scales to evaluate research. The relevance to priority setting for pharmaceutical innovation is that it offers a framework to incorporate consumer needs into the process of judging and allocating research grants.

6.6 Other examples

Besides the more general approaches presented above, there is a rich body of publications on examples of patient and citizen involvement in priority setting, health research, systematic reviews, clinical guideline development and health policy decision making.

IAPO Policy Framework

The International Alliance of Patient Organizations has a Policy Framework in which they state a number of priorities. Moreover, they put in place three methods to identify and prioritise policy issues and activities. These methods are: (i) input of members and stakeholders, (ii) identification of issues by IAPO staff and Governing Board facilitated by on-going research activities and (iii) annual online consultation of members.

Patient-Centered Outcomes Research Institute (PCORI)

PCORI helps people and their caregivers communicate and make informed health care decisions, allowing their voices to be heard in assessing the value of health care options. In 2010, the United States Patient Protection and Affordable Care Act created the PCORI. This was established to emphasize the critical importance of a patient-centred perspective in conducting research on comparative effectiveness of clinical interventions. Its mission statement commits to producing and promoting high-integrity research that is guided by patients, caregivers and the broader health care community. PCORI has proposed national priorities for research, following an extensive procedure of stakeholder consultations.

The Cochrane Agenda and Priority Setting Methods Group (CAPSMG)

In 2011 the CAPSMG was established. It is one of 16 Cochrane Methods Groups established to develop methodology and advise The Cochrane Collaboration on how the validity and precision of systematic reviews can be improved. The CAPSMG aims to inform the Cochrane entities about the empirical evidence available on methods to set a research agenda or establish top research priorities. In addition, it will endeavour to serve as a discussion forum.
Update on 2004 Background Paper, BP 8.5 Patient and Citizen Involvement

connecting people interested in methods to set research agendas or priorities inside and out of the Cochrane Collaboration.66

**Short bibliography of other examples**

The following short bibliography aims to illustrate the variety of patient and citizen involvement activities published in scientific journals. These articles mainly describe isolated instances of involvement across a variety of health research and policy making activities.

**(i) Priority setting**


Bruni RA, Laupacis A, Levinson W, Martin DK. Public involvement in the priority setting activities of a wait time management initiative: a qualitative case study. BMC Health Serv Res. 2007 Nov 16;7:186.

Buckley BS, Grant AM, Tincello DG, Wagg AS, Firkins L. Prioritizing research: patients, carers, and clinicians working together to identify and prioritize important clinical uncertainties in urinary incontinence. Neurourology and Urodynamics, 2010; 29: 708–714.


EURORDIS. Position paper “Patients” Priorities and Needs for Rare Diseases Research 2014 - 2020. [http://www.eurordis.org/sites/default/files/publications/what_how%20_are_disease_research_h_0.pdf](http://www.eurordis.org/sites/default/files/publications/what_how%20_are_disease_research_h_0.pdf)


Update on 2004 Background Paper, BP 8.5 Patient and Citizen Involvement


(ii) Involvement in Health Research


Patient Partner Project to promote the role of patient organizations in the clinical trials: context www.patientpartner-europe.eu (finalized in 2011)


(iii) Systematic reviews


(iv) Clinical guideline development


(v) Health policy

7. Roles and expertise of patients and citizens in health research & policy

The literature on roles of patients and citizens in health policy and research seems to reflect broad agreement on the idea that meaningful involvement requires more than a ‘tokenistic’ approach. Arnstein’s ladder of involvement and its variations illustrate a different levels of involvement, based on a measure of control over the decision making process. The rich variety of structures for involvement that have been employed in the field of health policy and research is a sign of a developing field of expertise and experience. One aspect of patient and citizen involvement however seems to lag behind in this process: developing good understanding of the expertise and the contribution of patients and citizens at different levels of involvement (i.e. consultation, collaboration and control) and in a variety of models.

There is a major lack of reflection of the very concept of patient and citizen involvement. What is it exactly that a patient or a citizen brings to the table in decision making processes? How can this be defined and measured? Concepts have been used interchangeably, with patient and citizen involvement variably defined and often poorly described. One of the few descriptions of different roles patients can play comes from EMA. In a report on the role of patients as members of scientific committees, EMA states: “The added value of having patients and consumers in the scientific committees is to bring a unique and critical input based on their real-life experience of being affected by a disease and its current therapeutic environment. This element fills a gap that other committee members (so-called scientific experts) cannot fill”. More in detail, EMA described the following roles:

1. Expertise
   Convey a combination of specific education, training or professional experience

2. Experience
   Convey practical disease knowledge obtained from direct contact with the disease (affected person or close contact with affected person, e.g. family, carer)

3. Advocacy
   Act on behalf of the affected patients in defence of their rights; provide patient-oriented public health/health care policy perspective

4. Empowerment
   Participate in decision making process within the committee; having access to information and process on behalf of patients.

Despite the value of this description, a deeper understanding of the nature and value of patient and citizen involvement is needed. Currently, the conceptual basis of patient and citizen involvement is limited to reference to experiential knowledge of patients. For citizens, being a ‘lay person’ is their task. For both, it remains an open question as to how their knowledge and perspective should be organized. Are patients asked to bring forward only their personal experience? Should patients and citizens involved collect the experiences and preferences from the groups they represent? Descriptions of levels and structures for involvement are not sufficient to answer these questions, and this is problematic since the concepts of patient and citizen knowledge and perspective form the building blocks of frameworks for involvement.

This point is well illustrated by a recent discussion of patient and public involvement by Ives et al. in their paper addressing a possible paradox in patient and public involvement (PPI); the “PPI paradox”. This paradox is constituted as follows; the value of patient and public
involvement is in the ‘lay’ perspective on research, it is the experience of being a service user or member of the public that justifies their involvement. Efforts to access this expertise can however compromise the ‘lay status’ of the patient or citizen involved. This risk of the lay perspective being tainted is absent at the lower levels of involvement, for example, if lay expertise is accessed through a simple consultative model. However, patient and public involvement in this form is not usually considered sufficient. Patients and citizens who are involved at a level that is higher on Arnstein’s ladder, need adequate training to be able to contribute substantially to the scientific process. But once a ‘lay person’ undergoes training, and becomes familiar enough with research to be substantially involved, their ‘lay’ status is compromised and they become ‘more expert’. And even though they can still contribute to the process in a way that is informed by their own experience of illness or disability, their lay perspective is at risk of being ‘tamed’ to make it more congruous with that of the professional researcher. A critique on this idea came from Staley, who argued that the views of the lay person are complementary to those of the technical experts. Lay people know what research would help them, how to make participation a positive experience and how best to communicate the findings to a lay audience.\textsuperscript{74}

Progress on developing a conceptual underpinning for patient and public involvement can resolve these uncertainties. A critical appraisal of different structures for involvement can identify different meaningful combinations of content, level and structure of patient and citizen contributions to the scientific process.\textsuperscript{75}

8. Evaluating the impact of patient and citizen involvement

The wide range of policies and other initiatives that have now been used to shape a practice of patient and citizen involvement, raise the question of their impact. A review of examples of public involvement at the design stage of primary health research by Boote et al. in 2010 found only one study that reported an explicit attempt to measure the impact this involvement.\textsuperscript{76} Other authors concluded that the evidence base on the impact and benefits of patient and citizen involvement in research is still small and that much of the evidence consists of descriptive, often retrospective, accounts of involvement.\textsuperscript{77,78,79,80,81,82} Stewart et al., analyzed literature on identifying research priorities and they found that only nine out of 258 papers which addressed this topic reported patient involvement.\textsuperscript{83} Oliver et al. systematically reviewed different methods of consumer involvement in research priority setting. They concluded that "what we know about the advantages and disadvantages of methods for involving consumers in agenda setting rests on weak short-term evidence and almost entirely speculative long-term evidence".\textsuperscript{84} Currently, calls are being made for more rigorous evaluation of the process and the impact of involvement.\textsuperscript{85,86}

8.1 Available evidence: what does it say?

Research into the impact of patient and citizen involvement in health research and policy can be categorized into knowledge of the impact of involvement on research processes and outcomes and impact on the patients and citizens who were involved. Finally, there is some knowledge on the impact of patient and citizen involvement on professionals.
Impact on research processes and outcomes

Recently, Barber et al. analyzed literature on evaluation of service involvement in identifying and prioritizing research. They conclude that a variety of impacts have been reported:

(i) Involving service users increases the range of research topics, highlighting issues of importance to service users and identifying new themes.
(ii) Service user involvement ‘pushed the science forward more quickly’.
(iii) Service user involvement at the research design stage lead to a more ethically acceptable research design, has contributed to improving trial consent procedures and enhanced recruitment and accrual rates.
(iv) Where studies have used service users as co-researchers and interviewers, the quality of the data was influenced in a positive way.
(v) Service user involvement in analyzing data includes questioning the interpretations of researchers and modifying researchers’ misinterpretations, and making adjustments to how findings have been reported.
(vi) Service user involvement in disseminating research findings was said to enhance the power and credibility of the findings, leading to wider and more accessible dissemination.

A few years earlier, Staley assessed where there appears to be the most evidence for the impact of public involvement in research and identified four themes:

(i) Public involvement was reported to increase recruitment to all types of research;
(ii) Public involvement was reported to be of particular value in qualitative research where participants are asked to share their views and experiences;
(iii) Public involvement was reported to be of particular value in clinical trials where it helped to improve trial design and ensured the use of relevant outcome measures;
(iv) Public involvement was most frequently reported to benefit the people involved as well as the research participants.

Nilsen et al. reviewed evidence from randomized controlled trials on methods of consumer involvement in developing healthcare policy and research, clinical practice guidelines and patient information material. They concluded that evidence of the effects of consumer involvement in healthcare decisions at the population level is weak, but also report some evidence for positive effects:

(i) Moderate quality evidence shows that involving consumers in the development of patient information material results in material that is more relevant, readable and understandable to patients, without affecting their anxiety. This ‘consumer-informed’ material can also improve patients’ knowledge;
(ii) Low quality evidence shows that using consumer interviewers instead of staff interviewers in satisfaction surveys can have a small influence on the survey results;
(iii) Low quality evidence that an informed consent document developed with consumer input (potential trial participants) may have little if any impact on understanding compared to a consent document developed by trial investigators only;
(iv) There is very low quality evidence that telephone discussions and face-to-face group meetings engage consumers better than mailed surveys in order to set priorities for community health goals. They also result in different priorities being set for these goals.

Despite these reports of limited evidence for the effects of patient and citizen involvement, there are also studies with opposing conclusions. Domecq Garces JP, et al. reported that they found ample evidence suggesting that engagement of patients in patient centered outcome
Update on 2004 Background Paper, BP 8.5 Patient and Citizen Involvement

Research improved study design (by choosing outcomes more meaningful to patients or designs that are more culturally sensitive or consistent with patients’ context), execution (improving subject recruitment and retention) and translation (better implementation, dissemination and uptake). Others identified tensions and barriers between different stakeholders at the research design stage concerning variable levels of understanding of service users about health research methods, time and costs, and difficulties raised when researchers used jargon and complex language.

Assessment of the impact of patient and citizen involvement is complicated by the way experiences are reported in the literature. In general, these descriptions are often brief and provide limited evidence of impact. Concepts like consultation, representation, and expertise have been used interchangeably, with patient and citizen involvement variably defined and often poorly described. Longer qualitative descriptions often provide a better insight into impact. However, while such descriptions can be very valuable, they provide no indication of the extent of impact, its magnitude or how it compares across different areas of impact.

**Impact on patients and citizens involved**

In a recent review of the literature on evaluation of service involvement in identifying and prioritizing research Barber et al., stated that service user involvement is associated with empowerment and strengthening of the service user voice. In addition, service users describe increased knowledge, skills and confidence, and support from others in user groups. A study of experiences of cancer patients with involvement activities in cancer services, palliative care and research, revealed that many participants described their involvement activity as a positive way to keep active, to combat depression and loneliness, and as a way to deal with their (cancer) diagnosis and treatment.

Fudge et al. assessed user involvement in health service development in an ethnographic study. They found that service users discussed the impact of involvement primarily in terms of personal gains. For example, they reported satisfaction in feeling that professionals were listening to them, that their ideas were acted on, and that their experience was being harnessed to help others. Service users were observed engaging with the programme for the social opportunities it provided. Finally, service users described their involvement as helping to increase their knowledge and understanding of their condition. When asked about how their involvement had improved services, few service users could directly answer the question.

In other studies, some negative consequences, such as feeling overburdened, reliving distressing memories, hearing stark medical details or being referred to as ‘professional users’, have also been reported.

**Impact on professionals**

We know little about the effects of service user involvement in research on researchers, but there are suggestions that such involvement has led to researchers developing a deeper understanding of service user issues, and prompted them to challenge their own beliefs and assumptions. However, Staley reported that researchers who have reflected on involvement of the public in research, conclude that it is difficult to assess the impact of involvement or to predict where involvement would have the greatest impact. Other patients have voiced perceived threats to professional skills and knowledge: “They are coming in and suddenly they
are the experts and they have done no studying, no qualifications and I think she feels a bit kind of like that’s not right, their experience cannot outweigh my academic qualifications and knowledge.”

Also, researchers generally seem to find it difficult to give up control in order to share knowledge and power and have learnt to espouse scientific methodologies that typically exclude “lay people”. Within professional groupings, Fudge et al. identified two categories. Firstly, professionals who viewed user involvement as an exercise in democracy and promoted patients’ expertise as valid as that of professionals were identified. Secondly, there were those who unquestionably enacted out the policy of involvement as a directive to be implemented as part of a patient centred NHS.

8.2 A framework for evaluating patient and citizen involvement

Ultimately, the effectiveness of any public participation or consultation process should be judged by some measure of the outcomes achieved. There is no agreement on desirable or appropriate outcomes. For example, a change in research priorities resulting from patient involvement may not necessarily be a change for the better for all patients. The reported effect that patient involvement ‘pushed the science forward more quickly’ may or may not have had a positive effect on the quality of the scientific result and a single patient may be a good representative for some patients from a certain country or (sub-)culture, but not for others. Debate within the public participation literature divides between those concerned more with process measures against those more interested in what the influence of involvement is on the final decisions taken. Abelson et al. argue for a stronger evidence base to evaluate patient and citizen involvement. To facilitate evaluation of deliberative processes they propose four elements that need to be assessed:

I **Representation:** To what extent are different types of representation achieved (e.g. geographic, demographic or political)? Consultation processes may also be assessed against criteria that emphasize both access to a consultation (by providing equal opportunities) as well as clarity and legitimacy in the selection process.

II **Structure of the process or procedures:** Are the procedural aspects of a consultation process legitimate, reasonable, responsive and fair? These are considered fundamental aspects of the evaluation process. Legitimacy and responsiveness principles are assessed by considering questions such as: What point in the decision making process is public input being sought? (i.e., is the public involved in significant aspects of decision making, such as agenda setting, or in minor decisions only?); At what level of the organization does the participation occur? Evaluations of deliberative processes in particular would also assess elements of the process such as: (1) Was ample time provided for discussion? (2) Did participants have the opportunity to challenge the information presented? (3) Was mutual respect and concern for others emphasized throughout deliberations?

III **Information:** What and how is information selected, presented and interpreted? These are crucial elements of any consultation process and are therefore important evaluation principles to consider.

IV **Outcomes and decisions arising from the process:** The final set of evaluation principles considers the various sets of potential outcomes of the public participation process. Elements to consider include an assessment of the extent to which public input was incorporated into the final decisions, how decisions and the public’s input into these decisions were
communicated to the public, and the degree to which the decision making authority was found to respond to the public’s input (i.e., what aspects of the input did they incorporate or not incorporate and why?). Secondly, participants must be satisfied with the process which must lead to a more informed citizenry with a better understanding of the issue. Thirdly, an important outcome is the extent to which consensus was achieved and finally, it must be asked if better decisions were taken and the participation process improved policy making (i.e., did the process make a difference to the final decision.

9. Conclusion and future strategies

The number of initiatives that have been employed to organize patient and citizen involvement in health research and policy reflect broad acknowledgement of its value and importance. The variety of efforts is, however, also a symptom of ambiguity and an unfinished search for best practices. In this section, we propose future (research) strategies to maximize the potential benefits of patient and citizen involvement in priority setting for pharmaceutical innovation. We refer to knowledge on patient and citizen involvement in the literature, combined with the results of a survey and the outcomes of two meetings with representatives from stakeholders (i.e. patient organizations, regulators, pharmaceutical industry and scientists).

9.1 Validity and representativeness

One of the main arguments for patient involvement concerns the contributions that patients could make to the relevance and quality of biomedical research based on their 'experiential knowledge'. However, the validity of patients' experiential knowledge in the context of biomedical research processes raises a number of questions: To what extent is the experienced perception of a patient representative credible? And, how can this specific knowledge be absorbed into the scientific process? What methods can be used to enhance the credibility of the contribution of patients and citizens to the decision making? Questions of validity need to be addressed since they limit acceptance of non-expert involvement. While patient and citizen organizations struggle to demonstrate credibility, their position may be undermined by ambiguity in their roles and the goals of their involvement in priority-setting and decision making.

The debate on representativeness of patients and citizens is long standing. Many researchers question whether or not anyone involved could be ‘representative’ of patients or the public in a broader sense – even when a study involved people who had experienced the condition being explored. On the contrary, supporters of involvement have insisted that we focus on inclusion and diversity of participants rather than representativeness. More work is needed to ascertain whether the views of those involved are the same as those not involved and whether user involvement is leading to inequalities—providing benefits to those involved over those who are not. The potential PPI paradox—the lay perspective being ‘tamed’ to fit the scientific process by training of patient and citizen representatives—needs to be addressed for its potential threat to validity and representativeness.
9.2 Framework development

Organizing meaningful patient and citizen involvement is highly complex. As stated above, the wide variety of approaches for patient and citizen involvement has added to experience, but this has not yet resulted in a widely accepted model or a framework for meaningful involvement. Such a framework is needed to ground patient and citizen involvement in an evidence base and to optimize its practice. In the literature, a call is made for consistent and explicit terminology to describe stakeholders and engagement methods. Taking the task of developing a framework, implies the opportunity to start clarifying some of the ambiguity that currently exists, for example by identifying the areas of impact that should be included in an instrument to ensure its content validity. It would also offer the opportunity of explaining how important elements such as the context and process of patient and citizen involvement are considered. Currently, several knowledge gaps hamper the development of a framework for patient and citizen involvement in priority setting for pharmaceutical innovation.

(i) Lack of oversight of initiatives for involvement. Patients and citizens are involved in health research and policy, but there is a lack of clarity on their role and expertise. The experiences reported in the literature stem from a broad field: from patient and citizen involvement in medical research (i.e. supporting the recruitment of research participants) to involvement in committees responsible for marketing authorization of new medicines (i.e. at the EMA). Among and within patient and citizen organizations, there is no consensus on the goals of involvement in priority setting. Experts involved in the meetings to support this background paper observed a lack of knowledge and understanding of patient and citizen involvement, both on the part of patient/citizens and experts (See Annex 8.5.2).

(ii) Models and frameworks. The general consensus is that a one-size-fits-all model for patient and citizen involvement seems unrealistic and unwanted. Based on the research in this background paper, we suggest that further research on different models for patient and citizen involvement should work from a combination of five variables. These are related to the following questions: (1) what is the goal of involvement; (2) who should be involved; (3) what is the role or expertise of the patient or representative involved; (4) what level of involvement is pursued and (5) what structure for involvement is suitable. The five variables all have different subcategories. For example, the goal of patient involvement may be to enhance transparency in the process of priority setting. Another goal of involvement is to give patients and citizens a say in the decision making process. Finally, it may be argued that control of end users over the priority setting process is a goal of patient and citizen involvement. The variable ‘level of involvement’ refers to the levels of citizen participation. For the purpose of patient and citizen involvement in priority setting for pharmaceutical innovation, it may be preferable to use the categories consultation, observation of the decision making process, partnership and lay control. As regards the patients or citizens that are involved and their role we distinguish four possibilities:

* The experienced individual (a patient or a carer): this person can inform the decision makers with a (non-representative) account of experiential knowledge acquired as a patient or a carer.

* A patient representative: is a person (not necessarily a patient) who gives input and feedback to decision makers about priorities and needs of groups of patients. This information should be representative for all relevant groups of patients. A patient representative also has a role in informing the public about priority setting.
Update on 2004 Background Paper, BP 8.5 Patient and Citizen Involvement

* A lay person: this person is not a member of the scientific community. He or she can give a non-expert input and feedback on the process and/or the outcome of priority setting

* A public representative: a person who has been chosen to provide representative input and feedback from the public's perspective on research priorities. They can also help increase public understanding of priority setting processes.

In Figure 8.5.2 we present a schematic overview of these variables

Figure 8.5.2: Initial framework for patient and citizen involvement (for further development)

<table>
<thead>
<tr>
<th>Who</th>
<th>Experienced patient or carer</th>
<th>Patient representative</th>
<th>Lay person</th>
<th>Public representative</th>
<th>Level of involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role</td>
<td>Observation of decision making</td>
<td>Observation of decision making</td>
<td>Observation of decision making</td>
<td>Observation of decision making</td>
<td>Transparency</td>
</tr>
<tr>
<td></td>
<td>Consultation</td>
<td>Partnership</td>
<td>Consultation</td>
<td>Partnership</td>
<td>Collaboration</td>
</tr>
<tr>
<td></td>
<td>Lay control</td>
<td>Lay control</td>
<td>User control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

We stress the point that Figure 8.5.2 is no more than a proposal for a starting point for further development: in each cell of the figure, research needs to be done to elaborate and substantiate the different categories. This should result in a more in-depth understanding of the roles: what expertise is a patient or citizen asked to bring to the decision making process? It may also lead to an alternative characterization of levels of involvement. We are currently not aware of examples of lay control in health research and policy making. This option may be removed or retained for reasons that are yet unrevealed.

The figure illustrates on the one hand, that forms of involvement that some may call 'tokenistic' are considered adequate to achieve a certain goal. For example, for the sake of achieving transparency in the process of priority setting, involving patients and citizens as observants of the decision making may be just as effective as and more cost-efficient than setting up a collaborative partnership. On the other hand, it becomes clear that:

(iii) Priority setting within patient and citizen organizations. Organizations of patients and citizens which may be involved in priority setting, have to clarify their approach towards priority setting for pharmaceutical innovation. Literature on this topic is lacking and patient organizations in our survey report no formal internal process for setting priorities. This lack of procedure and preparation is a threat to further development of patient and citizen involvement.
9.3 Evaluate and learn

There is a knowledge gap with regard to the effects of patient and citizen involvement. Few researchers have tried to assess benefits, costs and adverse effects of different types of involvement activities. The evaluation of benefits in relation to costs is virtually absent. A strategy to enhance patient and citizen involvement in priority setting for pharmaceutical innovation would be to assure structural outcome assessment of initiatives to involve patients and citizens. This will not only strengthen the evidence for patient and citizen involvement, it is also needed to justify policy making and the expenditures required to facilitate this involvement. Critical scrutiny of initiatives would not only involve description and effect measurement, but also a cost-benefit assessment.

At present the evidence base does not provide impact data in enough qualitative detail to be the only source in the development of an instrument to measure impact and there is a need for further (qualitative) exploration. Abelson et al. propose four elements that need to be addressed to facilitate evaluation of deliberative processes:
(i) Representation: To what extent are different types of representation achieved (e.g. geographic, demographic or political)?
(ii) Structure of the process or procedures: Are the procedural aspects of a consultation process legitimate, reasonable, responsive and fair?
(iii) Information: What and how is information selected, presented and interpreted?
(iv) Outcomes and decisions arising from the process: The final set of evaluation principles considers the various sets of potential outcomes of the public participation process. In addition, participants must be satisfied with the process which must lead to a more informed citizenry with a better understanding of the issue. Another important outcome is the extent to which consensus was achieved and finally, it must be asked if better decisions were taken and the participation process improved policy making (i.e., did the process make a difference to the final decision).

These could be a starting point for the development of impact measurement instrument for patient and citizen involvement in priority setting. In addition, economic analysis of patient and citizen involvement is not yet reported in the literature, which suggests that future collaborations with health economists could advance our understanding of how to develop economic appraisal of the impact of patient and citizen involvement.

9.4 Empowerment and capacity building

A model is essential but in the absence of people who are willing and able to realize its potential, it will remain a paper tiger: weak and indecisive. Hence, capacity building is needed to realize meaningful involvement of patients and citizens in priority setting for pharmaceutical innovation. In this background paper, several aspects are identified for which capacity building efforts are needed. Future strategies for involvement should be based on strong values and frameworks to ensure accountability, independence and transparency. In addition to the framework development discussed above, other efforts are needed to build a good practice, mainly in education and training. All stakeholders need to be prepared for decision making on priorities that involve patients and citizens. This requires the empowerment of patients and citizens and education and training for all the parties involved. Initiatives such as the IMI European Patients’ Academy on Therapeutic Innovation (EUPATI) will play an important role in this.
Update on 2004 Background Paper, BP 8.5 Patient and Citizen Involvement

(i) Empowerment and education. All stakeholders need to be prepared to for decision making on priorities that involves patients and citizens. In the literature, examples are given of how meaningful involvement of patients and citizens is complicated by the inequality of power in the decision making process between the expert community of scientists on the one hand and the patient and citizen representatives on the other. Feedback from people who have become actively involved in research, is that researchers should not underestimate the confidence it takes to get involved. Without emotional and psychological strength involvement is much more unlikely. A case study described how exclusion mechanisms (such as leaving certain people out or allowing less time for particular people to speak) and inclusion strategies (e.g. the lack of titles on name badges and the use of clear and informal language) can influence the process and outcomes of a dialogue meeting between researchers and service users. To resolve these issues, empowerment of patients and citizens is required as well as education of the other parties involved.

(ii) Equal information access. In the literature, a power imbalance is observed between experts/scientists who possess what seems to be the desired information, who control its dissemination and the forum within which it is debated on the one hand, and patients and citizens who do not have this control over information on the other. The asymmetry of information access was also identified as an important barrier at the first stakeholder meeting to support this background paper (see Annex 8.5.2). Priority setting for pharmaceutical innovation is currently not a transparent process. Patients and citizens often do not have access to information about decision making from pharmaceutical companies, regulators and governmental agencies. Asymmetry of information access creates asymmetry in power relations and hampers empowerment.

(iii) Ignored knowledge. Professionals generally control the interpretation of involvement and the ways that patients and citizens are involved. Patient organizations at our meetings reported the perceived lack of recognition of patients’ expertise as a major concern. The literature reports that members of drug reimbursement committees often believed that a patient’s ability to access information on the internet, and the presence of members of the public on the committee allowed sufficient access to patients. Some even speak of “intractable difficulties” including many scientists’ lack of conviction that service user involvement has the potential to contribute scientifically to such research; the dominance of positivist scientific paradigms that preclude engagement with experiential knowledge and anxiety that service users lack the requisite objectivity and familiarity with high-level abstraction adequately to participate. Including experiential knowledge of patients into the process of ‘doing science’ requires that the set of considerations allowed in decision making is broadened. Scientists and technical experts have a common knowledge base and a common language and patient experience and citizen preference are not sufficiently incorporated in the scientific discourse, it is ‘ignored knowledge’. This may have implications for the ability of patient and citizen involvement to bring about fundamental change.

There are several initiatives aimed at educating participants in decision making in health policy and research, for example NICE, IAPO, and INVOLVE. The European Union has played an active role by funding the PatientPartner Project, three-year EU Seventh Framework Programme (FP7) project investigating, enforcing and advising on the role of patient organizations in clinical trials. This project demonstrated the need for and willingness of patients to contribute to medical research. Subsequently, EU participated in
the Innovative Medicine Initiative project of the European Patients’ Academy on Therapeutic Innovation (EUPATI), which, started in 2012. Through these and other projects, knowledge on processes and mechanisms that may inhibit meaningful contribution of patients and citizens also has increased. Additional research and support is needed to identify barriers to meaningful involvement and to design measures to overcome them. It may also be important for patients to gather in patients’ organizations as this critical mass may better represent the needs and priorities of patients.

9.5 Dealing with conflict of interest

With the rise of patient and citizen involvement, the attention on conflicts of interest has also grown. Many patient and consumer groups accept pharmaceutical industry funding to support their activities. Some of them see this as a necessity to achieve their aims and they argue that patient groups are able to defend their independence from the influence of any sponsor. Other patient organizations refuse drug industry funding to maintain their autonomy. Another argument against financial relationships between commercial and civil society groups is voiced by Health Action International (HAI): “It is imperative to maintain the distinct view of each stakeholder in order to make balanced decisions about pharmaceutical regulation and health policy.” Accepting funding from the pharmaceutical industry clearly puts patient organizations in a condition of potential conflict of interest. Undue pressure can also come from other sponsors, such as public agencies or research institutes. The same holds for citizens’ organizations, who are also relevant parties from the perspective of private and public interests. Problems may arise when publication of conflict of interest information leads to diminished functioning of patient organizations and additional problems of validity and representativeness. Adequate strategies for dealing with conflicts of interest have to be designed. Potential adverse effects of conflicts of interest are a problem for many stakeholders in the pharmaceutical sector. Transparency is often advised as a way to resolve problems of conflicting interests. Regardless of the necessity of transparency, additional strategies are needed to ensure the primacy of the interests of patients and society. These ‘firewalls’ are still underdeveloped.

The EMA, for example, formulated criteria to be met by patients’ and consumers’ organizations involved in EMA activities. Problems may arise when information about funding sources is not disclosed, or if the relationship between the funding sources and activities of patient organizations is not appropriately addressed. This may lead to diminished trust in patient organizations and additional problems of validity and representativeness. Therefore, relationships with sponsors and common policies to maintain independence should be discussed transparently in order to avoid these problems.

Patient and citizen involvement can strengthen the quality and legitimacy of the decision-making process. Its potential is currently widely acknowledged and much experience is gained in the past decade. Thus, patient and citizen involvement is here to stay. However, to fully capture the value offered by such involvement, there is a need to invest in research in this area to identify appropriate groups, design frameworks for analysis, build sufficient capacity and address conflicts of interest. The European Commission (DG Research and Innovation) have a long history of establishing and supporting “Networks of Excellence”. Such an approach may be useful to support such needed research. The EUPATI project, supported by the EU through IMI, may be another model that could be adapted to focus on evaluation and learning from experience.
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Annex 8.3.2: Meeting report

IN INVOLVEMENT OF PATIENTS AND CITIZENS IN PRIORITY SETTING FOR PHARMACEUTICAL INNOVATION

Brussels 27 September 2012

Traditionally, the role of patients and citizens in pharmaceutical innovation is restricted to being research subjects and beneficiaries of research results. At the time of the development of the WHO Priority Medicines for Europe and the World 2004, patient participation in priority setting was uncommon and knowledge on the effects of such participation was limited. Over the past decade, the claim has been voiced by many that pharmaceutical innovation is misguided if patients and the public are not involved enough. Awareness of the need for a fully-fledged position for patients and citizens in the pharmaceutical innovation process is growing.

Currently, work is underway to update the 2004 WHO Priority Medicines Report. The Belgian Government offered to contribute to this update project by funding the development of a background paper on the role of patients and citizens in priority setting for pharmaceutical innovation. Belgium’s National Institute for Health and Disability Insurance (RIZIV/INAMI) agreed to organize two meetings to facilitate the production of a background paper. A group of experts on the topic joined a first meeting on September 27th 2012 (for a list of participants see Appendix) in Brussels. The goal of this meeting was to develop understanding of the role of patients and citizens in priority setting for pharmaceutical innovation.

A second larger meeting is planned for 22 February 2013, at which the draft background paper will be discussed in detail. In this report we summarize the ideas and conclusions of the first meeting.

The role of patients and citizens in priority setting for pharmaceutical innovation

WHO Priority Medicines for Europe and the World is concerned with priority setting for pharmaceutical innovation. Considering the limited literature and diverse experience with patient involvement in priority setting for pharmaceutical innovation, participants in this first meeting were invited to share as many experiences and viewpoints as possible, even if they came from patient involvement in for example regulatory bodies or reimbursement decision making.

It is important to note that patient involvement and citizen involvement in priority setting for pharmaceutical innovation are not the same. The societal perspective comprises the perspective of citizens as taxpayers, health care users and potential patients. The individual perspective is the perspective of the patient as expert by experience. These perspectives are complementary, but different. The contributions to this first meeting were generally focused on the role of patients. In this report, we discuss patient and citizen involvement together. However, the citizen’s perspective may have been under-represented. This raised the question of how to manage perspectives and biases from all groups involved in priority setting. Also, not all relevant patient groups have adequate representatives (for example children, prisoners).
Participants identified critical issues and suggestions on how to move forward. The issues presented and discussed are in this report summarized under four headings: (1) alignment of pharmaceutical innovation with medical need; (2) barriers to patient and citizen involvement; (3) moving forward and how to overcome barriers, and (4) what was agreed? This report aims to give a comprehensive and structured overview of the issues discussed and therefore, contributions from participants were grouped and merged.

1  **Alignment of pharmaceutical innovation with medical need**

Currently, priority setting mainly driven by scientists, research funding organizations and pharmaceutical companies. Priorities are thus set by the suppliers of pharmaceutical products. Patients introduce and emphasize issues that researchers, companies or regulators may not identify as important. In addition, implementation of innovations can be hampered if patients are not involved in the process of development. By working with patients, patient organizations and the public, innovation can be focused at pharmacotherapeutic interventions that reflect the views of patients and citizens, and meets their healthcare needs.

2  **Barriers to patient and citizen involvement**

The participants of the meeting shared their views and experiences on the existing barriers that hamper patient and citizen involvement in pharmaceutical innovation.

A  **‘Ignored knowledge’**

The perceived lack of recognition of patients’ expertise is a major concern. Patient organizations report that participation sometimes amounts to no more than ‘tokenism’. Tokenism is involvement in the form of information or consultation that aims to legitimize decisions and gain support from patients without giving them any actual influence on the decision making.

The goal to include experiential knowledge of patients in the process of ‘doing science’ and in decision making, is challenging for both patients and scientific experts. It requires a broadening of the set of considerations that are allowed in the decision making. Scientists and technical experts have a common knowledge base and a common language and patient experience and citizen preference are not sufficiently incorporated in the scientific discourse, it is ‘ignored knowledge’. Bringing this ignored knowledge to the process of priority setting is complicated by unequal power relations. Patients and citizens are challenged to legitimize their input. They struggle to meet this challenge and to find ways to demonstrate credibility. Experts who recognize the value of patient involvement, may experience problems when they have to translate experiential knowledge to evidence based language.

B  **No agreement on goals and process**

Patient and citizen involvement can serve several goals. For example, improving patient (health related) outcomes, increasing efficiency, achieving a more equal status of participants and gaining control over the process of priority setting are all mentioned in the literature. Among and within patient organizations and civil societal groups there is no clear consensus on the goals of their involvement in priority setting. With regard to process, there are also many unanswered questions. There is no oversight, guidance or best practice for patient and citizen involvement in pharmaceutical innovation processes. There is a need for case descriptions and examples of successes and failures. In the light of these omissions it is also very difficult to evaluate success or failure of involvement.
C Problems with legitimacy and representativeness
Organizing patient and citizen involvement is highly complex. Patients can sit in on meetings with researchers and regulators, but their presence has to be backed-up by a justified view on legitimacy and representativeness. This raises questions such as:
- Who is represented by the patient involved in priority setting?
- What is the legitimacy of involving (non-elected) citizen panels?
- How can we define the knowledge from the patient and the societal perspective that is relevant for priority setting?
These questions are pressing, since a possible lack of legitimacy and representativeness is an important barrier for empowerment of patients and citizens who are involved in priority setting.

D Absence of legal framework, knowledge and resources
There is a lack of knowledge and understanding of patient involvement both on the part of patients/citizens and experts. Capacity building is needed to learn to work together and to account for different perspectives in priority setting for pharmaceutical information. The general absence of a legal framework to organize and fund patient organizations is a barrier for organization of patient and citizen involvement and capacity building. In addition, patient organizations often have limited resources. This is a reason for patients not to get involved. And if they do, lack of funding may be a barrier to facilitate on-going improvement by evaluation and learning.

E Asymmetry of information access
The informational barrier is twofold. First, priority setting for pharmaceutical innovation is not a transparent process. Patients and citizens often do not have access to information about decision making from pharmaceutical companies, regulators and governmental agencies. Asymmetry of information access creates asymmetry in power relations and hampers empowerment. Second, there is no oversight on patient and citizen involvement. Patient and societal organizations are usually unaware of the activities and experiences of colleagues.

F Strict Conflicts of Interest (COI) policies
Strict policies on COI are the result of heightened attention for the adverse effects of conflicts of interest in the scientific community. Some patient organizations have experienced problems with these policies for their involvement in decision making (e.g. due to the funding of their organization). For example, new COI regulations at the EMA have made some patient representatives no longer eligible.

3 Moving forward: how to overcome barriers?
Participants identified barriers, but also shared ideas and examples of how patients organizations and civil society organizations can overcome these barriers and get involved in decision making on pharmaceutical innovation.

A Promote involvement
The participants of the meeting see the need to promote a much greater role for patient representatives in all aspects of the drug development process including priority setting for pharmaceutical innovation. To prepare all stakeholders for decision making that involves patients and the public, substantial efforts are needed. Partnerships should be based on
strong values and frameworks to ensure accountability, independence and transparency. In addition, the possibility of active measures should be considered. Some suggestions are:

- Patient involvement as a condition for funding (e.g. in EU projects);
- Horizon 2020 and IMI should provide grants to support patient involvement in priority setting and all aspects of drug development, and investigate the most impactful and appropriate models for patient involvement in these processes;
- Promote governments to set conditions to health R&D funding to ensure that this funding meets societal needs;
- Advocate conditions to public funding that ensure affordability and availability of the end product from the start of the innovation process.

B Describe models for involvement

Identifying the different roles of patients/citizens and the different contexts (or levels) on which involvement can be realized is seen as key element to improve involvement. The participants agree that it is unlikely that a one-size-fits-all model for patient and citizen involvement will be successful. Different models for different group-task combinations are needed.

Specification is needed of at least the following aspects of patient and citizen involvement to achieve a solid framework for different models:

- Expectations of all stakeholders;
- Goals of patient and citizen involvement;
- Role of patients and citizens in participation (experts working together with lay people);
- Added value of patient and citizen involvement;
- Degrees of involvement (depending on goal and process of setting priorities);
- Selection process of representatives;
- Outcome measures to evaluate patient and citizen involvement;

C Capacity-building

Identifying, collecting and sharing good practices on patient and citizen involvement is a good starting point to facilitate capacity building. With well-designed models for involvement – and supported by resources – patients, citizens and experts can be educated to enable meaningful involvement. Capacity building can also help empower patient and citizen representatives. The view that the debate on the added value of involvement needs evidence that can come from, for example, case studies and best practices is shared by the participants.

D Create transparency and look into COI management

Transparent decision making and information is important to make patient and citizen involvement possible. Regulators, companies, research funding organizations and governments should provide the necessary information for patients and citizens to facilitate involvement.

Conflicts of interest surrounding the development of pharmaceuticals is an issue that attracts a lot of societal attention. Mechanism to deal with conflict of interests are put in place. Unequal treatment of patient/citizen experts compared to scientific experts regarding conflict of interest should be avoided. Principles of transparency, adherence to codes of ethics and integrity, good governance and sound financial systems can guide the management of conflicting interests.
E  Advocate alternative innovation models and make use of the internet

The participants felt that opportunities for better patient and citizen involvement in priority setting could be found by looking at new ways of innovation and how to get patients and citizens involved there. One way to create space for priority-setting based on health needs to be determined by multi-stakeholder engagement, is by advocating for alternative innovation models that stimulate needs-driven innovation. In addition, in developing models for involvement, the internet should especially be investigated for its opportunities. There are several internet-communities of patients that are potentially useful for this task. Examples are www.patientslikeme.com and www.patientvoices.org.uk

4  What was agreed?

- The common objective of patient and citizen involvement is to achieve better alignment of pharmaceutical innovation with medical need.

- Patient and citizen involvement is necessary for reasons of legitimacy and efficiency.

- Legitimization of patient and citizen involvement needs to be explicated.

- Goals & motivations of patients and citizens to be involved should be researched.

- Models for involvement for different contexts need to be developed.

- There is a need for clarification of roles, settings and purpose of involvement.

- Transparency is necessary to enable meaningful involvement.

- An annotated bibliography will be made to gain insight in the work on patient involvement in the literature.

- A survey will be held among patient and reimbursement organizations with the aim to document case examples & best practices.

- We need to systematically describe several characteristics of patient and citizen involvement (who/which input/which role etc.).

- We need to look at methods to measure effects of patient involvement.

- There is a need for capacity building and education of all stakeholders.

- COI policies should be reviewed to identify unnecessary barriers for patient involvement.

- A second meeting will be held on February 22nd 2013. On the agenda will be the results of the survey, a draft of the annotated bibliography and a draft background paper on patient and citizen involvement.
ANNEX 6.8.3: Survey results

RESPONDENTS

A survey was held under members of the International Alliance of Patients’ Organizations (IAPO) and the European Patients Forum (EPF)
IAPO is a global alliance representing patients of all nationalities across all disease areas. EPF represents 55 chronic disease specific patient organizations operating at EU level and national coalitions of patients organizations. In addition a slightly adapted survey was sent out to the Pharmaceutical Pricing and Reimbursement Information Network.
PPRI is a networking and information-sharing initiative on burning issues of pharmaceutical policies from a public health perspective. It involves PPRI members of almost 70 institutions (mainly competent authorities and third party payers) from the whole European Union, plus Albania, Canada, Iceland, Norway, South Africa, Switzerland and Turkey.

Seventeen representatives of Patient Organizations, through the network of IAPO and EPF completed the survey;
Nine representatives of members the PPRI Network completed the survey.

Below we present the results of the survey. In view of the number of respondents it is questionable if the information is representative. The results may not fully reflect national differences in involvement of patient’s perspective. Nonetheless, the reactions we received to the presentation of these results at the second stakeholder meeting (see Annex 8.5.2) seemed to reflect endorsement rather than criticism.

RESULTS PATIENT ORGANIZATIONS

Involvement of patient organizations in Priority Setting
Patient organizations were asked: Are you/your organization/your members currently involved (as representatives, experts or lay people) in discussions around priority setting for biomedical innovation (pharmaceuticals, medical devices)?
Role or capacity
Patient organizations were asked: In what capacity do/did they act?

Table 2. Roles of patient representatives involved in health care policy and research

<table>
<thead>
<tr>
<th>Capacity</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative of patient organization</td>
<td>6 (35%)</td>
</tr>
<tr>
<td>Expert</td>
<td>0</td>
</tr>
<tr>
<td>Lay person</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>Not applicable</td>
<td>9 (53%)</td>
</tr>
</tbody>
</table>

*Total >100% because more than one answer was allowed

Experiences of patient organizations with involvement

Table 3. Experiences of patient organizations with involvement

<table>
<thead>
<tr>
<th>Experience</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priority setting</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Technology appraisal at NICE</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>Reimbursement</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>PCWP at EMA</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (35%)</td>
</tr>
<tr>
<td>None</td>
<td>9 (59%)</td>
</tr>
</tbody>
</table>

*Total >100% because more than one answer was allowed

Internal process of priority setting
Does your organization have a process for setting priorities in research or have activities involving patients within your own organization? If so, who is responsible for priority setting?

Table 4. Process for priority setting

<table>
<thead>
<tr>
<th>Priority setting by (N = 17)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual member of organization</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Organization as a group</td>
<td>4 (23%)</td>
</tr>
<tr>
<td>No formal process for priority setting</td>
<td>4 (23%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (47%)</td>
</tr>
</tbody>
</table>
Neglected groups
The question was asked: Are you aware of any ‘neglected patient groups’ with regard to patient representation and patient involvement? Could you provide us with examples?
YES 2 (12%) vestibular diseases, all long term conditions
NO 15 (88%)
UNKNOWN 1 (6%)

Capacity building
Are you aware of any efforts for capacity building for patients (e.g., courses for patient representatives)?
YES 3 (18%) via IAPO, EPF, EUPATI, EMA, etc.
NO 14 (82%)

Are you aware of efforts to educate professionals on how to incorporate patient experience/expertise in decision making or priority setting on pharmaceutical research?
YES 3 (18%) via Eduvital, EPF Value+ kit
NO 14 (82%)

Success factors and barriers
The patient organizations were asked: What are the factors that contribute to successful patient involvement in decision making or priority setting on pharmaceutical research? (e.g., education of patients/professionals, obligatory patient involvement)

Factors mentioned:
1 Patient support groups
2 Education of patients/professionals.
3 Obligatory patient involvement
4 Funding
5 Participating in congresses and raise our voice
6 Partnership and dialog with the appropriate stakeholders
7 Understand that involvement is a process, not a one-time event

Subsequently, the question was: What are the factors that hamper involvement of patients in decision making or priority setting on pharmaceutical research?

Factors mentioned:
1 Use of technical language
2 Heavy bureaucratic system
3 Lack of any ideas on what would be suitable drugs partly because the diseases are not understood
4 No close contribution between patients organizations and government institutions.
5 Lack of resources (always assuming that patients should do everything on volunteer basis).
6 Lack of education
Update on 2004 Background Paper, BP 8.5 Patient and Citizen Involvement

Lack of knowledge of where to find expert patients
The decision making stakeholders usually do not think that patients are part of the system or qualified to participate
Experts of pharmaceutical research are unaware of the needs of patients
Pharmacoeconomical aspects
Ethical issues
Genetic aspects
The whole process and language is designed for professionals and it is perceived as too much work and too complicated to involve patients.
There is confusion on the difference between a (individual) patient and a patient representative, and which one would be the right one
The perceived bias by patient representatives because of industry funding to their organizations. Sometimes it does not matter how responsibly and in which transparent way a patient group is doing this, it is just bad in itself and patients are assumed to be more naïve than healthcare professionals.

Finally, the respondents were invited to bring to our attention anything they considered relevant to the topic.
Response came from two organization representatives:
1. Strengthen relationship among patient organizations in the world in order to increase their voice.
2. Organize necessary educational programmes from WHO to involve patients in decision making in different fields of health system.
3. Patients leaders should be members in the WHO since they are representing the patients the best.
4. WHO should assist us to reach every relevant workshop or congress to bring the patients voice.

RESULTS PPRI NETWORK MEMBERS

Involvement of PPRI representatives in Health Care Policy and Research
PPRI members were asked: In your country are patients or citizens involved in decision making for pricing or reimbursement decisions. In addition, we asked if they knew of any examples of patients or citizens involvement in pharmaceutical innovation, market authorization, guideline development and biomedical research in their country. The results are summarized below.

PPRI network survey launched end October 2012
Update on 2004 Background Paper, BP 8.5 Patient and Citizen Involvement

Involvement of patients or citizens in pricing or reimbursement decisions

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>MT</td>
<td>AT</td>
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<tr>
<td>NO</td>
<td>BE</td>
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</table>

Who is involved in these discussions?
- Patient representatives
- Relevant patient organizations

What’s their role?
- Directly involved in the decision process
- Consultation

Involvement of patients or citizens in pharmaceutical innovation, market authorization, guideline development and biomedical research programs

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT (market authorization, innovation)</td>
<td>CZ</td>
</tr>
<tr>
<td>BE (guideline development)</td>
<td>HU</td>
</tr>
<tr>
<td>ES (market authorization)</td>
<td>MT</td>
</tr>
<tr>
<td>NO (innovation, guideline development)</td>
<td>SE</td>
</tr>
<tr>
<td>UK (market authorization, guideline development)</td>
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Awareness of neglected patient groups

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
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</thead>
<tbody>
<tr>
<td>NO (elderly people)</td>
<td>AT</td>
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<tr>
<td></td>
<td>BE</td>
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<td></td>
<td>HU</td>
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<td>UK</td>
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</tbody>
</table>
Update on 2004 Background Paper, BP 8.5 Patient and Citizen Involvement

Capacity building

Efforts for capacity building for patients and citizens (e.g. courses for patient or citizen representatives)

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>AT</td>
<td>CZ</td>
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<tr>
<td>BE</td>
<td>HU</td>
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<tr>
<td>NO</td>
<td>MT</td>
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<tr>
<td>UK</td>
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</tr>
</tbody>
</table>

Efforts to educate professionals on how to incorporate patient and citizen experience/expertise in decision making on priority setting on pharmaceutical research, pricing or reimbursement

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT</td>
<td>BE</td>
</tr>
<tr>
<td>(“economic prescription” courses)</td>
<td></td>
</tr>
<tr>
<td>CZ</td>
<td></td>
</tr>
<tr>
<td>HU</td>
<td></td>
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<td>MT</td>
<td></td>
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<tr>
<td>NO</td>
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<td>SE</td>
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<td>UK</td>
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</table>

Success factors and barriers

What are the factors that contribute to successful patient or citizen involvement in decision making on price or reimbursement setting?

- Adequate education (e.g. knowledge/understanding decision making criteria) is important
- No “conflict of interest”
- An obligatory “conflict of interest declaration” should be introduced
- Other stakeholders’ understanding of the importance of the participation of patients/citizens
- Timely information to the patient organizations
- Obligatory patient representative

What are the factors that hamper involvement of patients in decision making or priority setting on price or reimbursement setting?

- Inadequate education
- “Conflict of interest”
- Absence of a patient representative
- Unstructured patient support groups
- Unclear role of patient support groups
Update on 2004 Background Paper, BP 8.5 Patient and Citizen Involvement

- Absence of umbrella organizations
- Potential influence of marketing by pharmaceutical companies
- Low price sensitivity for medicines
- Too short deadlines in the decision making process

DISCLAIMER by PPRI:

The data contained in this summary have been provided by the members of the PPRI network and represent the current situation. The data do not have any legally binding value and are meant exclusively for the information of PPRI network members who are committed to sharing information on pharmaceutical pricing and reimbursement.
Annex 8.5.4: Viergever’s Checklist for health research priority setting

Table 1 Checklist for health research priority setting

**Preparatory work**

1. **Context**
   Decide which contextual factors underpin the process: What resources are available for the exercise? What is the focus of the exercise (i.e. what is the exercise about and who is it for)? What are the underlying values or principles? What is the health, research and political environment in which the process will take place?

2. **Use of a comprehensive approach**
   Decide if use of a comprehensive approach is appropriate, or if development of own methods is the preferred choice. These approaches provide structured, detailed, step-by-step guidance for health research priority setting processes from beginning to end.

3. **Inclusiveness**
   Decide who should be involved in setting the health research priorities and why. Is there appropriate representation of expertises and balanced gender and regional participation? Have important health sectors and other constituencies been included?

4. **Information gathering**
   Choose what information should be gathered to inform the exercise, such as literature reviews, collection of technical data (e.g. burden of disease or cost-effectiveness data), assessment of broader stakeholder views, reviews or impact analyses of previous priority setting exercises from other geographical levels.

5. **Planning for implementation**
   Establish plans for translation of the priorities to actual research (via policies and finding) as a priority at the beginning of the process. Who will implement the research priorities? And how?

**Deciding on priorities**

6. **Criteria**
   Select relevant criteria to focus discussion around setting priorities.

7. **Methods for deciding on priorities**
   Choose a method for deciding on priorities. Decide whether to use a consensus based approach or a metrics based approach (pooling individual rankings), or a combination

**After priorities have been set**

8. **Evaluation**
   Define when and how evaluation of the established priorities and the priority setting process will take place. Health research priority setting should not be a one-time exercise!
9. Transparency
Write a clear report that discusses the approach used: Who sets the priorities? How exactly were priorities set?
Annex 8.5.5: Saunders’ criteria and rating scales


Table 3 Final consumer review criteria and rating scales

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Range of scores a</th>
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</thead>
<tbody>
<tr>
<td><strong>Extent of benefit:</strong></td>
<td></td>
</tr>
<tr>
<td>Will the findings potentially have an important positive impact on human lives, including any of the following aspects: disease causation (identifying the biology of cancer and the fundamental mechanisms by which cancers arise), prevention, diagnosis, treatment, physical and/or mental and/or social wellbeing, quality of life, dignity, survival? When assessing this criterion, trained consumer reviewers may want to consider some or all of the following:</td>
<td>Nil (no information provided) = 0</td>
</tr>
<tr>
<td></td>
<td>Minor = 1</td>
</tr>
<tr>
<td></td>
<td>Moderate = 2</td>
</tr>
<tr>
<td></td>
<td>Substantial = 3</td>
</tr>
<tr>
<td>• Has the researcher explained how the research will generate tangible benefit/s to human life?</td>
<td></td>
</tr>
<tr>
<td>• Has the researcher indicated the probability, magnitude, and/or duration of these potential benefits?</td>
<td></td>
</tr>
<tr>
<td>• Does the research provide a number of benefits?</td>
<td></td>
</tr>
<tr>
<td><strong>Pathway for realizing the benefit:</strong></td>
<td></td>
</tr>
<tr>
<td>Is there a clear description of the steps required to reach the stated benefits of the research? When assessing this criterion, trained consumer reviewers may want to consider some or all of the following:</td>
<td>Nil = 0</td>
</tr>
<tr>
<td></td>
<td>Moderate = 1</td>
</tr>
<tr>
<td></td>
<td>Substantial = 2</td>
</tr>
<tr>
<td>• Has the researcher provided a brief description of the broad steps or stages required to reach the stated benefits of the research?</td>
<td></td>
</tr>
<tr>
<td>• Do the steps or stages appear reasonable?</td>
<td></td>
</tr>
<tr>
<td>• Are the steps or stages achievable?</td>
<td></td>
</tr>
<tr>
<td>• Do the steps or sages represent significant constraints to achieving the actual benefits of the research?</td>
<td></td>
</tr>
<tr>
<td><strong>Potential for application of findings:</strong></td>
<td></td>
</tr>
<tr>
<td>Is there potential for real-world application of findings in the long-term? When assessing this criterion, trained consumer reviewers may want to consider some or all of the following:</td>
<td>Nil = 0</td>
</tr>
<tr>
<td></td>
<td>Moderate = 1</td>
</tr>
<tr>
<td></td>
<td>Substantial = 2</td>
</tr>
<tr>
<td>• Is it likely that the research findings will be able to be put into practice (in either the short, medium or long term)?</td>
<td></td>
</tr>
<tr>
<td>• Are there likely to be significant barriers to putting the research findings into practice?</td>
<td></td>
</tr>
<tr>
<td>• How compatible are the research findings likely to be with existing laws, public policy, resources, etc.?</td>
<td></td>
</tr>
<tr>
<td>• Where relevant, does the researcher include the groups they will work with to overcome barriers to applying research findings?</td>
<td></td>
</tr>
<tr>
<td><strong>Equity:</strong></td>
<td></td>
</tr>
<tr>
<td>Is there adequate justification for the selection of the study sample that demonstrates potential for equity, e.g. the research does not exclude groups who could potentially benefit from its outcomes, and/or it addresses an understudied group and/or a group with a high burden of</td>
<td>Nil = 0</td>
</tr>
<tr>
<td></td>
<td>Moderate = 1</td>
</tr>
<tr>
<td></td>
<td>Substantial = 2</td>
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<tr>
<td>(also includes if more...</td>
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illness? When assessing this criterion, trained consumer reviewers may want to consider some or all of the following (the research is not required to meet all these expectations):

- Does the researcher explain how the findings could be generalized or applied to similar people outside the research?
- Does the research have the potential to provide benefit across all relevant persons, groups and/or places?
- Does the research address an understudied group?
- Does the research address a group with a considerable burden of illness?

**Consumer involvement:**

(a) Development phase: have experienced consumers (e.g. from consumer or cancer groups) been involved during the development of the research proposal?

(b) Ongoing involvement: is there a plan for ongoing consumer involvement in the research? Is consumer involvement described? Have the researchers identified the preferred approach of consumers for involvement in the research? Are there formal processes/structures in place that link the researchers with consumers?

**Dissemination of results:**

Is there a plan for circulating lay information about all research results to participants and/or the general community? Are there plans for consumers to be involved in the dissemination of research results?

<table>
<thead>
<tr>
<th>Level of reasonable explanation given by the researcher in the funding proposal against each criterion</th>
<th>than one option is addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>No = 0, Yes = 1</td>
<td>No = 0, Yes = 1</td>
</tr>
<tr>
<td>No = 0</td>
<td>No = 0</td>
</tr>
<tr>
<td>Participants or the general community = 1</td>
<td>Participants and the general community (or community only where no human participants) = 2</td>
</tr>
</tbody>
</table>

*a* Level of reasonable explanation given by the researcher in the funding proposal against each criterion
Appendix

<table>
<thead>
<tr>
<th>Participants</th>
<th>National</th>
<th>Involvement of Patients and Citizens in Priority Setting for Pharmaceutical Innovation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleemput, Irina</td>
<td>KCE Belgian Health Care Knowledge Centre, Belgium</td>
<td>Brussels 22 February 2013</td>
</tr>
<tr>
<td>De Cock, Jo</td>
<td>National Institute Health &amp; Disability Insurance, Belgium</td>
<td></td>
</tr>
<tr>
<td>De Ridder, Ri</td>
<td>National Institute Health &amp; Disability Insurance, Belgium</td>
<td></td>
</tr>
<tr>
<td>Delatte, Thérèse</td>
<td>National Institute Health &amp; Disability Insurance, Belgium</td>
<td></td>
</tr>
<tr>
<td>Duvieusart, Brigitte</td>
<td>Fondation Roi Baudouin, Belgium</td>
<td></td>
</tr>
<tr>
<td>Groves, Joanna</td>
<td>International Alliance of Patients’ Organizations, United Kingdom</td>
<td></td>
</tr>
<tr>
<td>Immonen-Charalambous, Kaisa</td>
<td>European Patients’ Forum, Belgium</td>
<td></td>
</tr>
<tr>
<td>Kaplan, Warren</td>
<td>School of Public Health Boston University, United States</td>
<td></td>
</tr>
<tr>
<td>Laing, Richard</td>
<td>World Health Organization, Switzerland</td>
<td></td>
</tr>
<tr>
<td>Livingstone, Heidi</td>
<td>National Institute for Health and Clinical Excellence, United Kingdom</td>
<td></td>
</tr>
<tr>
<td>Mellema, Tessel</td>
<td>Health Action International Europe, the Netherlands</td>
<td></td>
</tr>
<tr>
<td>Mertens, Raf</td>
<td>KCE Belgian Health Care Knowledge Centre, Belgium</td>
<td></td>
</tr>
<tr>
<td>Skoglund, Ulrich</td>
<td>IKK Arzeneimittel Veranlaste Leistungen, Germany</td>
<td></td>
</tr>
<tr>
<td>Stolk, Pieter</td>
<td>WHO Collaborating Centre Utrecht University, the Netherlands</td>
<td></td>
</tr>
<tr>
<td>Van Thiel, Ghislaine</td>
<td>University Medical Centre Utrecht, the Netherlands</td>
<td></td>
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<tr>
<td>Vandensande, Tinne</td>
<td>Fondation Roi Baudouin, Belgium</td>
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</tr>
<tr>
<td>Wirtz, Veronika</td>
<td>National Institute of Public Health, Mexico</td>
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Ghislaine van Thiel/Pieter Stolk November 2012

Meeting report 2

Involvement of Patients and Citizens in Priority Setting for Pharmaceutical Innovation

Brussels 22 February 2013

Patients have always been involved in research. For many years they were the subjects of research but often their involvement was through informed consent procedures. Some patients groups fundraised for research and did support research related to the disease they were interested in. In the 80s and 90s, two groups of patients became more active in advocating for research in their areas of concern. These were orphan diseases and AIDS.
Update on 2004 Background Paper, BP 8.5 Patient and Citizen Involvement

Through their advocacy changes such as the Orphan Drug Act in the United States was passed.

At the time the Priority Medicines Report was written in 2004, there was a limited literature on the topic of involvement of patients and citizens in pharmaceutical innovation. Since then, there has been increased attention for patient and citizen involvement and this is also reflected in a growing body of literature.

The European Commission have now requested that WHO update the 2004 Priority Medicines Report as a background study for Horizon 2020 planning and as an input to the planning for the next Innovative Medicines Initiative. The Belgium government (National Institute for Health and Disability Insurance) has offered to provide support for this process by funding an activity to be undertaken as part of this update project. NIHDI has agreed to organize two meetings. A first relatively small meeting was held on September 27th 2012 and focused on defining terms and concepts, sharing information and suggesting resources that could be used to develop a background paper on this topic. The background paper was the central topic of the second meeting. Several contributions were invited to give additional input for the background paper and to stimulate discussion on identifying the most pressing research questions. The meeting was chaired by Bert Leufkens from Utrecht University. In this report, we summarized the presentations and discussions held on 22 February 2013.

Introduction by Bert Leufkens

Professor Leufkens introduced the topic of the meeting. He referred to the experiences of the Medicines Evaluation Board (MEB) in the Netherlands. The MEB has developed closer interaction with patients’ and citizen’s organizations with the aim to:
(i) become better informed about pertinent practice needs of patients in the drug usage system (operational goal),
(ii) learn about shared and different values and perspectives when regulating medicines (tactical goal),
(iii) promote transparency, accountability and trust about benefit-risk decisions made by the MEB (strategic goal).
Professor Leufkens also reported about discussions among scientist and regulators who see the question of How to involve patients and citizens as an important issue.

Lessons from involving patients and citizens in research agenda setting

A series of articles and book chapters have been produced by Jacqueline Broerse and her colleagues at the Vrije (Free) University in Amsterdam. Professor Broerse made the opening remarks during the February 22nd meeting. During the past 25 years, Professor Broerse and her colleagues have developed and tested the Interactive Learning and Action (ILA) approach for patient and citizen participation in priority setting. In her presentation she gave an overview of cases and outlined the four basic principles of the Interactive Learning and Action Approach: (1) partnership; (2) participation; (3) knowledge integration and learning and (4) joint reflection and alignment. The process and practice of ILA was explained through the presentation of the case of policy agenda setting with the burns foundation. The lessons learned from experience with patient and citizen involvement in priority setting were:

1. Patients are able to set research priorities on a variety of topics, including biomedical research. They have attention for long-term research and provide with new research topics.
Update on 2004 Background Paper, BP 8.5 Patient and Citizen Involvement

2. Each stakeholder group in ILA has its ‘own’ priorities, although there is clear overlap as well.
3. It is difficult to address power differences adequately and subtle ways of exclusion can occur.
4. Empowerment of patients through good preparation is crucial, as well as process facilitation and support.
5. Patient and citizen involvement is approached with a mix of distrust and enthusiasm, and a mixed dialogue is mostly valued.
6. In general there is no adherence to quality criteria such as diversity, knowledge integration and reflection. Also transparency, validity and reproducibility are not warranted.
7. There is a lack of competences.
8. Incentives may be established through trans-disciplinary research programs.
9. Switch from a supply-driven towards a more problem-oriented research system requires a paradigm shift, which is never easy.
10. There is a lack of sense of urgency.
11. Dominant structures and procedures are an obstacle for patient involvement.
12. A learning network is of great importance as it can create a transition arena.

Past experiences by IAPO with Priority Medicines project
Joanna Groves from the International Alliance of Patients’ Organizations (IAPO) shared experiences with the Priority Medicines Project. IAPO responded to consultations during development of Priority Medicines Report in 2004 and based their response on consultation with IAPO members. In addition, patient representatives attended a meeting on the first Priority Medicines Report in Brussels in October 2004 and the launch in The Hague in November 2004. In those days, the key area of input was around the need and value of patient involvement. For IAPO, their involvement in the Priority Medicines project in 2004 was one of instigators of development of IAPO’s Policy Statement and Guidelines on Patient Involvement (published 2005). A case example of how patients/citizens have been able to influence priority setting for pharmaceutical innovation was presented, namely the Consumers Health Forum. In this Australian project, patients were involved in development of policy and guidelines on promoting and applying research. A high impact result was the overturning of a decision by Australian Government in 2011 which would have threatened access to vital medicines. The following conclusions were presented:

* Patients’ organizations are involved in priority setting for pharmaceutical innovation but there is much scope and need to support and promote involvement.
* There are many barriers to involvement including:
A lack of awareness, identification of patient groups, questions of representation, credibility and independence, a lack of evidence of impact, lack of knowledge (on both sides), understanding how to do it, lack of resources etc.

* All involvement should be based on strong values and frameworks to ensure accountability, independence, transparency and value.
* There is a need to promote greater research into patient involvement in all aspects of the drug development process including priority setting for pharmaceutical innovation to assess the impact of patient involvement to date and to investigate the most impactful and appropriate methods for involvement in these processes.
Where are we? Surveys
In addition the two patient’s organizations from Europe and internationally have helped undertake a short survey of their members. The PPRI network that works on pricing and reimbursement has also undertaken a survey of their members to discover what role patients and citizens play in pricing and reimbursement decisions.
- Patients & Citizens associations
- PPRI network
For the results of the surveys see Annex 8.5.3.

Presentation of the Background paper
The draft background paper was discussed in detail.

Session 2: Team discussion (three groups)
The presentations were followed by group discussions to encourage active interaction between the different groups. The meeting also had as an important goal to allow for a discussion of the background paper and to answer key questions about the role of patients and citizens in priority setting.

The participants were divided in three groups. Each group discussed the role of patients and citizens in priority setting. The discussions were guided by two questions:
* Which are the best models that could be used?
* What are the indicators (input and process) that could be used to measure or describe this involvement?
The chairs of the subgroup sessions were:
J. Groves (IAPO)
K. Immonen-Charalambous (EPF)
V. Thomas (NICE).

Session 3: Next steps
In session 3, a report was given of the three groups discussion. Rapporteurs were asked to address the following topics:
* What can be agreed?
* What research is needed to identify the most effective ways for patients and civil society to contribute to priority setting for research?
* Which recommendations could be included in the ‘Priority Medicines in Europe and the World 2013’ report?, Richard Laing (WHO)

Group 1 Report
Group 1 agreed on the following:
* Participation is a value in itself;
* No one model "fits all";
* But some key principles could be identified that should be applied across all situations;
* Clear goals and clear roles for all actors;
* Capacity building to support patient/citizen involvement; and
* Transparency is essential – relates to capacity of patients and citizens to give informed input;

Group 1 identified the following research topics:
* A specific research agenda should be developed
Update on 2004 Background Paper, BP 8.5 Patient and Citizen Involvement

* Theoretical framework
* Indicators – process and outcome
* Impact research on different levels
* Evaluation of initiatives
* Collecting and documenting models and initiatives

Group 1 Recommended:
* Regulatory framework for transparency is needed
* Develop research to identify best practice and the impact of participation, while bearing in mind that participation should not be seen instrumentally but as a value in itself
* (EPF): mandate or strongly prioritise research projects that include patients and citizens involvement in identifying the research priorities.

Group 2 Report
Group 2 agreed on the following:
* In general patient / citizen involvement has been acknowledged as important
* But it is recognised that it might be complicated and patients/citizens have interests and perspectives
* Roles and responsibilities regarding involvement are not clear enough
* Representativeness needs to be clear
* Components to underpin the involvement include: accountability, education, transparency.

Group 2 identified the following research topics:
* Develop a specific research agenda:
  * Indicators
  * Impact research, on different levels e.g. society
  * Develop theoretical framework
  * Evaluation of initiatives
  * Collecting and document models and initiatives – and at the same time develop indicators.

Group 2 Recommended:
* Not only use one model and replicate it
* Bring in different models
* Invest in research (how to do it and evaluation).

Group 3 Report
Group 3 agreed on the following:
* Involvement of patients from start is necessary
* Top-down and bottom-up approach
* Flexibility of methods
* Regulatory requirement
* Training and education in working with patients
* Patient involvement in research design (asking the right question)
* Transparency in declaring interests and resolving conflicts
* Skills and capacity building

Group 3 identified the following research topics:
* Build research networks on the role of patients
* Risk-benefits evaluations from the patients’ point of view
Update on 2004 Background Paper, BP 8.5 Patient and Citizen Involvement

* Value of paying participants
* Evaluation of measures of the added value of participation itself + of different models for participation.

Group 3 Recommended:
* Expand EUPATI
* Acknowledge the issues of a multilingual constituency.

In a closing session the results of the group meetings were presented.

Participants

<table>
<thead>
<tr>
<th>Name</th>
<th>Organization/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen Peter</td>
<td>European Federation of Pharmaceutical Industries and</td>
</tr>
<tr>
<td>Antonissen Yoeriska</td>
<td>INAMI National Institute for Health and Disability Insurance</td>
</tr>
<tr>
<td>Berens Catherine</td>
<td>European Commission DG Enterprise and Industry</td>
</tr>
<tr>
<td>Bouvy Jacoline</td>
<td>Erasmus University Rotterdam</td>
</tr>
<tr>
<td>Brennan David</td>
<td>European Federation of Allergy and Airways diseases Patients’</td>
</tr>
<tr>
<td>Associations</td>
<td>Associations</td>
</tr>
<tr>
<td>Broerse Jacqueline</td>
<td>Athena Institute VU university Amsterdam</td>
</tr>
<tr>
<td>Cassou-Mounat Blandine</td>
<td>Association Internationale de la Mutualité</td>
</tr>
<tr>
<td>Chevalier Pierre</td>
<td>INAMI National Institute for Health and Disability Insurance</td>
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<tr>
<td>Chlebus Magda</td>
<td>European Federation of Pharmaceutical Industries and</td>
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<tr>
<td>Cleemput, Irina</td>
<td>KCE Belgian Health Care Knowledge Centre</td>
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</tr>
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### Update on 2004 Background Paper, BP 8.5 Patient and Citizen Involvement

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Ghislaine van Thiel/Pieter Stolk March 2013