



DIRECTORATE-GENERAL FOR INTERNAL POLICIES

POLICY DEPARTMENT
ECONOMIC AND SCIENTIFIC POLICY **A**

Economic and Monetary Affairs

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Links between Pharmaceutical R&D Models and Access to Affordable Medicines

Study for the ENVI Committee



DIRECTORATE GENERAL FOR INTERNAL POLICIES
POLICY DEPARTMENT A: ECONOMIC AND SCIENTIFIC POLICY

Links between Pharmaceutical R&D Models and Access to Affordable Medicines

STUDY

Abstract

Each patient in the European Union has a right of access to care. National governments face the challenge to balance resources against healthcare demand to ensure that populations enjoy equitable access to effective, affordable and sustainable healthcare. This study describes the main challenges with regard to access to affordable medicines, including Research & Development, pricing and reimbursement of medicines and the influence of the economic crisis. Potential policy options to tackle these challenges are presented, drawing on best practices and a review of specific measures implemented in different European countries. This document was provided by Policy Department A for the Committee on the Environment, Public Health and Food Safety.

This document was requested by the European Parliament's Committee on Environment, Public Health and Food Safety.

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Original: EN

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Manuscript completed in September 2016

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LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
AMR	Antimicrobial Resistance
ASMR	Amélioration du Service Médical Rendu (<i>added therapeutic value</i>)
ATC	Anatomical Therapeutic Chemical
BIA	Budget Impact Analysis
CBA	Cost Benefit Analysis
CEA	Cost Effectiveness Analysis
CED	Coverage with Evidence Development
CMA	Cost Minimisation Analysis
CTD	Common Technical Document
CUA	Cost Utility Analysis
DCP	Decentralised procedure
DDD	Defined Daily Dosage
DRG	Diagnosis Related Group
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries
EGA	European Generic Medicines Association
EMA	European Medicines Agency
EMA	European Medicines Evaluation Agency
ENVI	Environment, Public Health and Food Safety
EP	European Parliament
ERP	External Reference Pricing

ERT	Enzyme Replacement Therapy
EU	European Union
EuroScan	International Information Network on New and Emerging health Technologies
GDP	Gross Domestic Product
GP	General practitioner
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
IMI	Innovative Medicines Initiative
IMS	Intercontinental Marketing Services
INN	International Non-proprietary Name
IP	Intellectual Property
IQWiG	Institute for Quality and Efficiency in Health care
IRP	Internal Reference Pricing
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IT	Information Technology
MA	Marketing authorisation
MAA	Marketing authorisation application
MCDA	Multi-criteria Decision Analysis
MEAs	Managed Entry Agreements

MoCA-OMP	Mechanism of Co-ordinated Access to Orphan Medicinal Products
MRP	Mutual Recognition Procedure
MS	Member States
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NME	New Molecular Entity
NOACs	New Oral Anticoagulants
OECD	Organisation for Economic Co-operation and Development
OTC	Over-the-counter
PACE	Patient and Clinical Engagement
PFS	Progression-free survival
PPI	Proton Pump Inhibitor
PPP	Purchasing Power Parity
PRIME	PRiority MEdicines
PVAs	Price Volume Agreements
QALY	Quality-adjusted life year
RA	Rheumatoid Arthritis
RCT	Randomised clinical trial
RMS	Reference Member State
R&D	Research and Development
SEK	Swedish Krona
SMC	Scottish Medicines Consortium

SME	Small and Medium-size Enterprises
TAU	Temporary Authorisation for Use
TLV	Tandvårds- och läkemedelsförmånsverket (<i>Dental and Pharmaceutical Benefits Agency</i>)
TVF	Transparent Value Framework
UK	United Kingdom
US	United States
VAT	Value-added tax
VBP	Value-based pricing
WHO	World Health Organization

GLOSSARY

The definitions provided here are mainly derived from glossaries provided in relevant and recent reports on the subject^{1,2} as well as the international HTA glossary³.

- Access** Refers to the patient's ability to obtain medical care, including medicines, and a measure of the proportion of a population that reaches appropriate health services, including medication. The ease of access is determined by such components as the availability of medical services and their acceptability to the patient, the location of healthcare facilities, transportation, hours of operation and cost of care.
- Adaptive pathways** A flexible approach to the current system of authorisation in which the licensing of medicines is prospectively planned.
- Added therapeutic value** Refers to medicines which fulfil the following criteria:
- Seen as innovative or a real therapeutic advance;
 - Appears to offer an advantage over current standard treatments;
 - Possibly helpful over existing medicines, or minimal or no clinical advantage compared to existing standard treatments;
 - Other categories, including not viewed as acceptable medicine for routine care, including safety concerns, and judgement reserved due to for instance to insufficient data currently available from clinical trials.
- Affordability** Affordability is not an unequivocal concept. The term refers to a securing standard of living at a price that 'does not impose, in the eyes of a third party (usually government), an unreasonable burden on household incomes'. With regard to medicines, this refers to the extent to which medicines and further healthcare products are available to the people who need them at a price they/their health system can pay.
- Biological medicine (biological)** A product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physical-chemical-biological testing, together with the production process and its control.
- Biosimilar medicine (biosimilar)** A biological medicine that is similar to another biological medicine that has already been authorised for use. Biosimilars can only be authorised for use once the period of data exclusivity on the original 'reference' biological medicine has expired. In general, this means that the biological reference medicine must have been authorised for at least

¹ WHO European Office, 2015, *Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research*, WHO: Copenhagen, available at: http://www.euro.who.int/_data/assets/pdf_file/0003/273819/WHO-Medicines-Report-FINAL2015.pdf?ua=1.

² Vogler, S., Zimmerman, N., 2013, *Glossary of Pharmaceutical Terms*, WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, Gesundheit Österreich GmbH: Vienna, available at: http://whocc.goeg.at/Literaturliste/Dokumente/MethodologyTemplate/PHIS%20Glossary_Update2013_final_ge_samt.pdf.

³ <http://htaglossary.net/HomePage>.

	10 years before a similar biological medicine can be made available by another company.
Budget impact analysis	An evaluation of the financial impact of the introduction of a technology or service on the capital and operating budgets of a government or agency.
Clinical trial	Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.
Co-payment	Insured patient's contribution towards the cost of a medical service covered by the insurer. Can be expressed as a percentage of the total cost of the service or as a fixed amount. Co-payment is a form of out-of-pocket payment. Co-payments might be designed in different formats. With regard to co-payment applied to the medicines, commonly applied variants in European countries are prescription fees, percentage reimbursement/co-payment rates and, but to a less extent, deductibles.
Cost benefit analysis	An economic evaluation consisting of comparing various options, in which costs and outcomes are quantified in common monetary units.
Cost effectiveness analysis	An economic evaluation consisting of comparing various options, in which costs are measured in monetary units, then aggregated, and outcomes are expressed in natural (non-monetary) units.
Cost minimisation analysis	An economic evaluation consisting of comparing various options presumed to produce equivalent outcomes and determining the least costly of those options.
Cost utility analysis	An economic evaluation consisting of comparing various options, in which costs are measured in monetary units and outcomes are measured in utility units, usually in terms of utility to the patient. This is a form of cost-effectiveness analysis in which the effectiveness of an option is adjusted on the basis of quality of life.
Distribution (of medicines)	The division and movement of pharmaceutical products from the premises of the manufacturer of such products, or another central point, to the end user thereof, or to an intermediate point by means of various transport methods, via various storage and/or health establishments.
Evergreening strategies	Refers to the strategy in which pharmaceutical companies seek to maintain sales of their patented products as they near the end of their patent life. This can include isomers such as esomeprazole versus omeprazole and escitalopram versus citalopram and fixed combinations.
External reference pricing	The practice of using the price(s) of a medicine in another 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.

First to market	The first product that created a new market, product category, or a substantial subdivision of a category.
Generic medicine (generic)	A medicine which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicine, and whose bioequivalence with the reference medicine has been demonstrated by appropriate bioavailability studies. The expiration of a patent removes the monopoly of the patent holder on drug sales licensing.
Gross domestic product	The gross expenditure on the final uses of the domestic supply of goods and services valued at purchasers values less imports of goods and services. Comparisons of gross domestic products are arguably best based on purchasing power parities and not on market exchange rates.
Health expenditure	<p>Health expenditure is defined as the sum of expenditure on activities that – through application of medical, paramedical, and nursing knowledge and technology – has the goals of:</p> <ul style="list-style-type: none"> • Promoting health and preventing disease; • Curing illness and reducing premature mortality • Caring for persons affected by chronic illness who require nursing care; • Caring for persons with health-related impairments, disability, and handicaps who require nursing care; • Assisting patients to die with dignity; • Providing and administering public health; • Providing and administering health programmes, health insurance and other funding arrangements.
Health technology assessment	<p>The application of scientific knowledge in healthcare and prevention. Health technology assessment is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased and robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient-focused and seek to achieve best value.</p>
Horizon scanning	A systematic examination of information to identify new medicines that could be potential threats, risks, emerging issues and opportunities, allowing for better preparedness of the health authority for the new medicine. Activities in some countries can start up to three years before likely European Medicines Agency approval.
Incremental cost effectiveness ratio	The additional cost of the more expensive intervention compared with the less expensive intervention, divided by the difference between the effects of the interventions on the patients (the additional cost per quality-adjusted life year, for example).
Innovative medicines	A common definition of what constitutes an ‘innovative medicine’ is currently lacking. From a public health perspective, the level of innovativeness of a medicine is primarily defined by the benefits the

	medicine generates for patients. These can be in the therapeutic, clinical or quality of life domains, but also in the socioeconomic domain.
Intellectual property	Includes patents for inventions, trademarks, industrial designs and geographical indications.
Internal price referencing	The practice of using the price(s) of identical medicines or similar products or even with therapeutically equivalent treatment (not necessarily a medicine) in a country in order to derive a benchmark or reference price for the purposes of setting or negotiating the price or reimbursement of the product in a given country. Patients typically pay the price difference for a more expensive medicine than the current referenced price medicine if they still wish this, e.g. the originator medicine where generics exist.
Managed entry agreement	An arrangement between a manufacturer and payer/provider that enables access to (coverage/reimbursement of) a health technology subject to specified conditions.
Marketing authorisation	A license issued by a medicines agency approving a medicine for market use based on a determination by authorities that the medicine meets the requirements of quality, safety and efficacy for human use in therapeutic treatment.
Marketing authorisation application	Entails all administrative information and documentation that is necessary to demonstrate the quality, safety and efficacy of a medicine.
Mark-up	The difference between the cost price and the selling price. In the case of the pharmaceutical distribution, it is one type of remuneration awarded to distribution actors such as wholesalers and pharmacies for handling their services.
Me-too medicines	Medicines that are comparable or similar to pre-existing medicines, medicines without added value to the patient.
Multi-criteria decision analysis	An analysis supporting complex decision-making situations, the objective of the analysis and the nature of decision-makers' preferences play an essential role in choosing the appropriate approach.
Opportunity costs	The value of the benefits of a better option that is given up when another option is chosen.
Orphan medicine	A product that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the European community, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the product in the Community would generate sufficient return to justify the necessary investment and that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the community or, if such method exists, that the product will be of significant benefit to those affected by that condition.

Over-the-counter medicines (OTC)	Medicines which may be dispensed without a prescription. In some countries they are available via self-service in pharmacies and/or other retail outlets (e.g. drugstores). Selected over-the-counter medicines may be reimbursed for certain indications in some countries.
Patented medicines	Medicines which are protected by a trademark.
Pharmaceutical expenditure	Total expenditure on pharmaceutical and other medical nondurables. This comprises medicinal preparations, branded and generic medicines, on-patent medicines, serums and vaccines, vitamins and minerals and oral contraceptives. Other medical nondurables comprise wide range of medical nondurables such as bandages, elastic stockings, incontinence articles, condoms and other mechanical contraceptive devices.
Price volume agreements	Agreements which focus on controlling financial expenditure with pharmaceutical companies refunding over budget situations. This is a form of a managed entry agreements.
Quality-adjusted life year (QALY)	A measure of outcome of an intervention where gains (or losses) of years of life subsequent to the intervention are adjusted on the basis of the quality of life during those years. This parameter can provide a common unit for comparing cost-utility across different interventions and health problems.
Randomised clinical trial	A study comparing at least two interventions, in which the eligible participants are allocated randomly to the intervention group, or groups, and the control group.
Rebate	A payment made to the purchaser after the transaction has occurred. Purchasers (either hospitals or pharmacies) receive a bulk refund from a wholesaler, based on sales of a particular product or total purchases from that wholesaler or manufacturer over a particular period of time.
Reimbursement	Coverage of the cost by a third-party payer (such as social health insurance or the national health service).
Research & Development	Comprises creative work undertaken on a systematic basis in order to increase the stock of knowledge, including knowledge of man, culture and society and the use of this stock of knowledge to devise new applications. Research & Development is a term covering three activities: basic research, applied research and experimental development.
Risk-sharing arrangements	Agreements concluded by payers and pharmaceutical companies to diminish the impact on the payer's budget of new and existing medicines brought about by either the uncertainty of the value of the medicine and/or the need to work within finite budgets. Managed entry agreements and risk-sharing arrangements are used inter-changeably. In recent years, managed entry agreements have become the term that is most used.
Tendering	Any formal and competitive procurement procedure through which tenders (offers) are requested, received and evaluated for the procurement of goods, works or services, and as a consequence of

which an award is made to the tenderer whose tender/offer is the most advantageous.

Transparent value framework Development of new approaches to the pricing of new medicines for orphan diseases, given concerns with current approaches (including ever increasing prices).

Value-added tax A sales-tax on products collected in stages by enterprises. It is a wide-ranging tax usually designed to cover most or all goods and services, including medicines.

Value-based pricing In general, it is meant that countries set prices for new medicines and/or decide on reimbursement based on the therapeutic value which medicine offers, usually assessed through HTA or economic evaluation.

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EXECUTIVE SUMMARY

Background

Around the globe concerns exist with regard to access to care, which is a patient's ability to obtain healthcare. Concerns about access have been particularly important in recent years, with the countries in the European Union (EU) facing economic crises. Economic crises pose threats to health and health systems performance due to scarce resources. As a result of limited financial and human resources, ageing populations, increases in chronic diseases, and technological developments, national governments face the challenge of ensuring that populations enjoy equitable access to effective, affordable and sustainable healthcare.

This report provides an overview of the main issues related to *access to medicines* in the EU and suggests options to policymakers to address the key challenges in order to improve access to medicines. This includes newer more expensive medicines to address unmet need. Information was collected through desk research of relevant policy documents and by a literature search in peer-reviewed (e.g. PubMed, Web of Science) databases.

Medicines can improve the quality of life of patients as well as save lives. Medicines are, therefore, important to public health as well as the European economy. In 2014, outpatient pharmaceutical expenditure accounted for 17.1% of total health expenditure and for 1.41% of Gross Domestic Product (GDP) in the EU. Pharmaceutical expenditure decreased during the past few years as a result of measures taken by health authorities including, for example, increased patient co-payments. However, this trend is changing due to the increased availability of newer and higher priced medicines.

The increased availability of newer medicines is due to a greater demand for access to medicines to treat diseases for which no treatment or diagnosis exists, or where there is limited effectiveness and/or concerns with the side effects of current treatments. However, the demand has to be balanced against available resources, especially with rising prices of new medicines in a number of disease areas, such as cancer.

Key factors related to access to medicines

Availability and affordability of medicines are the most important influencing factors with regard to access to medicines. These are linked to the value chain of medicines, pricing of medicines, as well as the cultural and economic context of EU Member States (MS).

Value chain

The pharmaceutical value chain consists of three main phases: manufacturing the medicine, distributing, and dispensing the medicine. The manufacturing phase is characterised by Research & Development (R&D), registration and authorisation (i.e. allowed to be sold) of medicines and quality control after the medicines are used in clinical practice. Access to new medicines can be accelerated by optimising these processes.

For example, a number of new strategies and models have been proposed to assist with increased productivity of R&D, including pharma-academic partnerships, biotech co-creation and innovation centres (Chapter 3.2).

With regard to the registration and authorisation of medicines, there are proposals to decouple the incentive system of the current EU regulation of medicines, which discriminates against the development of new medicines for short-term use, such as antibiotics (Chapter 7.5.1). These measures are in addition to the incentives surrounding the development and pricing strategies of new medicines to treat rare diseases as well as (other) life-threatening diseases such as cancer. Scarce resources are resulting in closer scrutiny over costs within the distribution system, including wholesaler and pharmacy remuneration (Chapter 4.2) and

is also leading to new models to optimise the use of new medicines. This starts prior to the authorisation of medicines and includes closer assessment of their potential value. The reason for this is because present systems and assessment methods are seen as not sufficiently rigorous to meet future challenges. Of all new medicines, 85-90% are believed to provide few or no advantages over existing ones (Chapter 0).

There are also ongoing initiatives to accelerate the introduction of new medicines that address disease areas for which there are currently no treatment options. One such initiative concerns so-called adaptive pathways. Adaptive pathways are a flexible approach to the current system of authorisation in which the licensing of medicines is prospectively planned. Inherent to adaptive pathways is a higher degree of uncertainty regarding the safety and effectiveness of a new medicine at the point of authorisation in comparison with traditional licensing. Its real potential has to be shown through studies performed once the medicine is used in clinical practice to ensure current medicines are used wisely to maximise patient benefits (Chapter 3.3.1). Payers, including health insurers, also have concerns as it is currently difficult to remove new medicines from reimbursement lists, other than for safety reasons, even though they appear no longer to provide value for money. Examples of such cases that have received ample media attention include medicines for treating patients with Pompe and Fabry disease, which are both rare conditions (Chapter 4).

Pricing of medicines and the role of EU MS

Pricing and reimbursement of medicines is the mandate of each EU MS. New approaches are needed to address the concerns among payers within EU MS with regard to increasing prices of new medicines. As a result, EU MS have instigated a number of market intelligence measures, called horizon scanning, to identify as early as possible priority medicines that could have a considerable impact on patients' health and healthcare budgets. Subsequently, it is important to track the progress of the development of these medicines as well as plan their entry for use in clinical practice. Planning the entry means that it is important to develop physician and patient educational guidelines for using the new medicines. Guidance may also include the development of quality indicators to optimise the use of these new medicines once available for use in patients.

In addition, ways to make new valued medicines affordable are needed. This includes payers entering into agreements with pharmaceutical companies, such as confidential discounts, as well as agreements in which the price of the new medicine is dependent on the volume used in practice. At the same time, accelerating strategies are taken to release resources to pay for new valued medicines whilst funding increased drug volumes due to the growing number of chronic diseases, such as cancer. Strategies include encouraging greater prescribing of low-cost medicines without compromising patient care. These strategies are growing as more standard medicines lose their patents and become available at appreciably lower prices. Some MS have also introduced tendering schemes to obtain low prices for medicines once they have lost their patent and are available via multiple sources (Chapter 4.1). Lessons learnt from previous experiences show that the lowest prices and, hence, resources released, are seen in countries that encourage the use of such medicines.

Other measures to improve access to new medicines focus on providing incentives and funding for innovative medicines whilst ensuring that health authorities do not pay higher prices for new medicines, that offer no or very limited health benefits compared to existing treatments. The effectiveness and/or safety of a medicine versus current standard treatments is a key consideration among payers when assessing the potential price for new medicines requested by pharmaceutical companies. Once the effectiveness and/or safety of a new medicine has been assessed, MS are typically divided into those that directly use such assessments to review potential prices, and those that assess the potential value of new

medicines based on the additional cost per quality-adjusted life year (QALY) versus current treatments. Nevertheless, only a minority of countries using the latter approach provide threshold levels for negotiation (Chapter 0).

The existing system for assessing the value of medicines, i.e. Health Technology Assessment (HTA), has the tools to carry out rigorous evaluations of the extent of patient benefits of the new medicines versus existing ones. However, there are concerns that current methods do not fully capture the value of new treatments. For example, suggestions have been made to establish minimum effectiveness targets for new cancer medicines as an improvement for consideration of higher prices (Chapter 4.4). There are also concerns that funding for certain patient groups may be enhanced by political forces and pressures. As a result, other patient populations may lose out within available budgets. Rigorous HTA techniques, as well as an integrative perspective towards HTA may help to address this. This means that HTA includes collecting information that is considered meaningful, relevant and plausible to all stakeholders, including the public and by explicating their values.

Another key consideration when assessing the value of a medicine includes the severity of the disease. The use of budget impact analysis (BIAs) as part of pricing and reimbursement negotiations is also growing. A BIA enables payers to assess the likely impact of the new medicine on healthcare budgets in all or sub-populations. The recent launch of new medicines to potentially cure patients with the hepatitis C virus (HCV) has accelerated this consideration, with the potential for quadrupling pharmaceutical budgets based on likely patient numbers with HCV and initial requested prices. These concerns resulted in strong price negotiations with the pharmaceutical industry by some European countries to improve their affordability for patients (Chapter 4.6.2).

The way forward - policy options

The report reveals that a number of barriers need to be overcome, as well as activities undertaken, to improve access to affordable medicines. This includes for new medicines:

- innovative ways to stimulate R&D into new medicines, including new antibiotics as well as potential ways to accelerate the availability and use of new medicines of value in patients through initiatives such as adaptive pathways;
- reduction of the fragmentation of regulatory agencies and improvement of their coordination to ensure faster authorisation for new medicines. Regulators, HTA bodies and payers must collaborate with a focus on minimising duplication of Randomised Clinical Trials (RCTs) and their applications. At the same time, ensuring meaningful outcomes are collected in RCTs and real world studies to enhance decision making, as there can be concerns with translating short-term measures into meaningful clinical improvements for patients;
- enhancing funding for, and availability of, new medicines in target populations where their health gain is greatest, through pro-active planning. This starts before the medicine enters the market and is typically part of horizon scanning activities;
- greater scrutiny over the value of new medicines so that higher prices are not being paid for new medicines with limited or no benefit compared with existing treatments, thus compromising available budgets for new medicines that have added therapeutic value;
- development of new approaches to the pricing of new medicines where there are concerns with current approaches, such as pricing for new medicines for rare diseases, i.e. the so-called Transparent Value Framework (TVF), developed through co-operation involving all key stakeholder groups.

For existing medicines potential measures include:

- ensuring rapid access to good quality medicines at low prices whilst ensuring a viable pharmaceutical market for these medicines in Europe;
- scrutinising the mark-ups for medicines in the distribution chain for both wholesalers and pharmacies given their impact on final prices charged to health authorities;
- exploring potential tendering opportunities when multiple sources become available for a given medicine;
- tackling issues of co-payments for patients where this is a concern with regard to attaining good health, especially following the economic crisis.

And for both new and existing medicines:

- strengthening HTA and related activities so that priorities can be more easily set and available medicines will have enhanced effectiveness and cost-effectiveness.

While these activities can contribute greatly to the goal of effective care within limited healthcare budgets, a critical perspective is important in interpreting this report. The fact is, as shown in the report, that present pharmaceutical R&D produces few new, innovative medicines for diseases for which no treatment exists. Systems to evaluate each medicine, including existing ones, are essential to identify these high-priority medicines. The goal of an effective and efficient healthcare system can only be met by full information on the effectiveness and cost-effectiveness of each medicine as well as processes in place that optimise available budgets. HTA and related activities, including pharmaceutical regulation, can help furnish this information.

1. GENERAL INFORMATION

1.1. Aim and scope of the study

This study was requested by the Committee on Environment, Public Health and Food Safety (ENVI) of the European Parliament (EP) and provides an overview of the main issues regarding access to affordable medicines. Consequently, a range of policy options for future consideration and debate are suggested to address the key challenges of access to affordable medicines in the EU.

Access refers to the patient's ability to obtain healthcare, including medicines⁴, as is a critical component of universal health coverage⁵. All MS have a mandate to provide resources to ensure equitable access to relevant, appropriate and efficient healthcare that closely matches the need of their population⁶, with no one barred from accessing care. With respect to medicines, access has been described under different frameworks^{7,8,9}, mainly focusing on the availability and affordability of medicines. Availability refers to manufacturing, forecasting, procurement, distribution and delivery of medicines¹⁰. Affordability refers to prices of medicines¹¹ and includes affordability to healthcare services, as well as to patients if there are co-payments. Providing access to medicines and ensuring affordability is essential in order to provide everyone with access to quality health services¹².

There is ongoing tension in every MS between rising healthcare costs and the ability to continue to provide comprehensive and relevant healthcare for everyone. This trade-off is becoming more difficult with respect to pharmaceutical expenditure for a number of reasons (Table 1).

Table 1: Key drivers and barriers leading to tensions within healthcare systems

Key factors that increase pharmaceutical expenditure (drivers)	Barriers influencing pharmaceutical expenditure
<ul style="list-style-type: none"> Ageing populations and rise in the prevalence of chronic diseases Improved scientific understanding with increasing knowledge of pharmacogenomics, leading to fragmentation of patient populations 	<ul style="list-style-type: none"> Concerns with public finances especially during times of recession/limited economic growth Payers' willingness to pay for new more expensive medicines, especially those with limited innovation, i.e. most new medicines

⁴ WHO European Office, 2015, *Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research*, WHO: Copenhagen, available at: http://www.euro.who.int/_data/assets/pdf_file/0003/273819/WHO-Medicines-Report-FINAL2015.pdf?ua=1.

⁵ Expert Panel on effective ways of investing in Health (EXPH), 2016, *Report on Access to Health Services in the European Union*, available at: http://ec.europa.eu/health/expert_panel/opinions/docs/015_access_healthservices_en.pdf.

⁶ Idem.

⁷ Penchansky, R. and Thomas, J.W., 1981, *The concept of access: definition and relationship to consumer satisfaction*, Medical Care, 19, p. 127–140.

⁸ World Health Organization, 2004, *Equitable access to essential medicines: a framework for collective action*, Policy Perspectives on Medicines, WHO: Geneva, available at: <http://apps.who.int/medicinedocs/pdf/s4962e/s4962e.pdf>.

⁹ Frost, L.J. and Reich, M.R., 2010, *How do good health technologies get to poor people in poor countries*, Boston, MA: Harvard Center for Population and Development Studies.

¹⁰ Bigdeli, M. et al., 2013, *Access to medicines from a health system perspective*, Health Policy Plan, 28, p. 692–704.

¹¹ World Health Organization, *Access to Medicines*, available at: <http://www.who.int/trade/glossary/story002/en/>.

¹² World Health Organization, 2014, *What is universal health coverage?*, Online Q&A, available at: http://www.who.int/features/qa/universal_health_coverage/en/.

Key factors that increase pharmaceutical expenditure (drivers)	Barriers influencing pharmaceutical expenditure
<ul style="list-style-type: none"> Number of new medicines entering the market enhanced by fragmentation of patient populations (which can lead to orphan status) 	<ul style="list-style-type: none"> Growth in risk-sharing arrangements and other mechanisms to moderate the prices of new medicines
<ul style="list-style-type: none"> Increasing prices for new medicines including those for patients with cancer enhanced by orphan status 	<ul style="list-style-type: none"> Potential growth in differential pricing arrangements across countries as seen with the new medicines for hepatitis C
<ul style="list-style-type: none"> Willingness of EU countries to allow greater leeway regarding pricing and reimbursement for new medicines that extend life at the end of life 	<ul style="list-style-type: none"> Many standard treatments available as low-cost generics, as well as increasing number of biosimilars, influencing pricing considerations for new medicines
<ul style="list-style-type: none"> No universal concept of what constitutes a fair price for a new medicine balanced against the desire for pharmaceutical companies to make profits. This is not helped by payers' limited leverage overall for price negotiations exacerbated by many not armed to establish 'willingness to pay' boundaries 	<ul style="list-style-type: none"> Growth in External Reference Pricing (ERP, Chapter 4.3.1)
<ul style="list-style-type: none"> Evidence-based guidelines lacking or ignored 	
<ul style="list-style-type: none"> Lack of comprehensive Information Technology (IT) systems routinely monitoring patient care across countries and suggesting ways to increase appropriate and efficient prescribing 	
<ul style="list-style-type: none"> Only a limited number of EU countries systematically approaching disinvestment using HTA principles 	
<ul style="list-style-type: none"> Under-investment in health promotion 	

Source: Adapted from Vandenbroeck et al.¹³, Godman et al.¹⁴, Hoen¹⁵, Iyengar et al.¹⁶, and the Expert Panel on effective ways of investing in health¹⁷.

In summary, firstly there is an increasingly elderly population with an increasing prevalence of chronic diseases including cancer, diabetes, and hypertension¹⁸.

¹³ Vandenbroeck, P. et al., 2016, *Future scenarios about drug development and drug pricing*. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). KCE Reports 271. D/2016/10.273/59.

¹⁴ Godman, B. et al., 2015, *Personalizing health care: feasibility and future implications*. BMC medicine. 2013;11:179.

¹⁵ Hoen, E., 2014, *Access to cancer treatment. A study of medicine pricing issues with recommendations for improving access to cancer medication. A report prepared for OXFAM*, available at: https://www.oxfam.org/sites/www.oxfam.org/files/file_attachments/rr-access-cancer-treatment-inequality-040215-en.pdf.

¹⁶ Iyengar, S. et al., 2016, *Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis*, PLoS medicine, 13(5):e1002032.

¹⁷ Expert Panel on effective ways of investing in Health (EXPH), 2016, *Report on Access to Health Services in the European Union*, available at: http://ec.europa.eu/health/expert_panel/opinions/docs/015_access_healthservices_en.pdf.

¹⁸ OECD, 2015, *Health at a Glance 2015: OECD Indicators*, OECD Publishing: Paris, available at: http://www.oecd-ilibrary.org/docserver/download/health_glance-2015-sum-en.pdf?expires=1447069970&id=id&accname=quest&checksum=BACE5CB3DED5B5C8D34BA9B86F6E24E1.

Secondly, there is a continuing unmet need for new medicines in Europe¹⁹. Unmet need is defined as a condition for which no treatment, therapy or diagnosis is addressed by available therapies²⁰. This will require more effective, new and often higher-priced medicines to improve population health. For example, the prices of new medicines for patients with cancer have risen ten-fold in recent years²¹. There are also typically high prices for new medicines to treat patients with rare diseases such as Pompe disease^{22,23}.

Thirdly, there are stricter clinical management targets and rising patient expectations. These, combined with the increased prevalence of chronic diseases, will increase the use of medicines and associated costs.

Continued access to medicines that are affordable to health systems is of utmost importance, both for public health and economic reasons. Medicines can improve the quality of life of patients as well as save lives. The European Federation of Pharmaceutical Industries (EFPIA) recently estimated that medicines have helped improve the lives of patients, which, together with other advances, have added an extra 30 years of life to people living in Europe compared to a century ago²⁴. Medicines are also important to the economy since they not only keep people in work, but also enhance employment. Pharmaceutical companies are major employers in Europe and they invest over €30 billion per year in R&D in Europe. However, there are concerns that Europe is losing its influence as a major force in the global pharmaceutical sector. For example, the United States (US) now accounts for 55% of the total sales of new medicines launched between 2009 and 2013, compared with just 23% for Europe²⁵.

To improve access to affordable medicines, new approaches have to be found. These approaches may include the development of new R&D models, new ways that can accelerate market access to new medicines that address unmet need, and models to optimise the use of new medicines that can improve the health of patients once available. It should, however, be considered that accelerated access has to be balanced against potential patient safety concerns, especially if there are considerable uncertainties regarding the possible adverse effects of a new medicine when used in routine clinical care (Chapter 3.3).

The new approaches could also include different activities that are linked to the lifecycle of a medicine. These include pre-launch, peri-launch and post-launch activities²⁶ (Chapter 5). Pre-launch activities include establishing information systems that can identify important new medicines that are likely to be launched within the next few years, as well as continually finding ways of saving resources to fund new, higher-priced medicines within available budgets. One successful method has been prescribing lower-cost medicines (so-called generics and biosimilars) instead of originator (so-called branded) medicines to treat the same disease without compromising patient care. There may also be the potential for savings from looking more critically at the value chain of medicines and its associated costs. This includes reviewing wholesaler and pharmacist remuneration when distributing medicines.

¹⁹ Kaplan, W. et al., 2013, *Priority Medicines for Europe and the World 2013 Update Report*, available at: http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf?ua=1.

²⁰ Bhatt, A., 2015, *Assessing unmet medical need in India: A regulatory ride*, *Perspect Clin Res*, 6(1), p. 1-3.

²¹ Kelly, R. and Smith, T., 2014, *Delivering maximum clinical benefit at an affordable price: engaging stakeholders in cancer care*. *The lancet oncology*, 15(3):e112-e8.

²² Simoens, S. et al., 2013, *Cost-effectiveness assessment of orphan drugs: a scientific and political conundrum*. *Applied health economics and health policy*. 11(1), p. 1-3.

²³ Cohen, P. and Felix, A. 2014, *Are payers treating orphan drugs differently?* *Journal of Market Access & Health Policy*, 2, p. 23513.

²⁴ European Federation of Pharmaceutical Industries and Associations, 2014, *The Pharmaceutical Industry in Figures. Key data 2014*, available at: http://www.efpia.eu/uploads/Figures_2014_Final.pdf.

²⁵ Idem.

²⁶ Godman, B. et al., 2015, *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?* *Expert review of clinical pharmacology*, 8(1), p. 77-94.

Peri-launch activities include assessing reimbursement, pricing and funding of new medicines. Potential developments include risksharing arrangements, value-based pricing (VBP) as well as multi-criteria decision analyses (MCDA), including those for new medicines for orphan diseases. Post-launch activities include assessing the effectiveness and safety of new medicines in routine clinical care and adjusting prices or prescribing guidance where necessary to improve prescribing efficiency.

Outside the scope of this report are proposals to increase the number and use of evidence-based guidelines to improve the quality and efficiency of prescribing. This can include encouraging the prescribing of well-proven, but less expensive medicines without compromising care^{27,28}. In addition, proposals to improve health promotion to reduce the prevalence of chronic diseases and their associated costs.

1.2. Methods used

Information presented in this report was collected through desk research of regulatory and other relevant policy documents (e.g. World Health Organization (WHO), European Commission (EC), Organisation for Economic Co-operation and Development (OECD)) as well as through an extensive literature search in peer-reviewed databases (PubMed/Medline, Scopus, Science Direct, Ovid and EconLit). In addition, we analysed the dataset 'Health expenditure indicators' from the OECD for the EU28 MS, whenever possible, and from 2005 to the last year available.

1.3. Setting the scene

Access to medicines has been regulated for over 50 years within the EU. In 1965, the first European Community rules on medicines were established. These rules aimed to protect public health by preventing medicines from entering the market if there were particular concerns, e.g. the safety of the products. Before this, MS applied national legislation to regulate medicines for human use. The regulatory framework has been frequently and substantially amended throughout the subsequent years.

A major landmark was the establishment of the European Medicines Evaluation Agency (EMA) in 1995 and the enforcement of new European licensing procedures. In the 2000s, EMA's responsibilities and tasks gradually expanded, resulting in a stronger role in the protection of public and animal health. Since 2009, the Agency has been known as the European Medicines Agency (EMA).

The current framework for the regulation of medicines is complex as there are different regulations for different types of medicines. In all cases, pharmaceutical companies are obliged to apply for a scientific evaluation of their product before they are allowed to launch it onto the European pharmaceutical market. The EMA is responsible for the scientific evaluation of applications from pharmaceutical companies for EU-wide single marketing authorisations (MA) (centralised procedure). Alternatively, pharmaceutical companies might choose to apply for a procedure at MS level, where national competent authorities are responsible for the authorisation of medicines (decentralised procedure (DCP)).

The pricing and reimbursement policy for new and existing medicines is the remit of national governments or health authorities of individual MS. Measures regarding pricing and reimbursement must be objective and verifiable, and may not discriminate against medicines

²⁷ Bach, P.B., 2013, *Reforming the payment system for medical oncology*. JAMA. 310(3), p. 261-262.

²⁸ Gustafsson, L. et al., 2011, *The 'wise list'- a comprehensive concept to select, communicate and achieve adherence to recommendations of essential drugs in ambulatory care in Stockholm*. Basic & clinical pharmacology & toxicology, 108(4), p. 224-233.

that are imported. They became regulated through Directive 89/105/EEC²⁹. The Directive was adopted to ensure that free movement of goods was not obstructed by domestic pricing and reimbursement legislation. Its goal was to facilitate the functioning of the internal market for medicines. This has stimulated MS to introduce cost-containment measures and other policies to manage the prescription and consumption of medicines to ensure equal access to care. The pricing of new medicines is also affected by reviews from key groups such as the WHO (Chapter 4).

As these measures affected the internal pharmaceutical market, an amended proposal of the Directive was adopted by the EP in 2013³⁰. The amended proposal of the Directive provides a series of procedural requirements to streamline and reduce the duration of national decisions on pricing and the reimbursement of medicines³¹. These include:

- Regulations for the pricing of new medicines as well as existing medicines, including generics, must be based on objective and verifiable criteria, which are independent from the origin of the product. In addition, intellectual property (IP) rights should not interfere with pricing and reimbursement decisions;
- Pricing and reimbursement decisions for new medicines must be completed within 180 days: 90 days for pricing, 90 days for reimbursement, or 180 days for combined pricing and reimbursement decisions;
- With regard to generic medicines, the time frame for pricing and reimbursement decisions is 90 days: 30 days for pricing and 60 days for reimbursement decisions, under the condition that the reference medicine is already reimbursed.

Based on the above-mentioned context, the report is structured as follows:

- Overview of pharmaceutical expenditure in the EU;
- Value chain of medicines, including (new) R&D models, registration and market access process, including proposals to accelerate the availability of new medicines to treat patients with unmet need;
- Key factors influencing prices of medicines including new medicines, generics and biosimilars;
- Models to optimise the use of new medicines including pricing, reimbursement and funding decisions;
- Barriers to access to medicines, including the impact of the recent economic crisis;
- Lessons learnt from previous experiences with new medicines;
- Conclusions and policy options to accelerate access to (new) medicines addressing unmet need.

²⁹ Council Directive of 21 December 1988, relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance system.

³⁰ COM(2013)168 final. Amended proposal for a Directive of the European Parliament and the council on the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of public health insurance systems.

³¹ Idem.

2. PHARMACEUTICAL EXPENDITURE IN THE EUROPEAN UNION

KEY FINDINGS

- From 2005 to 2014 there was a decline of pharmaceutical expenditure as a percentage of both total health expenditure and GDP in the EU.
- In 2014, pharmaceutical expenditure accounted for 17.1% of the total health expenditure and for 1.41% of GDP on average in the EU.
- Pharmaceutical expenditure increases if consumption of medicines in hospitals is included.
- Pharmaceutical expenditure went down during the last few years, but this trend may change with increasing utilisation of new, high-priced medicines.

2.1. Introduction

This chapter provides an overview of pharmaceutical expenditure in the EU MS. The most important determinants of pharmaceutical expenditure are the availability of new branded (patented) medicines and the patent expiry of medicines, which leads to the availability of low-cost generics and biosimilars³². Furthermore, Toumi and Rémuzat identified the following country-specific determinants of pharmaceutical expenditure: national demography and epidemiology; availability of alternatives on the national market; HTA requirements; cost-containment; and pricing policies³³.

Pharmaceutical spending has slowed down in many European countries in recent years, mainly due to the growing share of the generic market and cost-containment measures including reducing the prices of medicines³⁴.

According to the EU pharmaceutical expenditure forecast of 2012³⁵, the pharmaceutical market could likely continue to decrease because of 1) the increased use of generics, 2) the availability of biosimilars, and 3) increased requests for evidence of additional clinical and economic benefits during reimbursement and funding considerations, especially when requesting higher prices than current standards. More recently, the OECD has drawn attention to the long-term sustainability of pharmaceutical spending in light of new high-priced medicines, which target small populations and/or complex conditions, and may lead to a further rise in pharmaceutical spending³⁶.

Medicines may be used in the inpatient setting (e.g. hospitals, nursing and residential care facilities), and in the outpatient sector (mostly pharmacies and ambulatory healthcare). Subsequently, a distinction should be made between outpatient and inpatient pharmaceutical expenditure. On average, inpatient pharmaceutical expenditures are estimated to account for approximately 15% of the total pharmaceutical spending in European countries³⁷. In the Pharmaceutical Health Information System Hospital Pharma Report 2010, it was reported

³² Executive Agency for Health and Consumers, 2012, *Pharmaceutical expenditure forecast*, Final report, available at: http://ec.europa.eu/health/healthcare/docs/creativ_ceutical_eu_pharmaceutical_expenditure_forecast.pdf.

³³ Idem.

³⁴ OECD, 2015, *Health at a Glance 2015: OECD Indicators*, OECD Publishing: Paris.

³⁵ Executive Agency for Health and Consumers, 2012, *Pharmaceutical expenditure forecast*, Final report, available at: http://ec.europa.eu/health/healthcare/docs/creativ_ceutical_eu_pharmaceutical_expenditure_forecast.pdf.

³⁶ OECD, 2015, *Health at a Glance 2015: OECD Indicators*, OECD Publishing: Paris.

³⁷ Executive Agency for Health and Consumers, 2012, *Pharmaceutical expenditure forecast*, Final report, available at: http://ec.europa.eu/health/healthcare/docs/creativ_ceutical_eu_pharmaceutical_expenditure_forecast.pdf.

that less than one fourth of the pharmaceutical expenditure is spent in the inpatient sector³⁸. It is well-known that inpatient pharmaceutical expenditure is difficult to assess because of the different financing systems in European countries, with medicines used in hospitals usually funded out of hospital budgets and included in the Diagnosis Related Group (DRG) or DRG-like systems³⁹. In addition, there can be extensive discounts in the hospital sector. Subsequently, only data regarding outpatient pharmaceutical expenditure are taken into account in this report.

2.2. Sources of data

The online database OECD Health Statistics 2016⁴⁰ was the primary data source consulted to get data on pharmaceutical expenditure in the EU, followed by the European 'Health for all' database⁴¹. Data were collected for the EU28 MS, whenever possible and from 2005 to the last year available.

Pharmaceutical expenditure from the OECD includes spending on prescribed medicines and self-medication (often referred to as over-the-counter (OTC)) drugs⁴². It also includes pharmacists' remuneration when applicable, wholesale, retail margins and value-added tax (VAT)⁴³. For some countries, medical non-durable goods are also included⁴⁴.

Pharmaceutical expenditure may be evaluated through different indicators. The first one is represented by the amount of money spent on medicines per capita. However, inter-country comparisons can be difficult because of the exchange rates and the different economic situations across countries. This is why Power Purchasing Parities (PPPs) are increasingly used, as this reflects the relative price level in relation to the country's purchasing power. Differences in pharmaceutical spending per capita may reflect differences in volume, structure of consumption, clinical practice guidelines, and pharmaceutical prices⁴⁵. Furthermore, pharmaceutical spending can also be assessed with respect to the total health expenditure and to the GDP.

2.3. Total pharmaceutical expenditure in Euros/capita

Data on total pharmaceutical expenditure in PPPs US dollars/capita are available for all the countries except for Bulgaria, Croatia, Cyprus, Malta and Romania. Data are collected in terms of constant prices and constant PPPs, which means that PPPs are extrapolated starting from a fixed base year (2010). The use of constant PPPs allows capturing changes in volume but not in relative prices and is most used to analyse indicators across countries and over time. Data have been transformed in Euros taking into consideration the rates of conversion of PPPs for GDP (1 US dollar = 0.762604 Euro in 2010).

From 2005 to 2014 there was a mean increase of 0.1% in the pharmaceutical expenditure on average over all countries of which data were available (

Table 2). Nine countries showed an increase in pharmaceutical expenditure (mean: 17.6%; Min: 2.2%, United Kingdom (UK); Max: 42.7%, Latvia), while thirteen countries showed a decrease (mean: -12.0%; Min: -1.1%, Slovenia; Max: -34.9%, Portugal). The mean

³⁸ Vogler, S. et al., 2010, *PHIS Pharmaceutical Health Information System Hospital Pharma Report 2010*, available at: http://ec.europa.eu/health/healthcare/docs/phish_hospital_pharma_report_en.pdf.

³⁹ Vogler, S., Zimmermann, N. and Habi, C., 2013, *Understanding the components of pharmaceutical expenditure—overview of pharmaceutical policies influencing expenditure across European countries*, GaBI Journal, 2(4).

⁴⁰ OECD, 2016, *Health statistics*, available at: http://stats.oecd.org/index.aspx?DataSetCode=HEALTH_STAT.

⁴¹ WHO, 'Health For All' database, available at: <http://data.euro.who.int/hfad/>.

⁴² OECD, 2015, *Health at a Glance 2015: OECD Indicators*, OECD Publishing: Paris.

⁴³ Idem.

⁴⁴ OECD, 2016, *Pharmaceutical spending (indicator)*, available at: <https://data.oecd.org/healthres/pharmaceutical-spending.htm>.

⁴⁵ Idem.

expenditure across countries was €347.8/capita in 2014 (Min: €222.3, Estonia; Max: €517.1, Germany).

Table 2: Total pharmaceutical expenditure as PPPs Euros, 2010/capita (2005-2014)

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Δ%
Austria	388.8	397.0	417.1	429.3	399.3	399.6	404.6	405.2	402.5	416.6	7.1
Belgium	450.1	437.5	458.1	465.6	474.4	468.0	470.9	446.9	437.5	430.5	-4.4
Czech Republic	308.6	291.6	281.2	285.0	327.5	292.7	300.3	315.5	287.5	275.7	-10.7
Denmark	254.1	269.4	280.4	265.1	257.4	256.5	230.5	214.0	207.5	226.0	-11.1
Estonia	191.9	208.9	211.6	226.3	205.0	208.5	200.9	214.9	216.7	222.3	15.9
Finland	369.6	349.2	357.7	368.2	355.6	350.2	345.0	343.3	342.3	334.5	-9.5
France	486.2	481.8	485.0	481.9	485.6	481.4	478.9	466.9	455.7	462.2	-4.9
Germany	445.7	444.2	462.9	478.6	492.5	499.3	479.9	488.0	493.1	517.1	16.0
Greece	457.0	507.1	576.8	..	678.1	661.9	662.8	493.1	468.1	435.2	-4.8
Hungary	414.1	430.0	395.8	397.0	390.6	414.3	446.0	405.8	375.1	382.0	-7.7
Ireland	411.9	445.2	471.1	514.1	526.3	518.1	480.4	480.1	517.6	508.8	23.5
Italy	468.4	476.1	461.0	455.9	444.5	444.4	435.5	412.9	409.0	379.6	-19.0
Latvia	168.3	191.4	244.2	187.9	202.7	210.8	209.4	209.9	238.1	240.2	42.7
Lithuania	260.9	265.9	270.9	281.4	289.4	278.9	281.1	318.3	316.3	328.9	26.0
Luxembourg	352.7	337.6	344.7	332.4	334.8	323.0	258.3	256.0	253.2	248.8	-29.5
Netherlands	337.0	336.2	354.7	347.3	345.9	348.7	346.4	307.4	286.5	282.5	-16.2
Poland	219.1	224.8	224.1	235.7	249.7	248.8	251.7	234.3	238.1	238.6	8.9
Portugal	418.0	415.1	417.4	412.3	401.7	388.8	353.7	302.8	274.6	272.1	-34.9
Slovak Republic	327.6	345.6	378.5	397.4	418.3	427.0	410.2	395.9	395.7	379.7	15.9

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Δ%
Slovenia	335.8	343.9	333.5	342.2	353.2	357.8	354.6	362.9	361.7	332.1	-1.1
Spain	396.2	389.7	388.4	397.8	406.5	405.9	394.5	376.7	393.7	386.6	-2.4
Sweden	352.3	362.4	361.4	365.7	365.2	359.4	355.0	356.5	352.4	352.2	0.0
UK	340.2	347.7	2.2

2.4. Total pharmaceutical expenditure as percentage of total health expenditure (2005-2014)

Data on total pharmaceutical expenditure as percentage of total health expenditure are available for all the countries except for Bulgaria, Croatia, Cyprus, and Romania (Table 3). Data from Malta were collected through the WHO 'Health For All' database and were not available from the OECD. From 2005 to 2014, there was a decline by on average 2.9 percentage points in the pharmaceutical expenditure as percentage of total health expenditure (Min: -0.9, Austria; Max: -8.9, Poland). This contrasted with Greece, Latvia, Malta and the UK which showed an increase. The mean value across countries was 17.1% in 2014 (Min: 6.7%, Denmark; Max: 30.2%, Hungary).

Table 3: Total pharmaceutical expenditure as percentage of total health expenditure (2005-2014)

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Δ
Austria	13.3	13.4	13.6	13.6	12.5	12.4	12.5	12.2	12.1	12.4	-0.9
Belgium	17.1	16.5	16.8	16.4	15.9	15.7	15.5	14.6	14.1	13.8	-3.4
Czech Republic	25.7	23.5	22.2	20.9	22.1	20.4	20.4	21.5	19.7	17.1	-8.6
Denmark	8.6	8.7	8.9	8.3	7.6	7.7	7.0	6.5	6.3	6.7	-1.9
Estonia	24.0	23.8	21.7	21.6	20.0	20.5	19.9	20.2	19.4	18.8	-5.2
Finland	16.1	14.6	14.6	14.6	14.0	13.5	12.9	12.6	12.5	12.3	-3.8
France	17.6	17.3	17.3	17.0	16.6	16.4	16.0	15.5	15.0	15.0	-2.5
Germany	15.4	15.0	15.4	15.4	15.3	15.0	14.3	14.2	14.1	14.5	-1.0
Greece	22.3	23.6	25.8	..	29.7	30.4	34.8	29.3	28.4		+6.0
Hungary	31.3	32.0	31.6	31.9	32.9	33.3	35.0	32.6	30.3	30.2	-1.0
Ireland	15.5	16.5	16.4	16.0	15.1	14.8	14.4	14.1	14.5	14.1	-1.4
Italy	20.4	20.1	20.0	19.2	19.0	18.8	18.5	18.1	18.6	17.0	-3.4
Latvia	22.5	23.2	26.5	21.5	24.4	25.8	26.1	25.5	28.0	26.8	+4.3
Lithuania	34.3	31	28.5	26.1	26.7	26.7	26.0	28.9	28.2	27.8	-6.5

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Δ
Luxembourg	10.2	10.2	10.7	10.2	9.9	9.7	8.9	8.6	8.5	8.4	-1.8
Malta	14.6	15.7	16.4	17.6	17.6	18.1	19.4	18.0	18.3	..	+3.7
Netherlands	11.0	10.7	10.9	10.3	10.0	9.8	9.6	8.3	7.7	7.6	-3.4
Poland	29.8	28.8	26.5	24.6	24.6	24.3	24.1	22.3	21.5	20.9	-8.9
Portugal	22.1	22.3	22.1	21.2	20.2	19.3	18.4	16.6	15.6	15.4	-6.7
Slovak Republic	33.3	31.1	29.4	30.2	29.4	29.2	28.7	26.5	26.5	27.0	-6.3
Slovenia	21.3	21.1	20.1	19.1	19.7	19.8	19.6	20.2	20.4	18.6	-2.7
Spain	20.7	19.6	19.0	18.5	18.3	18.2	17.8	17.5	18.7	17.9	-2.7
Sweden	13.9	14.0	13.7	13.6	13.5	13.3	10.2	10.1	9.8	9.6	-4.3
UK	12.1	12.2	+0.1

2.5. Total pharmaceutical expenditure as percentage of gross domestic product (2005-2014)

Data on total pharmaceutical expenditure as percentage of GDP are available for all the countries except for Bulgaria, Croatia, Cyprus, Malta and Romania (Table 4). From 2005 to 2014, there was a decline of 0.12 percentage points on average (Min: -0.04, Estonia; Max: -0.70, Portugal), with the exception of Germany, Greece, Ireland, Latvia and Spain, which showed an increase and Austria and UK, which remained stable. In 2014, the mean value across countries was 1.41% ranging from 0.53% (Luxembourg) to 2.35% (Greece).

Table 4: Total pharmaceutical expenditure as percentage of GDP (2005-2014)

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Δ
Austria	1.28	1.27	1.29	1.31	1.27	1.25	1.24	1.23	1.23	1.28	0.00
Belgium	1.55	1.48	1.51	1.53	1.61	1.56	1.57	1.50	1.47	1.44	-0.11
Czech Republic	1.64	1.46	1.34	1.33	1.62	1.42	1.43	1.52	1.39	1.31	-0.33
Denmark	0.78	0.80	0.83	0.79	0.82	0.80	0.72	0.67	0.66	0.71	-0.07
Estonia	1.19	1.17	1.09	1.23	1.31	1.30	1.16	1.17	1.16	1.15	-0.04
Finland	1.29	1.17	1.15	1.18	1.25	1.20	1.16	1.17	1.18	1.17	-0.12
France	1.79	1.74	1.72	1.72	1.79	1.75	1.72	1.68	1.64	1.67	-0.12
Germany	1.58	1.52	1.53	1.56	1.70	1.65	1.53	1.53	1.54	1.60	+0.02

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Δ
Greece	2.01	2.12	2.34	..	2.90	2.99	3.30	2.63	2.56	2.35	+0.34
Hungary	2.51	2.51	2.30	2.28	2.40	2.52	2.66	2.45	2.21	2.17	-0.34
Ireland	1.18	1.24	1.28	1.45	1.59	1.57	1.43	1.43	1.52	1.42	+0.24
Italy	1.70	1.70	1.63	1.64	1.70	1.68	1.64	1.60	1.63	1.54	-0.17
Latvia	1.32	1.33	1.53	1.21	1.50	1.59	1.46	1.39	1.51	1.48	+0.15
Lithuania	1.94	1.81	1.64	1.64	1.96	1.82	1.69	1.82	1.73	1.73	-0.21
Luxembourg	0.74	0.69	0.67	0.68	0.74	0.69	0.55	0.57	0.55	0.53	-0.21
Netherlands	1.03	1.00	1.02	0.98	1.02	1.02	1.00	0.90	0.85	0.83	-0.20
Poland	1.74	1.68	1.56	1.58	1.63	1.56	1.51	1.38	1.38	1.34	-0.40
Portugal	2.08	2.04	2.01	1.98	1.99	1.89	1.75	1.56	1.42	1.39	-0.70
Slovak Republic	2.20	2.14	2.12	2.11	2.35	2.28	2.14	2.03	2.01	1.88	-0.32
Slovenia	1.70	1.65	1.50	1.50	1.69	1.70	1.68	1.77	1.78	1.59	-0.11
Spain	1.59	1.52	1.49	1.53	1.64	1.64	1.61	1.59	1.68	1.63	+0.04
Sweden	1.15	1.14	1.11	1.13	1.21	1.13	1.09	1.11	1.09	1.08	-0.07
UK	1.21	1.21	0.00

3. VALUE CHAIN OF MEDICINES AND APPROACHES TO INCREASE ACCESS TO MEDICINES

KEY FINDINGS

- The value chain of medicines consists of manufacturing the medicine, distributing and dispensing the medicine.
- In order for a pharmaceutical product to be placed on the market in Europe, MA is required. Despite the implementation of common frameworks to demonstrate the quality, safety and efficacy of a medicine, there remains fragmentation within the EU regarding marketing authorisation applications (MAA).
- Also, legislation with regard to the distribution of medicines needs to be reassessed as current legislation results in unnecessary costs that will increase the prices of medicines.
- There is an increasing request from health authorities and payers for real-world effectiveness and safety data of medicines. This has forced manufacturers to invest in the size, duration and design of their R&D plans for new medicines. These investments, however, do not necessarily lead to new medicines.
- New R&D models have been proposed to increase access to affordable (innovative) medicines, for example pharma-academic partnerships, biotech co-creation and innovation centres.
- To accelerate the decision-making processes in drug development, the adaptive pathways concept is seen as an innovative approach. Adaptive pathways aims to be a better compromise between patient access, evidence on a drug's risks and benefits, cost-effectiveness and returns on financial investment. Inherent to adaptive pathways is a higher degree of uncertainty at the point of MA in comparison with traditional licensing. Its real potential has to be shown through post-marketing studies.

3.1. Value chain

The pharmaceutical value chain consists of three main phases: manufacturing the medicine, distributing and dispensing the medicine. The manufacturing phase is characterised by R&D, registration and authorisation of medicines as well as quality assurance. Distribution focuses on the handling and delivery of the medicine as well as promotional and educational activities. Dispensing medicines is carried out by physicians and pharmacists⁴⁶. In this report, we mainly focus on the first two phases of the value chain.

3.1.1. Research & Development

Every medicine starts with basic research in which many compounds are screened in relation to their potential for treating new or existing conditions. In the preclinical testing phase, the number of relevant compounds is further reduced. Thereafter, clinical trials in patients are conducted⁴⁷. RCTs, i.e. studies that investigate the efficacy and safety of new medicines in humans, are important features of the pharmaceutical value chain and are required for MA.

⁴⁶ IMS Institute for healthcare informatics, 2014, *Understanding the pharmaceutical value chain*, available at: http://www.imshealth.com/imshealth/Global/Content/Corporate/IMS%20Health%20Institute/Insights/Understanding_Pharmaceutical_Value_Chain.pdf.

⁴⁷ International Federation of Pharmaceutical Manufacturers & Associations, 2011, *The pharmaceutical industry and global health: facts and figures*, available at: <http://www.ifpma.org/resource-centre/the-pharmaceutical-industry-and-global-health/>.

RCTs are performed in three developmental phases (so-called phase I/II/III trials)⁴⁸. In phase I trials, the safety of a medicine is tested among healthy volunteers. In phase II trials, the safety and efficacy of the medicine is tested among those with the disease. In phase III trials, more information is gathered on the safety and efficacy, using different dosages and different populations. The number of volunteers or patients testing the new medicine increases in each phase; from 20-100 in phase I, to 1,000-5,000 in phase III⁴⁹. To negotiate with the payers (such as health insurers) for subsequent reimbursement, so-called real-world effectiveness data gathered via phase IV trials or observational studies using patient registries are increasingly required by EU/MS legislations⁵⁰.

In the Pharmaceutical Sector Inquiry (2009)⁵¹, representatives of the pharmaceutical sector mentioned in a survey that an increasing volume of data is required during the evaluation procedure and that certain national authorities asked for duplicate assessments. Despite the current European regulatory framework, more coordination is requested by the pharmaceutical industry⁵².

R&D, as well as additional testing of a new therapy or product, is not arranged through one central body, but subject to partial harmonisation. MS individually control the regulation of RCTs, based on Council Directive 2001/20/EC⁵³. Although this Directive was intended to improve harmonisation of clinical trials, it raised several negative effects. It could not prevent a decline in the number of RCTs carried out, costs and delays of RCTs have doubled and, to date, it has been costly to conduct RCTs. In the R&D phase, it is clear that fragmentation exists because the MS are responsible for national regulation⁵⁴.

Because Directive 2001/20/EC did not achieve its goal to simplify and harmonise administrative provision governing clinical trials, the EP and the Council of the EU adopted Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use (repealing Directive 2001/20/EC) in 2014.

Despite several harmonisation initiatives set out in the Regulation, the majority of the authority for granting MA for new medicines remains at the individual MS level⁵⁵. According to the pharmaceutical industry, additional requirements posed by national competent authorities are some of the most important issues to be resolved. This issue is likely to remain, even after the enforcement of new European legislation on MA⁵⁶. This needs to be addressed in the future.

3.1.2. Market authorisation of medicines

In order for a new medicine to be placed on the market, MA is required for the targeted MS. There are several possibilities to receive MA for a new medicine.

As mentioned earlier (Chapter 1.3), the centralised procedure of MA came into operation in 1995. Via the centralised procedure, EMA grants MA of a product in all EU MS. In addition to

⁴⁸ <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm>.

⁴⁹ Idem.

⁵⁰ Annemans, L., Aristides, M. and Kubin, M., 2007, *Real-life data: A growing need*, ISPOR Connections, 13(5), p. 8-12.

⁵¹ European Commission, DG Competition, 2009, *Pharmaceutical Sector Inquiry*, final report, available at: http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf.

⁵² Idem.

⁵³ Mossialos, E., Mrazek, M. and Walley, T., 2004, *Regulating Pharmaceuticals In Europe: Striving For Efficiency, Equity And Quality*, European Observatory on Health Systems and Policies Series, McGraw-Hill Education: UK.

⁵⁴ Lezot, P.L., International Cooperation, 2013, *Convergence and Harmonization of Pharmaceutical Regulations - A Global Perspective*, Academic Press.

⁵⁵ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC [2014] OJ L158/1.

⁵⁶ Member state agreement upon conditions under which the RMS can start the MRP/DCP. CMDH/243/2001/Rev July 2013.

the central procedure, the national procedure exists. This consists of two options: the Mutual Recognition Procedure (MRP) and the DCP. Regarding the MRP, MA must be granted in a MS⁵⁷, which is called the Reference Member State (RMS). Via the RMS, regulatory authorities of other MS, called Concerned MS, could approve the medicine unless there are suspicions that the medicine could present a (high) risk for public health in the targeted MS. The MRP can only be used when there is a MA in at least one MS. If this is not the case, MA could be achieved through the DCP⁵⁸. A manufacturer could submit an application in a selected MS. In accordance with Article 17(2) of Directive 2001/83/EC on the Community code relating to medicinal products for human use⁵⁹, the MA for the same medicine cannot be granted in parallel in two or more MS by separate national procedures⁶⁰. In such cases, the DCP must be followed. In order to do so, the applicant has to request one MS to act as the RMS for the particular product⁶¹.

An MAA includes all administrative information and documentation that is necessary to demonstrate the quality, safety and efficacy of a medicine. A format that is internationally used for applications of medicines is the Common Technical Document (CTD)⁶². The CTD is quite coordinated and harmonised; however, MS are eligible to request additional data on issues of quality, safety, and efficacy when a national procedure (DCP and MRP) is used. Figure 1 depicts the European countries with additional national requirements. For example, countries including Bulgaria, Greece, Hungary, Poland, Portugal, Romania and Spain request a statement of MA transfer signed by all parties. In Hungary and Poland, declarations have to be made on packaging size and samples⁶³. Additional requests for such information can potentially delay the access and availability of medicines.

More than three quarters (77%) of the MA are currently submitted to competent authorities in Germany, Denmark, the UK and the Netherlands, because these MS are known for running an efficient operation. Although this does not create a fragmentation of the authorities, it results in an imbalance regarding the review of applications. This will eventually lead to delays of both the review and the product (potentially) reaching the market.

⁵⁷ Bachmann, P., 2013, *MRP & DCP step by step instructions how to apply and how the procedures are conducted*, EU 28: science, medicines, health, available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/05/WC500143592.pdf.

⁵⁸ Buanchetto, M.A., *Overview of Authorisation Procedures for Medicinal Products*, Regulatory Affairs Professionals Society, Chapter 17, available at:

http://www.raps.org/uploadedFiles/PDF_Assets/EU%20Fundamentals,%20Ch.%2017.pdf.

⁵⁹ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use, 28.11.2001, L 311/67.

⁶⁰ Bachmann, P., 2013, *MRP & DCP step by step instructions how to apply and how the procedures are conducted*, EU 28: science, medicines, health, available at:

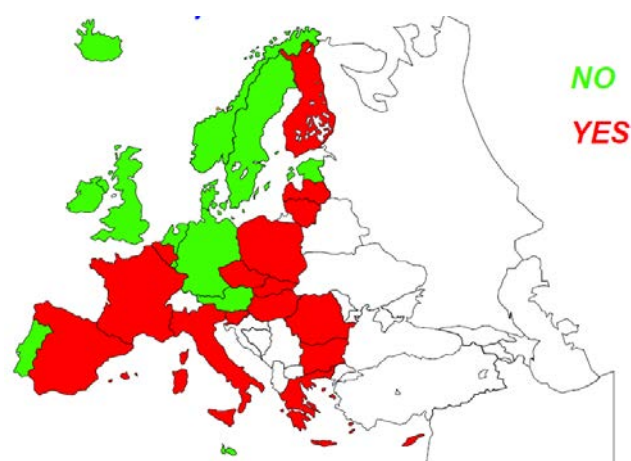
http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/05/WC500143592.pdf.

⁶¹ Buanchetto, M.A., *Overview of Authorisation Procedures for Medicinal Products*, Regulatory Affairs Professionals Society, Chapter 17, available at:

http://www.raps.org/uploadedFiles/PDF_Assets/EU%20Fundamentals,%20Ch.%2017.pdf.

⁶² Idem.

⁶³ Idem.

Figure 1: European countries with additional national requirements

Source: Bachmann⁶⁴.

3.1.3. Distribution of medicines

Distribution in the pharmaceutical value chain is also referred to as the supply chain of medicines. There are two pharmaceutical trader organisations at European level: the European Association of Pharmaceutical Full-line Wholesalers and the European Association of Euro-Pharmaceutical Companies for European parallel traders. However, no clear graphical display of the European pharmaceutical distribution chain is available. This makes it difficult for regulators and authorities to track the origin of a product. This could be a challenging task as the European pharmaceutical distribution system is extensive and, therefore, complex⁶⁵.

In general, regulation of the distribution of medicines in the EU has traditionally not been strong⁶⁶. Control of the supply chain was dependent on the judgement of the individual MS with the exception of Belgium, where clear requirements for the control of the supply chain of pharmaceutical and devices have been established. On 5 November 2013, legislation (Guidelines on Good Distribution Practice of Medicinal Products for Human Use)⁶⁷ was enacted to improve the situation. These guidelines were not received well by the pharmaceutical industry, as the new guidelines were judged to be overly burdensome and unrealistic⁶⁸. An example concerns the guideline to ship all pharmaceutical products in controlled temperature conditions⁶⁹. Despite the opinions of the stakeholders, this part of the value chain is now covered by clear EU-wide legislation. This legislation needs to be reassessed, as it results in

⁶⁴ Bachmann, P., 2013, *MRP & DCP step by step instructions how to apply and how the procedures are conducted*, EU 28: science, medicines, health, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/05/WC500143592.pdf.

⁶⁵ European Alliance for Access to Safe Medicines, 2013, *European supply chain complexity and confusion*, Patient Safety Rapport, Final Version, 2013, available at: http://www.eaasm.eu/cache/downloads/ab6tbljcsbkk4088048ko48sw/Patient_safety_report_FINAL%20VERSION%20p2.pdf.

⁶⁶ Idem.

⁶⁷ European Commission, 2013, *Information from European institutions, bodies, offices and agencies. Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use*, OJ C343/1.

⁶⁸ O'Donnell, P., 2012, *Europe's planned rules on drug distribution provoke industry accusations of red tape*, available at: <http://www.girp.eu/sites/default/files/documents/APM%20News-%20Europe's%20planned%20rules%20on%20drug%20distribution%20provoke%20industry%20accusations%20of%20red%20tap.pdf>.

⁶⁹ European Commission, 2013, *Information from European institutions, bodies, offices and agencies. Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use*. OJ C343/1.

unnecessary costs that will increase the prices of medicines (current margins in the distribution chain are discussed further in Chapter 4.2).

3.2. R&D models

The R&D models that are used by pharmaceutical companies have changed over the last 35 years. In the 1980s, companies typically used a centralised model. In this model, the medicine was developed in the headquarters of a pharmaceutical company. The R&D laboratories in each country, in which the medicine was meant to be sold, were in charge of the technology transfer and had to adapt the medicine based on local market demands. In the 1990s, there was a shift towards polycentric structures. This implies that the majority of the development of medicines was still performed at the headquarters of a pharmaceutical company; however, the local R&D laboratories became more (financially) independent and involved in research activities of their own. In the late 1990s, the independence of the R&D laboratories increased even more⁷⁰.

3.2.1. Key issues regarding current R&D models

Nowadays, real-world data are increasingly requested to determine the effectiveness of (innovative) medicines, gathered either via phase IV RCTs or observational studies using patient registries⁷¹. Consequently, pharmaceutical companies are increasingly forced to invest in size, duration and design of their R&D plans for new medicines. Investments in size and design of RCTs, which lead to rising R&D costs, are also driven by an increase in reporting requirements. This is mainly based on concerns regarding the safety or efficacy of other (similar) medicines. RCTs have to be more comprehensive to determine a clear effect size of a new medicine in comparison with (an) existing one(s). The R&D costs per Newly approved Molecular Entity (NME) have increased eightfold in the last 40 years. Development of a new medicine during clinical trials is now almost twice as expensive as pre-clinical research in which preliminary safety, among others, is investigated. In the 1970s, this situation was reversed⁷². These increased investments in R&D do not necessarily lead to an increase in new medicines; the number of newly approved medicines per year remains stable⁷³. As the pharmaceutical industry is dependent on the revenues from the sales of their medicines, they will adapt their prices accordingly. This may mean in some situations that R&D money is spent on the development of me-too medicines, also called follow-on medicines (i.e. medicines that are similar to pre-existing medicines, or medicines without added value to the patient), instead of on the development of new innovative medicines for areas of unmet medical need⁷⁴. By producing me-too medicines, companies reduce the market shares of their competitors, while lowering their own risks of failure inherent in the development of new, innovative medicines.

3.2.2. New R&D models to increase access to affordable medicines

New models of R&D need to be introduced to increase access to affordable (innovative) medicines. A non-exhaustive overview of such models and other relevant developments, mainly focussed on increased R&D productivity, is provided below. For a discussion of pricing issues that influence access to medicines, please refer to Chapter 4.

⁷⁰ Saur-Amaral, I. and Gouveia, J.J.B., 2007, *International R&D models applied to pharmaceutical industry: a preliminary outline of results*, available at: <http://www2.druid.dk/conferences/viewpaper.php?id=1861&cf=28>.

⁷¹ Annemans, L., Aristides, M. and Kubin, M., 2007, *Real-life data: A growing need*, ISPOR Connections, 13(5), p. 8-12.

⁷² Scannell, J.W., Hinds, S. and Evans, R., 2015, *Financial Returns on R&D: Looking Back at History, Looking Forward to Adaptive Licensing*, *Reviews on Recent Clinical Trials*, 10, p. 28-43.

⁷³ Morozova, A.H., and Stevenson, D., 2012, *R&D: pharmaceutical development – adapting to the future*, *Regulatory Rapporteur*, 9(10), p. 3.

⁷⁴ Hollis, A., 2004, *Me-too drugs: is there a problem?*, available at: http://www.who.int/intellectualproperty/topcis/ip/Me-tooDrugs_Hollis1.pdf.

a. New partnerships to access new sources of innovation

Traditionally, collaboration between researchers (academia) and pharmaceutical companies did not reach its full potential due to cultural differences (scientifically-driven research questions vs. profit-driven practices). This situation is currently changing with a growing realisation that there is a common interest: to provide better treatment and care to patients⁷⁵. Public-private partnerships, that bridge the translational gap, must be properly funded, and the rewards must be shared equitably to make these partnerships work.

Pharmaceutical companies already collaborate with public entities such as the EC, or national governments. The largest public-private partnership is the European Innovative Medicines Initiative (IMI), which is focused on improving the efficiency and effectiveness of the R&D of medicines in Europe⁷⁶. IMI was established in 2009 as a partnership between the EC and the EFPIA. In this partnership, important players such as universities, pharmaceutical companies, Small and Medium-size Enterprises (SMEs), patient organisations and medicines regulators are brought together to strengthen Europe's competitiveness in the pharmaceutical sector and make it more attractive for R&D investments. Such initiatives increase transparency and demand-driven R&D.

Another example of a public-private partnership is the creation of academic centres of excellence. Through these centres, agreements between a pharmaceutical company and one or more universities provide sustainable relations with leading academic researchers⁷⁷.

b. Innovation centres

Innovation centres are typically set up by pharmaceutical companies in life science parks (where universities and SMEs are also located) to facilitate collaborations with academic and entrepreneurs⁷⁸. Examples in Europe include innovation centres that are based in London (Johnson & Johnson) and in Berlin (Bayer).

c. Biotech co-creation

Venture capital funds of pharmaceutical companies are used to invest in biotech start-ups, but also in-kind, to support innovation. The benefits of such a co-creation are twofold: pharmaceutical companies benefit from the efficiency of the start-ups, while the start-ups benefit from the capabilities of large pharmaceutical companies.

d. Open crowdsourcing

A precompetitive innovation model that is used by a number of pharmaceutical companies to stimulate R&D is open crowdsourcing, also called open innovation. Companies communicate specific challenges related to R&D to an unknown group ('the crowd'), usually researchers from academic institutes or SMEs. Once solutions have been found, the organisations provide the 'solver' with a financial reward in return for the transfer of the IP. Initiating such collaboration in the early stages of drug development will result in increased innovation and will increase the translational potential of fundamental scientific research⁷⁹.

Crowdsourcing can also be part of a so-called not-for-profit 'parallel drug development track'⁸⁰. This means that governments first investigate which healthcare priorities must be

⁷⁵ Tralau-Stewart, C.J. et al., 2009, *Drug discovery: new models for industry-academic partnerships*, Drug Discovery Today, 14(1), p. 95-101.

⁷⁶ www.imi.europa.eu

⁷⁷ Wang, L., Plump, A., and Ringel M., 2015, *Racing to define pharmaceutical R&D external innovation models*, Drug Discovery Today, 20(3), p. 361-370.

⁷⁸ Idem.

⁷⁹ Lessl, M. et al., 2011, *Crowd sourcing in drug discovery*, Nature Reviews Drug Discovery, 10(4), p. 241-242.

⁸⁰ Vandenbroeck, P. et al., 2016, *Future scenarios about drug development and drug pricing*. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). KCE Reports 271. D/2016/10.273/59.

addressed. Areas of interest might especially be those in which industry is not keen to invest in, e.g. antibiotics or paediatric medicines. Public institutes are subsequently asked whether they have the tools and capabilities to solve the needs identified. Coalitions are formed, in which research institutes, payers, national authorities and patient organisations collaborate in demand-driven research projects. This form of collaboration is called parallel track because medicines are being developed in competition with the pharmaceutical industry. Prices of medicines are expected to be lower because the costs, e.g. marketing and high salaries and/or bonuses, will be absent. IP rights might be shared between the coalition members, or even become irrelevant when certain developments are not protected.

e. Pharmaceutical peer-shared risk partnerships

Pharmaceutical companies work in parallel on the discovery and development of medicines for the same disease in so-called peer-shared risk partnerships. Consequently, companies might encounter the same failures, resulting in considerable financial losses. If companies join forces, these losses may be redundant. However, because of the competitive nature that is inherent to the pharmaceutical industry, a real profit-sharing partnership is complex. Consequently, other partnerships such as partnerships with public institutes, are more common⁸¹.

f. Initiatives to enhance antibiotics R&D

The development of new antibiotics is urgently needed given the increase in antimicrobial resistance (AMR). In response, numerous R&D initiatives, of which many are based on partnerships between different stakeholders, are ongoing and these initiatives require coordination to ensure that unmet medical needs are targeted. Most initiatives are based on 'push' mechanisms (such as tax incentives, research grants, and product development partnership) while 'pull' mechanisms that reward the successful development of a medicine (such as patent buyouts or monetary prizes) are used to a lesser extent. This leads to a situation where the focus of R&D is shifted towards basic research and early drug development. For an extensive overview of gaps in the European R&D agenda for antibiotics, and recommended solutions, please refer to the report of the 2016 Dutch Presidency of the EU⁸². Some of these points are further discussed in Chapter 7.5.1.

3.3. Accelerated availability of medicines

3.3.1. Adaptive pathways

Since traditional assessments of medicines do not always provide the mechanism to continuously monitor new evidence on the safety and efficacy of a medicine, innovative methods could be developed by focussing on access for a certain population when granting provisional (conditional) reimbursement for a new medicine⁸³. The adaptive pathways concept is seen as an approach to accelerate the decision-making processes in drug development. However, there are also concerns.

Adaptive pathways are defined as "prospectively planned, flexible approach to regulation of medicines and biologics" that follows iterative phases of data gathering to "reduce

⁸¹ Wang, L., Plump, A., and Ringel M., 2015, *Racing to define pharmaceutical R&D external innovation models*, Drug Discovery Today, 20(3), p361-370.

⁸² Renwick, M.J., Simpkin, V. and Mossialos, E., 2016, *International and European Initiatives Targeting Innovation in Antibiotic Drug Discovery Development. The Need for a One Health – One Europe – One World Framework*, Report for the 2016 Dutch Presidency of the European Union, available at: <https://english.eu2016.nl/documents/reports/2016/02/10/2016-report-on-antibiotic-rd-initiatives>.

⁸³ Eichler, H.G. et al., 2015, *From adaptive licensing to adaptive pathways: Delivering a flexible life-span approach to bring new drugs to patients*, Clin Pharmacol Therap, 97(3), p. 234-246.

uncertainties, followed by regulatory evaluation and license adaptation"⁸⁴. With adaptive pathways, the regulatory decision is shifted to an earlier phase in drug development. This means that a medicine can be temporarily authorised to enter the market when it has demonstrated initial safety and efficacy. Subsequently, further evidence should be developed according to a proactive plan which needs to be drafted by both the manufacturer and the regulator⁸⁵. In this way, a pre-defined incremental regulation process is created in which the initial license will be continually revised and supported by additional evidence, instead of a definitive decision at one point in time. Adaptive pathways build on ongoing developments within countries to monitor the effectiveness and safety of new medicines in routine clinical care (Chapter 5.9). They aim for a better compromise between patient access (especially for medicines that address conditions with an (high) unmet medical need), evidence on a medicine's risks and benefits, cost-effectiveness and returns on financial investment⁸⁶.

The success of adaptive pathways depends on the collaboration of major stakeholders including patients, healthcare providers, payers, and regulators. Those stakeholders have to be aligned on the extent of risk and uncertainty that is acceptable when taking into account a medicine's benefit and safety⁸⁷. Inherent to adaptive pathways is a higher degree of uncertainty at the point of MA in comparison with traditional licensing. The uncertainty surrounding the potential cost and cost-effectiveness estimates (QALY⁸⁸, Chapter 0) has a wider range in preliminary phases of medicine development. This could make decision-making with adaptive pathways more complex for new medicines. To counter this, preliminary checks could be implemented along the process and after approval is granted. This could provide a complex scenario for price discussions, especially when a manufacturer is convinced of the benefit-risk profile of their new medicine and wants a premium price. The payer may prefer a price in line with the uncertainty surrounding the value and potential budget impact of the new medicine until this becomes clearer (managed entry agreements (MEAs), Chapter 5.6). In addition, there are concerns about potential lower standards regarding safety and efficacy. It would be beneficial for society to find a reward system that provides the right incentives to the manufacturer for drug development whilst acknowledging payer issues over affordability and access as well as patient safety issues. Patient safety issues include researching the new medicine in wider, more co-morbid populations until more clinical data becomes available.

In order to make adaptive pathways work, post-marketing studies have to be performed in clinical settings. If the new medicine does not provide the envisaged patient benefits, price re-evaluation should occur. In this process, a new post-marketing study is performed when the previous one has finished and valuable data is collected, safety is monitored and uncertainty regarding the new medicine is decreased. From previous studies, however, it is known that these commitments are hard to meet, as many post-surveillance studies are not

⁸⁴ Idem.

⁸⁵ Tsoi, B., 2013, *Panel Discussion. Possibilities for harmonization of HTA and regulator processes and evidentiary requirements in Canada*. Presentation, Edmonton, available at: [https://www.cadth.ca/media/symp-2013/2013-presentations/A4%20-%20CADTH%20Harmonization%20Panel%20Presenation%20\(2013-05-05\)%20FINAL%20-%20Salon%20B%20\(Chander%20Sehgal%20Section%20Removed\).pdf](https://www.cadth.ca/media/symp-2013/2013-presentations/A4%20-%20CADTH%20Harmonization%20Panel%20Presenation%20(2013-05-05)%20FINAL%20-%20Salon%20B%20(Chander%20Sehgal%20Section%20Removed).pdf).

⁸⁶ Rosano, G.M.C. et al., 2015, *Adaptive licensing — A way forward in the approval process of new therapeutic agents in Europe*, *Clinical Trials and Regulatory Science in Cardiology*, 1, p. 1–2.

⁸⁷ Eichler, H.G. et al., 2012, *Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval*, *Nature*, 91(3), p. 426-437.

⁸⁸ A QALY refers to the additional life years associated with a new medicine versus existing standards adjusted by the quality of life for that year with 1 equal to perfect health and zero equalling death.

started, completed or ended before scheduled completion^{89,90,91}. This needs to be addressed for in order for adaptive pathways to become commonplace in the future.

3.3.2. Other initiatives

Another development that is aimed at improving access to innovative medicines to patients is *PRIority Medicines (PRIME)*. PRIME is a voluntary scheme that was launched by the EMA in March 2016⁹². PRIME is based on early dialogue between EMA and the companies of promising medicines to improve RCT design in order to generate better data on the benefit and risks of new medicines to accelerate their evaluation by EMA and payers.

There are also several other initiatives at MS level to accelerate early access and funding of new medicines. Initiatives include conditional MA, risk management plans, periodic safety update reports, five-year renewal of MA, compassionate use programmes, staggered approval, conditional licensing and progressive approval. Some of these proposals contain elements of adaptive pathways⁹³.

Several countries have implemented an alternative to the traditional licensing system. French authorities, for instance, allow temporary authorisations (TAU) for unlicensed medicines in certain instances⁹⁴. In the UK, an 'Early Access to Medicines' scheme was implemented for medicines for which there is not yet an outcome on the regulatory decision⁹⁵. In the EU, conditional MA and risk management plans are applied to provide earlier access to patients with unmet medical needs.

⁸⁹ Eichler, H.G. et al., 2012, *Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval*, *Nature*, 91(3), p. 426-437.

⁹⁰ Barker, R.W. and Garner, S., 2015, *Realising the potential of adaptive development of medicines*, *Reviews on Recent Clinical Trials*, 10, p. 19-24.

⁹¹ Eichler, H.G., *Adaptive licensing a useful approach for drug licensing in the EU?*, 2012, EMA: London, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2012/04/WC500124930.pdf.

⁹² Enhanced early dialogue to facilitate accelerated assessment of PRIority Medicines (PRIME) http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202636.pdf

⁹³ Barker, R.W., 2012, *Adaptive drug development and licensing*, *Regulatory Rapporteur*, 9(10), p. 13-15.

⁹⁴ Barker, R.W. and Garner, S., 2015, *Realising the potential of adaptive development of medicines*, *Reviews on Recent Clinical Trials*, 10, p. 19-24.

⁹⁵ Idem.

4. KEY FACTORS INFLUENCING PRICES OF MEDICINES

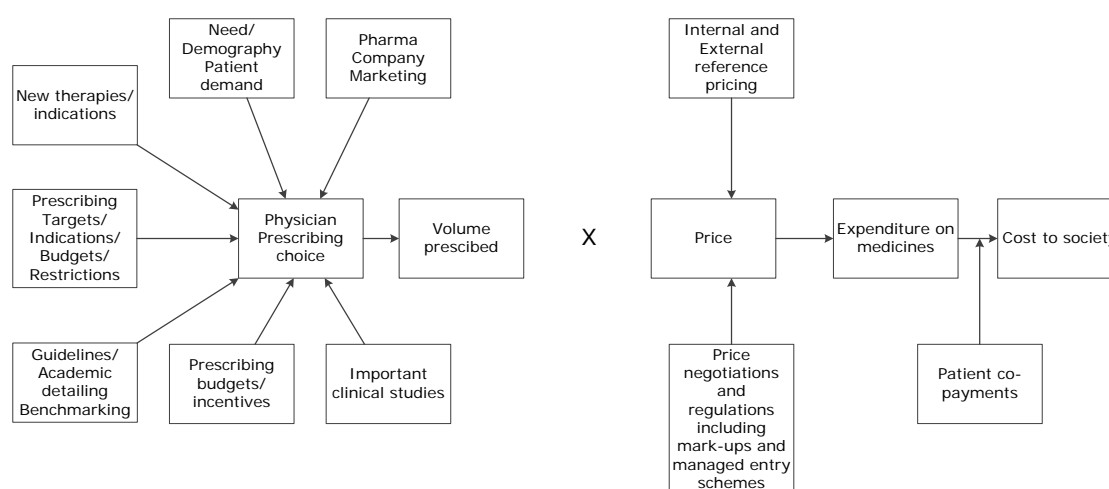
KEY FINDINGS

- The prices of medicines has been an important factor in the growth of overall healthcare expenditure in the past decades, leading to greater scrutiny over their prices, including distribution costs.
- There is considerable variation in the prices of generics across the EU, which is unsustainable, while there is less variation in the prices of new (patented) medicines with most European countries referencing others.
- There are concerns with the prices of new medicines, especially those for cancer and orphan diseases. As a result, EU MS are increasingly entering into MEAs including confidential discounts in order for new medicines to be reimbursed.
- There are also developments in proposed pricing strategies for new cancer medicines and those for orphan diseases, including establishing minimum effectiveness criteria as well as multi-criteria decision frameworks.
- There have been considerable differences in the pricing of new medicines to treat patients with HCV. This has resulted in discussions regarding affordability given the potential budget impact of these medicines as well as the development of consortia to better manage their entry and price.
- There will be growing use of biosimilars in the future as prices fall and concerns with their effectiveness and safety are addressed through educational and other activities.

4.1. Introduction

This chapter provides an overview of key factors that influence the prices of medicines.

Figure 2: Key factors influencing pharmaceutical expenditure



Source: Adapted from Godman et al.⁹⁶.

⁹⁶ Godman, B. et al., 2009, *Multifaceted national and regional drug reforms and initiatives in ambulatory care in Sweden*; global relevance, Expert Rev Pharmacoeconomics Outcomes Research, 9, p. 65-83.

Prices of medicines are important within healthcare, as pharmaceutical expenditure has been a major contributor to the overall growth of healthcare expenditure during the past years⁹⁷. Even high income countries are now struggling to fund new premium-priced medicines, including new therapies to treat patients with cancer, HCV and those with orphan diseases^{98,99,100,101}. Unless key issues are addressed, the number of European countries struggling to finance both new and existing medicines, given the extent of unmet need, will grow^{102,103,104}. Consequently, prices of current and future medicines in Europe are of prime importance to all key stakeholders in Europe. Having said this, prices of medicines do vary considerably across Europe. This includes new medicines for patients with HCV¹⁰⁵. When discussing prices of medicines, it is important to acknowledge that prices of medicines will differ according to the particular price component in question, e.g. ex-factory prices, being prices of medicines leaving the manufacturer, wholesale prices or the pharmacy price¹⁰⁶ (Chapter 4.2).

Prices of medicines will continue to differ among MS depending on their price-setting mechanisms for patented medicines (new and existing medicines), as well as those that have lost their patent, e.g. generics and biosimilars. This is because each MS regulates directly or indirectly their medicine prices through a variety of different mechanisms. Mechanisms can include caps on profits, pricing directives including ERP (Chapter 4.3.1) and compulsory price cuts^{107,108,109,110,111,112,113}.

⁹⁷ Barnieh, L. et al., 2014, *A synthesis of drug reimbursement decision-making processes in organisation for economic co-operation and development countries*, Value in health, 17(1), p. 98-108.

⁹⁸ Hofmarcher, T., Jönsson, B. and Wilking, N., 2014, *Access to high-quality oncology care across Europe*, IHE Report, 2, IHE: Lund, available at: <http://www.ihe.se/getfile.aspx?id=23042014>.

⁹⁹ Brennan, T. and Shrank, W., 2014, *New expensive treatments for hepatitis C infection*, JAMA, 312(6), p. 593-594.

¹⁰⁰ Simoens, S. et al., 2013, *Cost-effectiveness assessment of orphan drugs: a scientific and political conundrum*, Applied health economics and health policy, 11(1), p. 1-3.

¹⁰¹ Godman, B. et al., 2015, *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?*, Expert review of clinical pharmacology, 8(1), p. 77-94.

¹⁰² Malmstrom, R.E. et al., 2013, *Dabigatran - a case history demonstrating the need for comprehensive approaches to optimize the use of new drugs*, Frontiers in pharmacology, 4, p. 39.

¹⁰³ Kaplan, W. et al., 2013, *Priority Medicines for Europe and the World 2013 Update*, WHO Report, available at: http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf?ua=1.

¹⁰⁴ Mousnad, M.A., Shafie, A.A. and Ibrahim, M.I., 2014, *Systematic review of factors affecting pharmaceutical expenditures*, Health policy, 116(2-3), p. 137-146.

¹⁰⁵ Iyengar, S. et al., 2016, *Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis*, PLoS medicine, 13(5):e1002032.

¹⁰⁶ Vogler, S., Zimmermann, N. and Hahl, C., 2013, *Understanding the components of pharmaceutical expenditure - overview of pharmaceutical policies influencing expenditure across European countries*, GaBI Journal, 2(3), p. 178-187.

¹⁰⁷ Vogler, S., 2012, *The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries - an overview*, GaBI, 1(2), p. 93-100.

¹⁰⁸ COM(2013) 168 final. Amended proposal for a Directive of the European Parliament and the council on the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of public health insurance systems.

¹⁰⁹ Dylst, P., Vulto, A. and Simoens, S., 2014, *Analysis of European policy towards generic medicines*, GaBI Journal, 3(1), p. 34-35.

¹¹⁰ Mack, A., 2015, *Norway, biosimilars in different funding systems. What works?*, GaBI Journal, 4(2), p. 90-92.

¹¹¹ Leopold, C. et al., 2012, *Differences in external price referencing in Europe: a descriptive overview*, Health policy, 104(1), p. 50-60.

¹¹² Van Wilder, V. et al., 2015, *Towards a harmonised EU assessment of the added therapeutic value of medicines, study for the ENVI Committee*, available at: [http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU\(2015\)542219_EN.pdf](http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU(2015)542219_EN.pdf).

¹¹³ Paris, V. and Belloni, A., July 2013, *Value in Pharmaceutical Pricing*, OECD Health Working Paper, No 63, OECD Publishing: Paris.

Compulsory price cuts or freezes are typically instigated in response to budgetary pressures^{114,115}. Such practices tend to be greater in times of economic recession. Other pricing approaches in times of recession include increasing out-of-pocket expenditure (patient co-payment), which can negatively impact on access and affordability of medicines¹¹⁶.

The different mechanisms for pricing generics in Europe have resulted in the prices of some generics varying by 36 times or more across countries¹¹⁷, with the prices of some generic medicines as low as 2% to 4% of the pre-patent loss price of the originator (brand) medicine^{118,119}.

Overall, there is less variation in the prices for patented medicines among European countries compared with generics. This is due to the increasing use of ERP among European countries when setting prices^{120,121} (Chapter 4.3.1). Examples include biological medicines to treat patients with Rheumatoid Arthritis (RA), where prices varied between €10,760.9 and €21,349.2 per patient per year among the 28 EU MS with an average of €14,200.5. There has also been a price difference of only 146% for abacavir to treat patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) among European countries and between €458 to €782 for a 150mg vial of trastuzumab to treat patients with breast cancer^{122,123,124}. Recent research has shown that the prices of ten patented medicines, including less expensive and more expensive medicines, among 15 European countries remained relatively stable or decreased in recent years in Europe, i.e. between 2007 and 2012. However, prices in Germany were up to 27% more expensive than the average, and prices in Greece up to 32% cheaper than the average¹²⁵.

Recent studies have also shown that European countries with a high GDP per capita, e.g. Norway, the Netherlands, Finland, Austria and Belgium, tend to have higher ex-factory prices among a range of patented products versus European countries with a lower GDP per capita such as Spain, Greece and Portugal. The presence of external referencing pricing policies typically results in lower prices for medicines. Price differences between the originator

¹¹⁴ European Commission. et al., 2012, *Cost-containment policies in public pharmaceutical spending in the EU*, Economic Papers 461, available at: http://ec.europa.eu/economy_finance/publications/economic_paper/2012/pdf/ecp_461_en.pdf.

¹¹⁵ Leopold, C. et al., 2014, *Effect of the economic recession on pharmaceutical policy and medicine sales in eight European countries*, Bulletin of the World Health Organization, 92(9), p. 630-640d.

¹¹⁶ Maimaris, W. et al., 2013, *The influence of health systems on hypertension awareness, treatment, and control: a systematic literature review*, PLoS medicine, 10(7):e1001490.

¹¹⁷ Simoons, S., 2007, *International comparison of generic medicine prices*, Current medical research and opinion, 23(11), p. 2647-2654.

¹¹⁸ Godman, B. et al., 2009, *Multifaceted national and regional drug reforms and initiatives in ambulatory care in Sweden: global relevance*, Expert review of pharmacoeconomics & outcomes research, 9(1), p. 65-83.

¹¹⁹ Woerkom, M. et al., 2012, *Ongoing measures to enhance the efficiency of prescribing of proton pump inhibitors and statins in The Netherlands: influence and future implications*, Journal of comparative effectiveness research, 1(6), p. 527-538.

¹²⁰ Leopold, C. et al., 2012, *Differences in external price referencing in Europe: a descriptive overview*, Health policy, 104(1), p. 50-60.

¹²¹ European Commission, 2012, *Cost-containment policies in public pharmaceutical spending in the EU*, Economic Papers 461, available at: http://ec.europa.eu/economy_finance/publications/economic_paper/2012/pdf/ecp_461_en.pdf.

¹²² Vogler, S., Kilpatrick, K. and Babar, Z., 2015, *Analysis of medicine prices in New Zealand and 16 European Countries*, Value in health, 18(4), p. 484-492.

¹²³ Putrik, P. et al., 2014, *Inequities in access to biologic and synthetic DMARDs across 46 European countries*, Annals of the rheumatic diseases, 73(1), p. 198-206.

¹²⁴ Leopold, C. et al., 2013, *Personalised medicine as a challenge for public pricing and reimbursement authorities - A survey among 27 European countries on the example of trastuzumab*, Health policy, 113(3), p. 313-322.

¹²⁵ Idem.

(brand) medicines and generic versions ranged from 0% to 90% depending on the medicine and the country¹²⁶.

Other published studies have shown similar prices between countries with similar income levels¹²⁷, as well as higher prices for patented medicines in the US versus key European and OECD countries¹²⁸. However, there are also studies showing no consistency between the level of income of a country and the prices of medicines in that country¹²⁹. On balance, European countries with a higher GDP per capita tend to have higher prices for patented medicines. However, this is not the case for generics. Prices of generics will depend on the mechanisms within the country to lower these, with prices typically lower in countries with greater use of generics irrespective of their GDP per capital¹³⁰.

Prices can also vary considerably across healthcare sectors. Within the hospital sector, greater price reductions, including providing medicines free of charge, are typically granted for patients whose treatment is likely to continue in ambulatory care, i.e. after patients are discharged from hospital¹³¹. In this case, the full cost of the medicine is paid by the ambulatory care health authority. Consequently, justifying the approach by pharmaceutical companies to offer their medicines to hospitals at low prices or free of charge.

As a result, there can be appreciable price differences for the same molecule between hospital and ambulatory care sectors, depending on the level of discounts within hospitals^{132,133}, of an originator (brand medicine) or a generic^{134,135}. However, these developments, including MEAs (Chapter 5.6), make it increasingly difficult to document the actual prices paid for medicines, especially new medicines, among European countries compared with list prices within Intercontinental Marketing Services (IMS) databases. This must be acknowledged when reviewing the prices of medicines across countries.

Tendering programmes are also growing in ambulatory care, with price reductions appearing greater for medicines procured by central tendering processes than those obtained through decentralised procurement processes¹³⁶. At least seven European countries have now instigated tendering programmes in this sector¹³⁷, with tendering more popular in countries with a mature generic medicines market compared with those European countries with developing generic medicines markets. Central tendering procurement initiatives include (i) a public tendering system for simvastatin in Belgium, (ii) two-weekly assessments of prices for multiple-sourced products in Denmark, (iii) monthly tendering for generics in Sweden

¹²⁶ Leopold, C. et al., 2012, *Impact of external price referencing on medicine prices - a price comparison among 14 European countries*, Southern med review, 5(2), p. 34-41.

¹²⁷ Cabrales, A. and Jimenez-Martin, S., 2013, *The determinants of pricing in pharmaceuticals: are US prices really so high?*, Health economics, 22(11), p. 1377-1397.

¹²⁸ Kanavos, P. et al., 2013, *Higher US branded drug prices and spending compared to other countries may stem partly from quick uptake of new drugs*, Health affairs, 32(4), p. 753-761.

¹²⁹ Morel, C.M., McGuire, A. and Mossialos, E., 2011, *The level of income appears to have no consistent bearing on pharmaceutical prices across countries*, Health affairs (Project Hope), 30(8), p. 1545-1552.

¹³⁰ Dylst, P. and Simoens, S., 2011, *Does the market share of generic medicines influence the price level? a European analysis*. PharmacoEconomics, 29(10), p. 875-82.

¹³¹ Vogler, S. et al., 2013, *Discounts and Rebates Granted for Medicines for Hospital Use in Five European Countries*, The Open PharmacoEconomics & Health Economics Journal, 5, p. 1-10.

¹³² Vogler, S. et al., 2012, *Discounts and rebates granted to public payers for medicines in European countries*, Southern med review, 5(1), p. 38-46.

¹³³ Vogler, S. et al., 2013, *The role of discounts and loss leaders in medicine procurement in Austrian hospitals - a primary survey of official and actual medicine prices, Cost effectiveness and resource allocation*, 11(1), p. 15.

¹³⁴ Vogler, S., 2012, *How large are the differences between originator and generic prices? Analysis of five molecules in 16 European countries*, Farmeconomy. Health economics and therapeutic pathways, 13(suppl 3), p. 29-41.

¹³⁵ Vogler, S., Kilpatrick, K. and Babar, Z.U.D., 2015, *Analysis of medicine prices in New Zealand and 16 European Countries*, Value in health, 18(4), p. 484-492.

¹³⁶ Matusewicz, W. et al., 2015, *Improving the managed introduction of new medicines: sharing experiences to aid authorities across Europe*, Expert review of pharmacoEconomics & outcomes research, 15(5), p. 755-758.

¹³⁷ Dylst, P., Vulto, A. and Simoens, S., 2011, *Tendering for outpatient prescription pharmaceuticals: what can be learned from current practices in Europe?*, Health policy, 101(2), p. 146-152.

(with the winning company guaranteed a substantial proportion of prescriptions for the molecule the following month), (iv) three to six-monthly tendering in the Netherlands and yearly tendering in Germany, Latvia and New Zealand^{138,139,140,141}. The monthly tendering for multiple-sourced products in Sweden is expected to lower generic prices further (previously 4% to 10% of pre-patent loss prices for high volume generics¹⁴²), which is occurring in practice¹⁴³.

Tendering programmes can achieve savings in the short term. For instance, the introduction of the tender-like 'preference policy' for off-patent (generic) medicines in the Netherlands reduced pharmaceutical expenditure by €0.75 to €0.90 billion over five years¹⁴⁴. Savings realised through tenders and rebate contracts in Germany amounted to €2.09 billion in 2012¹⁴⁵. However, whilst such policies do achieve savings, the effects of long-term tendering are still unclear¹⁴⁶. This includes the potential for shortages of medicines if countries become financially unattractive for generic and other companies.

The various mechanisms within European countries for establishing prices of new medicines are explored in Chapter 0. This includes mechanisms for establishing prices of new medicines including those for cancer, orphan diseases, and infectious diseases. This will also include potential alliances among countries to improve negotiating stances and access such as current initiatives in Belgium, Luxembourg and the Netherlands¹⁴⁷, as well as alliances such as the GAVI Alliance (formerly known as the Global Alliance for Vaccines and Immunisation)¹⁴⁸. These are discussed further in Chapter 7.5.

4.2. Price components

Pharmaceutical expenditure is determined by combining a value component (cost) and a volume component (Figure 2). There are typically three price components which comprise the price of medicines in ambulatory care, and altering these can appreciably alter subsequent medicine prices. These include¹⁴⁹:

- The ex-factory price – typically the price set by the manufacturer (pharmaceutical company) in accordance with the pricing and reimbursement regulations for the country;

¹³⁸ Fraeyman, J. et al., 2013, *The potential influence of various initiatives to improve rational prescribing for proton pump inhibitors and statins in Belgium*, Expert review of pharmacoeconomics & outcomes research, 13(1), p. 141-151.

¹³⁹ Dylst, P. et al., 2013, *Generic medicines: solutions for a sustainable drug market?*, Applied health economics and health policy, 11(5), p. 437-443.

¹⁴⁰ European Commission, Carone, G., Schwierz, C. and Xavier, A., *Cost-containment policies in public pharmaceutical spending in the EU*, Economic Papers 461, September 2012, available at: http://ec.europa.eu/economy_finance/publications/economic_paper/2012/pdf/ecp_461_en.pdf.

¹⁴¹ PHARMAC, 2014, *PHARMAC tender reveals vibrant market for pharmaceuticals*, available at: <http://www.pharmac.health.nz/news/media-2014-02-12-tender/>.

¹⁴² Godman, B. et al., 2009, *Multifaceted national and regional drug reforms and initiatives in ambulatory care in Sweden: global relevance*, Expert review of pharmacoeconomics & outcomes research, 9(1), p. 65-83.

¹⁴³ Godman, B. et al., 2012, *Essential to increase the use of generics in Europe to maintain comprehensive health care?*, Farmeconomia: Health Economics and Therapeutic Pathways, 13(3S), p. 5-20.

¹⁴⁴ Dylst, P. et al., 2013, *Generic medicines: solutions for a sustainable drug market?*, Applied health economics and health policy, 11(5), p. 437-443

¹⁴⁵ Idem.

¹⁴⁶ Dylst, P., Vulto, A. and Simoens, S., 2011, *Tendering for outpatient prescription pharmaceuticals: what can be learned from current practices in Europe?*, Health policy, 101(2), p. 146-152.

¹⁴⁷ Vandenbroeck, P. et al., 2016, *Future scenarios about drug development and drug pricing*. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). KCE Reports 271. D/2016/10.273/59.

¹⁴⁸ GAVI, *The GAVI Alliance Vaccine Supply and Procurement Strategy for the period 2011-2015*, available at: <http://www.gavi.org/about/gavis-business-model/vaccine-supply-and-procurement/#>.

¹⁴⁹ Kanavos, P.G. and Vondoros, S., 2011, *Determinants of branded prescription medicine prices in OECD countries*, Health economics, policy, and law, 6(3), p. 337-367.

- The pharmacy purchasing price - price set at the level of the wholesaler, including their mark-ups (i.e. the difference between the cost price and the selling price);
- The pharmacy retail price - also called the 'consumer price' or 'end price', which is the price set at the pharmacy level by governments and health authorities, including the pharmacy margins. The pharmacy retail price (net) can be increased by further additions, such as duties and taxes, which results in the pharmacy gross retail price.

In addition, there is the 'reimbursed price', which is typically the price reimbursed by health authorities for the medicine. The total price includes any patient co-payment¹⁵⁰. The 'reimbursed price' or 'reimbursement price' is the maximum amount paid by public payers¹⁵¹. Among European health authorities, the term 'reimbursement price' is typically not explicitly indicated, except for Austria, which uses the term 'sickness fund price'. However, it can generally be calculated by deducting patient co-payments from the medicine or 'end price'. Most European countries^{152,153} ask patients for a specific percentage of the price of the medicine when it is dispensed, although this percentage can vary according to the perceived therapeutic need of the medicine, e.g. insulin is usually provided free of charge to patients with diabetes, whilst there is a high co-payment for medicines such as the proton pump inhibitors (PPIs) in some countries.

Patient co-payments can be substantial, which can negatively impact subsequent medicine use^{154,155}. For instance in Serbia, the co-payment for statins is 80% leading to low utilisation of statins at 3.3 defined daily doses (DDDs)/1.000 inhabitants/day in 2007 versus, for instance, the UK (England 93.6 DDDs/1.000 inhabitants/day in 2007, Scotland 127 DDDs/1.000 inhabitants/day in 2008). The high use of statins in the UK is caused by ongoing measures to identify and treat patients with cardiovascular disease, together with limited co-payment for these medicines^{156,157}.

Wholesale and pharmacy mark-ups usually apply to all medicines; however, they are limited to reimbursed and prescription-only medicines in some European countries¹⁵⁸. The remuneration for distributing medicines in the form of fixed mark-ups or regressive schemes will influence pharmacy retail prices. Several European countries have opted for regressive wholesale and pharmacy remuneration schemes, which decrease the mark-ups for higher cost medicines. The various strategies are discussed in.

¹⁵⁰ Godman, B. et al., 2010, *Comparing policies to enhance prescribing efficiency in Europe through increasing generic utilization: changes seen and global implications*, Expert review of pharmacoeconomics & outcomes research, 10(6), p. 707-722.

¹⁵¹ WHO Collaborating Centre for Pharmaceutical PaRP, *Pharmaceutical Health Information System Glossary*, 2011, available at: http://whocc.goeg.at/Literaturliste/Dokumente/MethodologyTemplate/PHIS%20Glossary_UpdatedApril2011.pdf.

¹⁵² Vogler, S., Zimmermann, N. and Hahl, C., 2013, *Understanding the components of pharmaceutical expenditure - overview of pharmaceutical policies influencing expenditure across European countries*, GaBI Journal, 2(3), p. 178-187.

¹⁵³ Vogler, S. et al., 2011, *Comparing pharmaceutical pricing and reimbursement policies in Croatia to the European Union Member States*, Croatian medical journal, 52(2), p. 183-197.

¹⁵⁴ Maimaris, W. et al., 2013, *The influence of health systems on hypertension awareness, treatment, and control: a systematic literature review*, PLoS medicine, 10(7):e1001490.

¹⁵⁵ Simoons, S. and Sinnaeve, P., 2014, *Patient co-payment and adherence to statins: a review and case studies*, Cardiovascular drugs and therapy, 28(1), p. 99-109.

¹⁵⁶ Bennie, M. et al., 2012, *Multiple initiatives continue to enhance the prescribing efficiency for the proton pump inhibitors and statins in Scotland*, Expert review of pharmacoeconomics & outcomes research, 12(1), p. 125-130.

¹⁵⁷ Godman, B. et al., 2010, *Policies to enhance prescribing efficiency in Europe: findings and future implications*, Frontiers in pharmacology, 1, p. 141.

¹⁵⁸ Kanavos, P., Schurer, W., and Vogler, S., 2011, *The pharmaceutical distribution chain in the European Union: structure and impact on pharmaceutical prices*, European Commission: Brussels, available at: http://eprints.lse.ac.uk/51051/1/Kanavos_pharmaceutical_distribution_chain_2007.pdf.

Table 5.

Pharmacy remuneration may also be designed independently from the price of the medicine, e.g. by providing a fee for service for a medicine whatever its cost, as currently occurs in the Netherlands or in the UK^{159,160}.

Increased regulation of the mark-ups for both wholesalers and pharmacies is part of health authority/government strategies across Europe to regulate the prices of their medicines. Key stakeholder incentives and disincentives need to be mapped out in advance to avoid any unexpected effects. This includes the number of wholesalers and pharmacies considered as part of any future country strategy¹⁶¹.

Table 5: Potential strategies for regulating the distribution mark-up as well as advantages and disadvantages of popular schemes

Strategy	Description and examples
Fixed or flat fee	A fixed amount for any item dispensed, e.g. UK
Differential fixed or regressive fee	Items in one category incur a higher/lower fixed amount than another
Regressive flat fee/amount	Higher cost items incur a lower fixed amount for wholesalers and pharmacies Advantages include reducing incentives among pharmacists to dispense higher cost medicines when these are prescribed Disadvantages include reducing the incentive for pharmacies to stick to high cost items. In addition, adding significantly to the price patients pay for their medicines in low-income countries where there are typically higher patient co-payments
Fixed percentage	A fixed percentage depending on the wholesaler price
Differential fixed or regressive percentage	Items in one category incur a higher/lower fixed amount than another category
Regressive percentage – whole or part of procurement prices	Higher cost items are associated with lower remuneration – typical in Europe

¹⁵⁹ Vogler, S., Zimmermann, N. and Habl, C., 2013, *Understanding the components of pharmaceutical expenditure - overview of pharmaceutical policies influencing expenditure across European countries*, GaBI Journal, 2(3), p. 178-187.

¹⁶⁰ Kanavos, P., Schurer, W., and Vogler, S., 2011, *The pharmaceutical distribution chain in the European Union: structure and impact on pharmaceutical prices*, European Commission: Brussels, available at: http://eprints.lse.ac.uk/51051/1/Kanavos_pharmaceutical_distribution_chain_2007.pdf.

¹⁶¹ Ball, D., on behalf of the WHO/HAI Project on Medicine Prices and Availability, 2011, *The Regulation of Mark-ups in the Pharmaceutical Supply Chain*, Review Series on Pharmaceutical Pricing Policies and Interventions, Working Paper 3, available at: <http://www.haiweb.org/medicineprices/05062011/Mark-ups%20final%20May2011.pdf>.

Strategy	Description and examples
	<p>Advantages include easy to implement and reduces the incentive for pharmacists to dispense higher cost vs. lower cost medicines where they can</p> <p>Disadvantages include the fact that high cost medicines may still attract large mark-ups and may not necessarily create an incentive for pharmacists to dispense less expensive items where this is a possibility</p>
Fixed maximum fee/percentage	<p>Maximum fixed amount, although lower amounts can be incurred. Maximum percentage is regulated among both wholesalers and pharmacists</p> <p>Advantages include an incentive for competition Disadvantages include the fact that such schemes may lead to reduced service quality or range of medicines available in pharmacies in order to lower their costs</p> <p>There is also a disincentive for pharmacists to sell/dispense lower cost medicines if there is inadequate competition or room to reduce their costs, while incentives still exist for pharmacists/retailers to sell/dispense more expensive medicines where they can</p>
Regressive maximum % fee	Higher cost items incur lower fixed amounts or percentages, according to defined thresholds among both wholesalers and pharmacies
Fixed maximum fee	Maximum fixed amount – although lower amounts can be incurred
Fixed maximum percentage	Maximum percentage of the cost price is regulated among both wholesalers and pharmacies
Regressive maximum % fee	Higher cost items incur lower fixed amounts or percentages according to defined threshold levels

Source: Adapted from Ball¹⁶².

The number of wholesalers varies considerably across Europe - ranging from between 5 and 160 wholesalers per country (low in, for instance, Germany and high in Greece¹⁶³, Table 6).

¹⁶² Ball, D., on behalf of the WHO/HAI Project on Medicine Prices and Availability, 2011, *The Regulation of Mark-ups in the Pharmaceutical Supply Chain*, Review Series on Pharmaceutical Pricing Policies and Interventions, Working Paper 3, available at: <http://www.haiweb.org/medicineprices/05062011/Mark-ups%20final%20May2011.pdf>.

¹⁶³ Idem.

In 2013, Vadoros and Stargardt documented 130 wholesalers in Greece versus 20 in the UK, nine in the Netherlands, three in Denmark and two in Finland. The high number in Greece, as compared to lower numbers in other countries, raises questions regarding the efficiency in the system in Greece. The number of wholesalers in Greece is likely to fall, now that margins for prescription medicines have decreased from 7.8% to 5.4%¹⁶⁴. Most wholesaler margins in the EU vary between 2% and 8% of the pharmacy retail price, although rates as high as 24% have been noted for a small number of medicines¹⁶⁵. In Croatia, this is 8.5% of ex-factory prices¹⁶⁶. Pharmacy mark-ups typically range between 18% and 25% as shown in a report for the EC published in 2012, although these have been as low as 12% and as high as 50%¹⁶⁷.

Table 6: Number of wholesalers among European countries and the average margins of wholesalers and pharmacies

Country	Wholesalers (Approximate number)	Av. WS margin (% PPP)	Av. Pharmacy margin (% PPP)	Type of wholesaler mark-up	Type of pharmacy mark-up
Austria	10	10.0%	10.2%	Regressive	Regressive + dispensing fee
Belgium	15	8.5%	na	Regressive	Regressive + dispensing fee
Czech Republic	30	4.3%	na	Regressive	Regressive
Denmark	5	6.5%	19.30%	Negotiations with manufacturers	Linear + dispensing fee
Estonia	50	na	19%	Regressive	Regressive
Finland	5	3.0%	24%	Negotiations with manufacturers	Regressive + dispensing fee
France	10	6.2%	na	Regressive	Regressive + dispensing fee
Germany	5	5,0%	24%	Regressive	Linear
Greece	160	4.0%	na	Regressive	Regressive
Hungary	10	6.2%	19%	Regressive	Regressive
Italy	70	3.0%	na	Na	Linear

¹⁶⁴ Vadoros, S. and Stargardt, T., 2013, *Reforms in the Greek pharmaceutical market during the financial crisis*, Health policy, 109(1), p. 1-6.

¹⁶⁵ Kanavos, P. and Wouters, O., 2014, *Competition issues in the distribution of pharmaceuticals*, Session III of the OECD Global Forum on Competition, Paris, available at: http://eprints.lse.ac.uk/56006/1/_lse.ac.uk_storage_LIBRARY_Secondary_libfile_shared_repository_Content_Wouters,%20Competition%20issues_Wouters_Competition%20issues_2014.pdf.

¹⁶⁶ Vogler, S. et al., 2011, *Comparing pharmaceutical pricing and reimbursement policies in Croatia to the European Union Member States*, Croatian medical journal, 52(2), p. 183-197.

¹⁶⁷ Kanavos, P. and Wouters, O., 2014, *Competition issues in the distribution of pharmaceuticals*, Session III of the OECD Global Forum on Competition, Paris, available at: http://eprints.lse.ac.uk/56006/1/_lse.ac.uk_storage_LIBRARY_Secondary_libfile_shared_repository_Content_Wouters,%20Competition%20issues_Wouters_Competition%20issues_2014.pdf.

Netherlands	10	18.0%	na	Negotiations with manufacturers	Dispensing fee
Poland	na	9.8%	na	Regressive	Regressive
Portugal	10	6.9%	18%	Regressive	Regressive
Slovenia	10	8.5%	na	Regressive	Regressive + dispensing fee
Slovakia	10	na	21%	Regressive	Regressive + dispensing fee
Spain	60	3.5%	na	Regressive	Regressive
Sweden	10	2.5%	21%	Negotiations with manufacturers	Regressive
UK	10	12.5%	na	Negotiations with manufacturers	Linear + dispensing fee

Source: Adapted from Carone et al.¹⁶⁸ and Kanavos et al.¹⁶⁹.

These findings compare with data published in 2003 and 2004 for a number of European countries (Table 7).

Table 7: Wholesaler and retail margins in Europe as a % of the total price

Country	Wholesale margin (% price)	Retail margin (% price)	VAT	Manufacturer (% price)
Austria	7.5%	24.1%	16.7%	51.8%
Belgium	8.5%	29.2%	8.5%	56.6%
Finland	2.6%	26.6%	7.4%	63.3%
France	3.8%	26.2%	5.2%	64.8%
Germany	7.7%	27.3%	13.8%	51.2%
Greece	5.5%	24.0%	7.4%	63.1%
Italy	6.7%	20.4%	9.1%	63.8%
Netherlands	10.8%	20.2%	5.7%	63.4%
Spain	6.7%	26.8%	3.8%	62.7%
Sweden	2.4%	20.0%	0%	77.6%
UK	10.3%	17.3%	0%	72.4%

Source: Adapted from Ball¹⁷⁰.

¹⁶⁸ European Commission, Carone, G., Schwierz, C. and Xavier, A., 2012, *Cost-containment policies in public pharmaceutical spending in the EU*, Economic Papers 461, available at: http://ec.europa.eu/economy_finance/publications/economic_paper/2012/pdf/ecp_461_en.pdf.

¹⁶⁹ Kanavos, P. and Wouters, O., 2014, *Competition issues in the distribution of pharmaceuticals*, Session III of the OECD Global Forum on Competition, Paris, available at: http://eprints.lse.ac.uk/56006/1/_lse.ac.uk_storage_LIBRARY_Secondary_libfile_shared_repository_Content_Wouters,%20Competition%20issues_Wouters_Competition%20issues_2014.pdf.

¹⁷⁰ Ball, D., on behalf of the WHO/HAI Project on Medicine Prices and Availability, 2011, *The Regulation of Mark-ups in the Pharmaceutical Supply Chain*, Review Series on Pharmaceutical Pricing Policies and Interventions, Working Paper 3, available at: <http://www.haiweb.org/medicineprices/05062011/Mark-ups%20final%20May2011.pdf>.

4.3. Reference pricing

In their guidance on pharmaceutical pricing policies, the WHO recommends that countries should consider using ERP as a method for negotiating or benchmarking prices and as part of an overall strategy, in combination with other methods, for setting the price of a medicine¹⁷¹. This is in addition to internal reference pricing (IRP) to conserve pharmaceutical expenditure¹⁷².

Reference pricing can include the following^{173,174,175}:

- ERP for both new and existing medicines, i.e. prices compared with other countries and potentially adjusted;
- IRP either by therapeutic area/class (Anatomical Therapeutic Chemical (ATC) Level 3 or 4), i.e. the disease area or pharmacological class, or by the molecule (ATC Level 5). Under this system, prices are typically set at the lowest price for a product in a therapeutic area/class or molecule, with the patients covering the additional cost themselves for a more expensive product.

4.3.1. External reference pricing

With respect to countries chosen for comparative purposes, European countries typically choose other European countries with similar economic comparability and/or geographic proximity for referencing¹⁷⁶. Consequently, lower-income European countries typically refer to other lower-income countries, and more wealthy European countries frequently use other high-income European countries as their reference for pricing purposes. However, this is not universal.

There is, however, an appreciable variation in the number of countries included in the reference country basket among European countries. However, the most common approach is to have less than 10 countries in the chosen basket for ease of comparison¹⁷⁷. This mirrors WHO recommendations when countries are developing an ERP system, i.e. countries instigating such systems should select comparator countries based on issues such as their economic status, pharmaceutical pricing systems and similar burden of disease¹⁷⁸.

A variety of prices are used for external referencing purposes across countries, although ex-factory prices are generally used¹⁷⁹. However, ERP rarely incorporates the actual prices paid by health authorities (payers), especially with the increase in MEAs, which include confidential rebates and discounts (Chapter 5.6)^{180,181}.

¹⁷¹ WHO, 2013, *WHO Guideline on Country Pharmaceutical Pricing Policies*, World Health Organization: Geneva, available at: <http://www.ncbi.nlm.nih.gov/books/NBK258631/>.

¹⁷² Simoens, S., 2012, *A review of generic medicine pricing in Europe*, GaBI Journal, 1(1), p. 8-12.

¹⁷³ Leopold, C. et al., 2012, *Differences in external price referencing in Europe: a descriptive overview*, Health policy, 104(1), p. 50-60.

¹⁷⁴ Godman, B. et al., 2015, *Pharmaceutical pricing in Croatia: a comparison of ordinances in 2013 versus 2009 and their potential savings to provide future guidance*, GaBI journal, 4 (2), p. 79-89.

¹⁷⁵ Dylst, P., Vulto, A. and Simoens, S., 2011, *The impact of reference-pricing systems in Europe: a literature review and case studies*, Expert review of pharmacoeconomics & outcomes research, 11(6), p. 729-737.

¹⁷⁶ Leopold, C. et al., 2012, *Differences in external price referencing in Europe: a descriptive overview*, Health policy, 104(1), p. 50-60.

¹⁷⁷ Idem.

¹⁷⁸ WHO, 2013, *WHO Guideline on Country Pharmaceutical Pricing Policies*, World Health Organization: Geneva, available at: <http://www.ncbi.nlm.nih.gov/books/NBK258631/>.

¹⁷⁹ Leopold, C. et al., 2012, *Differences in external price referencing in Europe: a descriptive overview*, Health policy, 104(1), p. 50-60.

¹⁸⁰ Ferrario, A. and Kanavos, P., 2013, *Managed entry agreements for pharmaceuticals: the European experience*, EMI-Net: Brussels, available at: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/mea_report_en.pdf.

¹⁸¹ Vogler, S. et al., 2012, *Discounts and rebates granted to public payers for medicines in European countries*, Southern med review, 5(1), p. 38-46.

In their study assessing the impact of ERP on the prices of a basket of 14 patented medicines among 14 European countries, Leopold et al. found that ERP leads to lower prices for medicines¹⁸². However, there was an appreciable variation in the ex-factory price of the basket of 14 medicines among the studied countries. As a result, this confirmed that the price levels of patented medicines in Europe are not only driven by ERP – where this exists – but also other factors, including pharmaceutical industry activity as well as national pricing and reimbursement policies, GDP per capita and total pharmaceutical expenditure.

The authors acknowledge that, whilst ERP is a widely used pricing policy in Europe, there is potential for improvement through implementing more detailed legislation¹⁸³. This is because there are concerns with reference pricing¹⁸⁴. Potential revisions include identifying alternative countries in case a particular medicine is not available among existing designated reference countries. There is also a need for more formal information sharing with other public pricing authorities to learn more about the different ERP methodologies, as well as the national experiences, to give future guidance. Such developments may help to address these concerns.

Concerns and controversies surrounding ERP include:

- Potential harm to the reference countries depending on their size and current patient co-payment levels¹⁸⁵;
- Prices of medicines among European countries may not reflect actual prices^{186,187} especially given the increase in the number of MEAs including confidential discounts (Chapter 5.6);
- Pharmaceutical companies may preferentially try and launch their new premium-priced medicines initially in higher-price countries. As a result, this may potentially increase reimbursed prices in those remaining countries that directly or indirectly reference them^{188,189}. This leads to discussions around VBP for new medicines (Chapter 5.6) in each country. VBP is based on key parameters including the prices of current standard treatments, ethical values and willingness-to-pay thresholds¹⁹⁰;
- There are concerns that ERP may, in time, lead to a convergence of willingness-to-pay economic thresholds (cost per QALY) for assessing potential prices for new medicines among European countries¹⁹¹. However, this is unlikely in the short term,

¹⁸² Leopold, C. et al., 2012, *Impact of external price referencing on medicine prices - a price comparison among 14 European countries*, Southern med review, 5(2), p. 34-41.

¹⁸³ Leopold, C. et al., 2012, *Differences in external price referencing in Europe: a descriptive overview*, Health policy, 104(1), p. 50-60.

¹⁸⁴ Barros, P.P., 2010, *Pharmaceutical policies in European countries*, Advances in health economics and health services research, 22, p. 3-27.

¹⁸⁵ Garcia Marinoso, B., Jelovac, I. and Olivella, P., 2011, *External referencing and pharmaceutical price negotiation*, Health economics, 20(6), p. 737-756.

¹⁸⁶ Leopold, C. et al., 2012, *Differences in external price referencing in Europe: a descriptive overview*, Health policy, 104(1), p. 50-60.

¹⁸⁷ Ferrario, A. and Kanavos, P., 2013, *Managed entry agreements for pharmaceuticals: the European experience*, EMI-Net: Brussels, available at: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/mea_report_en.pdf.

¹⁸⁸ European Commission, et al., 2012, *Cost-containment policies in public pharmaceutical spending in the EU*, Economic Papers 461, available at: http://ec.europa.eu/economy_finance/publications/economic_paper/2012/pdf/ecp_461_en.pdf.

¹⁸⁹ Leopold, C. et al., 2012, *Impact of external price referencing on medicine prices - a price comparison among 14 European countries*, Southern med review, 5(2), p. 34-41.

¹⁹⁰ Gandjour, A., 2013, *Reference pricing and price negotiations for innovative new drugs: viable policies in the long term?*, PharmacoEconomics, 31(1), p. 11-14.

¹⁹¹ Gandjour, A., 2015, *Convergence of decision rules for value-based pricing of new innovative drugs*, Expert review of pharmacoeconomics & outcomes research, 15(2), p. 209-213.

with most countries that use economic criteria in their pricing and reimbursement deliberations currently unwilling to set threshold levels¹⁹²;

- Price reductions in one reference country may not automatically apply to other reference countries, unless there are mechanisms in place to rapidly reassess prices and implement reductions. As a result, potential savings that could be accrued are reduced;
- Pharmaceutical companies could potentially withhold launching their new medicines in lower-priced countries if they believe this will adversely affect their overall profitability across Europe¹⁹³.

However, to mitigate against some of these concerns, initial reforms in Croatia, including changes in internal and ERP policies, resulted in 85 new medicines being added to the reimbursement list between 2009 and 2011, coupled with a deficit reduction¹⁹⁴. This was up from 47 new medicines between July 2009 and 2010, with 13 new medicines added to the list of expensive hospital products^{195,196}.

4.3.2. Internal reference pricing

Under this system, patients typically cover the difference in price for a more expensive medicine than the reference priced medicine, in addition to any existing co-payments for the pack dispensed¹⁹⁷.

In a recent study conducted by the European Generic Medicines Association (EGA), 80% of European countries had an IRP system for generics¹⁹⁸. When setting reference prices, the majority of countries took into account the prices of existing medicines with the reference price based on either the lowest-priced medicine (47% of countries), the lowest-priced generic medicine (21% of countries), the average price of medicines (11% of countries), the average price of generic medicines (5% of countries), or other measures (16% of countries). Reference prices were established by active substance (42% of countries), i.e. ATC Level 5, therapeutic class (31% of countries), i.e. ATC Level 4, or pharmacological class (ATC Level 3), i.e. disease area (18% of countries), or by another mechanism (9% of countries)¹⁹⁹.

In another recent publication involving the 28 EU MS and Norway, the authors found that 22 of the surveyed countries had also instigated an IRP system for generics, i.e. fixed reimbursement for groups of identical or similar medicines²⁰⁰. However, these authors found that most countries appear to cluster medicines with the same active ingredient, i.e. ATC Level 5, rather than by therapeutic group or class (ATC Levels 3 and 4). It is likely that clustering around the class/therapeutic area will help conserve resources given continual pressures in Europe.

¹⁹² Paris, V. and Belloni, A., 2013, *Value in Pharmaceutical Pricing*, OECD Health Working Paper No 63, OECD Publishing: Paris.

¹⁹³ European Commission, et al., 2012, *Cost-containment policies in public pharmaceutical spending in the EU*, Economic Papers 461, available at: http://ec.europa.eu/economy_finance/publications/economic_paper/2012/pdf/ecp_461_en.pdf.

¹⁹⁴ Brkicic, L.S. et al., 2012, *Initiatives to improve prescribing efficiency for drugs to treat Parkinson's disease in Croatia: influence and future directions*, Expert Rev Pharmacoecon Out Res, 12(3), p. 373-384.

¹⁹⁵ Godman, B. et al., 2015, *Pharmaceutical pricing in Croatia: a comparison of ordinances in 2013 versus 2009 and their potential savings to provide future guidance*, GaBI Journal, 4 (2), p. 79-89.

¹⁹⁶ Voncina, L. and Strizrep, T., 2011, *Croatia: 2009/2010 pharmaceutical pricing and reimbursement reform*, Eurohealth, 16(4), p. 20-22.

¹⁹⁷ Godman, B. et al., 2012, *Payers endorse generics to enhance prescribing efficiency: impact and future implications, a case history approach*, GaBI Journal, 1(2), p. 69-83.

¹⁹⁸ Simoens, S., 2012, *A review of generic medicine pricing in Europe*, GaBI Journal, 1(1), p. 8-12.

¹⁹⁹ Idem.

²⁰⁰ Vogler, S., 2012, *The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries - an overview*, GaBI Journal, 1(2), p. 93-100.

A systematic review by Galizzi et al.²⁰¹ suggested that IRP was typically associated with a decrease in the prices of medicines subject to this policy. This was particularly the case in virtually every country studied that had implemented a generic reference pricing policy once the patent had expired and generics became available for the molecule (ATC Level 5). However, to work well, the generics market must be competitive, as collusion amongst manufacturers represents a serious problem to potential prices and savings²⁰².

Galizzi et al. also found greater price decreases in sub-markets in which medicines were already facing generic competition prior to IRP, with price decreases varying according to the extent of generic competition, company strategies and country pricing regulations²⁰³. Overall, both therapeutic reference pricing (ATC levels 3 and 4) and generic reference pricing (ATC level 5) were associated with significant and consistent savings in the first years of application, with no apparent detrimental effect of therapeutic reference pricing on patient outcomes^{204,205,206,207}.

Galizzi et al. also found that the market share of generics significantly increased whenever pharmaceutical companies producing brand-named medicines did not lower their prices to the reference price, launched new dosages and/or formulations, or marketed substitute medicines still under patent protection (i.e. 'evergreening' strategies)²⁰⁸. Examples of 'evergreening' strategies used by pharmaceutical companies to protect their sales of medicines as they near the end of their patent life include esomeprazole versus omeprazole, levocetirizine versus cetirizine, desloratidine versus loratidine and escitalopram versus citalopram²⁰⁹.

4.4. Prices of new medicines for patients with cancer

A growing challenge across countries is the continued funding of new, high-priced medicines for patients with cancer. The management of patients with cancer is seen as increasingly important, but also an increasingly expensive disease area, causing concern to healthcare systems and patients^{210,211,212,213}.

²⁰¹ Galizzi, M.M., Ghislandi, S. and Miraldo, M., 2011, *Effects of reference pricing in pharmaceutical markets: a review*, *PharmacoEconomics*, 29(1), p. 17-33.

²⁰² Ghislandi, S., 2011, *Competition and the Reference Pricing Scheme for pharmaceuticals*, *Journal of health economics*, 30(6), p. 1137-1149.

²⁰³ Galizzi, M.M., Ghislandi, S. and Miraldo, M., 2011, *Effects of reference pricing in pharmaceutical markets: a review*, *PharmacoEconomics*, 29(1), p. 17-33.

²⁰⁴ Dylst, P., Vulto, A. and Simoons, S., 2011, *The impact of reference-pricing systems in Europe: a literature review and case studies*, *Expert review of pharmacoeconomics & outcomes research*, 11(6), p. 729-737.

²⁰⁵ Galizzi, M.M., Ghislandi, S. and Miraldo, M., 2011, *Effects of reference pricing in pharmaceutical markets: a review*, *PharmacoEconomics*, 29(1), p. 17-33.

²⁰⁶ Schneeweiss, S. et al., 2004, *Net health plan savings from reference pricing for angiotensin-converting enzyme inhibitors in elderly British Columbia residents*, *Medical Care*, 42(7), p. 653-660.

²⁰⁷ Schneeweiss, S. et al., 2003, *Clinical and economic consequences of reference pricing for dihydropyridine calcium channel blockers*, *Clinical pharmacology and therapeutics*, 74(4), p. 388-400.

²⁰⁸ Galizzi, M.M., Ghislandi, S. and Miraldo, M., 2011, *Effects of reference pricing in pharmaceutical markets: a review*, *PharmacoEconomics*, 29(1), p. 17-33.

²⁰⁹ Vernaz, N. et al., 2013, *Patented drug extension strategies on healthcare spending: a cost-evaluation analysis*, *PLoS medicine*, 10(6):e1001460.

²¹⁰ Chalkidou, K. et al., 2014, *Evidence-informed frameworks for cost-effective cancer care and prevention in low, middle, and high-income countries*, *The lancet oncology*, 15(3):e119-e31.

²¹¹ Sullivan, R. et al., 2011, *Delivering affordable cancer care in high-income countries*, *The lancet oncology*, 12(10), p. 933-980.

²¹² Zafar, S.Y. et al., 2013, *The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expenses and the insured cancer patient's experience*, *The oncologist*, 18(4), p. 381-390.

²¹³ Hoen, E., 2014, *Access to cancer treatment. A study of medicine pricing issues with recommendations for improving access to cancer medication*. A report prepared for OXFAM, available at: https://www.oxfam.org/sites/www.oxfam.org/files/file_attachments/rr-access-cancer-treatment-inequality-040215-en.pdf

Cancer is currently the second most common cause of death in the EU²¹⁴. If current trends continue, by 2030 there will be approximately 23.6 million new cancer cases globally each year, equivalent to an increase of 68% compared with 2012²¹⁵. In 2009, it was estimated that the treatment of cancer patients cost the EU €126 billion, of which €51.0 billion was related to healthcare costs²¹⁶. These costs will rise with increasing prevalence rates and increasing costs of new cancer medicines. Expenditure on anti-cancer medicines worldwide was US\$91 (€83.72) billion in 2013, up from US\$71 (€65.32) billion in 2008²¹⁷. Currently, medicine costs account for approximately one quarter of total medical costs for patients with cancer, although this varies considerably^{218,219}, with the contribution of medicines likely to increase.

There are a number of facts that appear undeniable with respect to cancer care. Firstly, more activities and initiatives can be undertaken by European countries to diagnose and manage most types of cancer, including increasing prevention strategies²²⁰. Secondly, the cost of cancer care has increased markedly in recent years, and is projected to increase at an unsustainable rate with the prices of new cancer medicines rising appreciably in recent years and likely to continue rising (Table 8)^{221,222,223}. High prices of new cancer medicines are exacerbated by pharmaceutical companies typically seeking orphan status for their new targeted anticancer medicines²²⁴. This is despite the fact that the results of personalised medicine approaches in oncology, including targeted oncology medicines, have to date not been as encouraging as was initially hoped^{225,226}. Thirdly, there appears to be limited or no correlation between the number of deaths per 100,000 population in a country and their overall expenditure on cancer per patient²²⁷. Lastly, issues such as early diagnosis, rapid access to health services, treatment approaches in elderly patients and changing lifestyle, including stopping smoking and reducing weight, have a greater impact on subsequent outcomes than the spend on cancer treatments, including medicines^{228,229}. This is important given the substantial number of new cancer medicines in development and their envisaged

²¹⁴ Kaplan, W. et al., 2013, *Priority Medicines for Europe and the World 2013 Update*, WHO Report, available at: http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf?ua=1.

²¹⁵ McGuire, A. et al., 2015, *End of life or end of the road? Are rising cancer costs sustainable? Is it time to consider alternative incentive and funding schemes?*, Expert review of pharmacoeconomics & outcomes research, 15(4), p. 599-605.

²¹⁶ Idem.

²¹⁷ Howard, D.H. et al., 2015, *Pricing in the Market for Anticancer Drugs*, Journal of Economic Perspectives, 29(1), p. 139-162.

²¹⁸ Luengo-Fernandez, R. et al., 2013, *Economic burden of cancer across the European Union: a population-based cost analysis*, The lancet oncology, 14(12), p. 1165-1174.

²¹⁹ Aggarwal, A., Ginsburg, O. and Fojo, T., 2014, *Cancer economics, policy and politics: What informs the debate? Perspectives from the EU, Canada and US*, Journal of Cancer Policy, 2(1), p 1-11.

²²⁰ Chalkidou, K. et al., 2014, *Evidence-informed frameworks for cost-effective cancer care and prevention in low, middle, and high-income countries*, The lancet oncology, 15(3):e119-e31.

²²¹ Howard, D.H. et al., 2015, *Pricing in the Market for Anticancer Drugs*, Journal of Economic Perspectives, 29(1), p. 139-162.

²²² Kelly, R.J. and Smith, T.J., 2014, *Delivering maximum clinical benefit at an affordable price: engaging stakeholders in cancer care*, The lancet oncology, 15(3):e112-e8.

²²³ Experts in Chronic Myeloid Leukemia, 2013, *The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts*, Blood, 121(22), p. 4439-4442.

²²⁴ Mullard, A., 2012, *FDA drug approvals*, Nature reviews Drug discovery, 11(2), p. 91-94.

²²⁵ Kantarjian, H.M. et al., 2013, *Cancer drugs in the United States: Justum Pretium--the just price*, Journal of clinical oncology, 31(28), p. 3600-3604.

²²⁶ Garattini, L., Curto, A. and Freemantle, N., 2015, *Personalized medicine and economic evaluation in oncology: all theory and no practice?*, Expert review of pharmacoeconomics & outcomes research, 15(5), p. 733-738.

²²⁷ Uyl-de Groot, C.A. et al., 2014, *Dispelling the myths around cancer care delivery: It's not all about costs*, Journal of Cancer Policy, 2, p. 22-29.

²²⁸ Aggarwal, A., Ginsburg, O. and Fojo, T., 2014, *Cancer economics, policy and politics: What informs the debate? Perspectives from the EU, Canada and US*, Journal of Cancer Policy, 2(1), p 1-11.

²²⁹ Coleman, M.P. et al., 2011, *Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data*, Lancet, 377(9760), p. 127-138.

requested prices²³⁰. The growing spend on new cancer medicines at increased prices means potentially less monies are available to fund current and new treatments in other priority disease areas²³¹ within fixed budgets. This concept, known as opportunity costs, potentially threatens the ability of European countries to continue providing equitable and comprehensive healthcare²³².

Table 8: Prices for new cancer medicines

Author	Prices for new medicines to treat patients with cancer
Bach	Median monthly price of anticancer medicines increased from US\$1,600 (€1,472) in the early 1960s to more than US\$4,000 (€3,680) for new anticancer medicines approved between 2000 and 2005 (2010 US\$, 2016 €) ²³³ .
Howard et al.	In 1995, patients and their insurers paid US\$54,100 (€49,772) for a year of life. In 2005, they paid US\$139,100 (€127,972) for the same benefit. By 2013, this had reached US\$207,000 (€190,440) ²³⁴ . These figures include the findings from modelling studies where there are concerns with the relationship between disease or progression free survival, complete responses and overall survival, especially in patients with solid tumours ^{235,236,237,238} .
McGuire et al.	Currently, cancer therapies targeted for specific patient populations have higher reimbursed prices than non-targeted cancer treatments ²³⁹ .
Kelly and Smith	Currently, new medicines to treat patients with cancer typically cost between US\$6,000 (€5,520) to US\$10,000 (€9,200) per month. There is often little relationship between the reimbursed prices for cancer medicines and their associated health benefit (Box 1) ^{240,241,242} .

²³⁰ European Federation of Pharmaceutical Industries and Associations, 2013, *HEALTH & GROWTH – Evidence Compendium*, available at: http://www.efpia.eu/uploads/Modules/Documents/health-and-growth_evidence-compendium.pdf.

²³¹ Haycox, A., 2016, *Why Cancer?*, *PharmacoEconomics*, 34(7), p. 625-7.

²³² Ghinea, N., Kerridge, I. and Lipworth, W., 2015, *If we don't talk about value, cancer drugs will become terminal for health systems*, *The Conversation*, available at: <http://theconversation.com/if-we-dont-talk-about-value-cancer-drugs-will-become-terminal-for-health-systems-44072>.

²³³ Bach, P.B., 2013, *Reforming the payment system for medical oncology*, *JAMA*, 310(3), p. 261-262.

²³⁴ Howard, D.H. et al., 2015, *Pricing in the Market for Anticancer Drugs*, *Journal of Economic Perspectives*, 29(1), p. 139-162.

²³⁵ Kantarjian, H.M. et al., 2013, *Cancer drugs in the United States: Justum Pretium--the just price*, *Journal of clinical oncology*, 31(28), p. 3600-3604.

²³⁶ Henshall, C. et al., 2014, *Understanding the Role and Evidence Expectations of Health Technology Assessment and Coverage/Payer Bodies: What Are They Looking for, and How and Why Does This Differ From What Regulators Require?*, *Therapeutic Innovation & Regulatory Science*, 48(3), p. 341-46.

²³⁷ Prasad, V. et al., 2015, *The Strength of Association Between Surrogate End Points and Survival in Oncology: A Systematic Review of Trial-Level Meta-analyses*, *JAMA internal medicine*, 175(8), p. 1389-98.

²³⁸ Cortazar P, Zhang, L. et al., 2014, *Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis*, *Lancet*, 384(9938), p. 164-172.

²³⁹ McGuire, A. et al., 2015, *End of life or end of the road? Are rising cancer costs sustainable? Is it time to consider alternative incentive and funding schemes?*, *Expe Rev Pharmacoecon Out Res*, 15(4), p. 599-605.

²⁴⁰ Kelly, R.J. and Smith, T.J., 2014, *Delivering maximum clinical benefit at an affordable price: engaging stakeholders in cancer care*, *The lancet oncology*, 15(3):e112-e8.

²⁴¹ Experts in Chronic Myeloid Leukemia, 2013, *The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts*, *Blood*, 121(22), p. 4439-4442.

²⁴² Kantarjian, H.M. et al., 2013, *Cancer drugs in the United States: Justum Pretium--the just price*, *Journal of clinical oncology*, 31(28), p. 3600-3604.

Box 1: Limited relationship between requested prices in the US and the extent of health gain for new cancer medicines

- Out of the 12 cancer medicines that were approved by the US Food and Drug Administration (2012), nine had a price of more than US\$10,000 per month. However, only three prolonged survival, with two of them by less than two months;
- In patients with renal cell carcinoma:
 - Seven targeted therapies were approved in the US between 2005 and 2012 including sunitinib, everolimus, pazopanib and axitinib;
 - All improved median progression-free survival (PFS) between three to six months;
 - However, this was associated with minimal or no impact on overall patient survival times, at a cost of US\$70,000 (€64,400) to US\$140,000 (€128,800) annually²⁴³.

The concern with increasing prices of new cancer medicines has resulted in growing interest among key stakeholder groups to establish minimum effectiveness criteria for valuing new cancer medicines based on survival benefits^{244,245,246}. This is because there are concerns with linking surrogate markers, such as progression free survival and response rates, with outcome measures (Box 1), especially in patients with solid tumours^{247,248}. Prices of new cancer medicines will increasingly include funding accompanying diagnostic tests as a 'joint product', with new targeted therapies being developed to potentially improve effectiveness rates²⁴⁹ as well as the need to confirm effectiveness with real world data. Outcomes-based schemes can play an important role in such situations (see also Chapter 5.6). However, this will be dependent on available information systems to routinely collect appropriate patient level data as well as link data sets to fully capture patient data on outcomes. Currently only a minority of EU countries and regions are able to do this routinely.

A number of authors are suggesting a minimum median improvement in survival for patients with advanced cancer of at least three to six months for a new cancer medicine to be seen as an advance^{250,251,252,253}. Other authors have suggested a minimum median improvement in survival of 2.5 to 6 months as a clinically meaningful improvement for a new medicine in patients with advanced colorectal cancer, e.g. a relative meaningful median improvement in

²⁴³ Idem.

²⁴⁴ Idem.

²⁴⁵ Ferguson, J. et al., 2000, *New treatments for advanced cancer: an approach to prioritization*, British Journal of cancer, 83(10), p. 1268-1273.

²⁴⁶ Noonan, A. and Bekaii-Saab, T., 2015, *Second-line outcomes in metastatic colorectal cancer - raising the bar for the high jump rather than the doing the limbo*, Expert review of pharmacoeconomics & outcomes research, 15(1), p. 133-143.

²⁴⁷ Henshall, C. et al., 2014, *Understanding the Role and Evidence Expectations of Health Technology Assessment and Coverage/Payer Bodies: What Are They Looking for, and How and Why Does This Differ From What Regulators Require?* Therapeutic Innovation & Regulatory Science, 48(3), p.341-346.

²⁴⁸ Kantarjian, H.M. et al., 2013, *Cancer drugs in the United States: Justum Pretium--the just price*, Journal of clinical oncology, 31(28), p.3600-3604.

²⁴⁹ Godman, B. et al., 2013, *Personalizing health care: feasibility and future implications*, BMC medicine, 11, p. 179.

²⁵⁰ Kantarjian, H.M. et al., 2013, *Cancer drugs in the United States: Justum Pretium--the just price*, Journal of clinical oncology, 31(28), p.3600-3604.

²⁵¹ Ferguson, J.S. et al., 2000, *New treatments for advanced cancer: an approach to prioritization*, British journal of cancer, 83(10), p. 1268-1273.

²⁵² Ellis, L.M. et al., 2014, American Society of Clinical Oncology perspective: *Raising the bar for clinical trials by defining clinically meaningful outcomes*, Journal of clinical oncology, 32(12), p. 1277-1280.

²⁵³ van de Vooren, K., Curto, A. and Garattini, L., 2013, *Optional copayments on anti-cancer drugs*, BMJ (Clinical research ed), 346, p.f349.

overall survival of 20%²⁵⁴. This corresponds to recent recommendations from the American Society of Clinical Oncology^{255,256}. Below this, prices for new cancer medicines should be similar to those for existing cancer medicines.

Other authors have suggested co-payments for new, more expensive cancer medicines with minimal improvement in overall survival. Health authorities would cover the price of current standard treatments for the particular tumour type. Patients would subsequently have the opportunity, if wished, to cover the additional costs themselves for new cancer medicines. However, this approach is principally seen as providing extra emotional comfort rather than any real health benefit²⁵⁷. There are also concerns with the concept of equity within European healthcare systems.

It is recognised these developments will require longer-term clinical trials than those often required by regulatory bodies, such as the EMA²⁵⁸. However, this must be balanced against the need for health authorities to make robust and transparent funding decisions within finite budgets alongside ever-increasing requested prices for new cancer medicines^{259,260}.

It is likely such debates will continue.

4.5. Prices of new medicines to treat patients with orphan diseases

Whilst new medicines are required to address areas of unmet need, there are increasing challenges regarding future funding of new medicines for orphan diseases, including targeted cancer therapies^{261,262}. New targeted medicines for cancer are included, since pharmaceutical companies typically seek orphan status for these²⁶³.

Orphan medicines are defined by the EMA, and among a number of MS, as medicines of benefit to patients with rare disease with a prevalence equal to or less than 5/10,000 citizens in Europe^{264,265}. However, some European countries have established their own definitions, e.g. the UK uses a prevalence of 1 in 50,000 inhabitants, whilst Sweden and Denmark have a definition of 1 in 10,000²⁶⁶. There are also different definitions in Canada and the US²⁶⁷.

²⁵⁴ Noonan, A.M. and Bekaii-Saab, T., 2015, *Second-line outcomes in metastatic colorectal cancer - raising the bar for the high jump rather than the doing the limbo*, Expert review of pharmacoeconomics & outcomes research, 15(1), p. 133-143.

²⁵⁵ Ellis, L.M. et al., 2014, *American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes*, Journal of clinical oncology, 32(12), p. 1277-1280.

²⁵⁶ Noonan, A.M. and Bekaii-Saab, T., 2015, *Second-line outcomes in metastatic colorectal cancer - raising the bar for the high jump rather than the doing the limbo*, Expert review of pharmacoeconomics & outcomes research, 15(1), p. 133-143.

²⁵⁷ van de Vooren, K., Curto, A. and Garattini, L., 2013, *Optional copayments on anti-cancer drugs*, BMJ (Clinical research ed), 346, p.f349.

²⁵⁸ Henshall, C. et al., 2014, *Understanding the Role and Evidence Expectations of Health Technology Assessment and Coverage/Payer Bodies: What Are They Looking for, and How and Why Does This Differ From What Regulators Require?* Therapeutic Innovation & Regulatory Science, 48(3), p.341-346.

²⁵⁹ Howard, D.H. et al., 2015, *Pricing in the Market for Anticancer Drugs*, Journal of Economic Perspectives, 29(1), p. 139-162.

²⁶⁰ Kelly, R.J. and Smith, T.J., 2014, *Delivering maximum clinical benefit at an affordable price: engaging stakeholders in cancer care*, The lancet oncology, 5(3):e112-e118.

²⁶¹ Cohen, J. and Felix, A., 2014, *Are payers treating orphan drugs differently?*, Journal Of Market Access & Health Policy, 2, p. 23513.

²⁶² Mullard, A., 2012, *FDA drug approvals*, Nature reviews Drug discovery, 11(2), p. 91-94.

²⁶³ Idem.

²⁶⁴ Morel, T. et al., 2013, *Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries*, Orphanet journal of rare diseases, 8, p. 198.

²⁶⁵ European Commission, Directorate-general enterprise and industry, Habl, C. and Bachner, F., 2011, *EMINET – Initial investigation to assess the feasibility of a coordinated system to access orphan medicines*, WHO: Vienna, available at: <http://ec.europa.eu/DocsRoom/documents/7611?locale=nl>.

²⁶⁶ Idem.

²⁶⁷ Douglas, C.M. et al., 2015, *Why orphan drug coverage reimbursement decision-making needs patient and public involvement*, Health policy, 119(5), p. 588-596.

Challenges to funding new medicines for patients with orphan diseases arise from the fact that, whilst individual cases may be small in number, there are perceived to be approximately 7,000 rare diseases, growing by approximately 250 new diseases annually. Currently, they affect approximately 30–40 million people across the EU^{268,269,270}. In addition, whilst only 878 orphan medicines have been approved by EMA (as of December 2012), the number of approved medicines is growing²⁷¹ with an estimated 1,800 new orphan medicines in development²⁷². These numbers are expected to continue growing with ongoing developments in genomic sequencing, greater stratification of different cancer types to smaller and smaller patient populations, and incentives for research. Current incentives include 10 years of market exclusivity in Europe (up to seven years in the US), assistance with protocol development, reductions in fees from the EMA centralised procedures, and grants for undertaking trials regarding orphan medicines^{273,274,275}. Limited clinical trial data have also been enough to secure MA in Europe. In some cases, MA has been granted on uncontrolled Phase II, as well as studies involving less than 200 patients²⁷⁶. Thirdly, a positive opinion has been seen in over 80% of cases of new orphan medicines submitted to the EMA, with only a limited number receiving a negative opinion^{277,278}.

Challenges to funding also arise as the prices of orphan medicines can be appreciably more expensive than other medicines, especially where no other treatments exist²⁷⁹. A number of new orphan medicines are now priced at US\$300,000 (€276,000) to US\$400,000 (€368,000) per patient per year or more^{280,281}, although prices are lower for orphan medicines that are second or more to the market to treat those particular orphan diseases^{282,283}. Second or more to the market means that treatments already exist, and are reimbursed, in order to treat that particular orphan disease. Examples of the prices of current orphan medicines include idursulfase (Elaprase®), where the annual medicine costs for treating a 40 kg patient suffering from Morbus Hunter⁶ is approximately €500,000²⁸⁴ (lower for average annual costs

²⁶⁸ Joppi, R., Bertele, V. and Garattini, S., 2013, *Orphan drugs, orphan diseases. The first decade of orphan drug legislation in the EU*, European journal of clinical pharmacology, 69(4), p. 1009-1024.

²⁶⁹ Garattini, S., 2012, *Time to revisit the orphan drug law*, European journal of clinical pharmacology, 68(2), p. 113.

²⁷⁰ Hughes-Wilson, W. et al., 2012, *Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments?*, Orphanet journal of rare diseases, 7, p. 74.

²⁷¹ Hutchings, A. et al., 2014, *Estimating the budget impact of orphan drugs in Sweden and France 2013-2020*, Orphanet journal of rare diseases, 9, p. 22.

²⁷² Douglas, C.M. et al., 2015, *Why orphan drug coverage reimbursement decision-making needs patient and public involvement*, Health policy, 119(5), p. 588-596.

²⁷³ Drummond, M. and Towse, A., 2014, *Orphan drugs policies: a suitable case for treatment*, The European journal of health economics, 15(4), p. 335-40.

²⁷⁴ Joppi, R., Bertele, V. and Garattini, S., 2009, *Orphan drug development is not taking off*, British journal of clinical pharmacology, 67(5), p. 494-502.

²⁷⁵ Michel, M. and Toumi, M., 2012, *Access to orphan drugs in Europe: current and future issues*, Expert review of pharmacoeconomics & outcomes research, 12(1), p. 23-29.

²⁷⁶ Joppi, R., Bertele, V. and Garattini, S., 2013, *Orphan drugs, orphan diseases. The first decade of orphan drug legislation in the EU*, European journal of clinical pharmacology, 69(4), p. 1009-1024.

²⁷⁷ Idem.

²⁷⁸ Michel, M. and Toumi, M., 2012, *Access to orphan drugs in Europe: current and future issues*, Expert review of pharmacoeconomics & outcomes research, 12(1), p. 23-29.

²⁷⁹ Rollet, P., Lemoine, A. and Dunoyer, M., 2013, *Sustainable rare diseases business and drug access: no time for misconceptions*, Orphanet journal of rare diseases, 8(1), p. 109.

²⁸⁰ Cohen, J. and Felix, A., 2014, *Are payers treating orphan drugs differently?*, Journal Of Market Access & Health Policy, 2: 23513.

²⁸¹ Kaiser, J., 2012, *Personalized medicine. New cystic fibrosis drug offers hope, at a price*, Science, 335(6069), p. 645.

²⁸² Rollet, P., Lemoine, A. and Dunoyer, M., 2013, *Sustainable rare diseases business and drug access: no time for misconceptions*, Orphanet journal of rare diseases, 8(1), p. 109.

²⁸³ Picavet, E. et al., 2014, *Shining a light in the black box of orphan drug pricing*, Orphanet journal of rare diseases, 9, p. 62.

²⁸⁴ European Commission, Directorate-general enterprise and industry, Habl, C. and Bachner, F., 2011, *EMINET – Initial investigation to assess the feasibility of a coordinated system to access orphan medicines*, WHO: Vienna, available at: <http://ec.europa.eu/DocsRoom/documents/7611?locale=nl>.

– Table 9), and Naglazyme® (galsulfase) costing over €1 million per patient per year in France, Germany, Italy and Spain²⁸⁵.

Table 9 contains further details of a number of orphan medicines currently available, which cost on average US\$295,000 (€271,400)/patient/year.

Table 9: Orphan medicines with average annual costs in the US of US\$295,000 (€271,400) or greater

Orphan medicine (brand name)	Indication	Average annual cost/patient (US\$)(€, 2016)
Teduglutide (GATTEX®)	Short bowel syndrome	295,000 (271,400)
Imiglucerase (CEREZYME®)	Type 1 Gaucher disease	300,000 (276,000)
Galsulfase (NAGLAZYME®)	Mucopolysaccharidosis VI	441,000 (405,720)
Idursulfase (ELAPRASE®)	Mucopolysaccharidosis I and II	475,000 (437,000)
Eculizumab (SOLIRIS®)	Paroxysmal nocturnal haemoglobinuria	486,000 (447,120)
C1 esterase inhibitor (CINRYZE®)	Hereditary angioedema prophylaxis	487,000 (448,040)

Source: Adapted from Cohen and Felix²⁸⁶ and Picavet et al.²⁸⁷.

The average annual cost per patient for orphan medicines in France, Germany, Italy, Spain and the UK was generally over €150,000 in a paper published in 2012²⁸⁸. Prices for orphan medicines in non-oncology disease areas that are first to market (i.e. no recognised treatment currently available for the disease, 44% of all orphan medicines), have an average cost of €200,000/patient/year, with prices for second to market and oncology orphan medicines lower at €16,000 to €35,000/patient/year²⁸⁹.

A recent study among the five main EU countries suggested that expenditure and utilisation of orphan medicines is growing rapidly causing concern. Expenditure increased from 13% to 28% per annum and utilisation from 7% to 17% per annum in these EU countries in 2010 compared to 2009^{290,291}. This may be facilitated by off-label use, e.g. imatinib²⁹². Other

²⁸⁵ Michel, M. and Toumi, M., 2012, *Access to orphan drugs in Europe: current and future issues*, Expert review of pharmacoeconomics & outcomes research, 12(1), p. 23-29.

²⁸⁶ Cohen, J. and Felix, A., 2014, *Are payers treating orphan drugs differently?*, Journal Of Market Access & Health Policy, 2: 23513.

²⁸⁷ Picavet, E. et al., 2014, *Shining a light in the black box of orphan drug pricing*, Orphanet journal of rare diseases, 9, p. 62.

²⁸⁸ Michel, M. and Toumi, M., 2012, *Access to orphan drugs in Europe: current and future issues*, Expert review of pharmacoeconomics & outcomes research, 12(1), p. 23-29..

²⁸⁹ Douglas, C.M. et al., 2015, *Why orphan drug coverage reimbursement decision-making needs patient and public involvement*, Health policy, 119(5), p. 588-596.

²⁹⁰ Morel, T. et al., 2013, *Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries*, Orphanet journal of rare diseases, 8, p. 198.

²⁹¹ Muscolo, L.A.A. et al., 2012, PHP39 *The "Weight" of Orphan Drugs in the European Pharmaceutical Policy. A Focus on the Expenditure and the Utilization of Orphan Drugs in Five European Union Countries*, Value in Health, 15:A20.

²⁹² Kesselheim, A.S. et al., 2012, *The prevalence and cost of unapproved uses of top-selling orphan drugs*, PloS one, 7(2):e31894.

authors, though, have noted lower growth rates and contributions^{293,294}. This could be due to issues such as fully capturing all medicines likely to lose their patents in the coming years and their lower prices, as well as not fully capturing any off-label use.

To date, reimbursement has typically been more easily obtained among European authorities for new medicines to treat orphan diseases versus those for other disease areas^{295,296}.

This is illustrated firstly by the considerable controversy that surrounded the reimbursement for enzyme replacement therapy (ERT) for the symptomatic treatment of Fabry disease in the Netherlands at an incremental cost per QALY of €3.3 million. The Dutch reimbursement body argued that continued reimbursement would reduce available resources for other, more cost-effective health technologies, including medicines. There was a similar situation for alglucosidase alfa to treat Pompe's disease at an estimated cost per QALY of €0.3–0.9 million for the classic form, and up to €15 million/QALY for the non-classic form. This was based on the evidence collected during the 4-year follow-up study²⁹⁷. However, the draft advice to remove these medicines from the reimbursement list was leaked before its official release. This resulted in vocal opposition and resultant pressure on the Ministry of Health to ignore the advice. Subsequently, both these orphan medicines were reimbursed for all indications²⁹⁸, although they were, associated with a confidential price reduction.

Secondly, by ivacaftor in the UK, which was granted MA to treat the 5% of patients with cystic fibrosis who carry a particular genetic mutation (G551D)²⁹⁹. Reimbursement was granted in England at a cost per QALY of GB£285,000 (€373,350) to GB£1.077million (€1.41million), even after an agreed discount³⁰⁰. The decision by the National Health Service (NHS) Commissioning Board to recommend funding at this price put pressure on Scotland, which resulted in a funding recommendation, despite earlier advice from the Scottish HTA agency not to recommend its use based on concerns with the cost per QALY^{301,302}.

Thirdly, a survey conducted in 2010 among European countries, including the Baltic countries, showed the following^{303,304}:

- 5 of 22 responding European countries publicly funded access to new orphan products at requested prices;

²⁹³ Hutchings, A. et al., 2014, *Estimating the budget impact of orphan drugs in Sweden and France 2013-2020*, Orphanet journal of rare diseases, 9, p. 22.

²⁹⁴ Hughes-Wilson, W. et al., 2012, *Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments?*, Orphanet journal of rare diseases, 7, p. 74.

²⁹⁵ WHO European Office. *Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research*. Copenhagen: 2015.

²⁹⁶ Simoens, S. et al., 2013, *Cost-effectiveness assessment of orphan drugs: a scientific and political conundrum*, Applied health economics and health policy, 11(1), p. 1-3.

²⁹⁷ Idem.

²⁹⁸ Kanters, T.A. et al., 2015, *Access to orphan drugs in western Europe: can more systematic policymaking really help to avoid different decisions about the same drug?*, Exp Rev Pharmacoecon Out Res, 15(4), p. 557-559.

²⁹⁹ O'Sullivan, B.P., Orenstein, D.M. and Milla, C.E., 2013, *Pricing for orphan drugs: will the market bear what society cannot?*, JAMA, 310(13), p. 1343-1344.

³⁰⁰ NHS Commissioning Board, 2012, *Clinical Commissioning Policy: Ivacaftor for Cystic Fibrosis*, available at: <https://www.england.nhs.uk/wp-content/uploads/2013/04/a01-p-b.pdf>.

³⁰¹ Godman, B. et al., 2015, *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?*, Expert review of clinical pharmacology, 8(1), p. 77-94.

³⁰² Scottish Medicines Consortium, 2012, *Ivacaftor 150mg film-coated tablets (Kalydeco®) SMC No. (827/12) – Resubmission*, available at: https://www.scottishmedicines.org.uk/files/advice/ivacaftor_Kalydeco_FINAL_December_2012_amended_11_01_13_for_website.pdf.

³⁰³ Michel, M. and Toumi, M., 2012, *Access to orphan drugs in Europe: current and future issues*, Expert review of pharmacoeconomics & outcomes research, 12(1), p. 23-29.

³⁰⁴ European Commission, Directorate-general enterprise and industry, Hahl, C. and Bachner, F., 2011 *EMINET – Initial investigation to assess the feasibility of a coordinated system to access orphan medicines*, WHO: Vienna, available at: <http://ec.europa.eu/DocsRoom/documents/7611?locale=nl>.

- 11 out of 22 countries stated that access was granted in most cases, but could be subject to specific conditions, including prior approval of the initial prescription from a specialist or other administrative procedures before therapy was started/reimbursed;
- 5 out of 22 countries stated that access to new orphan medicines was limited due to budgetary constraints; in only one country, public coverage was not guaranteed for expensive new orphan medicines, again because of budget concerns;
- Typically, if reimbursed, there is no additional co-pay for such medicines among patients.

The major reasons given in this survey for new orphan medicines not to be included within national formularies or reimbursement lists included³⁰⁵:

- The new orphan medicine in question had not yet received MA, although it was made available to patients via compassionate use or other similar programmes, e.g. TAU in France;
- The orphan medicine is not (yet) available in a country despite being authorised for use (MA) because (a) commercialisation requires administrative clearance by the country's authorities, e.g. price agreements and inclusion in the pharmacy sales list, and this has not yet been completed; and (b) no patients have yet been diagnosed, e.g. with Pompe's disease in Estonia and Latvia;
- The MA holder had not yet applied for reimbursement, e.g. Myozyme® (αglucosidase alfa) in Finland;
- Reimbursement was denied by the reimbursement agency as not being cost-effective, e.g. Kuvan® in Sweden;
- Reimbursement is pending.

Fourthly, to date, there has been limited reimbursement hurdles for new orphan medicines at high prices among European countries, as illustrated with earlier examples. Linked to this, there currently appears to be no appropriate benchmarks and metrics within Europe gauging whether prices for new orphan medicines are too low or too high relative to expectations³⁰⁶. To date, it has been accepted by European health authorities that it is considered desirable to develop treatments for conditions with high disease severity, or where this is still significant unmet medical need, irrespective of the rarity of the condition.^{307,308} This could be encouraged by reimbursing such medicines at high prices (Table 9).

However, the pricing and reimbursement landscape for new orphan medicines is changing in Europe. This is illustrated by several authors^{309,310,311,312}:

³⁰⁵ Idem.

³⁰⁶ Kanavos, P. and Nicod, E., 2012, *What is wrong with orphan drug policies? Suggestions for ways forward*, Value in health, 15(8), p. 1182-1184.

³⁰⁷ Kaplan, W. et al., *Priority Medicines for Europe and the World 2013 Update*, WHO Report, 2013, available at: http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf?ua=1.

³⁰⁸ Kanavos, P. and Nicod, E., 2012, *What is wrong with orphan drug policies? Suggestions for ways forward*, Value in health, 15(8), p. 1182-1184.

³⁰⁹ Michel, M. and Toumi, M., 2012, *Access to orphan drugs in Europe: current and future issues*, Expert review of pharmacoeconomics & outcomes research, 12(1), p. 23-29.

³¹⁰ Cote, A. and Keating, B., 2012, *What is wrong with orphan drug policies?*, Value in health, 15(8), p. 1185-1191.

³¹¹ Whalen, J. and Spencer, M., 2011, *Sanofi Wins Long-Sought Biotech Deal, Acquisition of Genzyme for More Than \$20 Billion Will Give French Company Coveted Research Base in Massachusetts*, The Wall Street Journal, available at: <http://www.wsj.com/articles/SB10001424052748703373404576147483489656732>.

³¹² Kesselheim, A.S. et al., 2012, *The prevalence and cost of unapproved uses of top-selling orphan drugs*, PloS one, 7(2):e31894.

- The reimbursement potential for new, high-priced medicines for orphan diseases is decreasing among European countries, especially where there are alternative medicines available;
- Of the 36 new medicines for orphan diseases that have recently been reviewed by National Institute for Health and Care Excellence (NICE) in the UK, there are 15 negative recommendations (not reimbursed), with 12 conditionally reimbursed (i.e. subject to certain regulations);
- Out of 92 medicines for orphan diseases reviewed by the Dutch Health Insurance Board (now National Health Care Institute) between 1983 and 2013, 13 (14%) were denied reimbursement, and 22 (24%) were conditionally reimbursed;
- Growing concerns among health authority personnel in Europe, that orphan medicines have been viewed as a good business opportunity for pharmaceutical companies, e.g. Sanofi's purchase of Genzyme at a considerable price (over US\$20billion³¹³, €18,4 billion) in view of the perceived willingness of payers to accept higher prices for these medicines. In addition, companies launching their new medicines aiming for orphan status first and hoping high prices will be maintained as new indications are launched and/or used in off-label indications, e.g. imatinib;
- Concerns with a growing unjustified cost differential between medicines for orphan disease versus medicines for other disease areas, as more standard medicines lose their patent and become available at lower prices.

Concerns with the ever-increasing prices of new medicines to treat patients with orphan diseases and continued budgetary pressures is leading to^{314,315,316}:

- New approaches to value new orphan medicines - including the development of multi-faceted approaches, especially as new orphan medicines are unlikely to meet current cost-effectiveness thresholds (Incremental Cost Effectiveness Ratio (ICER) levels) where these exist;
- Growth in MEAs among European countries to facilitate their reimbursement (Chapter 5.6).

The need to develop new approaches to the pricing of orphan medicines is further endorsed by recent assessments, suggesting that orphan medicine development projects typically have higher success rates and shorter development times than non-orphan disease areas. Secondly, pharmaceutical companies generate potential life-time revenues similar to non-orphan disease areas, despite considerably smaller target populations. Thirdly, studies published in 2013 suggest that annual sales of orphan medicines are already US\$90 (€82.8) billion and growing rapidly as, collectively, there are more patients with orphan diseases than

³¹³ Whalen J, Spencer M. *Sanofi Wins Long-Sought Biotech Deal. Acquisition of Genzyme for More Than \$20 Billion Will Give French Company Coveted Research Base in Massachusetts*, available at: <http://www.wsj.com/articles/SB10001424052748703373404576147483489656732>.

³¹⁴ Morel, T. et al., 2013, *Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries*, Orphanet journal of rare diseases, 8, p. 198.

³¹⁵ European Commission, *Process on Corporate Social Responsibility in the Field of Pharmaceuticals Platform on Access to Medicines in Europe Working Group on Mechanism of Coordinated Access to Orphan Medicinal Products (MoCA-OMP) - TRANSPARENT VALUE FRAMEWORK*, available at: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/orphans_conclusions_en.pdf2012.

³¹⁶ Hughes-Wilson, W. et al., 2012, *Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments?* Orphanet journal of rare diseases, 7, p.74.

those with cancer³¹⁷. However, other authors have suggested a lower budget impact, especially for medicines for ultra orphan diseases^{318,319}.

However, considerable unmet need still persists for many rare diseases³²⁰. Consequently, there is a need to continue to incentivise the development of new orphan medicines³²¹. This is especially the case where there are no current treatments available. This has to be balanced, though, against issues of affordability and equity for the remainder of the population^{322,323}, i.e. whether orphan medicines should continue to be singled out for special status for reimbursement consideration (Table 10).

Table 10: Public preferences regarding orphan medicines

<ul style="list-style-type: none"> • In a survey among 4,118 adults in the UK concerning public preferences for medicine prioritisation criteria, the special funding status for treatments of rare diseases was not supported³²⁴; • However, public respondents did express a preference for treating diseases where there are no alternative treatments currently available, and for treating more severe diseases, even when the costs were higher than the costs of currently available treatments, although not when their effectiveness was less. • A recent survey among a random sample of 1,547 Norwegian citizens focussing on orphan diseases showed there was limited evidence that there is a societal preference for rare diseases, if treatment of these patients is at the expense of treatment of those with more common conditions. However, there appears to be strong support for equal treatment of patients with rare diseases in general³²⁵.
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If current approaches are not addressed, this may be seen as giving preferential treatment to the loudest voices among patient advocates, which typically include those with orphan diseases. This is not necessarily equitable^{326,327}, potentially resulting in patients with chronic diseases in non-orphan disease areas losing out as the number of patient advocacy groups are less. However, others have argued it is difficult to initiate such discussions before fully discussing issues on what constitutes high prices for orphan medicines³²⁸.

³¹⁷ Fagnan, D.E. et al., 2014, *Financing drug discovery for orphan diseases*, Drug discovery today, 19(5), p.533-538.

³¹⁸ Hutchings, A. et al., 2014, *Estimating the budget impact of orphan drugs in Sweden and France 2013-2020*, Orphanet journal of rare diseases, 9, p. 22.

³¹⁹ Schlender, M., Adarkwah, C.C. and Gandjour, A., 2015, *Budget impact analysis of drugs for ultra-orphan non-oncological diseases in Europe*, Expert review of pharmacoeconomics & outcomes research, 15(1), p. 171-179.

³²⁰ Kaplan, W. et al., *Priority Medicines for Europe and the World*, Update Report, 2013, available at: http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf?ua=1.

³²¹ Rollet, P., Lemoine, A. and Dunoyer, M., 2013, *Sustainable rare diseases business and drug access: no time for misconceptions*, Orphanet journal of rare diseases, 8(1), p. 109.

³²² Drummond, M. and Towse, A., 2014, *Orphan drugs policies: a suitable case for treatment*, The European journal of health economics, 15(4), p.335-340.

³²³ McCabe, C., Claxton, K. and Tsuchiya, A., 2005, *Orphan drugs and the NHS: should we value rarity?* BMJ, 331(7523), p. 1016-1019.

³²⁴ Linley, W.G. and Hughes, D.A., 2013, *Societal views on NICE, cancer drugs fund and value-based pricing criteria for prioritising medicines: a cross-sectional survey of 4118 adults in Great Britain*, Health economics, 22(8), p. 948-964.

³²⁵ Desser, A.S. et al., 2010, *Societal views on orphan drugs: cross sectional survey of Norwegians aged 40 to 67*. BMJ, 341,c4715.

³²⁶ Cohen, P. and Felix, A., 2014, *Are payers treating orphan drugs differently?* Journal of Market Access & Health Policy, 2, p. 23513.

³²⁷ Haycox, A., 2016, *Why Cancer?* PharmacoEconomics, 34(7), p. 625-627.

³²⁸ Kanavos, P. and Nicod, E., 2012, *What is wrong with orphan drug policies? Suggestions for ways forward*, Value in health, 15(8), p. 1182-1184.

To help address these issues, models that have recently been developed among key stakeholder groups to improve the level of decision-making for new, premium-priced orphan medicines. These include:

- Multi-Criteria Decision Analysis (MCDA) for valuing new orphan medicines based on the 8 categories proposed by Sussex et al.³²⁹;
- Framework for evaluation of new medicines for orphan diseases based on 10 criteria and 3 price differential categories (model of Hughes-Wilson et al.)³³⁰;
- TVF developed by a consultative process through the EU³³¹.

The proposed framework of Hughes-Wilson et al. to assist with value considerations for new orphan medicines is included in Table 11. These considerations contained a number of similar categories to the model proposed by Sussex et al.

Table 11: Proposed criteria for the evaluation of orphan medicines and potential parameters

Criteria	Price Differential		
	Lower prices	Medium prices	Higher prices
Rarity	1:2,000 - 1:20,000	1:20,000 - 1:200,000	Less than 1:200,000
Level of research	Literature review research	Building on existing knowledge of research findings	Starting R&D in an unknown area to the company
Level of uncertainty surrounding effectiveness	Immature data but this is promising	Appropriate surrogate end-points	Robust clinical end-points
Manufacturing complexity	Not complex to produce	Moderately complex to produce	Highly complex biological and galenic forms
Follow-up measures (additional benefits/costs)	Moderate to none envisaged	Research undertaken to answer specific questions arising from the studies	Safety and efficiency studies undertaken to evaluate these more closely in patients
Disease severity	Morbidity seen	Morbidity/severe invalidity in adulthood seen	Mortality/severe invalidity seen in infants
Available alternatives/unmet need	Alternatives with similar characteristics	Alternatives, but offering improvements	No current treatment alternatives available

³²⁹ Sussex, J. et al., 2013, *A pilot study of multicriteria decision analysis for valuing orphan medicines*, *Value in health*, 16(8), p. 1163-1169.

³³⁰ Hughes-Wilson, W. et al., 2012, *Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments?* *Orphanet journal of rare diseases*, 7, p. 74.

³³¹ European Commission, Process on Corporate Social Responsibility in the Field of Pharmaceuticals Platform on Access to Medicines in Europe Working Group on Mechanism of Coordinated Access to Orphan Medicinal Products (MoCA-OMP) - TRANSPARENT VALUE FRAMEWORK, available at: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/orphans_conclusions_en.pdf.

Criteria	Price Differential		
	Lower prices	Medium prices	Higher prices
	available for treatment	(innovation) to future management	
Level of impact of the condition/disease modification	Low impact of the new medicine	Medium impact	Strong impact of the new medicine
Use in a unique indication	Existing indications for the same molecule	Potential for multiple indications with the new medicine	Unique indication only for the new medicine

There has also been the development of the TVF among European authorities and other key stakeholder groups, including pharmaceutical companies³³². Challenges in the 'Terms of Reference' when the TVF was being developed included:

- Data, information, knowledge and expertise on the therapy or alternative therapies – if available – are often scarce. This limits available evidence on efficacy and (real life) effectiveness, especially at the time of MA;
- Registers and registries – if available – have been limited in a number of countries in terms of their capacity to produce solid (high-quality) evidence in rare diseases, including the number of patient entries;
- Availability of adequate dosages/packages may be limited, which may result in 'waste' when protocols are adapted to treat individual patients;
- Calculations that the average cost of treatment per year for common ailments or conditions is believed to be approximately €250 per year. This compares to orphan medicines, which average €30,000/patient/year (when first proposed) and are now higher at over €150,000³³³ or more (Table 9);
- Uncertainty on the extent to which the price of existing orphan medicines will fall when their period of exclusivity finishes, with the first approved orphan medicines losing exclusivity as of August 2012.

The deliberations resulted in the development of the TVF (Table 12). The TVF consists of four elements of value, coupled with a measure of the extent to which the degree each criteria is met. The main intended use of the TVF, as stated in the final report of the MoCA-OMP (Mechanism of Co-ordinated Access to Orphan Medicinal Products) working group, is for collaborative value-based discussions between reimbursement agencies and pharmaceutical companies. The framework is '*indicative, non-prescriptive and non-binding*', which means that EU MS still have the responsibility for reimbursement decisions with regard to new orphan medicines in their country.

There are four principal elements to the TVF (Table 12)³³⁴. The first element of the TVF is '*available alternatives/unmet need*'. This is defined by the MoCA-OMP working group as the

³³² Idem.

³³³ Michel, M. and Toumi M, 2012, *Access to orphan drugs in Europe: current and future issues*, Expert review of pharmacoeconomics & outcomes research, 12(1), p. 23-29.

³³⁴ Godman, B. et al., 2015, *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?*, Expert review of clinical pharmacology, 8(1), p. 77-94.

degree to which the new orphan medicines address the unmet need over existing therapies. Their non-pharmaceutical treatments can be used where no pharmaceutical treatment currently exists. The second element of the TVF '*(relative) effectiveness/degree of net benefit*' is defined as the net benefit that the new orphan medicines provide compared with current treatment approaches. The net benefit includes, for instance, the extent of clinical improvement, including improved quality-of-life, measured against the side effects of the new orphan medicine. This element may be informed by HTAs³³⁵.

The third element of the TVF is the '*response rate*'. This will vary depending on which measure and time frame being used, as well as available clinical data. Response rates will differ for different orphan diseases, e.g. response rates for new enzyme replacement therapies are expected to be greater than response rates for new medicines for late stage cancer. The fourth element of the TVF is the '*degree of certainty/documentation*'. This is defined as the certainty of the claim being made by the pharmaceutical company for the new orphan medicines. The level of evidence may be low when an orphan medicine has conditional approval, but compelling evidence is expected at a later stage for continued reimbursement at granted prices³³⁶.

Table 12: TVF for valuing new orphan medicines

Criterion	Low Degree	Medium Degree	High Degree
Available Alternatives as well as level of unmet Need	Yes The new medicine does not address current unmet need	Yes Major unmet need still exists with the new medicine	No No alternatives exist except supportive care, and the major unmet need is met by the new medicine
(Relative) Effectiveness, Degree of Net Benefit relative to alternatives including no treatment	Incremental benefit compared with current treatments	Major clinical benefit with the new medicine	The new medicine is curative for the disease area in question
Response Rate	<30%	30-60%	>60%
Degree of Certainty	Promising, but the health gain is not well-documented	Plausible with available evidence	Unequivocal improvement with the new medicine

There is ongoing research among European health authorities to assess the utility of the TVF in practice and make subsequent recommendations to aid future decision-making³³⁷. The results should help improve pricing and reimbursement decision-making for new medicines for orphan diseases, given the continued pressure on resources.

³³⁵ Michel, M. and Toumi M, 2012, *Access to orphan drugs in Europe: current and future issues*, Expert review of pharmacoeconomics & outcomes research, 12(1), p. 23-29.

³³⁶ Idem.

³³⁷ Godman, B. et al., 2015, *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?*, Expert review of clinical pharmacology, 8(1), p. 77-94.

4.6. Prices of medicines for infectious diseases

In this section, we focus on prices of medicines for the following infectious diseases: HIV, HCV and Ebola.

4.6.1. Human immunodeficiency virus

At the end of 2012, almost 10 million people globally living with HIV were receiving antiretroviral treatment. A viable market for antiretroviral medicines in low- and middle-income countries is key to the continued scale-up of antiretroviral treatments and their use across countries. Overall, for low- and middle-income countries, for 10 first- and 7 second-line adult and paediatric treatments between 2003 and 2012, the median price paid for adult first-line treatment regimens per treatment-year decreased from US\$499 to US\$122 (€459 to €112), and second-line regimens from US\$2,934 to US\$497 (€2,700 to €457). In 2005, adult regimens were typically sold for a price 170% higher than the cost of the active ingredients, i.e. the cost of goods, with the margin decreasing to 28% in 2012³³⁸.

Between 2004 and 2013, the price of paediatric treatments per treatment year decreased from US\$585 to US\$147 (€538 to €135) for first-line treatments and from US\$763 to US\$288 (€702 to €265) for second-line treatments³³⁹.

4.6.2. New medicines for hepatitis C virus

There have been considerable negotiations by payers across Europe in the price of new curative treatments for patients with the HCV without the side effects associated with previous regimes.

The reasons for this are as follows. Firstly, at current prevalence rates for HCV, initial list prices of US\$84,000 (€77,280) for a standard 12-week course of sofosbuvir in the US and US\$54,000 in the UK (€48,000) could potentially quadruple countries' total medicine budgets³⁴⁰. Total potential sales of US\$15trillion (€13.8 trillion) were envisaged if an estimated 180 million people worldwide with HCV were treated at these prices with sofosbuvir³⁴¹. Secondly, prices were as low as US\$900 (€828) for a treatment course in countries such as Egypt, Pakistan and other developing countries, where there is no patent protection^{342,343}. Thirdly, the cost of a 12-week course of sofosbuvir can be as low as US\$68-\$136³⁴⁴ (€63-€125), with Indian licensees currently selling generic sofosbuvir at prices between US\$161 and \$312 (€148 and €287) for a 28-tablet pack³⁴⁵. In view of this, the authorities in France were initially being charged sofosbuvir at 756 times the cost of its production prior to reimbursement negotiations³⁴⁶.

³³⁸ Perriens, J.H. et al., 2014, *Prices paid for adult and paediatric antiretroviral treatment by low- and middle-income countries in 2012: high, low or just right?*, *Antiviral therapy*, 19(Suppl 3), p. 39-47.

³³⁹ Idem.

³⁴⁰ Brennan, T. and Shrank, W., 2014, *New expensive treatments for hepatitis C infection*, *JAMA*, 312(6), p. 593-594.

³⁴¹ Montazerhodjat V, Weinstock DM, Lo AW, 2016, *Buying cures versus renting health: Financing health care with consumer loans*, 8(327), p. 1-8.

³⁴² Brennan, T. and Shrank, W., 2014, *New expensive treatments for hepatitis C infection*, *JAMA*, 312(6), p. 593-594.

³⁴³ Iyengar, S, et al., 2016, *Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis*. *PLoS medicine*, 13(5):e1002032.

³⁴⁴ Fraser, J., 2014, *WHO Guidelines May Help With Price Reductions For Hepatitis C Drugs*, *Intellectual Property Watch*, available at: <http://www.ip-watch.org/2014/04/09/who-guidelines-may-help-with-price-reductions-for-hepatitis-c-drugs/>.

³⁴⁵ Iyengar, S, et al., 2016, *Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis*. *PLoS medicine*, 13(5):e1002032.

³⁴⁶ Phelan, M. and Cook, C., 2014, *A treatment revolution for those who can afford it? Hepatitis C treatment: new medications, profits and patients*. *BMC Infect Dis*, BioMed Central Ltd; 14 Suppl 6(Suppl 6):S5.

Consequently, across Europe and other countries, Gilead Sciences has now entered into a number of MEAs for sofosbuvir (Sovaldi®). These include:

- with the Italian Reimbursement Agency - the new arrangement is for the cost for the 'initial patients' at €37,000/patient/course dropping to €4,000 for the 'last' patients, averaging €18,000 per patient. As a result, the yearly overall expenditure for sofosbuvir in Italy is expected to be less than €500 million, which is seen as acceptable to all parties³⁴⁷;
- In France with the Economic Committee for Health Products - they initially agreed a price of €13,667 per 28-tablet pack, i.e. around €5,000 lower than the initial list price, at an overall negotiated price of €41,000 (US\$51,000) for a 12-week course. However, prices are likely to go lower due to the potential budget impact and the launch of additional medicines to help cure HCV³⁴⁸. This includes the combination of sofosbuvir and ledipasvir (Harvoni®) leading to a potential cure initially at €48,000/treatment course³⁴⁹;
- The Spanish Ministry of Health has undertaken deals with the pharmaceutical industry to pay for treatment for 5000 to 6000 patients per year with HCV in Spain at a price of €25,000/course³⁵⁰. Recent negotiations further suggest a price drop to achieve the lowest price in Europe through budget ceiling caps and discounts³⁵¹.

In addition, the Brazilian government appears to be negotiating a price of US\$7,000 (€6,440) for a 12-week course of sofosbuvir³⁵². The situation will be closely monitored.

4.6.3. New medicines for Ebola

We have not looked at prices for new vaccines to help reduce future outbreaks of Ebola as these are still in an experimental stage and not commercially available.

4.7. Prices of new medicines for immunological diseases

There is considerable scrutiny regarding the utilisation and prices of biological medicines (to treat patients with RA) and other conditions of biological disease modifying anti-rheumatic medicines, as expenditure on these medicines now exceeds \$US25 billion (€23 billion) per year³⁵³. This expenditure is helped by their recognised place in the management of patients with RA, although there are still concerns with the price and cost-effectiveness of some of these medicines^{354,355}, with RA affecting approximately 1% of the population³⁵⁶. As mentioned

³⁴⁷ Fraser, J., 2014, *WHO Guidelines May Help With Price Reductions For Hepatitis C Drugs*, Intellectual Property Watch, available at: <http://www.ip-watch.org/2014/04/09/who-guidelines-may-help-with-price-reductions-for-hepatitis-c-drugs/>.

³⁴⁸ Taylor, P., 2014, *France agrees lowest Sovaldi pricing in EU: Government brings cost of hepatitis C drug to €5,000 below list price*, PMLIVE, available at: http://www.pmlive.com/pharma_news/france_agrees_lowest_sovaldi_pricing_in_eu_618661.

³⁴⁹ News H, 2015, *French Strike Deal for Sofosbuvir*, available at: <http://www.baseline-hiv.co.uk/hepatitis-articles/2015/10/26/french-strike-deal-for-sofosbuvir>.

³⁵⁰ Ministerio de Sanidad SSeI, 2014, *Sanidad traslada a las CC AA su compromiso para hacer llegar a los pacientes los nuevos medicamentos para la hepatitis C en condiciones de equidad*, available at: <http://www.msssi.gob.es/gabinete/notasPrensa.do?id=3518>.

³⁵¹ Campillo-Artero, C., García-Armesto, S., and Bernal-Delgado, E., 2016, *The merry-go-round of approval, pricing and reimbursement of drugs against the Hepatitis C virus infection in Spain*. Health policy, <http://dx.doi.org/10.1016/j.healthpol.2016.07.005>.

³⁵² Sovaldi and Harvoni, *Sofosbuvir Cost*, available at: <http://esofosbuvir.com/sofosbuvir-drug/sofosbuvir-cost/>.

³⁵³ Monaco, C. et al., 2015, *Anti-TNF therapy: past, present and future*, International immunology, 27(1), p. 55-62.

³⁵⁴ Iannazzo, S. et al., 2013, *A review of cost-effectiveness evaluations as part of national health technology assessments of biologic DMARDs in the treatment of rheumatoid arthritis*, Expert review of pharmacoeconomics & outcomes research, 13(4), p. 455-468.

³⁵⁵ de Oliveira Junior, H.A. et al., 2015, *Poorer functionality is related to better quality of life response following the use of biological drugs: 6-month outcomes in a prospective cohort from the Public Health System (Sistema Único de Saude)*, Minas Gerais, Brazil, Expert review of pharmacoeconomics & outcomes research, 15(3), p 403-412.

³⁵⁶ Idem.

in the introduction of Chapter 4, annual prices of biological disease modifying anti-rheumatic medicines average €14,200.5 per patient (€10,760.9 to €21,349.2) among the 28 EU MS^{357,358}.

However, 10 out of 46 countries from the WHO European region that were recently surveyed do not reimburse biological medicines for RA. This severely impacts on their subsequent utilisation and patient care, with their utilisation also significantly reduced where there is currently high patient co-payment³⁵⁹. The availability of considerably less expensive biosimilars could alter this situation.

4.8. Prices of generics

European countries typically have different approaches to the pricing of generics. However, they can be categorised under three headings^{360,361} including:

- **Price regulated systems** (prescriptive pricing) – where there are established rules for setting the prices of generics, e.g. Croatia, France and Norway^{362,363,364};
- **Free pricing** - where manufacturers are (relatively) free to set the prices of generics, e.g. Germany, Netherlands, Sweden and the UK^{365,366,367};
- **Combination/mixed approach** - A combination of the two approaches, e.g. Austria³⁶⁸.

These different approaches can lead to substantial differences in the prices of generics among the different European countries, e.g. prices of generics can vary 36-fold or more across countries depending on the molecule and the price-setting mechanisms³⁶⁹. Prices of some generics in Europe are as low as 2% to 4% of their pre-patent loss, e.g. for generic simvastatin and omeprazole in the Netherlands^{370,371,372}, with prices of generics typically lower in high versus low volume generic markets. A study published in 2011 showed that

³⁵⁷ Putrik, P. et al., 2014, *Inequities in access to biologic and synthetic DMARDs across 46 European countries*, Annals of the rheumatic diseases, 73(1), p. 198-206.

³⁵⁸ Monaco, C. et al., 2015, *Anti-TNF therapy: past, present and future*, International immunology, 27(1), p. 55-62.

³⁵⁹ Putrik, P. et al., 2014, *Inequities in access to biologic and synthetic DMARDs across 46 European countries*, Annals of the rheumatic diseases, 73(1), p. 198-206.

³⁶⁰ Simoens, S., 2012, *A review of generic medicine pricing in Europe*, GaBI Journal, 1(1), p. 8-12.

³⁶¹ Godman, B. et al., 2012, *European payer initiatives to reduce prescribing costs through use of generics*, GaBI Journal, 1(1), p. 22-27.

³⁶² Sermet, C. et al., 2010, *Ongoing pharmaceutical reforms in France: implications for key stakeholder groups*, Applied health economics and health policy, 8(1), p. 7-24.

³⁶³ Godman, B. et al., 2011, *Combination of prescribing restrictions and policies to engineer low prices to reduce reimbursement costs*, Expert review of pharmacoeconomics & outcomes research, 11(1), p. 121-129.

³⁶⁴ Brkičić, L.S. et al., 2015, *Pharmaceutical pricing in Croatia: a comparison of ordinances in 2013 versus 2009 and their potential savings to provide future guidance*, GaBI Journal, 4(2), p. 79-89.

³⁶⁵ Andersson, K.A. et al., 2008, *Influence of mandatory generic substitution on pharmaceutical sales patterns: a national study over five years*, BMC health services research, 8, p. 50.

³⁶⁶ Bennie, M. et al., 2012, *Multiple initiatives continue to enhance the prescribing efficiency for the proton pump inhibitors and statins in Scotland*, Expert review of pharmacoeconomics & outcomes research, 12(1), p. 125-130.

³⁶⁷ Woerkom, M. et al., 2012, *Ongoing measures to enhance the efficiency of prescribing of proton pump inhibitors and statins in The Netherlands: influence and future implications*, Journal of comparative effectiveness research, 1(6), p. 527-538.

³⁶⁸ Godman, B. et al., 2008, *Insight into recent reforms and initiatives in Austria: implications for key stakeholders*, Expert review of pharmacoeconomics & outcomes research, 8(4), p. 357-371.

³⁶⁹ Simoens, S., 2007, *International comparison of generic medicine prices*, Current medical research and opinion, 23(11), p. 2647-2654.

³⁷⁰ Godman, B. et al., 2009, *Multifaceted national and regional drug reforms and initiatives in ambulatory care in Sweden: global relevance*, Expert review of pharmacoeconomics & outcomes research, 9(1), p. 65-83.

³⁷¹ Bennie, M. et al., 2012, *Multiple initiatives continue to enhance the prescribing efficiency for the proton pump inhibitors and statins in Scotland*, Expert review of pharmacoeconomics & outcomes research, 12(1), p. 125-130.

³⁷² Woerkom, M. et al., 2012, *Ongoing measures to enhance the efficiency of prescribing of proton pump inhibitors and statins in The Netherlands: influence and future implications*, Journal of comparative effectiveness research, 1(6), p. 527-538.

medicine prices among 35 active substances that had lost their patents dropped by 43.2% by the end of the study in high volume markets versus only 21.6% among low volume markets³⁷³.

The population size of a country is not a barrier to obtaining low prices for generics, for instance in Lithuania and the Republic of Srpska^{374,375} despite comments to the contrary³⁷⁶. However, there are concerns that continued low prices for generics will threaten the viability of the generic industry in Europe potentially leading to shortages^{377,378}. This must be guarded against.

The differences in the various approaches to the pricing of generics among European countries can also lead to substantial differences between originator and generic prices. For instance, Greece, Ireland and Spain are currently displaying lower price differentials than Denmark, Finland and Sweden³⁷⁹.

Initiatives and measures used among MS to encourage the prescribing and/or dispensing of generics can be found in Godman et al.³⁸⁰, Dylst, Vulto and Simoens³⁸¹, and Hassali et al.³⁸².

Patient care is not compromised with studies showing no difference in outcomes between good-quality generics and originators (brand-named medicines) across classes^{383,384,385,386}. In fact, patient adherence can be improved through increased use of generics where co-payment is a concern^{387,388,389}.

However, there are still concerns regarding the effectiveness and/or safety of generic medicines among physicians and patients in some countries³⁹⁰. This includes Greece³⁹¹. There can also be confusion among some patients if they are dispensed a variety of different

³⁷³ Dylst, P. and Simoens, S., 2011, *Does the market share of generic medicines influence the price level?: a European analysis*, *PharmacoEconomics*, 29(10), p 875-882.

³⁷⁴ Garuoliene, K. et al., 2011, *European countries with small populations can obtain low prices for drugs: Lithuania as a case history*, *Expert review of pharmacoeconomics & outcomes research*, 11(3), p. 343-349.

³⁷⁵ Markovic-Pekovic, V. et al., 2012, *Ongoing initiatives in the Republic of Srpska to enhance prescribing efficiency: influence and future directions*, *Expert review of pharmacoeconomics & outcomes research*, 12(5), p. 661-671.

³⁷⁶ McKee, M., Stuckler, D. and Martin-Moreno, J.M., 2010, *Protecting health in hard times*, *BMJ*, 341:c5308.

³⁷⁷ Dylst, P. et al., 2013, *Generic medicines: solutions for a sustainable drug market?* *Applied health economics and health policy*, 11(5), p. 437-443.

³⁷⁸ Expert Panel on effective ways of investing in Health (EXPH), 2016, *Report on Access to Health Services in the European Union*, available at: http://ec.europa.eu/health/expert_panel/opinions/docs/015_access_healthservices_en.pdf.

³⁷⁹ McKee, M., Stuckler, D. and Martin-Moreno, J.M., 2010, *Protecting health in hard times*, *BMJ*, 341:c5308.

³⁸⁰ Godman B, et al., 2012, *Payers endorse generics to enhance prescribing efficiency: impact and future implications, a case history approach*. *GaBI*, 1(2), p. 21-35.

³⁸¹ Dylst, P., Vulto, A. and Simoens, S., 2013, *Demand-side policies to encourage the use of generic medicines: an overview*. *Expert review of pharmacoeconomics & outcomes research*, 13(1), p. 59-72.

³⁸² Hassali, M. et al., 2014, *The experiences of implementing generic medicine policy in eight countries: A review and recommendations for a successful promotion of generic medicine use*. *Saudi Medical Journal*, 22: 491-503.

³⁸³ Kesselheim, A. et al., 2008, *Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis*, *JAMA*, 300(21), p. 2514-2526.

³⁸⁴ Kesselheim, A. et al., 2010, *Seizure outcomes following the use of generic versus brand-name antiepileptic drugs: a systematic review and meta-analysis*, *Drugs*, 70(5), p. 605-621.

³⁸⁵ Paton, C., 2006, *Generic clozapine: outcomes after switching formulations*, *The British journal of psychiatry*, 189, p. 184-185.

³⁸⁶ Veronin, M., 2011, *Should we have concerns with generic versus brand antimicrobial drugs? A review of issues*, *JPHSR*, 2, p. 135-150.

³⁸⁷ Barbui, C. and Conti, V., 2014, *Adherence to generic v. brand antidepressant treatment and the key role of health system factors*, *Epidemiology and psychiatric sciences*, p. 1-4.

³⁸⁸ Shrank, W.H. et al., 2006, *The implications of choice: prescribing generic or preferred pharmaceuticals improves medication adherence for chronic conditions*, *Archives of internal medicine*, 166(3), p. 332-337.

³⁸⁹ Dylst, P., Vulto, A. and Simoens, S., 2015, *Societal value of generic medicines beyond cost-saving through reduced prices*, *Expert review of pharmacoeconomics & outcomes research*, 15(4), p. 701-711.

³⁹⁰ Dunne, S. et al., 2013, *A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study*, *BMC pharmacology & toxicology*, 14, p. 1.

³⁹¹ Tsiantou, V. et al., 2009, *Generic medicines: Greek physicians' perceptions and prescribing practices*, *Journal of clinical pharmacy and therapeutics*, 34(5), p. 547-554.

branded generics on different occasions, leading potentially to over- and under-dosing³⁹². Both situations need to be addressed to enhance potential savings from the increasing availability of standard medicines as generics. Potential measures and initiatives can include fining companies for misinformation, as happened in France following the extent of misinformation regarding generic clopidogrel from the originator company³⁹³, as well as increasing International Non-proprietary Name (INN) prescribing. High INN prescribing rates are seen in the UK through physician education, starting in medical school, with up to 98-99% of prescriptions across a variety of products and disease areas³⁹⁴.

There are also a variety of measures and initiatives that health authorities can use to encourage physicians to increase their prescribing of generics versus patented products in a class to save resources without compromising on care^{395,396,397}. These are also described in various publications^{398,399,400}. This can lead to appreciable differences in expenditure between countries when coupled with measures to obtain low prices for generics. For instance, expenditure on the PPIs and statins in Ireland was over ten times that in Sweden in 2007 when adjusted for population sizes. This difference was due to multiple measures in Sweden to encourage the prescribing of generic PPIs and statins as opposed to patented products in the class versus limited initiatives in Ireland to combat marketing activities of the manufacturers of patented medicine in these two classes⁴⁰¹. Care is not compromised as the medicines in these classes are seen as essentially similar at therapeutic doses^{402,403}.

These are part of the general measures across Europe to enhance the appropriate and affordable use of medicines. They are also a key component of care, especially for non-communicable disease, given the growing prevalence across Europe.

Documenting the effectiveness of measures to enhance the prescribing of generics versus originators (brand names) or patented products and potential savings, including their potential societal value, is outside the scope of this report. However, summaries can be found

³⁹² Olsson, E. et al., 2014, *Pharmacist-patient communication in Swedish community pharmacies*, Research in social & administrative pharmacy, 10(1), p. 149-155.

³⁹³ Editorial, 2013, *Generic bashing: effective but illegal*, PRESCRIRE INTERNATIONAL, 22(144), p. 307.

³⁹⁴ Godman, B. et al., 2013, *Reforms and initiatives in Scotland in recent years to encourage the prescribing of generic drugs, their influence and implications for other countries*. Expert review of pharmacoeconomics & outcomes research. 13(4), p. 469-482.

³⁹⁵ Corrao, G. et al., 2014, *Similarity between generic and brand-name antihypertensive drugs for primary prevention of cardiovascular disease: evidence from a large population-based study*, European journal of clinical investigation, 44(10), p. 933-939.

³⁹⁶ Usher-Smith, J. et al., 2008, *Evaluation of the clinical outcomes of switching patients from atorvastatin to simvastatin and losartan to candesartan in a primary care setting: 2 years on*, International journal of clinical practice, 62(3), p. 480-484.

³⁹⁷ Sakshaug, S. et al., 2007, *Switching statins in Norway after new reimbursement policy: a nationwide prescription study*, British journal of clinical pharmacology, 64(4), p. 476-481.

³⁹⁸ Godman, B. et al., 2010, *Comparing policies to enhance prescribing efficiency in Europe through increasing generic utilisation: changes seen and global implications*. Expert Rev. Pharmacoeconomics Outcomes Res 10: 707-722.

³⁹⁹ Godman, B. et al., 2014, *Multiple policies to enhance prescribing efficiency for established medicines in Europe with a particular focus on demand-side measures: findings and future implications*. Frontiers in Pharmacology. Focused Review 5 (Article 106): 1-9.

⁴⁰⁰ Moon, J. et al., 2014, *Different initiatives across Europe to enhance losartan utilization post generics: impact and implications*. Frontiers in pharmacology. 5:219.

⁴⁰¹ Godman, B. et al., 2010, *Comparing policies to enhance prescribing efficiency in Europe through increasing generic utilisation: changes seen and global implications*. Expert Rev. Pharmacoeconomics Outcomes Res 10: 707-722.

⁴⁰² Idem.

⁴⁰³ Weng, T. et al., 2010, *A systematic review and meta-analysis on the therapeutic equivalence of statins*. Journal of clinical pharmacy and therapeutics. 35(2), p. 139-151.

in reviews by Babar, Kan and Scahill⁴⁰⁴, Dylst et al.⁴⁰⁵, Dylst, Vulto and Simoens^{406,407}, Moe-Byrne et al.⁴⁰⁸, as well as Vogler et al. in addition to Godman et al.^{409, 410,411} (see also Chapter 6.2.4.).

4.9. Prices of biosimilars

The increasing use of biological medicines at appreciably higher prices than small molecules, e.g. biological medicines for cancer, immunological diseases and orphan diseases, is enhancing the attractiveness of biosimilars to health authorities^{412,413}. However, their uptake to date has been hampered by limited price reductions at 15% to 30% versus originators, as well as concerns with their effectiveness and safety, including immunogenicity, versus originators^{414,415}. Concerns with safety, including immunogenicity, have been heightened by misconceptions about the extent of clinical trials necessary for biosimilars to obtain MA, as well as the level misinformation^{416,417}. The extent of misinformation prompted the EC to issue documents and suggested strategies to all key stakeholder groups to address areas of concern. For instance, in the patient Q & A section, the EU Commission stated the following: *'Qu: 11. Is there any difference in safety between the biosimilar and the reference product? Answer - No, an approved biosimilar medicine and its reference medicine are expected to have the same safety and efficacy profile. EU legislation defines the studies that need to be performed for the biosimilar medicine to demonstrate similarity in quality, safety and efficacy (therapeutic effect) in relation to its reference medicine, and that there is no significant clinical difference to the reference medicine. Based on the information published on the EMA website, no specific safety issue has been identified for approved and marketed biosimilar medicines at the time of publication of this consensus information document'*⁴¹⁸.

The usage of biosimilars should increase in the future. For instance, the combined hospital group in Norway in 2015 will be obtaining biosimilar infliximab at a 69% discount compared with the originator tender price (REMICADE®) and a 72% discount compared with its list

⁴⁰⁴ Babar, Z.U., Kan, S.W, and Scahill, S., 2014, *Interventions promoting the acceptance and uptake of generic medicines: A narrative review of the literature*, Health Policy, 117(3), p. 285-96.

⁴⁰⁵ Dylst, P. et al., 2013, *Generic medicines: solutions for a sustainable drug market?*, Applied health economics and health policy, 11(5), p. 437-443.

⁴⁰⁶ Dylst, P., Vulto, A. and Simoens, S., 2015, *Societal value of generic medicines beyond cost-saving through reduced prices*, Expert review of pharmacoeconomics & outcomes research, 15(4), p. 701-711.

⁴⁰⁷ Dylst, P., Vulto, A. and Simoens, S., 2013, *Demand-side policies to encourage the use of generic medicines: an overview*, Expert review of pharmacoeconomics & outcomes research, 13(1), p. 59-72.

⁴⁰⁸ Moe-Byrne, T. et al., 2014, *Behaviour change interventions to promote prescribing of generic drugs: a rapid evidence synthesis and systematic review*, BMJ open, 4(5):e004623.

⁴⁰⁹ Godman, B. et al., 2013, *Ongoing measures to enhance prescribing efficiency across Europe: implications for other countries*, J Health Tech Assess, 1, p. 27-42.

⁴¹⁰ Godman, B. et al., 2012, *Payers endorse generics to enhance prescribing efficiency: impact and future implications, a case history approach*, GaBI Journal, 1(2), p. 69-83.

⁴¹¹ Godman, B. et al., 2012, *Essential to increase the use of generics in Europe to maintain comprehensive healthcare?*, Farmeonomia: Health Economics and Therapeutic Pathways, 13(3), p. 5-20.

⁴¹² Höer, H. et al., 2012, *Saving money in the European healthcare systems with biosimilars*. GaBI, 1(3-4), p. 120-126.

⁴¹³ Befrits, G., 2013, *The case for biosimilars—a payer's perspective*. GaBI 2(1), p. 12.

⁴¹⁴ Godman, B., 2013, *Editorial – Health authority perspective on biosimilars*. GaBI Journal. 2(1), p. 10-11.

⁴¹⁵ Declerck, P. and Simoens, S., 2012, *A European perspective on the market accessibility of biosimilars*. Biosimilars 2: 33-40.

⁴¹⁶ NEFARMA., 2013, *Biosimilars – biopharmaceuticals and biosimilars*, available at: www.nefarma.nl/stream/com-biologicals-and-biosimilars.

⁴¹⁷ Lee, J., Litten, B., and Grampp, G., 2012, *Comparability and biosimilarity: considerations for the healthcare provider*, Curr Med Res Opin, 28(6), p. 1053-1058.

⁴¹⁸ European Commission. *What you need to know about Biosimilar Medicinal Products*. A consensus information document, available at: <http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEwiVnb-IjPXNAhUGzxQKHbYcAXgQFggcMAA&url=http%3A%2F%2Fec.europa.eu%2FDocsRoom%2Fdocuments%2F8242%2Fattachments%2F1%2Ftranslations%2Fen%2Frenditions%2Fnative&usq=AFQjCNFTThS0xnIASOEer3pfGpGSBrpl2mQ&bvm=bv.127178174,d.bGs>.

price^{419,420}. Possible concerns with potential side effects, including issues of immunogenicity, are being addressed by the Ministry of Health in Norway, which is funding the 'NOR-SWITCH' study. The 'NOR-SWITCH' study compares the effectiveness and safety of originators and biosimilars in routine clinical care⁴²¹.

⁴¹⁹ Huizinga, T.W.J. and Gröndal, G., 2016, *Drivers of costly treatment strategies in rheumatoid arthritis*, The Lancet, 388(May), p. 213-214.

⁴²⁰ Mack A. Norway, 2015, *biosimilars in different funding systems*. What works? Generics and Biosimilars Initiative Journal. 4(2), p. 90-92.

⁴²¹ Idem.

5. MODELS TO OPTIMISE THE USE OF NEW MEDICINES

KEY FINDINGS

- New models to improve the managed entry of new medicines are based on three pillars, starting at pre-launch, through peri-launch and progressing to post-launch activities.
- Pre-launch activities include horizon scanning of new medicines as well as forecasting expenditures for planning and budget purposes. This will increase the use of BIAs in decision-making.
- Different European countries have different (peri-launch) approaches to the pricing and reimbursement of new medicines, including use of comparators, cost considerations, and analytical methods.
- There is currently no agreement regarding the definition of innovation among European countries. Developments in the pricing of new medicines include greater scrutiny over their value given the limited innovation with most new medicines. This includes developments with MEAs as well as developments around VBP and MCDA.
- Post-launch activities include patient registries to assess the effectiveness and safety of new medicines in routine clinical care, as well as monitoring prescribing against agreed guidance and any developed quality indicators.

5.1. Introduction

As mentioned, financial pressures on European health authorities are growing due to ageing populations and stricter clinical targets⁴²². There are also growing concerns among European health authorities with ever-increasing prices for new specialty medicines, which are straining health budgets, even for high-income countries⁴²³. Among 33 OECD countries, expenditure on medicines reached US\$800 billion (€736 billion) in 2013, with new, premium-priced medicines coupled with rising patient demand likely to continue to push pharmaceutical expenditure higher unless addressed⁴²⁴. These concerns have resulted in the development of new models to optimise the managed entry of new medicines, whilst still ensuring access for new, valued medicines (Figure 3)^{425,426,427}.

⁴²² Godman, B. et al., 2015, *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?* Expert review of clinical pharmacology, 8(1), p.77-94.

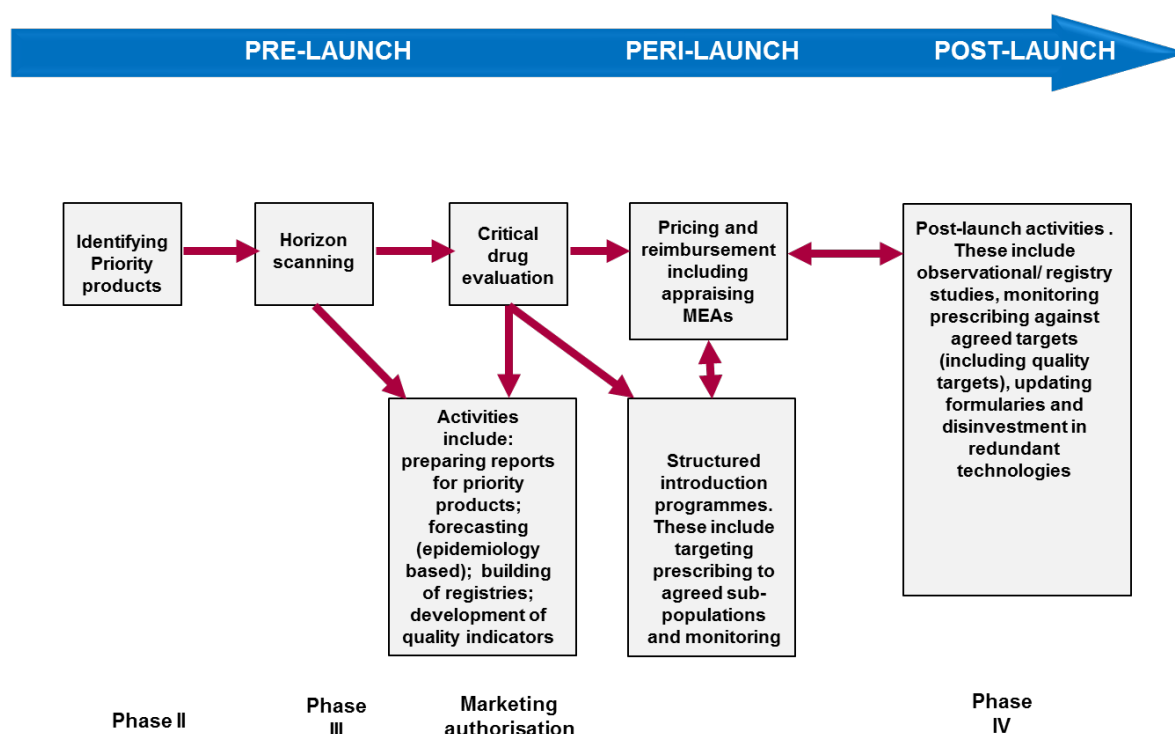
⁴²³ WHO European Office, *Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research*, 2015, WHO: Copenhagen, available at: <http://www.euro.who.int/en/health-topics/Health-systems/medicines/publications2/2015/access-to-new-medicines-in-europe-technical-review-of-policy-initiatives-and-opportunities-for-collaboration-and-research>.

⁴²⁴ OECD, 2015, *Health at a Glance 2015: OECD Indicators*, OECD Publishing: Paris, available at: http://www.oecd-ilibrary.org/docserver/download/health_glance-2015-sum-en.pdf?expires=1447069970&id=id&accname=quest&checksum=BACE5CB3DED5B5C8D34BA9B86F6E24E1.

⁴²⁵ Godman, B. et al., 2015, *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?* Expert review of clinical pharmacology, 8(1), p.77-94.

⁴²⁶ WHO European Office, 2015, *Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research*, WHO: Copenhagen, available at: <http://www.euro.who.int/en/health-topics/Health-systems/medicines/publications2/2015/access-to-new-medicines-in-europe-technical-review-of-policy-initiatives-and-opportunities-for-collaboration-and-research>.

⁴²⁷ Malmstrom, R. et al., 2013, *Dabigatran - a case history demonstrating the need for comprehensive approaches to optimize the use of new drugs*, Frontiers in pharmacology, 4, p. 39.

Figure 3: Pro-active measures to improve the managed entry of new medicines

Source: Adapted from Godman et al.⁴²⁸, Malmstrom et al.⁴²⁹ and Permanand and Bak Pedersen⁴³⁰.

The proposed model (Figure 3) is based around three pillars of pre-, peri-, and post-launch activities. This model was developed by health authority and health insurance company personnel from across Europe in response to budgetary concerns with new medicines, as well as with concerns regarding new oral anticoagulants (NOACs) in routine clinical care^{431,432} (Chapter 7.2). There are also concerns that promising evidence from clinical trials does not always translate into improvements in patient outcomes^{433,434,435}. As a result, there is an increasing need for pharmaceutical companies to focus on meaningful patient outcomes during drug development to enhance potential funding. In addition, there will be an increasing focus by health authorities and others post-launch to assess the effectiveness and value of new medicines in routine patient care to help ensure the optimal use of available

⁴²⁸ Godman, B. et al., 2015, *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?* Expert review of clinical pharmacology, 8(1), p.77-94.

⁴²⁹ Malmstrom, R.E. et al., 2013, *Dabigatran - a case history demonstrating the need for comprehensive approaches to optimize the use of new drugs*, Frontiers in pharmacology, 4, p.39.

⁴³⁰ Permanand, G., Bak Pedersen H., 2015, *Managing new premium-priced medicines in Europe*. Journal of pharmaceutical policy and practice, 8(Suppl 1), p. 1-3.

⁴³¹ Godman, B. et al., 2015, *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?* Expert review of clinical pharmacology, 8(1), p.77-94.

⁴³² Malmstrom, R.E. et al., 2013, *Dabigatran - a case history demonstrating the need for comprehensive approaches to optimize the use of new drugs*, Frontiers in pharmacology, 4, p.39.

⁴³³ Naci, H. and Ioannidis, J.P., 2015, *How good is "evidence" from clinical studies of drug effects and why might such evidence fail in the prediction of the clinical utility of drugs?* Annual review of pharmacology and toxicology, 55, p. 169-189.

⁴³⁴ Prescrire, 2015, *"Adaptive licensing" or "adaptive pathways": Deregulation under the guise of earlier access*, available at: http://english.prescrire.org/Docu/DOCSEUROPE/20151019_AdaptiveLicensing.pdf.

⁴³⁵ Eichler, H. et al., 2011, *Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response*. Nature reviews Drug discovery. 10(7), p. 495-506.

resources^{436,437} (similar to approaches for adaptive pathways, Chapter 3.3.1). There will also be increased focus by health authorities post-launch to enhance the prescribing of new medicines against agreed guidance and indicators (Chapter 5.9.1).

These developments will require greater interaction between pharmaceutical companies and health authorities during drug development and pre-launch activities. This will help ensure clinical trials and their interpretation meet the needs of health authorities when coming to assess their role and value⁴³⁸.

5.2. Pre-launch activities

Pre-launch activities include horizon scanning/early warning systems of new medicines. Horizon scanning has been defined as *"identifying new medicines or new uses of existing medicines that are expected to receive MA from the Regulatory Authority in the near future and estimating their potential impact on patient care"*^{439,440}.

Other authors and agencies have defined horizon scanning/early warning systems as: *"An effective early warning system is a system which: identifies innovations in the field of health technology likely to have a significant impact; and disseminates information relevant to the needs of the customer which is timely, so as to enable appropriate decision making (such as resource allocation), facilitate appropriate adoption, and identify further research requirements"*⁴⁴¹.

There are a number of examples of different countries instigating horizon scanning approaches^{442,443,444}. Since 1999, countries in Europe, North America, and the Asia-Pacific region have been collaborating under the EuroScan project (International Information Network on New and Emerging Health Technologies)^{445,446}. Each member agency is unique in its approach. However, they all have a common goal to inform particularly health authorities and hospital managers about new and emerging technologies that could have a

⁴³⁶ Godman, B. et al., 2015, *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?* Expert review of clinical pharmacology, 8(1), p.77-94.

⁴³⁷ Naci, H. and Ioannidis, J.P., 2015, *How good is "evidence" from clinical studies of drug effects and why might such evidence fail in the prediction of the clinical utility of drugs?* Annual review of pharmacology and toxicology, 55, p. 169-189.

⁴³⁸ Wonder, M., 2014, *What can be gained from increased early-stage interaction between regulators, payers and the pharmaceutical industry?* Expert review of pharmacoeconomics & outcomes research, 14(4), p.465-467.

⁴³⁹ Wild, C. et al., 2009, *Information service on new and emerging health technologies: identification and prioritization processes for a European union-wide newsletter*, International journal of technology assessment in health care, 25, Suppl 2, p.48-55.

⁴⁴⁰ Packer, C., Fung, M. and Stevens, A., 2012, *Analyzing 10 years of early awareness and alert activity in the United Kingdom*, International journal of technology assessment in health care, 28(3), 308-314.

⁴⁴¹ Murphy, K. et al., 2007, *Effective early warning systems for new and emerging health technologies: developing an evaluation framework and an assessment of current systems*, International journal of technology assessment in health care, 23(3), p.324-330.

⁴⁴² Wettermark, B. et al., 2010, *Einführung neuer Arzneimittel in europäische Gesundheitssysteme (Introduction of new medicines into European healthcare systems)*, GGW, 10(3), p. 24-34.

⁴⁴³ Miles, I. and Saritas, O., 2012, *The depth of the horizon: searching, scanning and widening horizons*, Foresight, 14(6), p.530-545.

⁴⁴⁴ Sun, F. and Schoelles, K., *A systematic review of methods for health care technology horizon scanning*, (Prepared by ECRI Institute under Contract No. 290-2010-00006-C.) AHRQ Publication No. 13-EHC104-EF, August 2013, Agency for Healthcare Research and Quality: Rockville MD, available at: <http://www.effectivehealthcare.ahrq.gov/>.

⁴⁴⁵ Packer, C., Fung, M. and Stevens, A., 2012, *Analyzing 10 years of early awareness and alert activity in the United Kingdom*, International journal of technology assessment in health care, 28(3), 308-314.

⁴⁴⁶ Nachtnebel, A. et al., 2012, *Scanning the horizon: development and implementation of an early awareness system for anticancer drugs in Austria*, Health policy, 104(1), p. 1-11.

significant budget impact^{447,448}. Horizon scanning typically consists of five sequenced components (Table 13).

Table 13: Sequenced components for horizon scanning activities

Step	Activity
1	Identifying new medicines and filtering them
2	Priority setting for topics/medicines
3	Early assessment of new medicines
4	Disseminating findings for key stakeholder groups
5	Monitoring the information provided, including feedback from stakeholders and updates

The key characteristics of any horizon scanning/early warning system must include the relevance of the data provided to key stakeholder groups, the independence of the assessors, adequate resourcing, a clear pathway for distributing the findings (outputs) in order to reach key decision makers and a defined set of customers⁴⁴⁹.

Information sources for new medicines (Step 1) include pharmaceutical companies, regulatory agencies, the medical scientific literature, conference presentations, newspaper articles as well as online information, portals/providers of information, such as Medscape^{450,451,452}. Filtering and prioritisation medicines as well as topics for further evaluation (Steps 1 & 2) typically include the potential health benefits of new medicines (health gain versus current standards), as well as their potential budget impact, with the latter also including potential savings where pertinent. Prioritisation of topics is key given the appreciable number of new medicines in development⁴⁵³.

Pre-launch (early) assessments of new medicines (Step 3) are typically undertaken up to three years before their likely launch date⁴⁵⁴. One example of a well-established horizon scanning operation is Italy, namely the Italian Horizon Scanning Project⁴⁵⁵. This group provides critical reports on new emerging medicines in a timely fashion, including their potential budget impact, to the Italian National Health System to improve health authority planning. The Italian group issues several reports following filtering and prioritisation (Steps 3 to 5). The first reports are issued up to 36 months before likely MA by EMA.

⁴⁴⁷ Simpson, S. et al., 2009, *A toolkit for the identification and assessment of new and emerging health technologies*, EuroScan Birmingham ISBN: 0704427257/9780704427259, p. 1-30.

⁴⁴⁸ Martino, O. et al., 2012, *Innovation and the burden of disease: retrospective observational study of new and emerging health technologies reported by the EuroScan Network from 2000 to 2009*, Value in health, 15(2), p.376-380.

⁴⁴⁹ Murphy, K. et al., 2007, *Effective early warning systems for new and emerging health technologies: developing an evaluation framework and an assessment of current systems*, International journal of technology assessment in health care, 23(3), p.324-330.

⁴⁵⁰ Wettermark, B. et al., 2010, *Einführung neuer Arzneimittel in europäische Gesundheitssysteme (Introduction of new medicines into European healthcare systems)*, GGW, 10(3), p. 24-34.

⁴⁵¹ Miles, I. and Saritas, O., 2012, *The depth of the horizon: searching, scanning and widening horizons*, Foresight, 14(6), p.530-545.

⁴⁵² Nachtnebel, A. et al., 2012, *Scanning the horizon: development and implementation of an early awareness system for anticancer drugs in Austria*, Health policy, 104(1), p. 1-11.

⁴⁵³ European Federation of Pharmaceutical Industries and Associations, *HEALTH & GROWTH – Evidence Compendium*, 2013, available at: http://www.efpia.eu/uploads/Modules/Documents/health-and-growth_evidence-compendium.pdf.

⁴⁵⁴ Wettermark, B. et al., 2010, *Einführung neuer Arzneimittel in europäische Gesundheitssysteme (Introduction of new medicines into European healthcare systems)*, GGW, 10(3), p. 24-34.

⁴⁵⁵ Joppi, R. et al., 2009, *The Italian Horizon Scanning Project*, European journal of clinical pharmacology, 65(8), p.775-781.

The English National Horizon Scanning Centre is another good example of pre-launch activities. A recent analysis suggested the centre performed well in terms of its sensitivity in predicting medicines that could impact on the UK National Health System. However, they believed, based on a recent analysis, that the filtration criteria for new medicines could be improved for increased efficiency⁴⁵⁶.

Forecasting of the potential utilisation and expenditure of new medicines is essential to improve planning and resource allocation to enhance their rational introduction^{457,458}. Planning may include (i) the development of guidelines for the prescribing of new medicines based on a critical evaluation of available evidence and current practices; (ii) instigation of educational activities around a new medicine to optimise its use following launch, especially if there are concerns with patient safety in wider, more co-morbid populations; (iii) budget-setting, including potentially developing quality indicators to guide subsequent use; and (iv) potentially developing registries to monitor the safety and/or effectiveness of new medicines in routine clinical practice^{459,460,461}.

Concerns with traditional models that have been used for forecasting uptake and expenditures of new medicines, especially new, high-cost biological medicines⁴⁶², led to the development of a new forecasting model in Stockholm County Council Sweden⁴⁶³. This model involves 23 medical and scientific groups, with regression analyses conducted on aggregate sales data. Predicted trends are adjusted for likely changes, including any patent expiries among key therapeutic areas, new guidelines, reimbursement decisions and/or the introduction of new medicines. There have been similar examples for medical devices⁴⁶⁴. This builds on current concerns with the early assessment of new medical devices⁴⁶⁵.

5.3. Peri-launch activities

Peri-launch activities typically centre around the pricing and reimbursement of new medicines, with members of the public and other stakeholders increasingly involved in decision making, e.g. UK through NICE and Scottish Medicines Consortium (SMC)^{466,467}.

⁴⁵⁶ Packer, C., Fung, M. and Stevens, A., 2012, *Analyzing 10 years of early awareness and alert activity in the United Kingdom*, International journal of technology assessment in health care, 28(3), 308-314.

⁴⁵⁷ WHO European Office, *Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research*, 2015, WHO: Copenhagen, available at: <http://www.euro.who.int/en/health-topics/Health-systems/medicines/publications/2015/access-to-new-medicines-in-europe-technical-review-of-policy-initiatives-and-opportunities-for-collaboration-and-research>.

⁴⁵⁸ Wettermark, B. et al., 2010, *Forecasting drug utilization and expenditure in a metropolitan health region*, BMC health services research, 10, p. 128.

⁴⁵⁹ Godman, B. et al., 2015, *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?* Expert review of clinical pharmacology, 8(1), p.77-94.

⁴⁶⁰ Campbell, S.M. et al., 2015, *Quality indicators as a tool in improving the introduction of new medicines*, Basic & clinical pharmacology & toxicology, 116(2), p. 146-157.

⁴⁶¹ Matusewicz, W. et al., 2015, *Improving the managed introduction of new medicines: sharing experiences to aid authorities across Europe*, Expert review of pharmacoeconomics & outcomes research, 15(5), p.755-758.

⁴⁶² Hartz, S. and John, J., 2009, *Public health policy decisions on medical innovations: what role can early economic evaluation play?* Health policy, 89(2), p. 184-192.

⁴⁶³ Wettermark, B. et al., 2010, *Forecasting drug utilization and expenditure in a metropolitan health region*, BMC health services research, 10, p. 128.

⁴⁶⁴ Kolominsky-Rabas, P.L. et al., 2015, *Technology foresight for medical device development through hybrid simulation: The ProHTA Project*, Technological Forecasting & Social Change, 97, p. 105-114.

⁴⁶⁵ Markiewicz, K., van Til, J.A. and IJzerman, M.J., 2014, *Medical devices early assessment methods: systematic literature review*, International journal of technology assessment in health care, 30(2), p. 137-146.

⁴⁶⁶ Rosenberg-Yunger, Z.R. et al., 2012, *Stakeholder involvement in expensive drug recommendation decisions: an international perspective*, Health policy, 105(2-3), p. 226-235.

⁴⁶⁷ Ford, J.A. et al., 2012, *NICE guidance: a comparative study of the introduction of the single technology appraisal process and comparison with guidance from Scottish Medicines Consortium*, BMJ open, 2(1):e000671.

However, the purpose of and the methods used for stakeholder engagement need to be clear for transparency reasons⁴⁶⁸.

New medicines are considered of value when they improve the health of patients either because they are more effective, have less side-effects, or are easier to administer than current standard medicines, and thus are seen as more cost-effective^{469,470,471}. This requires rigorous, transparent and careful evaluation using HTA methods to assess their potential role and value versus current standards, given the ever-increasing pressure on available resources within countries^{472,473,474,475}.

The WHO, in their guideline on country pricing policies for new medicines, recommended a number of considerations, including greater use of HTA in pricing considerations (Table 14).

Table 14: Summary of recommended policies by the WHO for pricing of new medicines

Policy Intervention	Recommendations
Cost-plus pricing	<ul style="list-style-type: none"> Countries generally should not use cost-plus as an overall pharmaceutical pricing policy as better alternatives are available and concerns with, for instance, obtaining accurate figures on the cost of R&D; If used, authorities should consider replacing or complementing the cost-plus approach with other policies such as VBP
ERP (building on Chapter 4.3.1)	<ul style="list-style-type: none"> Countries may well consider using ERP as a method for pricing new medicines as part of an overall pricing strategy, in combination with other methods; When developing an ERP system, countries should define transparent methods and processes as this is not always the case; Countries/payers should select comparator countries based on issues such as the economic status of comparator countries, their pharmaceutical pricing systems, publication of actual versus negotiated or concealed prices (where these can be obtained,

⁴⁶⁸ Kreis, J. and Schmidt, H., 2013, *Public engagement in health technology assessment and coverage decisions: a study of experiences in France, Germany, and the United Kingdom*, Journal of health politics, policy and law, 38(1), p.89-122.

⁴⁶⁹ Sermet, C. et al., 2010, *Ongoing pharmaceutical reforms in France: implications for key stakeholder groups*, Applied health economics and health policy, 8(1), p. 7-24.

⁴⁷⁰ Malmstrom, R.E. et al., 2013, *Dabigatran - a case history demonstrating the need for comprehensive approaches to optimize the use of new drugs*, Frontiers in pharmacology, 4, p. 39.

⁴⁷¹ Godman, B. et al., 2013, *Ongoing measures to enhance prescribing efficiency across Europe: implications for other countries*, J Health Tech Assess, 1, p. 27-42.

⁴⁷² Van Wilder, V. et al., 2015, *Towards a harmonised EU assessment of the added therapeutic value of medicines, study for the ENVI Committee*, available at: [http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU\(2015\)542219_EN.pdf](http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU(2015)542219_EN.pdf).

⁴⁷³ Elbarbary, M., 2010, *Health technology assessment (HTA) in cardiac field*. Journal of the Saudi Heart Association, 22(2), p. 77-84.

⁴⁷⁴ WHO European Office. *Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research*. Copenhagen: 2015.

⁴⁷⁵ Fischer, K.E., Grosse, S.D. and Rogowski, W.H., 2011, *The role of health technology assessment in coverage decisions on newborn screening*, International journal of technology assessment in health care, 27(4), p. 313-21.

Policy Intervention	Recommendations
	<p>acknowledging particularly in Europe that negotiations are often confidential⁴⁷⁶), and similar burden of disease;</p> <ul style="list-style-type: none"> • However, there are increasing concerns with this approach. This is likely to lead to further refinements for assessing the value of new medicines including issues of affordability.
Use of HTA	<ul style="list-style-type: none"> • Countries should use HTA as a tool to support reimbursement decision-making as well as price-setting/negotiations, potentially combining HTA with other policies and strategies, including ERP as well as IRP; • Countries should consider the following approaches: (i) review the applicability and potential adaptation of HTA reports from other countries; (ii) whether to review health economic evaluations submitted by pharmaceutical companies; (iii) alternatively, conducting their own assessments based on local information and local data (considerably more time-consuming and costly). The choices will depend on issues such as the technical capacity within a country, available resources and timings, e.g. to fit in with national or Pan-European guidelines; • Countries should take a stepwise approach to develop legislative and technical capacity, including defining the roles and responsibilities of key decision-makers and other stakeholders, as well as the process of decision-making; • HTA processes should be transparent and, where practical, assessments and decisions should be made publicly available to help other HTA organisations; • Where the incremental cost per QALY for a new medicine is less than a country's per capita GDP, the new medicine should invariably be considered as cost-effective. New medicines and other technologies, where the incremental cost per QALY is more than three times a country's per capita GDP, should typically be seen as not cost-effective⁴⁷⁷. • Countries/health authorities should collaborate to promote the exchange of information and develop common requirements for HTA to help conserve resources.

Whatever pricing approaches are used, there needs to be a balance against the desire to reward innovation against the needs of health authorities in Europe to continue providing equitable and comprehensive healthcare. This has led to the growth in concepts such as fair

⁴⁷⁶ Ferrario, A. and Kanavos, P., 2013, *Managed entry agreements for pharmaceuticals: the European experience*, EMINet: Brussels, available at: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/mea_report_en.pdf.

⁴⁷⁷ Rawlins, M., 2007, *Paying for modern cancer care--a global perspective*, *The lancet oncology*, 8(9), p.749-751.

pricing^{478,479}. Concerns with the prices of new medicines are heightened among health authorities as they perceive a limited level of innovation of most new medicines. This compares with ever-increasing requested prices of new medicines from pharmaceutical companies⁴⁸⁰. For instance, since the mid-1990s, independent published reviews have suggested that 85-90% of all new medicines provide few or no clinical advantages for patients compared with existing standard medicines⁴⁸¹. The authorities in Canada came to similar decisions⁴⁸². Only 67 out of 824 new medicine applications submitted to the authorities in Belgium for reimbursement considerations between 2002 and 2004 claimed 'added therapeutic value' versus current standards, i.e. envisaging higher prices than current standards. Out of these, only half were eventually granted 'added therapeutic value' status by the Belgium authorities⁴⁸³.

Prescrire, an independent critical drug information journal in France, believed only 2% of new indications for existing medicines or new medicines in France were truly innovative and/or offered a real therapeutic advantage over existing treatments, despite the hype (Table 15). Similarly, the *Geneesmiddelenbulletin*, an independent Dutch information bulletin on medicines, when evaluating 92 medicines between 2000 and 2011, believed none were therapeutic advances versus existing standard treatments and only 5.4% were considered to have added value for patients⁴⁸⁴.

Table 15: Percentage ratings by *Prescrire* of the level of innovation of new medicines and new indications introduced in France between 2007 to 2011

Prescrire ratings/criteria	2007	2008	2009	2010	2011	2012
Total number of new medicines/new indications	141	120	104	97	92	82
Seen as innovative or a real therapeutic advance	2%	0%	0%	1%	0%	1%
Appears to offer an advantage over current standard treatments	10%	5%	3%	3%	3%	4%
Possibly helpful over existing medicines, or minimal or no clinical advantage compared to existing standard treatments	75%	68%	73%	73%	72%	68%
Other categories including not viewed as acceptable medicine for routine care, including safety concerns, and	13%	27%	24%	23%	25%	27%

⁴⁷⁸ Expert Panel on effective ways of investing in Health (EXPH), 2016, *Report on Access to Health Services in the European Union*, available at:

http://ec.europa.eu/health/expert_panel/opinions/docs/015_access_healthservices_en.pdf.

⁴⁷⁹ Hill SR, Bero L, McColl G, and Roughead E, 2015, Expensive medicines: ensuring objective appraisal and equitable access. *Bulletin of the World Health Organization*. 93(1), p. 4.

⁴⁸⁰ Vandenbroeck, P. et al., 2016, Future scenarios about drug development and drug pricing. *Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE)*. 2016. KCE Reports 271. D/2016/10.273/59.

⁴⁸¹ Light, D. and Lexchin, J., 2012, *Pharmaceutical research and development: what do we get for all that money?*, *BMJ*, 345: e4348.

⁴⁸² Lexchin, J., 2012, *International comparison of assessments of pharmaceutical innovation*, *Health policy*, 105(2-3), p. 221-225.

⁴⁸³ Van Wilder, P. and Dupont, A., 2008, *Introducing evidence-based medicine in reimbursement procedures: does it affect the outcome?*, *Value in health*, 11(4), p. 784-787.

⁴⁸⁴ Lexchin, J., 2012, *International comparison of assessments of pharmaceutical innovation*, *Health policy*, 105(2-3), p. 221-225.

judgement reserved due to for
instance to insufficient data currently
available from clinical trials

Source: Adapted from *Prescrire* editorial reference⁴⁸⁵.

There are differences in the way HTA agencies and programmes in each country are organised, operated, and deal with pricing and reimbursement decisions for new medicines⁴⁸⁶. Within Europe, competent authorities use a variety of approaches to assess potential pricing and reimbursement of new medicines^{487,488} based on prices initially proposed by pharmaceutical companies. The competent authorities typically employ methods and principles of HTA to assess the level of innovation and the extent of the added value of a new medicine. Methods include assessing the level of clinical benefit of a new medicine in comparison with current standard treatments for that disease.

The perceived level of innovation of new medicines is used as a basis for pricing and reimbursement negotiations in, for example, Austria, France and Germany (Table 16).

Table 16: Criteria used for the reimbursement of new medicines in Austria, France and Germany (based on perceived value versus current standards)

Country	Extent of innovation and subsequent reimbursed prices
Austria: Innovation divided into three categories	<p>The three groupings used by the authorities in Austria to categorise the level of innovation of new medicines include:</p> <ul style="list-style-type: none"> • <i>Substantially</i> added clinical benefit based on assessments by an expert committee. Reimbursed prices are based on an average of prices among selected European countries with a pharmaco-economic study required to justify the requested price; • Added clinical benefit (again, based on an assessment by an expert committee). Reimbursed prices will be a maximum of 10% above the prices of current standard medicines for a particular disease area in Austria, depending on population size (total population or sub-population); • Marginal clinical benefit or similar benefit. Reimbursed price will be a minimum of 10% below the current standard medicines for that disease area in Austria. <p>New medicines are subsequently assigned a different colour code (and have different price levels), which influences their potential prescribing post-launch:</p> <ul style="list-style-type: none"> • a red box/code means a severely restricted medicine that requires the approval of the Chief Medical Officer of the relevant Sickness Fund before reimbursement (otherwise 100% self-pay) • a yellow box/code means a medicine restricted to a defined patient population (may or may not need prior approval)

⁴⁸⁵ Editorial, 2012, *New drugs and indications in 2011. France is better focused on patients' interests after the Mediator scandal, but stagnation elsewhere*, *Prescrire International*, 21(126), p. 106-107

⁴⁸⁶ Sorenson, C. and Chalkidou, K., 2012, *Reflections on the evolution of health technology assessment in Europe*. Health economics, policy, and law, 7(1), p. 25-45.

⁴⁸⁷ WHO European Office, 2015, *Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research*. Copenhagen.

⁴⁸⁸ Paris, V. and Belloni, A., 2013, *Value in Pharmaceutical Pricing*, OECD Health Working Paper No 63, July 2013, OECD Publishing: Paris.

Country	Extent of innovation and subsequent reimbursed prices
<p>France: divided into 5 categories</p>	<ul style="list-style-type: none"> a green box/code means that physicians can prescribe the new medicine without restrictions The ASMR (added therapeutic value) for a new medicine is assessed by the Transparency Commission in France; ASMR I-II-III (ASMR I and II represent a major or significant improvement in efficacy and/or side-effects versus current standard treatments judged by an expert commission, with ASMR III representing a modest improvement) means that the reimbursed price for the new medicine will be based on prices of the new medicine in selected European countries (Germany, Spain, Italy and the UK); ASMR IV represents a minor improvement with typically similar prices to current standard treatments in France being granted for reimbursement; ASMR V represents no or inadequate improvement versus current standard treatments in France at that time. As a result, the prices will be lower than the current standard treatments for reimbursement. <p>Since 2012, the French authorities have been seeking to combine both the Service Médical Rendu (assessment of the level of unmet medical need by the expert commission) and ASMR ratings into a single score.</p> <p>They have also been undertaking medico-economic assessments of selected new medicines. As of October 2014, the National Health Authority had selected 20 medicines comprising principally expensive and/or innovative medicines, including those for cancer, HIV, HCV and those for rare diseases for such assessments.</p>
<p>Germany: divided into six groups</p>	<ul style="list-style-type: none"> New medicines are assessed by an independent HTA organisation and assigned one of six groups. The groups are based on the degree of innovation versus current standard treatments, primarily based on randomised clinical trials. The six groups are: <ul style="list-style-type: none"> Substantial/major added benefit; Considerable added benefit; Small/minor added benefit; Unquantifiable additional benefit; No additional added benefit; Less benefit than current therapies. The assessments include a systematic review of all published and unpublished data, an estimate of the number of patients who could benefit from the new medicine in Germany and an estimate of the medicine costs; The assessments by the Institute for Quality and Efficiency in Health Care (IQWiG), and independent HTA organisation, subsequently drive reimbursed prices: <ul style="list-style-type: none"> Either assigned to a pre-existing reference price group (typically limited or no added benefit);

Country	Extent of innovation and subsequent reimbursed prices
	– Otherwise, price negotiations between the Sickness Funds and manufacturer take place, based on the level of health gain and prices in 15 European countries (including any current discounts).

Source: Adapted from Paris and Belloni⁴⁸⁹, Sermet et al.⁴⁹⁰, Godman et al.⁴⁹¹.

The categories in Table 16 (operationalised by IQWiG into an algorithm) are based on⁴⁹²:

- The relevance of the outcome measure (measure used in clinical trials to assess the effectiveness of the new medicine versus current standard treatments), e.g. survival is weighted higher by the HTA agency than a non-serious adverse event. This also includes the relevance of any proposed surrogate marker for that condition;
- The magnitude of the treatment effect versus current standards in Germany.

Using this algorithm, IQWiG firstly determines the extent and probability of the added benefit of the new medicine versus current standard treatments separately for each patient-relevant benefit and adverse effect (side-effect). Secondly, the agency aggregates the findings into an overall balance of the benefits and harm from the new medicine to determine the overall net added benefit for its use versus current standard treatments in its subsequent deliberations⁴⁹³. These developments in Germany have increased the scrutiny over the value of new medicines, e.g. in 2011, Novartis removed the combination of Aliskiren and Amlodipine (Rasilamlo®) from the market during its early evaluation by the HTA agency due to a disagreement about the appropriate comparator and concerns with the actual level of health benefit in practice, given the choice of comparator used by the company⁴⁹⁴.

Alternatively, clinical and economic assessments are combined when appraising potential reimbursement/funding for new medicines. European countries including Ireland, Norway, Poland, Slovakia, Sweden and the UK, in addition to Australia, Canada and Korea, assess the level of health gain/innovation of new medicines versus current standards in terms of an

⁴⁸⁹ Paris, V. and Belloni, A., *Value in Pharmaceutical Pricing*, OECD Health Working Paper No 63, July 2013, OECD Publishing: Paris.

⁴⁹⁰ Sermet, C. et al., 2010, *Ongoing pharmaceutical reforms in France: implications for key stakeholder groups*, *Applied health economics and health policy*, 8(1), p. 7-24.

⁴⁹¹ Godman, B. et al., 2012, *Improving the managed entry of new medicines: sharing experiences across Europe*, *Expert review of pharmacoeconomics & outcomes research*, 12(4), p.439-441.

⁴⁹² Horn, H. et al., 2014, *Early benefit assessment of new drugs in Germany - Results from 2011 to 2012*, *Health Policy*, 116(2-3), p. 147-153.

⁴⁹³ Idem.

⁴⁹⁴ Hao, Y. and Thomas, A., 2013, *Health technology assessment and comparative effectiveness research: a pharmaceutical industry perspective*, *Expert review of pharmacoeconomics & outcomes research*, 3(4), p. 447-454.

increase in the number of QALYs gained^{495,496,497,498,499,500,501,502}. This is typically termed the incremental cost-effectiveness ratio (ICER), with QALYs seen as an appropriate method for assessing value and funding for new medicines across disease areas and classes⁵⁰³.

Reimbursement deliberations can also include considerations of the budget impact of the new medicine, e.g. Poland^{504,505}.

Table 17 contains details of current guidelines among some of the European countries that use economic criteria as part of the reimbursement decision-making process for new medicines. Table 18 contains the requirements for suggested comparators among a number of European countries irrespective of the approach used, whilst Table 19 contains details of the suggested perspective for any economic analysis as well as suggested cost considerations. Typically, only direct medical costs, i.e. medical costs directly incurred by the health system, are considered by the authorities in Europe rather than both medical and societal cost considerations. Societal cost considerations include loss of work (productivity or production loss) and are referred to as 'indirect costs'. However, this is not an universal definition. Whilst different European authorities recommend different approaches for measuring utility weights of different health states (to determine the QALY), in practice the assessments by the relevant European authorities (reimbursement agencies) typically rely on the information provided by pharmaceutical companies⁵⁰⁶.

⁴⁹⁵ Van Wilder, V. et al., 2015, *Towards a harmonised EU assessment of the added therapeutic value of medicines, study for the ENVI Committee*, available at: [http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU\(2015\)542219_EN.pdf](http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU(2015)542219_EN.pdf).

⁴⁹⁶ Malmstrom, R.E. et al., 2013, *Dabigatran - a case history demonstrating the need for comprehensive approaches to optimize the use of new drugs*, *Frontiers in pharmacology*, 4, p. 39.

⁴⁹⁷ Svensson, M., Nilsson, F.O. and Arnberg, K., 2015, *Reimbursement Decisions for Pharmaceuticals in Sweden: The Impact of Disease Severity and Cost Effectiveness*, *PharmacoEconomics*, 33(11), 1229-1236.

⁴⁹⁸ Festoy, H. et al., 2008, *Norway – Pharmaceutical Pricing and Reimbursement Information*, available at: https://ppri.goeg.at/Downloads/Results/Norway_PPRI_2008.pdf.

⁴⁹⁹ Ford, J.A. et al., 2012, *NICE guidance: a comparative study of the introduction of the single technology appraisal process and comparison with guidance from Scottish Medicines Consortium*, *BMJ open*, 2(1), p. e000671.

⁵⁰⁰ Kolasa, K. et al., 2011, *A review of Health Technology Assessment (HTA) recommendations for drug therapies issued between 2007 and 2009 and their impact on policymaking processes in Poland*, *Health Policy*, 102(2-3), p. 145-151.

⁵⁰¹ Schwarzer, R. et al., 2015, *Systematic overview of cost-effectiveness thresholds in ten countries across four continents*, *Journal of comparative effectiveness research*, 4(5), p. 485-504.

⁵⁰² Vitry, A.I., Shin, N.H. and Vitre, P., 2013, *Assessment of the therapeutic value of new medicines marketed in Australia*, *Journal of pharmaceutical policy and practice*, 6, p. 2.

⁵⁰³ Hoey R., 2007, *Experts disagree over NICE's approach for assessing drugs*, *Lancet*, 370(9588), p. 643-644.

⁵⁰⁴ Kolasa, K. et al., 2011, *A review of Health Technology Assessment (HTA) recommendations for drug therapies issued between 2007 and 2009 and their impact on policymaking processes in Poland*, *Health Policy*, 102(2-3), p. 145-151.

⁵⁰⁵ Van de Vooren, K. et al., 2014, *A critical systematic review of budget impact analyses on drugs in the EU countries*, *Applied health economics and health policy*, 12(1), p. 33-40.

⁵⁰⁶ Barnieh, L. et al., *A synthesis of drug reimbursement decision-making processes in organisation for economic co-operation and development countries*, *Value in health*, 17(1), p. 98-108.

Table 17: Perspective and analytical approaches used by pertinent European countries when assessing potential reimbursement for new medicines

Country	Perspective and preferred health economic technique
Belgium	<ul style="list-style-type: none"> • Perspective: healthcare payer (the social insurance and patients); • Analytical methods: <ul style="list-style-type: none"> – If improving life expectancy is the main objective and the most important outcome for the patient. The most relevant method is a cost effectiveness analysis (CEA), e.g. cost per life year saved; – If the treatment has an impact on health-related quality of life that is significant to the patient. Or if there are multiple patient-relevant clinical outcome parameters expressed in different units in the evidence for the new medicine that cannot be translated into one common unit in a valid way - the most relevant analysis is a Cost Utility Analysis (CUA).
Netherlands	<ul style="list-style-type: none"> • Perspective: societal; • Analytical methods: These include a CEA or CUA – no Cost Minimisation Analysis (CMA).
Norway	<ul style="list-style-type: none"> • Perspective: Limited Societal perspective – mainly direct medical costs; • Analytical methods: CMA (where the outcomes are the same and the analysis is focusing on differences in costs between the new and standard treatments), CEA, CUA, and Cost Benefit Analysis (CBA) are all accepted. However, the choice of the economic technique must be justified by the pharmaceutical company submitting the analysis.
Sweden	<ul style="list-style-type: none"> • Perspective: Societal; • Analytical methods: <ul style="list-style-type: none"> – CEA/CUA are recommended; CBA where QALYs are difficult to use; – If the effects of the new medicines are comparable to those of the best current comparable treatment, a cost comparison is sufficient (CMA).
UK – England and Wales	<ul style="list-style-type: none"> • Perspective: National Health System and Personal Social Services; • Analytical methods: CEA or CUA are the preferred methods.
UK – Scotland	<ul style="list-style-type: none"> • Perspective: National health system and patients; • Analytical methods include: <ul style="list-style-type: none"> – CMA, CEA, CUA or CBA are all accepted; – The choice of the technique needs to be justified.

Source: Adapted from Paris and Belloni⁵⁰⁷.

⁵⁰⁷ Paris, V. and Belloni, A., *Value in Pharmaceutical Pricing*, OECD Health Working Paper No 63, July 2013, OECD Publishing: Paris.

Table 18: Guidance on the choice of comparators among selected European countries when assessing the value of new medicines for pricing and reimbursement considerations

Country	Guidance regarding the choice of comparator (consolidated)
Belgium	<ul style="list-style-type: none"> • The analysis should be constructed involving the identification of all relevant treatments for the indication(s) of the new medicines and population, and the calculation of the ICERs of all interventions compared to the next best alternative; • The comparator(s) can be a medicine and/or non-medical treatments. "Off-label" used medicines or services should not be used unless there is evidence of their clinical safety and efficacy; • The choice of the comparator(s) should always be justified; • Indirect comparisons are allowed but only under specific conditions. However, usually a direct comparator is sought.
France	<ul style="list-style-type: none"> • In practice, the therapeutic improvement ((Amélioration du Service Médical Rendu (added therapeutic value, AMSR)) is typically assessed against the best available and reimbursed treatment(s) for that condition at the time of submission of the new medicine.
Germany	<ul style="list-style-type: none"> • For medicines with new active ingredients, the additional benefit is assessed for each indication, by comparison to the "appropriate comparator" as defined by law. These include: <ul style="list-style-type: none"> – The comparator must be authorised in Germany for the specific indication assessed; – If the comparator is a non-medical treatment, it must be evaluated according to the perspective of the health insurance in Germany; – There is a preference towards therapeutic alternatives, whose benefits for patient have already been assessed by the combined German Health Insurers; – The comparator should be an appropriate therapy according to the state of medical knowledge that is generally accepted at that time in Germany; – In case of various alternatives, the choice should be given to the cheapest medicine.
Sweden	<ul style="list-style-type: none"> • The most appropriate alternative treatment (e.g. the most used); • This could be a medicine, another treatment or no treatment at all; • In undertaking health economic evaluations, the reference point should be a treatment that is applicable in the health system of Sweden. If existing randomised control trials with the new medicine do not offer a relevant treatment alternative for Swedish conditions, the analysis should be supplemented by a model calculation (indirect comparison); • The calculations carried out should be adequately documented so that the assumptions and procedures made in any model are evident, understandable and robust.

Country	Guidance regarding the choice of comparator (consolidated)
Netherlands	<ul style="list-style-type: none"> Standard treatment (i.e. used in daily practice) for which effectiveness has been proved; If there is no “standard treatment”, usual treatment may be considered, which can be either a medical treatment or non-medical treatment. However, this must be justified.
UK – England and Wales	<ul style="list-style-type: none"> Therapies routinely used in the NHS, including interventions (including medicines) regarded as current best practice (this could also be no intervention).

Source: Adapted from Paris and Belloni⁵⁰⁸.

Table 19: Perspective and cost considerations for health economic evaluations among selected European countries

Country	Perspective and costs considered
Belgium	<ul style="list-style-type: none"> Economic evaluation is required for new medicines in class 1, i.e. with demonstrable added therapeutic value versus current standard medicines) and may be considered for other applications; Perspective adopted: ‘all healthcare payers’; Only direct medical costs typically considered; Costs which are not related to healthcare (e.g. absence from work) and which are considered to be important for a specific treatment may be separately presented. However, this needs to be justified in the analysis.
Denmark	<ul style="list-style-type: none"> Perspective: socio-economic; All relevant costs, regardless of whether they are direct, indirect or intangible are considered (although most attention is given to direct medical costs); Indirect costs should be indicated separately (human capital method is recommended).
Norway	<ul style="list-style-type: none"> Perspective: limited societal; All relevant societal costs and cost to health insurance should be included and be presented separately.
Sweden	<ul style="list-style-type: none"> Perspective adopted: societal; Direct costs, indirect costs; Production loss and sickness can be included, estimated by human capital method. However, indirect costs have to be justified.
UK – England and Wales	<ul style="list-style-type: none"> Potential direct and indirect resource costs for the NHS and social services; Most focus lies on direct medical costs.
UK – Scotland	<ul style="list-style-type: none"> Principally direct healthcare resources; Other costs considered, e.g. patient costs, when justified.

Source: Adapted from Paris and Belloni⁵⁰⁹.

⁵⁰⁸ Idem.

⁵⁰⁹ Idem.

European countries that use cost per QALY considerations when reviewing potential prices and reimbursement for new medicines are further divided into those that give guidance on cost per QALY thresholds (minority) and those that adopt a more humanistic approach with variable threshold limits, based on issues such as disease severity and unmet medical need^{510,511,512}.

A recent study of 49 cancer medicines showed that there was an association between the health gain, i.e. improvement in health, in terms of the extent of the number of QALYs in the UK analysis and the ASMR rating in France (Table 16). The association was maintained in a multivariate analysis, including the site of the cancer, the date of medicine approval, the place of the new medicine in the treatment paradigm and whether an active treatment was available to treat patients should the medicine not be listed⁵¹³.

Incremental cost per QALY threshold levels among European countries include in ascending order: €19,776-€28,840 (Slovakia), €25,000 (Slovenia 1.5 times GDP), €29,200 (Poland), GB£20,000 (€26,000), GB£30,000 (€39,300) for the UK, €45,000 (Ireland) and up to €80,000 in the Netherlands^{514,515,516,517,518,519}. Until recently, there was no threshold guidance in Hungary, although threshold levels were believed similar to Poland⁵²⁰. More recently in Hungary, new medicines for public funding have been declared as cost-effective if they come under the threshold of 2xGDP per capita/QALY. They are proclaimed not cost-effective if the ICER is higher than 3xGDP per capita/QALY⁵²¹. The current threshold for economic effectiveness in Poland is ≤ 3xGDP per capita (currently PLN119,600; €29,200) for all medicines, including orphan medicines. The value of new medicines in Poland is helped by narrowing the indications to sub-populations where the new medicine has the greatest impact on the health of patients, coupled with risk-sharing schemes such as price volume agreements (PVAs), or confidential discounts to reduce their price⁵²².

In Slovakia, the criteria for determining potential pricing and reimbursement for new medicines include their effectiveness, safety, cost-effectiveness versus current standards, and whether or not the new medicine is the first to market. Other considerations include the severity of the disease and the value of the new medicine to society, e.g. whether the new

⁵¹⁰ Godman, B. et al., 2013, *Ongoing measures to enhance prescribing efficiency across Europe: implications for other countries*, J Health Tech Assess, 1, p. 27-42.

⁵¹¹ Paris, V. and Belloni, A., *Value in Pharmaceutical Pricing*, OECD Health Working Paper No 63, July 2013, OECD Publishing: Paris.

⁵¹² Barnieh, L., et al., 2014, *A synthesis of drug reimbursement decision-making processes in organisation for economic co-operation and development countries*, Value in health, 17(1), p. 98-108

⁵¹³ Idem.

⁵¹⁴ Van Wilder, V. et al., 2015, *Towards a harmonised EU assessment of the added therapeutic value of medicines, study for the ENVI Committee*, available at: [http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU\(2015\)542219_EN.pdf](http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU(2015)542219_EN.pdf).

⁵¹⁵ Paris, V. and Belloni, A., *Value in Pharmaceutical Pricing*, OECD Health Working Paper No 63, July 2013, OECD Publishing: Paris.

⁵¹⁶ Barry, M., Usher, C. and Tilson, L., 2010, *Public drug expenditure in the Republic of Ireland*, Expert review of pharmacoeconomics & outcomes research, 10(3), p. 239-245.

⁵¹⁷ Raftery, J.P., 2014, *NICE's Cost-Effectiveness Range: Should it be Lowered?* Pharmacoeconomics, 32(7), p. 613-615.

⁵¹⁸ Matuszewicz, W. et al., 2015, *Improving the managed introduction of new medicines: sharing experiences to aid authorities across Europe*, Expert review of pharmacoeconomics & outcomes research, 15(5), p. 755-758.

⁵¹⁹ Gulacsi, L. et al., 2014, *Health technology assessment in Poland, the Czech Republic, Hungary, Romania and Bulgaria*, The European journal of health economics, 15(1), p. S13-25.

⁵²⁰ Gulacsi, L., 2007, *The time for cost-effectiveness in the new European Union member states: the development and role of health economics and technology assessment in the mirror of the Hungarian experience*, The European journal of health economics, 8(2), p. 83-88.

⁵²¹ Gulacsi, L. et al., 2014, *Health technology assessment in Poland, the Czech Republic, Hungary, Romania and Bulgaria*, The European journal of health economics, 15(1), p. S13-25.

⁵²² Matuszewicz, W. et al., 2015, *Improving the managed introduction of new medicines: sharing experiences to aid authorities across Europe*, Expert review of pharmacoeconomics & outcomes research, 15(5), p. 755-758.

medicine will treat an orphan disease or not⁵²³. The law in Slovakia states that new medicines must be below 24 times the average monthly salary to be reimbursed (in 2015, this was €19,776/QALY) and up to 35 times for conditional reimbursement (up to €28,840 in 2015). There can be exceptions for highly innovative compounds that exceed these limits based on specific market access schemes, e.g discounts or PVAs⁵²⁴.

In the UK, NICE and its advisory bodies, as well as SMC, are unlikely to reject as cost-ineffective a medicine with an incremental cost per QALY <GB£20,000 (€26,000). They are increasingly likely to reject a new medicine as cost-ineffective above these levels. This means a new medicine is seen as not cost-effective at an incremental cost per QALY of >GB£20,000 (€26,000)–GB£30,000 (€39,300). Consequently, it has a low probability of funding^{525,526,527}. Having said that, there appears to be no theoretical rationale for these threshold levels, and they appear to have been derived from precedents⁵²⁸. In addition, decisions by NICE do vary according to issues such as the level on unmet medical need and disease severity. This includes new medicines that prolong life by at least three months in patients with a life expectancy of less than 24 months^{529,530}.

However, there have been concerns with 'end-of-life' premiums with some authors finding no ethical justification for this⁵³¹. There has also been controversy in the UK surrounding additional budgets for such medicines, such as the Cancer Drugs Fund^{532,533,534}. It was found in a study of NICE on societal values that UK citizens did endorse greater funding for new treatments (for severe diseases that address current unmet medical need) provided the new medicines offered substantial health benefits versus current standard treatments. However, UK citizens did not support end-of-life premiums, nor the special status for treatments for rare diseases or the concept of the Cancer Drugs Fund⁵³⁵.

Recent research from the University of York also suggested that the cost per QALY threshold for new medicines is too high in the UK and should be lowered to just under GB£13,000 (€17,000)/QALY. However, this research has been criticised. Criticisms included the number and range of assumptions made⁵³⁶. Currently, the UK is less rigid in its cost per QALY threshold levels than Poland, Slovakia and Slovenia, despite some authors advocating lower

⁵²³ Van Wilder, V. et al., 2015, *Towards a harmonised EU assessment of the added therapeutic value of medicines, study for the ENVI Committee*, available at: [http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU\(2015\)542219_EN.pdf](http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU(2015)542219_EN.pdf).

⁵²⁴ Idem.

⁵²⁵ Schwarzer, R. et al., 2015, *Systematic overview of cost-effectiveness thresholds in ten countries across four continents*, Journal of comparative effectiveness research, 4(5), p. 485-504.

⁵²⁶ Raftery, J.P., 2014, *NICE's Cost-Effectiveness Range: Should it be Lowered?* Pharmacoeconomics, 32(7), p. 613-615.

⁵²⁷ Mihajlovic, J. et al., 2015, *Reimbursement of Targeted Cancer Therapies Within 3 Different European Health Care Systems*, Clinical therapeutics, 37(2), p. 474-480.

⁵²⁸ Raftery, J.P., 2014, *NICE's Cost-Effectiveness Range: Should it be Lowered?* Pharmacoeconomics, 32(7), p. 613-615.

⁵²⁹ McGuire, A. et al., 2015, *End of life or end of the road? Are rising cancer costs sustainable? Is it time to consider alternative incentive and funding schemes?*, Expert review of pharmacoeconomics & outcomes research, 15(4), p. 599-605.

⁵³⁰ Schwarzer, R. et al., 2015, *Systematic overview of cost-effectiveness thresholds in ten countries across four continents*, Journal of comparative effectiveness research, 4(5), p. 485-504.

⁵³¹ Cookson, R., 2013, *Can the NICE "end-of-life premium" be given a coherent ethical justification?* Journal of health politics, policy and law, 38(6), p. 1129-1148.

⁵³² Editorial, 2010, *New 50 million pound cancer fund already intellectually bankrupt*, Lancet, 376(9739), p.389.

⁵³³ Marshall, H., 2013, *UK Cancer Drugs Fund receives £400 million boost*, The Lancet, 14:e494.

⁵³⁴ Haycox, A., 2016, *Why Cancer?* Pharmacoeconomics, 34(7), p. 625-627.

⁵³⁵ Linley, W.G. and Hughes, D.A., 2013, *Societal views on NICE, cancer drugs fund and value-based pricing criteria for prioritising medicines: a cross-sectional survey of 4118 adults in Great Britain*, Health economics, 22(8), p. 948-964.

⁵³⁶ Raftery, J.P., 2014, *NICE's Cost-Effectiveness Range: Should it be Lowered?*, Pharmacoeconomics, 32(7), p. 613-615.

threshold levels with increased budgetary pressures^{537,538}. As a result, new medicines have and will continue to be funded at higher cost per QALY levels in the UK in disease areas of high unmet medical need. These include new medicines at the end of life⁵³⁹ and where there are limited treatment choices currently available. This is because the incremental cost per QALY of a new medicine versus existing standards is not the only consideration in decision making. There are acknowledged modifiers including current unmet need in the disease area, as well as the extent of health benefits with the new medicine that may not be fully captured using traditional techniques⁵⁴⁰.

In a recent analysis assessing SMC's decisions for new cancer therapies, among the approved indications the incremental cost per QALY varied from GBE1,790 (€2,327) per QALY to GBE56,343 (€73,809) per QALY. Some 5 out of the 26 positive recommendations were given to new cancer therapies with a cost per QALY increase greater than GBE30,000 (€39,300) per QALY. Conversely, negative recommendations for new cancer therapies corresponded to cost per QALYs ranging from GBE22,445 (€29,402) per QALY to GBE376,475 (€493,182)/QALY; and, in 2 out of 18 cases, the pharmaceutical company's estimates were below GBE30,000 (€39,300) per QALY. Decision modifiers included whether this was a disease area of unmet need and whether available treatments were available. This applied in the assessment of seven of the new cancer therapies, contributing to positive decisions in six of these. Overall, the proportion of new medicines recommended for funding by SMC and NICE are similar, although SMC generally publishes guidance more quickly than NICE⁵⁴¹.

Additional countries with variable ICER threshold levels depending on issues such as unmet medical need and societal benefits include Norway and Sweden^{542,543}, although others have disagreed^{544,545}. A recent study in Sweden analysing 102 decisions by the Dental and Pharmaceutical Benefits Agency in Sweden (TLV) found that the lowest cost per QALY of declined reimbursements was Swedish Krona (SEK) 700,000 (€79,100), with the highest cost per QALY at SEK1,220,000 (€135,600)⁵⁴⁶. The authors believed that, based on their analysis, at an incremental cost per QALY of SEK702,000 for non-severe diseases (€79,400) and SEK988,000 for severe diseases (€111,700), the likelihood of reimbursement for a new medicine was estimated at 50/50. The authors of the published paper believed this showed that TLV places substantial weight on both cost effectiveness and disease severity in their reimbursement decisions, with the implied willingness to pay for a QALY higher than often cited in Swedish policy debates⁵⁴⁷. Belgium also does not set explicit ICER thresholds.

⁵³⁷ Idem.

⁵³⁸ Towse, A., 2009, *Should NICE's threshold range for cost per QALY be raised? Yes*, BMJ, 338:b181.

⁵³⁹ Raftery, J.P., 2014, *NICE's Cost-Effectiveness Range: Should it be Lowered?* Pharmacoeconomics, 32(7), p. 613-615.

⁵⁴⁰ Matusiewicz, W. et al., 2015, *Improving the managed introduction of new medicines: sharing experiences to aid authorities across Europe*, Expert review of pharmacoeconomics & outcomes research, 15(5), p. 755-758.

⁵⁴¹ Ford, J.A. et al., 2012, *NICE guidance: a comparative study of the introduction of the single technology appraisal process and comparison with guidance from Scottish Medicines Consortium*, BMJ open, 2(1), p. e000671.

⁵⁴² Van Wilder, V. et al., 2015, *Towards a harmonised EU assessment of the added therapeutic value of medicines, study for the ENVI Committee*, available at: [http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU\(2015\)542219_EN.pdf](http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU(2015)542219_EN.pdf).

⁵⁴³ Godman, B. and Gustafsson, L.L., 2013, *A new reimbursement system for innovative pharmaceuticals combining value-based and free market pricing*, Applied health economics and health policy, 11(1), p. 79-82.

⁵⁴⁴ Schwarzer, R. et al., 2015, *Systematic overview of cost-effectiveness thresholds in ten countries across four continents*, Journal of comparative effectiveness research, 4(5), p. 485-504.

⁵⁴⁵ Persson, U., Svensson, J. and Pettersson, B., 2012, *A new reimbursement system for innovative pharmaceuticals combining value-based and free market pricing*, Applied health economics and health policy, 10(4), p. 217-225.

⁵⁴⁶ Svensson, M., Nilsson, F.O. and Arnberg, K., 2015, *Reimbursement Decisions for Pharmaceuticals in Sweden: The Impact of Disease Severity and Cost Effectiveness*, Pharmacoeconomics, 33(11), 1229-1236.

⁵⁴⁷ Idem.

However, it is unlikely that the authorities in Belgium would reimburse new medicines with an additional cost per QALY of €80,000 or more⁵⁴⁸.

As can be seen, there are perhaps more differences than similarities with the different HTA approaches across countries^{549,550}.

It is likely that cost per QALY thresholds may be revisited as cost pressures grow across Europe. This is because some European health authorities already believe current threshold levels are difficult to sustain⁵⁵¹. However, this has to be balanced against the costs of financing and producing new medicines.

It is also likely that transparency in decision making will grow with increased resource pressures. Currently, the highest standard of transparency in terms of transparency in decision making among reimbursement groups assessing the value of new medicines are seen in only five OECD countries. This includes transparency in assessing both the clinical and cost evidence for new medicines, and the potential to appeal against decisions⁵⁵².

Regardless of the method employed, reimbursement authorities across Europe increasingly require manufacturers to demonstrate meaningful improvements in the efficacy and/or safety of their new medicine in all or specific subpopulations of patients in order to justify higher (premium) prices versus current treatments. Increasingly, effectiveness data obtained from real-life settings, i.e. routine clinical care, are required to make a final coverage decision as part of risk-sharing arrangements/MEAs^{553,554} as well as proposed developments with adaptive pathways (Chapter 3.3.1).

Any clinical evidence generated needs to take account of the different requirements of both reimbursement and/or HTA agencies, as well as regulatory agencies such as the EMA⁵⁵⁵. Box 2 describes some of the additional evidence requirements currently sought by reimbursement and/or HTA agencies across Europe and other countries. This is likely to change with developments in adaptive pathways and the collection of real world data as part of continued MA and funding.

⁵⁴⁸ Paris, V. and Belloni, A., *Value in Pharmaceutical Pricing*, OECD Health Working Paper No 63, July 2013, OECD Publishing: Paris.

⁵⁴⁹ Van Wilder, V. et al., 2015, *Towards a harmonised EU assessment of the added therapeutic value of medicines, study for the ENVI Committee*, available at: [http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU\(2015\)542219_EN.pdf](http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU(2015)542219_EN.pdf).

⁵⁵⁰ Schwarzer, R. and Siebert, U., 2009, *Methods, procedures, and contextual characteristics of health technology assessment and health policy decision making: comparison of health technology assessment agencies in Germany, United Kingdom, France, and Sweden*, *International journal of technology assessment in health care*, 25(3), p. 305-314.

⁵⁵¹ Raftery, J.P., 2014, *NICE's Cost-Effectiveness Range: Should it be Lowered?*, *Pharmacoeconomics*, 32(7), p. 613-615.

⁵⁵² Barnieh, L., et al., 2014, *A synthesis of drug reimbursement decision-making processes in organisation for economic co-operation and development countries*, *Value in health*, 17(1), p. 98-108

⁵⁵³ WHO European Office, 2015, *Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research*. Copenhagen.

⁵⁵⁴ Ferrario, A. and Kanavos, P., 2013, *Managed entry agreements for pharmaceuticals: the European experience*, EMI-net: Brussels, available at: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/mea_report_en.pdf.

⁵⁵⁵ Henshall, C., et al., 2014, *Understanding the Role and Evidence Expectations of Health Technology Assessment and Coverage/Payer Bodies What Are They Looking for, and How and Why Does This Differ From What Regulators Require?*, *Therapeutic Innovation & Regulatory Science*, 48(3), p. 341-346.

Box 2: Additional evidence requirements by reimbursement and HTA agencies

- An improvement in patient-relevant outcomes, such as quality of life, in addition to improvements in clinically-defined endpoints, such as a reduction in hospitalisations or earlier discharge from hospitals. In some cases, there may also be interest in the wider impact of the new medicine, such as those on caregivers' quality of life and or the economy/social system, such as reduction in the number of people unemployed;
- Longer-term clinical outcomes than those typically required for regulatory review that more accurately reflect the clinical course of disease, such as a reduction in subsequent heart attacks (following the first event) or improved survival (for a new cancer medicine);
- Relevance of the study population to the patients likely to receive the medicine as part of routine clinical care in the health system, for which the reimbursement body is responsible;
- Costs to the healthcare system, its budget impact, cost-effectiveness, and/or value for money (for VBP approaches);
- Performance of the new medicine in these regards compared with the most appropriate comparator for the health system for which the reimbursement body is responsible, i.e. the treatment patients are likely to receive in the absence of the new medicine. This will normally involve a comparison with another medicine acknowledging that the comparator may vary among healthcare systems according to prevailing clinical practice in that country at that time and the requested place of the therapy in clinical practice.

Source: Adapted from Henshall et al.⁵⁵⁶.

5.4. Assessing the level of innovation of new medicines

There is no universally established methodology among European countries for assessing the level of innovation for new medicines versus current standards, i.e. their added therapeutic value.

Research groups in Italy developed and published in 2005 a suggested algorithm for assessing the level of innovation of new medicines⁵⁵⁷. For each new medicine, the degree of therapeutic innovation was assessed by (I) determining the availability of previous treatments, and (II) the extent of the therapeutic effect. For both (I) and (II), scores of A, B or C were assigned in decreasing order of importance. Box 3 contains more details.

⁵⁵⁶ Idem.

⁵⁵⁷ Motola, D. et al., 2005, *Therapeutic innovation in the European Union: analysis of the drugs approved by the EMA between 1995 and 2003*, British journal of clinical pharmacology, 59(4), p. 475-478.

Box 3: Proposed model developed in Italy for assessing the level of innovation of new medicines**I) Availability of previous treatments:**

- A = medicines for diseases without recognised standard treatment;
- B = medicines for diseases where certain patients are less responsive to existing medicines and/or other treatments;
- C = medicines for diseases responsive to existing medicines or other treatments, and which are:
 - C1 = effective or safer compared to existing medicines;
 - C2 = pharmacological innovation, i.e. new medicines with better kinetics or new mechanism of action;
 - C3 = technological innovation, i.e. a new chemical or biotechnological medicine with a role in treatment similar to already existing ones).

II) Therapeutic effect:

- A = A major clinical benefit based on clinical end-points, e.g. increased survival rates for new cancer medicines and/or quality of life, or validated surrogate end-points (e.g. blood pressure in patients with diabetes);
- B = partial benefit on the disease in question based on clinical or validated surrogate end-points, or not sufficient evidence to show a major benefit;
- C = temporary or a small (minor) benefit of the new medicine on a few aspects of the disease, e.g. only partial symptomatic relief of a serious disease.

Source: Adapted from Motola et al.⁵⁵⁸.

The overall degree of important/moderate therapeutic innovation of new medicines (receiving marketing approval between 1995 and 2003) assessed by the authorities in Italy was 47% (32% important; 15% moderate). Most (80%) of the EMA-approved new medicines were for serious diseases. The other 20% included risk factors (7%) and non-serious diseases (13%)⁵⁵⁹.

A more recent analysis by the authorities in Italy showed similar figures. Among all new medicines, 49 out of 176 (28%) were classified as having an important degree of therapeutic innovation⁵⁶⁰. Among biological medicines, 15 out of 60 (25%) were considered as important therapeutic innovations⁵⁶¹. However, this percentage of new medicines considered as having innovation by the Italian authorities was appreciably greater than the level of innovation of new medicines assessed by other health and drug information authorities in Canada, France and the Netherlands^{562,563,564} (Chapter 0).

⁵⁵⁸ Motola, D. et al., 2005, *Therapeutic innovation in the European Union: analysis of the drugs approved by the EMA between 1995 and 2003*, British journal of clinical pharmacology, 59(4), p. 475-478.

⁵⁵⁹ Motola, D. et al., 2006, *An update on the first decade of the European centralized procedure: how many innovative drugs?*, British journal of clinical pharmacology, 62(5), p. 610-616

⁵⁶⁰ Idem.

⁵⁶¹ Idem.

⁵⁶² WHO European Office, 2015, *Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research*. Copenhagen.

⁵⁶³ Lexchin, J., 2012, *International comparison of assessments of pharmaceutical innovation*, Health Policy, 105(2-3), p. 221-225.

⁵⁶⁴ Editorial, 2013, *New drugs and indications in 2012 - Sluggish progress, timid measures to protect patients*, Prescrire International, 22(137), p. 105-107.

More recently, Aronson et al. developed the concept of 'rewardable innovation for new medicines'. They defined this as *"a medicinal product that provides, through a step change, something novel, with the potential or proven ability to yield, for individuals and/or their society, a treatment not previously available or a clinically significant improvement in treatment, with large health gains and a favourable benefit to harm balance, at an acceptable cost"*. The level of reward, i.e. the reimbursed price versus current standards, will depend on the perceived degree of innovativeness and the payer's willingness to pay the requested prices⁵⁶⁵.

5.5. Budget impact analysis

Many, if not most, EU countries, now consider the budget impact of the new medicine in their deliberations when considering reimbursement for a new, higher-priced medicine alongside, for instance, cost per QALY considerations^{566,567,568,569}.

The budget impact of a new medicine is defined as its overall budget impact to the healthcare system in terms of the opportunity costs involved. Such information cannot usually be calculated from cost per QALY analyses. BIA is a relatively new technique to provide useful additional information for reimbursement and funding decisions for new medicines⁵⁷⁰. BIAs are increasingly seen as a valuable step in the HTA process, which allow health authorities to evaluate whether a new medicine is safe, effective and efficient as well as affordable to all or a sub-population within European healthcare systems⁵⁷¹. Consequently, BIAs may be useful to decision makers when seeking to maximise the health gain of populations within finite budgets⁵⁷².

For instance, manufacturers applying for reimbursement to the Norwegian Medicines Agency are required to include a BIA together with the cost-utility analysis, e.g. a cost per QALY analysis. If total costs exceed "the bagatelle limit" (NOK 5 million (€5.250,000) in the fifth year after introduction), the final decision is taken in parliament⁵⁷³. BIAs also play an important role in regional decision making in Sweden and Denmark, alongside considerations of the efficacy and safety of the new medicine versus current standards^{574,575}.

Having said this, some health economists have argued that BIA undermines CEA⁵⁷⁶. However, other authors have argued the need and usefulness of BIAs for policymakers⁵⁷⁷. There are concerns that BIA is not yet a well-established technique and that BIAs conducted by

⁵⁶⁵ Aronson, J., Ferner, R., and Hughes, D., 2012, *Defining rewardable innovation in drug therapy*, Nature reviews Drug discovery, 11(4), p. 253-254.

⁵⁶⁶ Godman, B. et al., 2013, *Ongoing measures to enhance prescribing efficiency across Europe: implications for other countries*, J Health Tech Assess, 1, p. 27-42.

⁵⁶⁷ Paris, V. and Belloni, A., *Value in Pharmaceutical Pricing*, OECD Health Working Paper No 63, July 2013, OECD Publishing: Paris.

⁵⁶⁸ Mihajlovic, J. et al., 2015, *Reimbursement of Targeted Cancer Therapies Within 3 Different European Health Care Systems*, Clinical therapeutics, 37(2), p.474-480.

⁵⁶⁹ Yim, E. et al., 2012, *Assessment of pharmacoeconomic evaluations submitted for reimbursement in Korea*, Value in health, 15(1 Suppl):S104-110.

⁵⁷⁰ Van de Vooren, K. et al., 2014, *A critical systematic review of budget impact analyses on drugs in the EU countries*, Applied health economics and health policy, 12(1), p. 33-40.

⁵⁷¹ Faleiros, DR., Alvares, J., Almeida, AM., et al., 2016, *Budget impact analysis of medicines: updated systematic review and implications*. Expert review of pharmacoeconomics & outcomes research, 16(2), p. 257-266.

⁵⁷² Cohen, J.P., Stolk, E. and Niezen, M., 2008, *Role of budget impact in drug reimbursement decisions*, Journal of health politics, policy and law, 33(2), p. 225-247.

⁵⁷³ WHO European Office. Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research. Copenhagen: 2015.

⁵⁷⁴ Idem.

⁵⁷⁵ Godman, B. et al., 2009, Multifaceted national and regional drug reforms and initiatives in ambulatory care in Sweden: global relevance, Expert review of pharmacoeconomics & outcomes research, 9(1), p. 65-83.

⁵⁷⁶ Trueman, P., Drummond, M. and Hutton, J., 2001, *Developing guidance for budget impact analysis*, Pharmacoeconomics, 19(6), p. 609-621.

⁵⁷⁷ Niezen, M.G. et al., *Finding legitimacy for the role of budget impact in drug reimbursement decisions*, International journal of technology assessment in health care, 25(1), p. 49-55.

pharmaceutical companies appear to be tailored to demonstrate short-term savings, which is not ideal for long-term planning, and may be open to bias^{578,579}. However, this technique is here to stay. Authors have recently categorised BIAs as having the following characteristics⁵⁸⁰:

- the budget holders' perspective;
- with a short-time horizon (up to 3 years);
- within a clearly specified setting;
- where results are expressed as undiscounted cost differences between the new scenario (including the new medicine) and the current scenario;
- taking account of the potential trade-offs in healthcare resources (opportunity costs) with the new medicine;
- examining the results using sensitivity analyses responsive to the uncertainty surrounding future market developments (like a scenario analysis) and making them easy for budget holders (payers) to understand, e.g. similar to the analysis of extremes.

However, without reliable data regarding current prevalence rates for the diseases (epidemiology) in question in the country, as well as robust utilisation and expenditure data (unit prices and utilisation rates in routine clinical care), it can be difficult to obtain reliable estimates of the likely budget impact for new medicines⁵⁸¹. Robust forecasting approaches based on data from reliable and robust patient-level databases are one way forward to address this concern⁵⁸².

5.6. Risk-sharing arrangements and managed entry agreements

MEAs and risk-sharing arrangements are both used in the literature. However, the term MEA seems to be increasing rather than 'risk-sharing arrangements' in recent years^{583,584}. Definitions include:

- Risk sharing⁵⁸⁵: Agreements made between pharmaceutical companies and payers to lower the budget impact of particularly new medicines brought about by either the uncertainty of the value of the new medicine and/or the need to work within agreed budgets. In practice, the agreement lies in setting the scope and realising the mutual obligations amongst both payers and pharmaceutical companies, depending on the occurrence of an agreed condition, i.e. the 'risk'. The 'risk' varies by situation and can include pharmaceutical expenditure higher than agreed limits, or the actual level of health gain from the new medicine lower in practice, thereby reducing its value to the healthcare system;

⁵⁷⁸ Faleiros DR, Alvares J, Almeida AM, et al., 2016, *Budget impact analysis of medicines: updated systematic review and implications*. Expert review of pharmacoeconomics & outcomes research, 16(2), p. 257-266.

⁵⁷⁹ Van de Vooren, K. et al., 2014, *A critical systematic review of budget impact analyses on drugs in the EU countries*, Applied health economics and health policy, 12(1), p. 33-40.

⁵⁸⁰ Idem.

⁵⁸¹ Van de Vooren, K. et al., 2014, *A critical systematic review of budget impact analyses on drugs in the EU countries*, Applied health economics and health policy, 12(1), p. 33-40.

⁵⁸² Wettermark, B. et al., 2010, *Forecasting drug utilization and expenditure in a metropolitan health region*, BMC health services research, 10, p. 128.

⁵⁸³ Klemp, M., Fronsdal, K.B. and Facey, K., 2011, *What principles should govern the use of managed entry agreements?*, International journal of technology assessment in health care, 27(1), p. 77-83.

⁵⁸⁴ van de Vooren, K. et al., 2015, *Market-access agreements for anti-cancer drugs*, Journal of the Royal Society of Medicine, 108(5), p. 166-70.

⁵⁸⁵ Adamski, J. et al., 2010, *Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers*, BMC health services research, 10, p. 153.

- MEA⁵⁸⁶: An arrangement between a manufacturer and payer/provider that enables access to (coverage/reimbursement of) a new medicine (or other technology) subject to specified conditions. These arrangements include various mechanisms addressing the uncertainty about the (cost-)effectiveness of a new medicine, or to manage its adoption in clinical practice in order to maximise effective use, and/or limit the budget impact.

Typically, MEAs can be divided into financial or health-outcome (for example, improvement in quality of life) schemes^{587,588,589}. Financial-based schemes do not typically follow the principle of VBP especially if appreciable discounts are needed to reimburse the new medicine schemes (see also Chapter 5.7). The rationale for choosing between the different MEA schemes will depend on the health authority/health insurance company objectives⁵⁹⁰.

Increasing resource pressures, coupled with increasing availability of new, higher-priced medicines, increasing patient expectations, and the commercial necessity for pharmaceutical companies to achieve reimbursement of their new medicines in Europe, is leading to an increasing number of MEAs across Europe^{591,592}. MEAs potentially reduce the uncertainty regarding reimbursement for new medicines where there are concerns with their value and/or effectiveness^{593,594}. In addition, depending on the scheme, limit the prescribing of new medicines in populations for which they are not seen as cost-effective⁵⁹⁵.

Despite the growth in the number of MEAs with, for example, 133 active schemes in Belgium, England, the Netherlands and Sweden by December 2012⁵⁹⁶, there is still confusion surrounding their terminology and definitions. This potentially arises as the nature of such arrangements can be very different within and between countries⁵⁹⁷. Despite this growth, MEAs still only represent a minority of medicines within a European country's reimbursement lists⁵⁹⁸. However, this is expected to change, especially given the number of new biological medicines in development⁵⁹⁹. This is in addition to, pharmaceutical manufacturers' pricing strategies having no consistent bearing on the level of income of countries/their affordability

⁵⁸⁶ Klemp, M., Fronsdal, K.B. and Facey, K., 2011, *What principles should govern the use of managed entry agreements?*, International journal of technology assessment in health care, 27(1), p. 77-83.

⁵⁸⁷ Ferrario, A. and Kanavos, P., 2015, *Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden*, Social science & medicine, 124, p. 39-47.

⁵⁸⁸ Jaroslawski, S. and Toumi, M., 2011, *Market Access Agreements for pharmaceuticals in Europe: diversity of approaches and underlying concepts*, BMC health services research, 11, p. 259.

⁵⁸⁹ Navarria, A. et al., 2015, *Do the current performance-based schemes in Italy really work? "Success fee": a novel measure for cost-containment of drug expenditure*, Value in health, 18(1), p. 131-136.

⁵⁹⁰ Ferrario, A. and Kanavos, P., 2013, *Managed entry agreements for pharmaceuticals: the European experience*, EMINet: Brussels, available at: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/mea_report_en.pdf.

⁵⁹¹ Idem.

⁵⁹² Ferrario, A. and Kanavos, P., 2015, *Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden*, Social science & medicine, 124, p. 39-47.

⁵⁹³ Garrison, L. P. et al., 2013, *Performance-based risk-sharing arrangements—good practices for design, implementation, and evaluation: report of the ISPOR good practices for performance-based risk-sharing arrangements task force*, Value in Health, 16(5), p. 703-719.

⁵⁹⁴ Eckermann, S. and Willan, A.R., 2013, *Optimal global value of information trials: better aligning manufacturer and decision maker interests and enabling feasible risk sharing*, Pharmacoeconomics, 31(5), p. 393-401.

⁵⁹⁵ Idem.

⁵⁹⁶ Ferrario, A. and Kanavos, P., 2015, *Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden*, Social science & medicine, 124, p. 39-47.

⁵⁹⁷ Idem.

⁵⁹⁸ Idem.

⁵⁹⁹ Evaluate Pharma, *Surveying Tomorrow's BioPharma Landscape. The NASDAQ Biotech Index Up Close*, June 2012, available at: http://info.evaluatepharma.com/rs/evaluatepharmaltd/images/EvaluatePharma_NBI_Up_Close_2012.pdf.

for new, premium-priced medicines⁶⁰⁰, and the continuing instigation of ERP for new medicines in Europe⁶⁰¹ (Chapter 4.3.1). Having said this, the body of evidence for the implementation of MEAs is currently weak, with few studies exploring their merits and impact^{602,603,604}.

The recent report by Ferrario et al. suggests the most common MEAs among European countries are PVAs (39%), followed by requirements for data collection (29.5%) and limiting the access to eligible patients (13.1%). PVAs are widely used in Italy, Portugal, and Lithuania, while data collection for new medicines is a common requirement in Italy, the Netherlands, the Czech Republic and Sweden to assess their value in clinical practice post-launch. In addition, Italy, the Czech Republic and Belgium also limit access to certain medicines to eligible patients to further manage their budget impact and use⁶⁰⁵.

Not surprisingly, in view of their high costs and often limited health gain, a significant proportion of MEAs (37%) surround anti-cancer and immune modulating agents, with most MEAs in Europe currently undertaken in Italy^{606,607,608}. An analysis published in 2015 stated that, since July 2006, there have been 44 MEA contracts in force for 33 medicines in Italy⁶⁰⁹. In the UK, the Department of Health has signed 42 contracts covering 32 medicines since October 2007. Approximately half of the UK schemes involved anti-cancer therapies. The authors concluded that simple, financial-based contracts seemed more efficient as a means for health services to reduce their expenditure on new, high-priced anti-cancer medicines and enhance access for patients⁶¹⁰.

However, despite similar cited reasons for MEA implementation across countries, only in a minority of cases have countries implemented an agreement for the same medicine and indication. When they do, a different type of agreement is often implemented, which may be due to issues such as differences in governance across countries. This could arise from the fact that, in some countries MEAs are proposed following initial deliberations by pricing and reimbursement bodies, i.e. reactively. However, in other situations and countries, these may be proposed proactively⁶¹¹.

⁶⁰⁰ Morel, C.M., McGuire, A. and Mossialos, E., 2011, *The level of income appears to have no consistent bearing on pharmaceutical prices across countries*, Health affairs, 30(8), p. 1545-1552.

⁶⁰¹ Leopold, C. et al., 2012, *Impact of external price referencing on medicine prices - a price comparison among 14 European countries*, Southern med review, 5(2), p.34-41.

⁶⁰² Ferrario, A. and Kanavos, P., 2015, *Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden*, Social science & medicine, 124, p. 39-47.

⁶⁰³ Garrison, L. P. et al., 2013, *Performance-based risk-sharing arrangements—good practices for design, implementation, and evaluation: report of the ISPOR good practices for performance-based risk-sharing arrangements task force*, Value in Health, 16(5), p. 703-719.

⁶⁰⁴ Eijkenaar, F. et al., 2013, *Effects of pay for performance in health care: a systematic review of systematic reviews*, Health Policy, 110(2-3), p. 115-130.

⁶⁰⁵ Ferrario, A. and Kanavos, P., 2013, *Managed entry agreements for pharmaceuticals: the European experience*, EMiNet: Brussels, available at: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/mea_report_en.pdf.

⁶⁰⁶ Idem.

⁶⁰⁷ van de Vooren, K. et al., 2015, *Market-access agreements for anti-cancer drugs*, Journal of the Royal Society of Medicine, 108(5), p. 166-70.

⁶⁰⁸ Navarria, A., et al., 2015, *Do the current performance-based schemes in Italy really work? "Success fee": a novel measure for cost-containment of drug expenditure*, Value in health, 18(1), p. 131-136.

⁶⁰⁹ van de Vooren, K. et al., 2015, *Market-access agreements for anti-cancer drugs*, Journal of the Royal Society of Medicine, 108(5), p. 166-70.

⁶¹⁰ Idem.

⁶¹¹ Ferrario, A. and Kanavos, P., 2015, *Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden*, Social science & medicine, 124, p. 39-47.

MEA schemes in Italy include both outcome-based and financial schemes across a number of drug classes^{612,613}. However, recent analysis suggests there have been limited refunds to date for such schemes in Italy since 2006. Refunds equated to €121 million out of a total of €3,696 million spent on these medicines by the Italian National Health System for the 22 MEA schemes introduced and agreed between 2006 and 2012. This has led to suggestions of paying a success fee ex-post, i.e. after an analysis of the actual improvement in health alongside cost considerations, with the medicine provided initially free of charge by the pharmaceutical company. The first scheme is now in operation in Italy for Pirfenidone for the management of mild-to-moderate idiopathic pulmonary fibrosis. The outcome is based on forced vital capacity⁶¹⁴. This scheme is being closely monitored by the authorities in Italy as a potential exemplar for such schemes in the future, where there are clearly defined and agreed outcome measures.

However, there are concerns among health authorities and providers of the potential level of administration involved with such schemes. For example, recent research for some of the schemes in the UK for new cancer medicines highlighted the following^{615, 616}:

- 73% of hospitals reported they did not have sufficient human resources (especially pharmacy staff) to manage, co-ordinate and track the pertinent patients. This is especially the case if hospital personnel have to spend time manually tracking patients, retrospectively adjusting stock control systems and ensuring the necessary systems are in place to fully realise any savings, including accepting free goods;
- A need for greater flexibility around the time limits for processing claims, especially if only short time sales are included;
- A need for good communication between key stakeholder groups, e.g. in the case of Bortezomib, every missed claim resulted in a loss of £12,000 (€15,720) to the hospital;
- The need to ensure savings are passed back to the payers in terms of revised contracts, etc. This is not happening in 47% of hospitals.

These concerns in the UK were heightened by the early experiences regarding the risk-sharing scheme for multiple sclerosis established in 2002. This scheme was established due to concerns with the effectiveness and value of the beta-interferons in routine clinical care. However, there were issues with the model used in this risk-sharing study, and how the scheme was established^{617,618,619}. The first major analysis conducted in late 2009 showed that disease progression was not only worse than predicted in the model used by NICE when drafting the scheme, but was worse than the untreated control group⁶²⁰. However, a more recent analysis, including patients from the British Columbia multiple sclerosis database (Canada), found that treatment with interferon beta or glatiramer acetate led to

⁶¹² Garrison, L. P. et al., 2013, Performance-based risk-sharing arrangements—good practices for design, implementation, and evaluation: report of the ISPOR good practices for performance-based risk-sharing arrangements task force, *Value in Health*, 16(5), p. 703-719.

⁶¹³ Garattini, L. and Casadei, G., 2011, Risk sharing agreements: what lessons from Italy? *International journal of technology assessment in health care*, 27(2), p. 169-172.

⁶¹⁴ Idem.

⁶¹⁵ Adamski, J. et al., 2010, *Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers*, *BMC health services research*, 10, p. 153.

⁶¹⁶ Williamson, S., 2010, *Patient access schemes for high-cost cancer medicines*, *The lancet oncology*, 11(2), p. 111-112.

⁶¹⁷ Adamski, J. et al., 2010, *Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers*, *BMC health services research*, 10, p. 153.

⁶¹⁸ Boggild, M. et al., 2009, *Multiple sclerosis risk sharing scheme: two year results of clinical cohort study with historical comparator*, *BMJ*, 339, p.b4677.

⁶¹⁹ Palace, J. et al., 2014, *UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model*, *BMJ open*, 4(1), p. e004073.

⁶²⁰ Raftery, J., 2010, *Multiple sclerosis risk sharing scheme: a costly failure*, *BMJ*, 340, p.c1672.

improvements in disability in patients with relapsing-remitting multiple sclerosis. These were maintained with treatments seen as cost effective over the six years. The authors concluded that similar modelling approaches could be applied to other chronic diseases for which long-term controlled trials are not feasible⁶²¹. However, this would need careful consideration regarding funding.

These concerns with MEAs prompted groups such as the International Society for Pharmacoeconomics and Outcomes Research to develop guidance on key issues and practices⁶²². These are summarised in Table 20.

Table 20: Key issues surrounding the implementation, governance and reporting of MEAs

Issue	Key considerations
Implementation	<ul style="list-style-type: none"> Will the scheme measure appropriate outcomes? Are the costs acceptable to the healthcare system, including issues such as the complexity of implementation and opportunity costs? Is the time horizon realistic for all concerned, including the potential long-term consequences on health and overall costs? Are the funding arrangements clear and transparent? Is the data collection methodology efficient, e.g. not too cumbersome? Is the process for reviewing and analysing the evidence to make revised decisions on prices and reimbursement clear and agreed by all parties? This includes agreed timescales for payment of any discounts/rebates.
Governance	<ul style="list-style-type: none"> The extent of good governance will depend on the type of scheme; Where MEAs involve agreements among multiple stakeholders, the need for formal governance structures is greater. This could involve a steering committee with a formal governance structure to ensure transparency of the nature/aims of the scheme, accountability and a means to resolve any conflict.
Evaluation/Reporting	<ul style="list-style-type: none"> Has the MEA achieved its objective? This will typically involve multiple perspectives; How will the results be reported given limited reporting to date – especially as the evidence generated could be a public good, as there have been few studies published to date evaluating the overall economic impact of MEAs? This should include the knock-on effect of perversely keeping the list price of new medicines high, and the resultant effect on other countries that reference those particular countries for pricing considerations of new medicines.

Source: Adapted from Ferrario and Kanavos⁶²³, Garrison et al.⁶²⁴ and Jaroslawski and Toumi⁶²⁵.

⁶²¹ Palace, J. et al., 2015, *Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK Multiple Sclerosis Risk Sharing Scheme at 6 years: a clinical cohort study with natural history comparator*, *Lancet neurology*, 14(5), p.497-505.

⁶²² Garrison, L. P. et al., 2013, *Performance-based risk-sharing arrangements—good practices for design, implementation, and evaluation: report of the ISPOR good practices for performance-based risk-sharing arrangements task force*, *Value in Health*, 16(5), p. 703-719.

⁶²³ Ferrario, A. and Kanavos, P., 2015, *Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden*, *Social science & medicine*, 124, p. 39-47.

⁶²⁴ Garrison, L. P. et al., 2013, *Performance-based risk-sharing arrangements—good practices for design, implementation, and evaluation: report of the ISPOR good practices for performance-based risk-sharing arrangements task force*, *Value in Health*, 16(5), p. 703-719.

⁶²⁵ Jaroslawski, S. and Toumi, M., 2011, *Market Access Agreements for pharmaceuticals in Europe: diversity of approaches and underlying concepts*, *BMC health services research*, 11, p. 259.

There are also concerns among health authorities that pharmaceutical companies may not always lower their prices or withdraw their products if post-launch studies demonstrate concerns with the cost-effectiveness of their medicine in routine clinical care. This is illustrated by the considerable controversy surrounding the reimbursement for ERT for the symptomatic treatment of Fabry disease and alglucosidase alfa to treat Pompe's disease in the Netherlands (Chapter 4.5). Having said that, there are an increasing number of MEAs for new orphan medicines in Europe given their requested prices and uncertainty with their effectiveness⁶²⁶. This growth is likely to continue given the number of medicines for orphan diseases in development⁶²⁷.

These concerns with obtaining price reductions post launch have prompted some authors to suggest that MEAs should principally be based on price discounts⁶²⁸. However, other authors have suggested that discount or rebate schemes are better suited for pricing considerations and outcome-based schemes more suited to addressing issues of uncertainty that surround the cost-effectiveness of new medicines⁶²⁹.

The potential advantages and disadvantages of MEAs from the perspective of different stakeholders are summarised in A number of these issues were further consolidated in the report of Ferrario et al. regarding the strengths, weaknesses, opportunities and threats from MEAs. These are contained in Table 22.

Table 21. Whether to propose or accept an MEA as part of reimbursement considerations for new medicines will be a business decision by the pharmaceutical company, as well as a business/political decision by the payer/health authority. In any event, there must be a valid and efficient process for evidence collection and this is feasible, acceptable and realistic within a given country⁶³⁰.

A number of these issues were further consolidated in the report of Ferrario et al.⁶³¹ regarding the strengths, weaknesses, opportunities and threats from MEAs. These are contained in Table 22.

Table 21: Advantages and disadvantages of MEAs from different stakeholder perspectives

Stakeholder	Advantages	Disadvantages
Pharmaceutical company	<ul style="list-style-type: none"> Provides access to markets for new medicines where affordability will be an issue and/or concerns with effectiveness and value in routine clinical care; 	<ul style="list-style-type: none"> Costs and bureaucracy involved; Payback or price reductions if agreed outcomes are not met; Limits access to new medicines once budget caps are reached (if this is pertinent to the scheme);

⁶²⁶ Morel, T. et al., 2013, *Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries*, Orphanet journal of rare diseases, 8, p. 198.

⁶²⁷ Douglas, C.M. et al., 2015, *Why orphan drug coverage reimbursement decision-making needs patient and public involvement*, Health Policy, 119(5), p.588-596.

⁶²⁸ Wladysiuk, M., Tabor, A. and Godman, B., 2013, 'HTA for Crisis': sharing experiences during the 7th EBHC Symposium, Expert review of pharmacoeconomics & outcomes research, 13(1), p.47-49.

⁶²⁹ Kolasa, K., Kalo, Z. and Hornby, E., 2015, *Pricing and reimbursement frameworks in Central Eastern Europe: a decision tool to support choices*, Expert review of pharmacoeconomics & outcomes research, 15(1), p. 145-55.

⁶³⁰ Garrison, L. P. et al., 2013, *Performance-based risk-sharing arrangements—good practices for design, implementation, and evaluation: report of the ISPOR good practices for performance-based risk-sharing arrangements task force*, Value in Health, 16(5), p. 703-719.

⁶³¹ Ferrario, A. and Kanavos, P., 2013, *Managed entry agreements for pharmaceuticals: the European experience*, EMI-Net: Brussels, available at: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/mea_report_en.pdf.

Stakeholder	Advantages	Disadvantages
	<ul style="list-style-type: none"> Targeted use to specific patient sub-populations enhances the value of the new medicine and, hence, potential reimbursement. 	<ul style="list-style-type: none"> Real-world clinical effectiveness could be compared to effectiveness in clinical trials involving optimal patients.
Provider/payer	<ul style="list-style-type: none"> Provides the new medicine in such a way that it demonstrates value to the healthcare system; Provides early access and shares the risk if the new medicine is not performing as agreed; Limits the total budget impact, or helps control this; Building an evidence base to address current uncertainties regarding the clinical performance and value of the new medicine in routine clinical care for further discussions regarding prices and usage/funding. 	<ul style="list-style-type: none"> Costs and bureaucracy involved; Potential duplication of schemes with the lack of transparency; Possibility of providers managing multiple schemes without the necessary infrastructure, including IT infrastructure; Potential that small and low-income countries will lose out from confidential schemes if they do not have sufficient bargaining power; Potentially penalise those countries that rely on ERP to establish the price of their new medicines if this is based on high prices in reference countries; Concerns with withdrawing the new medicine purely on economic grounds if its value is not seen in clinical practice and Pharmaceutical Companies are reluctant to lower their prices; Deciding who owns the data/who pays for inputting the details into databases; Companies putting pressure on regions to implement MEAs for new medicines (if introduced region by region, e.g. Canada).
Patient/society	<ul style="list-style-type: none"> Access to promising new medicines, thus permitting greater choice/access if no prior treatments available; Promoting investment in innovation. 	<ul style="list-style-type: none"> Barriers to participation, e.g. a new medicine is only available in specialist centres; Risk that the new medicine does not demonstrate the expected benefit in clinical practice; Potential for the new medicine to be withdrawn at the end of the agreement;

Stakeholder	Advantages	Disadvantages
		<ul style="list-style-type: none"> • Data protection issues; • Other more robust research is not undertaken.

Source: Adapted from Ferrario and Kanavos⁶³², Malmstrom⁶³³ and Godman et al.⁶³⁴.

Table 22: Analysis of MEAs

Component	Summary of key areas
Strength	<p>A) <i>General strengths</i></p> <ul style="list-style-type: none"> • From a literature perspective, there seems to be a general agreement that MEAs can, under certain conditions, address post-licensing uncertainty regarding the clinical benefits and value of a new medicine. As a result, they enable early access to new innovative treatments; • In general, MEAs offer flexibility in dealing with new and often expensive new medicines, which are characterised by significant levels of uncertainty; • Different types of schemes exist in order to address different needs. <p>B) <i>Agreements including a health-outcome component (e.g. Coverage with Evidence Development (CED), payment for performance schemes)</i></p> <ul style="list-style-type: none"> • Collection of information on the use of the medicine and its effectiveness in different sub-groups of patients under real-life clinical conditions, i.e. outside a clinical trial, to update treatment guidance, reduce uncertainty and reach a final reimbursement decision. <p>C) <i>Pure financial agreements, no health outcome component (e.g. PVAs, price/dose capping, price-match, etc.)</i></p> <ul style="list-style-type: none"> • Improve the cost-effectiveness of new medicines through discounts offered by the pharmaceutical company on the official price (list price) or a payback agreement for non-responders; • A more reasonable cost-effectiveness will increase the probability of a new medicine receiving a positive recommendation by HTA agencies and reimbursement authorities; • Evidence of savings from price: volume arrangements, e.g. France. <p>D) <i>Strengths from a payer perspective</i></p> <p>Depending on the type of agreement and its objective, such schemes may enable better control of budgets, increase the cost-effectiveness of the new medicine, and/or limit the use of new medicines to defined patient populations, where their clinical and economic value is greatest.</p> <p>E) <i>Strengths from a patient perspective</i></p>

⁶³² Ferrario, A. and Kanavos, P., 2013, *Managed entry agreements for pharmaceuticals: the European experience*, EMINet: Brussels, available at: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/mea_report_en.pdf.

⁶³³ Malmstrom, R. et al., 2013, *Dabigatran - a case history demonstrating the need for comprehensive approaches to optimize the use of new drugs*. *Frontiers in pharmacology*. 4:39.

⁶³⁴ Godman, B. et al., 2015 *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?* Expert review of clinical pharmacology, 8(1), p. 77-94.

Component	Summary of key areas
	<p>Improves access to new medicines that had been, or were likely to be, rejected on initial cost-effectiveness grounds by the reimbursement authority.</p> <p><i>F) Strengths from a manufacturer perspective (e.g. pharmaceutical company)</i></p> <p>MEAs enable companies to obtain reimbursement for their new medicines, which were likely to be rejected by reimbursement agencies based on their initial assessments.</p>
Weaknesses	<p><i>A) General weaknesses</i></p> <ul style="list-style-type: none"> • There is little evidence to support the claimed benefits of MEAs versus the challenges involved in their implementation, e.g. monitoring requirements, and transaction costs; • Frequent lack of transparency on implemented agreements, e.g. confidential discounts, their objectives, and evaluation of their impact. This is preventing cross-country learnings and severely limits the ability of key stakeholder groups to engage with MEA processes; • Voluntary versus the non-voluntary nature of MEAs varies among European countries, which can create confusion among different stakeholders; • Variability in the perception of MEAs across countries and what actually constitutes such schemes, as these may differ across settings. <p><i>B) Agreements, including a health-outcome component (e.g. payment for performance)</i></p> <ul style="list-style-type: none"> • Despite collecting useful data that could enable the effectiveness and/or safety of new medicines to be reassessed in routine clinical care, and their price potentially renegotiated according to their impact on health and overall cost-effectiveness in real life, few countries to date leverage this opportunity (where this is feasible); • This may be due to difficulties involved with routinely collecting clinical data in practice, which will depend on the level of sophistication of IT systems/electronic health records in the country and the motivation of healthcare professionals to input the data, e.g. few European countries have access to linked patient-level data; • Concerns with assessing the evidence in clinical practice post-MEA implementation. <p><i>C) Pure financial agreements, no health outcome component (PVAs, price/dose capping, price-match, etc.)</i></p> <ul style="list-style-type: none"> • Although these schemes are designed to address budget impact concerns, without requesting data on the target expenditure vs. the achieved expenditure, it is generally not possible to say whether the schemes that are implemented succeed in managing the budget impact (France, which publishes its savings estimates on an annual basis, is an exception). <p><i>D) Schemes aiming to manage utilisation to optimise performance</i></p>

Component	Summary of key areas
	<ul style="list-style-type: none"> Although the schemes seem to be designed to achieve optimal utilisation in clinical care, it is not clear if they really succeed in limiting reimbursement to specific patient sub-groups; PVAs, for example, are used in France in an attempt to limit the use of medicines to the approved indication. However, the data collected do not enable verification whether the medicines were prescribed for the approved indication or not. <p><i>E) Weaknesses from a payer perspective</i></p> <ul style="list-style-type: none"> Additional efforts are required to make a new medicine available to patients, such as the extent of time needed for negotiations, monitoring of patient responses, data collection efforts, and efforts involved with developing patient registries; There can be limited capacity within countries to implement and assess the evidence generated and its robustness - especially if the data are provided by pharmaceutical companies and there is no routine access to patient-level data in the country. <p><i>F) Weaknesses from a patient perspective</i></p> <ul style="list-style-type: none"> Generally limited opportunities to engage with the development of MEAs; Not all patient groups are aware of what MEAs do, let alone know about individual schemes within their country. <p><i>G) Weaknesses from a manufacturer (pharmaceutical company) perspective</i></p> <p>Concessions need to be made, such as refunds for non-respondent patients, discounts, collection of additional data, etc., affecting potential profitability.</p>
Opportunities	<p><i>A) General opportunities</i></p> <p>Coverage with evidence generation schemes potentially increase the opportunity for the health system to re-evaluate the effectiveness of new medicines at a later stage and re-negotiate the price based on real-life effectiveness data, as opposed to Phase III clinical trials.</p> <p><i>B) Linking with other activities and initiatives</i></p> <ul style="list-style-type: none"> Streamlining post-marketing studies with data collection requirements as part of MEAs and/or adaptive pathways, e.g. reducing the data collection burden; Potential to link data collection as part of MEAs with EU initiatives on registries and adaptive pathways. Pulling evidence from different countries will generate a larger pool of data and increase the statistical significance of the results. <p><i>C) Managed introduction of new medicines</i></p>

Component	Summary of key areas
	<p>Opportunity to limit the budget impact of new, high-priced medicines by integrating MEAs into the process of the managed introduction of new medicines⁶³⁵.</p> <p><i>D) Opportunities from a payer perspective</i></p> <p>Re-evaluation of the effectiveness and/or safety of a new medicine in routine clinical care and the potential for re-negotiation of prices as new evidence becomes available.</p> <p><i>E) Opportunities from a patient perspective</i></p> <p>Greater transparency and opportunities to engage in the MEA process could enable patients to obtain faster access to new medicines.</p> <p><i>F) Opportunities from a manufacturer (pharmaceutical company) perspective</i></p> <ul style="list-style-type: none"> • Public relation and other benefits from the willingness to take responsibility for the use of a new medicine in real-life; • If integrated with post-marketing data collection including adaptive pathways, there is the potential of reducing data collection requirements in the future.
Threats	<p><i>A) General</i></p> <ul style="list-style-type: none"> • Proliferation of MEAs as quick-fix ad-hoc solutions, which are not always integrated into a comprehensive process of the managed entry of new medicines; • Their proliferation is likely to cause considerable additional burden to the healthcare system and manufacturers if not adequately addressed. <p><i>B) Threats from a payer perspective</i></p> <ul style="list-style-type: none"> • If MEA agreements proliferate without integrating with other activities and initiatives, the burden of such schemes is likely to become too great; • As MEAs become more common, there is a threat that pharmaceutical companies could start proposing higher entry prices for their new medicines in expectation of having discussions to lower prices for reimbursement; • If opportunities to synergise across initiatives (e.g. adaptive pathways, EU initiatives on registries, etc.) and to pull together evidence from different registries/databases and sharing of evidence between countries are not improved, duplication of data collection will occur and the evidence available to individual countries/regions within a country is likely to remain weak and potential fragmentary; • This could result in pharmaceutical companies putting pressure on health authorities to fund their new medicine without such schemes. <p><i>C) Threats from a patient perspective</i></p>

⁶³⁵ Godman, B. et al., 2014, *Dabigatran - a continuing exemplar case history demonstrating the need for comprehensive models to optimize the utilization of new drugs*, *Frontiers in pharmacology*, 5, p. 109.

Component	Summary of key areas
	<ul style="list-style-type: none"> • If MEAs become too burdensome for payers and pharmaceutical companies, the latter might become less willing to engage with such schemes, thus affecting the availability of new medicines; • This means that fewer instruments could be available to facilitate access to new medicines at affordable prices. <p><i>D) Threats from a manufacturer perspective</i></p> <p>If MEAs are going to add to other requirements (e.g. post-marketing data collection and surveillance) without reducing them, pharmaceutical companies could become more and more reluctant to engage with health authorities for reimbursement of their new medicine.</p>

Source: Adapted from Ferrario et al.⁶³⁶

In view of this, potential approaches in Europe to the pricing and reimbursement of new medicines could include a mixture of those approaches in Austria⁶³⁷ (Box 4) coupled with incremental cost per QALY considerations based on, for instance, the current situation in Poland, Slovenia and Slovakia^{638,639} and recommendations from the WHO (Table 14). The rationale for these suggestions are contained in Box 4. Alternatively, to further develop VBP approaches or MCDA frameworks (Chapters 5.6 and 0), adding to ongoing developments.

⁶³⁶ Ferrario, A. and Kanavos, P., 2013, *Managed entry agreements for pharmaceuticals: the European experience*, EMINet: Brussels, available at:

http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/mea_report_en.pdf.

⁶³⁷ Godman, B. et al., 2008, *Insight into recent reforms and initiatives in Austria: implications for key stakeholders*, Expert review of pharmacoeconomics & outcomes research, 8(4), p.357-371.

⁶³⁸ Matusiewicz, W. et al., 2015, *Improving the managed introduction of new medicines: sharing experiences to aid authorities across Europe*, Expert review of pharmacoeconomics & outcomes research, 15(5), p.755-758.

⁶³⁹ Van Wilder, V. et al., 2015, *Towards a harmonised EU assessment of the added therapeutic value of medicines, study for the ENVI Committee*, available at: [http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU\(2015\)542219_EN.pdf](http://www.europarl.europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU(2015)542219_EN.pdf).

Box 4: Potential advantages of considering pricing approaches to new medicines based on the approach in Austria

- Potential advantages include (building on Table 16):
 - Transparent and predictable approach to the pricing of an appreciable number of new medicines, i.e. those with similar, marginal or added therapeutic benefit compared to current standards, which constitute the vast majority of new medicines Table 15;
 - Provide an enhanced negotiating stance on potential prices/discounts for new medicines if current suggested prices do not meet the agreed criteria for pricing of new medicines, with only marginal or added therapeutic benefits compared to current standards. This could be part of any MEAs;
 - As a result, greater prediction among health authorities regarding future pharmaceutical expenditure when including new medicines in future reimbursement lists;
 - Reduced need for comprehensive health economic evaluations supplied by pharmaceutical companies, thus limiting the extent of internal resources within health authorities to assess these as well as the need for pharmaceutical companies to undertake an appreciable number of costly economic analyses. This reflects growing concerns among European authorities regarding surrogate markers that are used in health economic evaluations to justify premium prices where there are concerns with linking surrogate outcomes with subsequent impact on patients' quality of life and survival⁶⁴⁰. For example, surrogate endpoints such as PFS for cancer patients with solid tumours and overall survival^{641,642,643} as well as initial concerns with ezetimibe^{644,645}.
- This controversy surrounding surrogate markers can lead to considerable differences between estimations of the ICERs between academic groups and between academic groups and authorities, e.g. ICER differences between US\$50,000 (€46,000) and US\$150,000 (€138,000) were noted for sunitinib among different authors⁶⁴⁶. Adoption of the approach in Austria helps to resolve such controversies.

Source: Godman et al.⁶⁴⁷.

⁶⁴⁰ Svensson, S., Menkes, D. and Lexchin, J., 2013, *Surrogate outcomes in clinical trials: a cautionary tale*. JAMA internal medicine, 173(8), p. 611-612.

⁶⁴¹ Kantarjian, H. et al., 2013, *Cancer drugs in the United States: Justum Pretium--the just price*, Journal of clinical oncology, 31(28), p.3600-3604.

⁶⁴² Prasad, V. et al., 2015, *The Strength of Association Between Surrogate End Points and Survival in Oncology: A Systematic Review of Trial-Level Meta-analyses*. JAMA internal medicine, 175(8), p. 1389-1298.

⁶⁴³ Cortazar, P. et al., 2014, *Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis*. Lancet, 384(9938), p. 164-172.

⁶⁴⁴ Mitka, M., 2014, *Ezetimibe prescribing fails to keep up with evidence*, JAMA, 311(13), p. 1279-1280.

⁶⁴⁵ Godman, B. et al., 2009, *Update of recent reforms in Germany to enhance the quality and efficiency of prescribing of proton pump inhibitors and lipid-lowering drugs*, PharmacoEconomics, 27(5), p.435-438.

⁶⁴⁶ Jönsson, B., Ramsey, S. and Wilking, N., 2014, *Cost effectiveness in practice and its effect on clinical outcomes*, Journal of Cancer Policy, 2, p. 12-21.

⁶⁴⁷ Godman, B. et al., 2008, *Insight into recent reforms and initiatives in Austria: implications for key stakeholders*, Expert review of pharmacoeconomics & outcomes research, 8(4), p.357-371.

5.7. Value-based pricing

VBP has been defined by the UK Department of Health as “a mechanism for ensuring patients can get access to the medicines they need by linking the prices the NHS pays medicine providers to the value of the treatment”. This resulted in discussions to use an MCDA to include patient benefits not fully captured using a QALY approach⁶⁴⁸.

VBP is seen by some key stakeholders as potentially the most innovative tool for the pricing of new medicines⁶⁴⁹. However, others are concerned that setting prices based on value may not be efficient as it may not maximise societal value, especially if this leads to increased taxes or health insurance contributions⁶⁵⁰.

There are also concerns that VBP could drive up the cost of new medicines, especially if manufacturers aim toward upper cost per QALY threshold levels in their submissions where economic analyses are used in reimbursement decisions⁶⁵¹. There are also concerns that an increasing use of VBP will lead to an increase in MEAs, such as confidential discounts and PVAs to enhance potential reimbursement, especially where countries reference each other (ERP, Chapter 4.3.1). Without MEAs, the benefits from the introduction of new, expensive medicines shift to pharmaceutical companies in the form of increased profits⁶⁵².

VBP approaches may lead to differences in potential reimbursed prices for new medicines based on issues such as income per capita and current price levels for standard treatments among European countries⁶⁵³. VBP may also have an effect on IRP as more standard medicines lose their patent and there is limited innovation that leads to new medicines. Proposals by a UK Group (Office of Fair Trading) to introduce a form of IRP, based on approaches in other European countries, were rejected by pharmaceutical companies when negotiating new agreements between companies and the Ministry of Health⁶⁵⁴.

This recognises that achieving efficient pricing of medicines between and within countries is a complex conceptual and policy problem. At the same time, there is a recognised requirement to stimulate research and funding into new medicines that address appreciable unmet medical need in Europe. Concurrent with this is the recognised need to optimise the use of existing medicines, at often appreciably lower prices, to maintain equitable and comprehensive healthcare^{655,656}. As a result, different approaches may be needed across countries. This includes different approaches to valuing the level of innovation of new medicines and price trade-offs, including MEAs⁶⁵⁷.

Finally, there are ongoing debates and discussions on the extent of differences in reality between VBP and current approaches used across Europe to assess and value new medicines⁶⁵⁸. For instance, Rawlins et al. pointed out that the proposed VBP in the UK is not

⁶⁴⁸ Sussex, J., Towse, A. and Devlin, N., 2013, *Operationalizing value-based pricing of medicines: a taxonomy of approaches*, *PharmacoEconomics*, 31(1), p. 1-10.

⁶⁴⁹ Levaggi, R., 2014, *Pricing schemes for new drugs: a welfare analysis*, *Social science & medicine*, 102, p. 69-73.

⁶⁵⁰ Expert Panel on effective ways of investing in Health (EXPH), 2016, *Report on Access to Health Services in the European Union*, available at:

http://ec.europa.eu/health/expert_panel/opinions/docs/015_access_healthservices_en.pdf.

⁶⁵¹ Webb, D.J. and Walker, A., 2007, *Value-based pricing of drugs in the UK*, *Lancet*, 369(9571), p. 1415-1416.

⁶⁵² Idem.

⁶⁵³ Danzon, P., Towse, A. and Mestre-Ferrandiz, J., 2013, *Value-based Differential Pricing: Efficient Prices For Drugs in a Global Context*, *Health economics*.

⁶⁵⁴ Godman, B. et al., 2008, *Having your cake and eating it: office of fair trading proposal for funding new drugs to benefit patients and innovative companies*, *PharmacoEconomics*, 26(2), p. 91-98.

⁶⁵⁵ Idem.

⁶⁵⁶ Kaplan, W. et al., 2013, *Priority Medicines for Europe and the World*, Update Report, available at: http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf?ua=1.

⁶⁵⁷ Docteur, E. and Lopert, R., 2015, *Adapting pharmaceutical reimbursement policies to manage spending on high-priced drugs*, *Journal of pharmaceutical policy and practice*, 10(8(Suppl 1):O2.

⁶⁵⁸ Godman, B. and Gustafsson, L.L., 2013, *A new reimbursement system for innovative pharmaceuticals combining value-based and free market pricing*, *Applied health economics and health policy*, 11(1), p. 79-82.

that different from current approaches within NICE because appraisal committees do take into account issues such as the underlying severity of the disease, as well as treatments that prolong life at the end of life, in their deliberations⁶⁵⁹.

These concerns are likely to be resolved as the momentum builds for VBP approaches to the pricing and reimbursement of new medicines across countries.

5.8. Multi-criteria decision analysis

To improve the quality of decision-making, for example around reimbursement decisions, decision-makers need structured, explicit and transparent approaches. MCDA is one of these approaches⁶⁶⁰.

In 2014, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) established an MCDA Emerging Good Practices Task Force to identify best practice guidelines for MCDA. The Task Force presents a stepwise process of conducting an MCDA. The objective of the analysis and the nature of decision-makers' preferences play an essential role in choosing the appropriate approach. For example, value measurement approaches (constructing and computing numerical scores) should be selected when decision-makers consider decision-making criteria (e.g. budget impact and severity of the disease) to be compensatory; that is, an improvement in one criterion can compensate for a worsening in another. Outranking methods (pairwise comparison of alternatives on each criterion) may be useful if the goal is to identify a small subset of alternatives that fulfil a minimum requirement from a large set of alternatives (because developing a total value score using weighted-sum models for each alternative is not efficient).

The Task Force confirmed that MCDA might be applied to decisions informed by HTA. Some formal MCDA applications in HTA are discussed in the literature⁶⁶¹. Examples are MCDA in electing appraisal criteria for the introduction and delisting of health technologies (Italy) and the inclusion of patient involvement in HTA (Germany). For example, IQWiG piloted two MCDA techniques to ascertain patients' preferences as an indirect, unintended outcome in HTA and healthcare decision-making in 2010. In MCDA, health outcomes, disease impact, and implementation of the intervention are mostly used as decision criteria. When using economic criteria, cost-effectiveness criteria and total costs/budget impact of an intervention are considered. The process of including economic aspects, however, differs between countries.

Overall, it can be concluded that MCDA can be used to support the HTA process, but methodological challenges need to be addressed before its full-scale implementation⁶⁶² in practice.

5.9. Post-launch activities

Post-launch activities include assessing the utilisation of new medicines against agreed guidance and/or quality indicators, in addition to assessing the effectiveness and safety of new medicines in routine clinical care. These activities are growing as part of MEAs (Chapter 5.6), proposed developments such as adaptive pathways (Chapter 3.3.1), as well as a recognised need by health authorities to optimise the use of their limited resources.

⁶⁵⁹ Rawlins, M.D., Dillon, A. and Leng, G., 2013, *What's happening at NICE?*, Clinical medicine (London, England), 13(1), p. 13-15.

⁶⁶⁰ Thokala, P. et al., 2016), *Multiple criteria decision analysis for health care decision making-an introduction: Report 1 of the ISPOR MCDA emerging good practices task force*. Value in Health, 19(1), p. 1-13.

⁶⁶¹ Adunlin, G., Diaby, V., and Xiao, H., 2015, *Application of multicriteria decision analysis in health care: A systematic review and bibliometric analysis*. Health Expectations, 18(6), p. 1894-1905.

⁶⁶² Wahlster, P., et al., 2015, *Balancing costs and benefits at different stages of medical innovation: a systematic review of multi-criteria decision analysis (MCDA)*. BMC Health Services Research, 15, p. 262.

The type of post-launch study undertaken will depend on the availability and access to patient level, as well as other utilisation data within a country. Studies assessing time trends in the uptake of new medicines can be conducted with aggregated drug utilisation data, i.e. not involving access to patient level data. Studies assessing the safety and/or effectiveness and/or the appropriateness of the prescribing of new medicines in clinical practice require access to patient level data linked to clinical information⁶⁶³.

Table 23 contains details of post-launch studies undertaken among a number of European countries to assess the uptake, effectiveness and safety of new medicines in routine clinical practice.

Table 23: Examples of post-launch studies across countries assessing usage, effectiveness and safety of new medicines

Country/Region and medicine	Summary of studies undertaken
France – Benfluorex ⁶⁶⁴	<ul style="list-style-type: none"> • The Système National d'Information Inter-Régimes de l'Assurance Maladie and Programme de médicalisation des systèmes d'information were used to review benfluorex and the risk of valvular cardiopathy; • Several cases of valvular cardiopathy were reported in benfluorex-treated patients. This suggested an increase in risk with this medicine marketed, mainly for hypertriglyceridemia, but more recently in patients with diabetes; • Analysis of the risk of hospitalisation in 2007 and 2008 for a diagnosis of cardiac valvular insufficiency in diabetic patients exposed, or not, to benfluorex indicated an increased risk, leading to its removal from the market place.
Italy and Sweden – with dronedarone ⁶⁶⁵	<ul style="list-style-type: none"> • This study assessed how the subsequent reimbursement of dronedarone affected the prescribing of other antiarrhythmic medicines; • There was an increase in the prescribing of antiarrhythmic medicines in Sweden following the launch of dronedarone without any changes in amiodarone use. In the Emilia Romagna region of Italy, reimbursement of dronedarone did not influence the prescribing patterns of overall antiarrhythmics or amiodarone; • The authors concluded that, whilst clinical guidelines place dronedarone among first-choice treatments for atrial fibrillation, the prescribing of amiodarone was not affected in either country by the entry of dronedarone. They believed this was probably due to a cautious approach to prescribing by clinicians in accordance with regulatory recommendations and safety warnings.

⁶⁶³ Wettermark, B., 2013, *The intriguing future of pharmacoepidemiology*, European journal of clinical pharmacology, 69 Suppl 1, p.43-51.

⁶⁶⁴ Godman, B. et al., 2012, *Improving the managed entry of new medicines: sharing experiences across Europe*, Expert review of pharmacoeconomics & outcomes research, 12(4), p.439-441.

⁶⁶⁵ Piccinni, C. et al., 2013, *Trends in antiarrhythmic drug use after marketing authorization of dronedarone: comparison between Emilia Romagna (Italy) and Sweden*, European journal of clinical pharmacology, 69(3), p.715-720.

Country/Region and medicine	Summary of studies undertaken
Sweden - RA ⁶⁶⁶	<ul style="list-style-type: none"> • A study involving all clinics in Sweden specialising in rheumatology showed the following among patients with RA treated with biological medicines: <ul style="list-style-type: none"> – They are not at increased risk of invasive melanoma; – They are not at increased overall risk of cancer, but have a 50% increased relative risk of invasive melanoma. • Given the small increase in absolute risk, the authors concluded that these results do not shift the overall risk-benefit balance of biological medicines in clinical practice to treat RA patients. However, it might have shifted this balance with regard to RA patients that have a high risk of developing melanoma for other reasons.
Sweden – Levodopa/Carbidopa (Duodopa®) ⁶⁶⁷	<ul style="list-style-type: none"> • In late 2003, the manufacturer of Duodopa® applied for reimbursement from the Swedish Reimbursement Agency (TLV). The TLV granted reimbursement in 2005 to enable the manufacturer to submit an economic evaluation dossier; • The re-submission was considered inadequate by the authorities to judge its cost effectiveness; consequently, the TLV granted an extension; • The manufacturer initiated an economic evaluation using patient level data; • Data from a pre-planned interim analysis were used in the model. The TLV had concerns with its cost-effectiveness for new patients (existing patients were still reimbursed); • The manufacturer collected the necessary data and improved the economic model, resulting in reduced uncertainty and a lower cost-effectiveness ratio, and led to subsequent reimbursement for new and existing patients.
Sweden – Antiobesity medicines ⁶⁶⁸	<ul style="list-style-type: none"> • The routine collection of patient level data allowed the authorities in Sweden to assess the characteristics and utilisation of patients prescribed with various weight-loss medicines. The findings showed: <ul style="list-style-type: none"> – There was limited persistence with these therapies among patients in routine clinical practice; 77% of patients continued treatment for less than one year; – 28% of patients prescribed rimonabant and 32% of patients prescribed sibutramine had a history of

⁶⁶⁶ Raaschou, P. et al., 2013, *Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden*, BMJ, 346, p.f1939.

⁶⁶⁷ Willis, M. et al., 2010, *Reducing uncertainty in value-based pricing using evidence development agreements: the case of continuous intraduodenal infusion of levodopa/carbidopa (Duodopa(R)) in Sweden*, Applied health economics and health policy, 8(6), p.377-386.

⁶⁶⁸ Forslund, T. et al., 2011, *Usage, risk, and benefit of weight-loss drugs in primary care*, Journal of obesity, 2011, 459263.

Country/Region and medicine	Summary of studies undertaken
	<p>depression or antidepressant treatment. This is a specific contraindication for rimonabant;</p> <ul style="list-style-type: none"> – 41% of patients prescribed sibutramine had a history of hypertension and/or cardiovascular disease. This is a contraindication with sibutramine; – 36% of patients had no documented weight change after treatment, suggesting a lack of effectiveness.

Source: Godman et al.⁶⁶⁹.

5.9.1. Quality indicators for new medicines

Quality indicators are increasingly used across countries for the benchmarking of physician-prescribing habits, as an auditing tool, or to measure the effect of interventions including medicines^{670,671}. Many indicators now integrate the prescribing of medicines with other aspects of the quality of care; alternatively, linking to a procedure such as changes in treatment^{672,673}. Specific indicators have also been developed to enhance the appropriate use of medicines^{674,675}.

Quality indicators have typically not been developed to optimise the prescribing of new medicines at launch. The reasons for this are as follows:

- often a weak evidence base;
- a mismatch between efficacy and effectiveness (expectations from clinical trials);
- conflicting views between different stakeholder groups, e.g. on how rapidly new medicines should be introduced into routine clinical care;
- difficulties in establishing robust prescribing indicator levels for treatment with limited information;
- typically only a small number of patients are included in Phase III clinical trials^{676,677}.

This is changing with an increasing requirement for indicators at launch to optimise the prescribing of new medicines that treat unmet need within available resources. However, the development of quality indicators or new medicines requires a number of careful

⁶⁶⁹ Godman, B. et al., 2015, *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?* Expert review of clinical pharmacology, 8(1), p. 77-94.

⁶⁷⁰ Wettermark, B., et al., 2009, *Soft regulations in pharmaceutical policy making: an overview of current approaches and their consequences*, Applied health economics and health policy, 7(3), p. 137-147

⁶⁷¹ Marshall, M.N., et al., 2000, *The public release of performance data: what do we expect to gain? A review of the evidence*, JAMA, 283(14), p. 1866-1874.

⁶⁷² Martirosyan, L. et al., 2010, *A systematic literature review: prescribing indicators related to type 2 diabetes mellitus and cardiovascular risk management*, Pharmacoepidemiology and drug safety, 9(4), p.319-334.

⁶⁷³ Campbell, S.M. et al., 2009, *Effects of pay for performance on the quality of primary care in England*, The New England journal of medicine, 361(4), p.368-378.

⁶⁷⁴ Martirosyan, L. et al., 2010, *A systematic literature review: prescribing indicators related to type 2 diabetes mellitus and cardiovascular risk management*, Pharmacoepidemiology and drug safety, 9(4), p.319-334.

⁶⁷⁵ Hoven, J.L., Haaijer-Ruskamp, F.M. and Vander Stichele, R.H., 2005, *Indicators of prescribing quality in drug utilisation research: report of a European meeting (DURQUIM, 13-15 May 2004)*, European journal of clinical pharmacology, 60(11), p.831-834.

⁶⁷⁶ Campbell, S.M. et al., 2015, *Quality indicators as a tool in improving the introduction of new medicines*, Basic & clinical pharmacology & toxicology, 116(2), p. 146-157.

⁶⁷⁷ Eichler, H.G. et al., 2011, *Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response*, Nature reviews Drug discovery, 10(7), p.495-506.

considerations among health authorities. Box 5 summarises key areas that health authorities need to address and consider before introducing quality indicators for new medicines.

Box 5: Key factors when considering quality indicators for new medicines

- Define quality and the attributes of quality to be measured for the new medicine among the intended patient population;
- Address how to measure each aspect of defined quality of medicine use;
- Decide who the target person is, e.g. a physician;
- Ensure transparent recording of conflicts of interests among all stakeholders involved in the development of quality indicators for new medicines;
- Identify the appropriate unit of analyses (macro-meso-micro) and the availability of feasible and reliable data sources to measure this;
- Instigate data collection systems that underpin the measurement of agreed quality indicators before quality improvement begins with the new medicine ("know your baselines");
- There should be multiple approaches targeting quality and safety within a health systems-based strategy for a new medicine;
- A mix of structure, process and outcomes indicators can be considered for new medicines;
- A mixture of top-down and bottom-up approaches should be considered for new medicine;
- Validate, field/pilot-test the proposed indicators before general use.

Source: Adapted from Campbell et al.⁶⁷⁸.

⁶⁷⁸ Campbell, S.M. et al., 2015, *Quality indicators as a tool in improving the introduction of new medicines*, Basic & clinical pharmacology & toxicology, 116(2), p. 146-157.

6. ACCESS TO MEDICINES AND THE IMPACT OF ECONOMIC CRISIS

KEY FINDINGS

- Access to medicines refers to the patient's possibility to obtain medicines and is influenced by several factors. Availability and affordability are the most important ones.
- Regulatory policies have an impact on the availability of medicines among EU MS. Key issues are pricing policies, lag-time between marketing approval and pricing, generic competition, prescribing schedules.
- The affordability of a medicine is mostly dependent on the extent to which it is covered by the health insurer/payer. Reimbursement restrictions and co-payment deeply impact access to medicines.
- In recent years, the EU faced an economic crisis, which varied from country to country and posed a threat to health and health systems performance.
- Patients living in countries that suffered from economic crisis faced increased difficulties in accessing medicines.

6.1. Introduction

Access to medicines is recognised internationally as an important quality indicator of health service provision⁶⁷⁹. Access to medicines, defined as the patient's possibility to obtain medicines, concerns if and how people are obtaining their medicines, including how they use them, how much they pay for them and what is the burden of this payment on the overall personal income. Access to medicines has been described under different frameworks, as highlighted in the paper by Bigdeli et al⁶⁸⁰:

- The WHO-MSH 2000⁶⁸¹, based on availability, accessibility, acceptability and affordability;
- The WHO 2004⁶⁸² "Equitable access to essential medicines framework", encompassing four dimensions: rational selection, affordable prices, sustainable financing and reliable health and supply system;
- The Frost and Reich 2010⁶⁸³, based on 4As: architecture, availability, affordability and adoption.

The three frameworks, albeit different, have availability and affordability in common. Availability, which refers to manufacturing, forecasting, procurement, distribution and delivery of medicines⁶⁸⁴, is linked to pre-launch, peri-launch and post-launch activities.

⁶⁷⁹ Donabedian, A., *Defining and measuring the quality in health care*, in *Assessing Quality Health Care*, In: Wenzel RP (ed) Perspectives for Clinicians, 1992, Williams and Wilkins: Baltimore.

⁶⁸⁰ Bigdeli, M. et al., 2013, *Access to medicines from a health system perspective*, Health Policy Plan, 28, p. 692–704.

⁶⁸¹ Penchansky, R. and Thomas, J.W., 1981, *The concept of access: definition and relationship to consumer satisfaction*, *Medical Care*, 19, p. 127–140.

⁶⁸² World Health Organization, 2004, *Equitable access to essential medicines: a framework for collective action*, Policy Perspectives on Medicines, WHO: Geneva, available at: <http://apps.who.int/medicinedocs/pdf/s4962e/s4962e.pdf>.

⁶⁸³ Frost, L.J. and Reich, M.R., 2010, *How do good health technologies get to poor people in poor countries*, Boston, MA: Harvard Center for Population and Development Studies.

⁶⁸⁴ Bigdeli, et al., 2013, *Access to medicines from a health system perspective*, Health Policy Plan, 28, p. 692–704.

Affordability, which refers to the prices of medicines, is probably the dimension most affected by globalisation⁶⁸⁵.

Providing access to medicines and ensuring their affordability is essential according to the global coalition on universal health coverage⁶⁸⁶. In this context, in particular peri-launch activities, including pricing and reimbursement methods and policies, it may be fundamental to secure accessibility and affordability of medicines.

Nevertheless, according to Bigdeli et al.⁶⁸⁷, the above mentioned frameworks do not reflect the complexity and dynamics of healthcare systems. In fact, barriers to access can stem from both the demand and the supply side. From the demand-side, health-seeking behaviours and attitudes, both related to individual preferences and cultural and social customs, should be considered. From the supply side, barriers may be linked to the health service delivery, the health sector organisation, the public policies and the international and national context⁶⁸⁸. In this respect, the recent economic crisis has posed a threat to health and health systems performance. In fact, an economic crisis is a situation in which the country's economic activities, such as investments, national earnings, capital circulation and employment, are reduced to the extent that they eventually lead to decreasing credits and negative economic growth⁶⁸⁹. In recent years, the EU, in the context of a global general decline, faced an economic crisis with scale and timing varying from country to country. Some 4.4% of EU GDP was lost in 2009, slightly recovering in 2010 (+2.1%) and 2011 (+1.7%) and declining again in 2012 (-0.5%)⁶⁹⁰. Unemployment in the EU28 rose from 6.7% in March 2008 to 11.6% in September 2012 and it is currently at 9.5% (August 2015)⁶⁹¹. Due to the economic situation, a budget shortage was faced by governments of countries in economic recession and this led those governments to make their expenditures more efficient, as well as to adopt measures to limit public expenditure; for example⁶⁹², wage freezes or wage cuts in the public sector; staffing freezes or personnel cuts in the public sector; postponing retirement age criteria; tightening of eligibility criteria for unemployment and assistance benefits; reduction of housing benefits; cuts and restrictions in care-related benefits/allowances/facilities; increase in fees for publicly subsidised services (healthcare fees, transport fees, etc.); VAT and other tax increases.

These measures, together with the economic crisis itself, inevitably affected the social security systems as well. As a result, the percentage of population at risk of poverty or social exclusion increased during their period 2010-2012. In Greece, the number of people at risk with regard to social exclusion or poverty increased from about 29% pre-crisis level to 31.0% in 2011, 34.6% in 2012, 35.7% in 2013 and 36% in 2014. In Italy, the number of people at risk increased from about 26% pre-crisis level to 28.2% in 2011 and 29.9% in 2012, settling at 28.4% in 2013 and at 28.1% in 2014, while in Spain the number of people at risk increased from about 24% pre-crisis level to 26.1% in 2010, 26.7% in 2011, 27.2% in 2012, 27.3% in 2013 and 29.2% in 2014⁶⁹³. On the other hand, during the same period, the number of people at risk of poverty or social exclusion remained stable in countries that faced fewer

⁶⁸⁵ World Health Organization, *Access to Medicines*, available at: <http://www.who.int/trade/glossary/story002/en/>.

⁶⁸⁶ World Health Organization, 2014, *What is universal health coverage?*, Online Q&A, available at: http://www.who.int/features/qa/universal_health_coverage/en/.

⁶⁸⁷ Bigdeli, M., et al., 2013, *Access to medicines from a health system perspective*, Health Policy Plan, 28, p. 692–704.

⁶⁸⁸ Idem.

⁶⁸⁹ Alcorta, L. and Nixon, F., 2011, *The Global Financial Crisis and the Developing World: Impact on and Implications for the Manufacturing Sector*, United Nations Industrial Development Organization: Vienna, available at: https://www.unido.org/fileadmin/media/documents/pdf/Publications/110905/WP062010_Ebook.pdf.

⁶⁹⁰ Eurostat, 2015, available at: <http://ec.europa.eu/eurostat/>.

⁶⁹¹ Idem.

⁶⁹² Glassner, V., 2010, *The public sector in the crisis*, ETUI aisbl: Brussels, available at: <https://www.etui.org/Publications2/Working-Papers/The-public-sector-in-the-crisis>.

⁶⁹³ Eurostat, 2015, available at: <http://ec.europa.eu/eurostat/>.

difficulties such as Austria, Belgium, France, Finland, the Netherlands, Germany, and Sweden⁶⁹⁴. Nevertheless, economic shocks increased people's need for healthcare, but made it more difficult for them to access the care they needed⁶⁹⁵.

This chapter is based on a systematic literature review and focuses on the determinants of access to medicines, taking into consideration both the supply and the demand side, and on the impact of the economic crisis. The access to medicines has been tackled with regard to pre-launch (drug discovery, R&D, regulatory framework), peri-launch (governance of medicines, prices settlement, reimbursement, financing) and post-launch (delivery and supply systems and individual and household determinants) levels. A paragraph is also dedicated to specific sub-markets, e.g. generic and orphan medicines.

6.2. Determinants of access to medicines

6.2.1. Pre-launch level

Achieving long-term sustainability of healthcare systems and assuring universal access to new medicines for patients is one of the biggest challenges for health and medicines systems in Europe. Pre-launch activities, such as horizon scanning, forecasting, budget impact and critical medicine evaluation, assist policymakers with a forward-looking perspective on new medicines, thus allowing the use of long-term strategic approaches⁶⁹⁶ (as discussed in Chapter 5.2).

Regulatory policies as well as other supply and demand-side factors, such as overall expenditure on medicines and level of medicine use (market dynamics), are factors influencing the availability of medicines among EU MS. The EURO-Medicines project⁶⁹⁷ found that the number of medicines available varies across the EU, with the greatest number available in Germany and the UK and the lowest in the Scandinavian countries.

The major regulatory barriers to medicines' availability are discussed by Kanavos et al.⁶⁹⁸ in a report for the Directorate General for Internal Policies. Pharmaceutical companies apply for MA in every country, but do not market the medicine in all of them fearing that price regulation will jeopardise their pricing strategies elsewhere and could also lead to parallel trade (discussed in Chapter 4.3.1). This is particularly true for smaller markets, where overall access to medicines is significantly lower as a result of several factors, such as historical context, national budgets and reimbursement policies. By marketing products in EU MS that can afford the highest price or reimbursement level first, such as the UK and Germany, pharmaceutical companies intend to achieve higher prices in less wealthy countries. As a result, creating a barrier in both accessibility and affordability in smaller markets. In fact, some companies shifted exports from countries with lower prices to countries with higher prices. This was a consequence of the interventions on price regulation which have been made by several countries following the economic crisis⁶⁹⁹. However, the serious shortage of

⁶⁹⁴ Idem.

⁶⁹⁵ Maresso, A. et al., 2015, *Economic crisis, health systems and health in Europe: country experience*, *Observatory Studies series*, WHO Regional Office for Europe on behalf of the European Observatory on Health Systems and Policies, available at: http://www.euro.who.int/_data/assets/pdf_file/0010/279820/Web-economic-crisis-health-systems-and-health-web.pdf?ua=1.

⁶⁹⁶ WHO European Office, 2015, *Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research*, WHO: Copenhagen, available at: http://www.euro.who.int/_data/assets/pdf_file/0003/273819/WHO-Medicines-Report-FINAL2015.pdf?ua=1.

⁶⁹⁷ Folino-Gallo, P. et al., 2001, *Availability of medicines in the European Union: results from the EURO-Medicines project*, *Eur J Clin Pharmacol*, 57, p. 441-446.

⁶⁹⁸ Kanavos, P. et al., 2010, *Differences in costs of and access to pharmaceutical products in the EU*, Study for the Directorate General for Internal Policies, Policy Department A: Economic and scientific policy, available at: <http://www.europarl.europa.eu/activities/committees/studies.do?language=EN>.

⁶⁹⁹ Vogler, S. et al., 2011, *Pharmaceutical policies in European countries in response to the global financial crisis*, *South Med Rev*, 4(2), p. 69-79.

medicines that took place in Greece⁷⁰⁰ was not registered in other countries⁷⁰¹. Because of the economic constraints, the Greek healthcare system budget was drastically cut, thus affecting the structure and overall function of public healthcare, including hospitals, because of understaffing, deficits, shortages or even complete lack of medicines and other basic medical and surgical supplies⁷⁰².

Also, the time lag between marketing approval and pricing and reimbursement decisions may influence the access to new medicines, as shown by Cohen et al.⁷⁰³ in a comparative analysis between the US, the UK, France and the Netherlands. Furthermore, overall access to and affordability of pharmaceutical treatments may be influenced by the availability of cheap generic alternatives to expensive branded medicines. Generic availability can be explained by several factors, such as the generic competition, the time delay to generic entry and the demand for generics as dictated by physicians and pharmacies. Across EU MS, there is a significant variability in generic availability, market entry and competition after patents expire. In the Pharmaceutical Sector Inquiry⁷⁰⁴ it was concluded that it takes on average seven months for generic medicines to become available.

6.2.2. Peri-launch level

In addition to regulatory policies, peri-launch activities, in particular price and reimbursement policies, influence medicine affordability⁷⁰⁵.

While MA has been harmonised in the EU, pharmaceutical pricing and reimbursements are set at national level (Chapter 0). Pricing refers to the act of setting a price for a medicine; reimbursement is the full or partial coverage of the cost of the medicine by a third-party payer, such as a social health insurance or a NHS. In practice, pricing and reimbursements are closely linked, in order to secure accessibility and affordability of medicines, and to minimise their cost to third-party payers. EU MS policies regarding the pricing and reimbursement of new medicines clearly also have an impact on the pharmaceutical industry and its incentives for research. Such policies have consequences for patients' access to medicines in terms of both availability and affordability. Because of the limit they impose to the access to new medicines, pricing and reimbursement are sometimes referred to as the fourth hurdle, after the first traditional hurdles of safety, efficacy and quality⁷⁰⁶.

Several studies have analysed the impact of policies on pricing and reimbursement and on the access to new medicines, revealing differences in the uptake of new medicines across Europe, as broadly examined in the WHO technical report on the access to new medicines in Europe⁷⁰⁷. The affordability of medicines varies across EU MS as a result of, amongst others, the variance in national GDP, GDP per capita, the health system and available health budgets. The affordability of a medicine at the patient level depends on, amongst others, the extent

⁷⁰⁰ Karamanoli, E., 2012, *Greece's financial crisis dries up drug supply*, Lancet, 379, p. 302.

⁷⁰¹ Taylor, L., 2013, *Greece: temporary ban on parallel exports*, Pharmatimes Online, available at: <http://www.pharmatimes.com/Article/13-01-31/Greece-temporary-ban-on-parallel-exports.aspx>.

⁷⁰² Ifanti, A.A. et al., 2013, *Financial crisis and austerity measures in Greece: their impact on health promotion policies and public health care*, Health Policy, 113(1-2), p. 8–12.

⁷⁰³ Cohen, J. et al., 2007, *Patient access to pharmaceuticals: an international comparison*, Eur J Health Econ, 8, p. 253–266.

⁷⁰⁴ European Commission, DG Competition, 2009, *Pharmaceutical Sector Inquiry*, final report, available at: http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf.

⁷⁰⁵ WHO European Office, 2015, *Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research*, WHO: Copenhagen, available at: http://www.euro.who.int/_data/assets/pdf_file/0003/273819/WHO-Medicines-Report-FINAL2015.pdf?ua=1.

⁷⁰⁶ Cohen, J., Stolk, E. and Niezen, M., 2007, *The increasingly complex fourth hurdle for pharmaceuticals*, Pharmacoeconomics, 25, p. 727–734.

⁷⁰⁷ WHO European Office, 2015, *Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research*, WHO: Copenhagen, available at: http://www.euro.who.int/_data/assets/pdf_file/0003/273819/WHO-Medicines-Report-FINAL2015.pdf?ua=1.

to which a medicine is covered by the health insurer, combined with the cost-sharing burden placed on the patient⁷⁰⁸.

European countries use different approaches to limit pharmaceutical expenditures, and reimbursement systems are one of the main forms of cost containment strategies (Discussed further in Chapter 0).

The effects on pharmaceutical use and healthcare utilisation of a pharmaceutical policy, restricting the reimbursement of selected medicines/drug classes put in place in Denmark and Norway, were summarised in a Cochrane systematic literature review by Green et al.⁷⁰⁹ From the review, it appears that the impact of policies varied with regard to medication class and the implementation of restrictions. The review revealed that restrictions decreased third-party pharmaceutical spending, but they also diminished the use of some of the target medicines without increasing the use of other health services, as in the case of gastric-acid suppressant and non-steroidal anti-inflammatory drug classes. However, targeting second generation antipsychotic medicines increased treatment discontinuity and the use of other health services without reducing overall pharmaceutical expenditure, highlighting the risk of cost-shifting and of negative health outcome effects⁷¹⁰.

In addition to reimbursement restrictions, there are other forms of cost containment strategies employed by governments in relation to medicines. Among them are price and profit controls applied to pharmaceutical companies, distributors and sellers; cost-sharing strategies, including patient co-payments; the use of prescriptions and OTC medication; the use of reference pricing, generic substitution, and the use of lists of reimbursable medicines. Setting a budget for how much a country will spend on prescription medication is another adopted fiscal measure⁷¹¹.

From a systematic literature review performed by Barnieh et al.⁷¹², it is revealed that the majority of OECD countries use some form of cost-sharing strategy, mainly co-payments, as cost containment measures. The use of these measures varies across and within countries and is related to age, socioeconomic status, and presence of chronic condition(s). In Europe, some countries apply fixed forms of co-payments (i.e. Austria, Italy, the UK), while others use percentage-based co-payments (i.e. Belgium, Denmark, France, Luxemburg, Portugal, Spain), some further countries use both fixed and percentage co-payments forms (i.e. Finland, Germany), while some use cap-based co-payments, so that charges are either per medicine prescribed, per pack of a given medicine or per item on a prescription form (i.e. Ireland, Sweden).

The problem with co-payments, as the study from Barnieh highlights, is that they can create a barrier to seeking necessary medications and to treatment adherence, thus negatively affecting clinical outcomes for chronic conditions⁷¹³. Subsequently, increasing co-payment increases the number of vulnerable citizens, particularly among the elderly and people with a lower socioeconomic status. In fact, co-payments are likely to impact on patients' treatment decisions, particularly for those on a low income. Schafheutle et al.⁷¹⁴ explored how charges

⁷⁰⁸ Kanavos, P. et al., 2010, *Differences in costs of and access to pharmaceutical products in the EU*, Study for the Directorate General for Internal Policies, Policy Department A: Economic and scientific policy, available at: <http://www.europarl.europa.eu/activities/committees/studies.do?language=EN>.

⁷⁰⁹ Green, C.J. et al., 2010, *Pharmaceutical policies: effects of restrictions on reimbursement (review)*, The Cochrane Library, Issue 8.

⁷¹⁰ Idem.

⁷¹¹ The Scottish Government, 2006, *Review of prescription charges in Western Europe, North America and Australasia*, available at: <http://www.gov.scot/Resource/Doc/92240/0022048.pdf>.

⁷¹² Barnieh, L. et al., 2014, *A systematic review of cost-sharing strategies used within publicly-funded drug plans in Member Countries of the Organization for Economic Co-Operation and Development*, PLoS ONE, 9(3):e90434.

⁷¹³ Idem.

⁷¹⁴ Schafheutle, E. et al., 2001, *Access to medicines: cost as an influence on the views and behaviour of patients*, Health Soc Care Community., 10, p. 187-195.

for medicines incurred by patients influence their decisions for managing acute or chronic conditions, and whether prescription costs and affordability issues are discussed in the general practitioner (GP)–patient encounter. The study revealed that the behaviour of those participants who had to pay for their prescriptions, particularly those from less-affluent or deprived backgrounds and on a low or moderate income, was influenced by the cost dimension. However, cost was not the most important factor; these were severity of the condition, necessity and effectiveness of the treatment.

The issue of cost was reflected in the various strategies taken by participants to reduce medication cost, including taking smaller doses or buying an OTC product. Cost and affordability are, indeed, major barriers limiting access to medicines, as emerged from a Spanish study by Costa-Font et al.⁷¹⁵, revealing that use of medicines is dependent on several factors such as income, health insurance, patient co-payment and health status. Because co-payments in Spain are not associated with an individual's income, but depend on age and disability, the result is an unequal access to medicines, such that patients with low income and who do not meet the eligibility criteria may have to pay 40% of the cost of their medicines.

As part of cost containment policies, some countries have a special concern with controlling pharmaceutical expenditure and adopt a demand-side policy to control pharmaceutical expenditure, such as deductibles. A study from Kambia-Chopin et al.⁷¹⁶ evaluated whether the introduction of mandatory deductibles modified patients' purchasing behaviour of prescription medicines in France. The results confirmed the affordability concerns that such restrictions put on the more deprived; they showed that, when all other factors were kept equal, individuals' probability of having modified their consumption of medicines following the introduction of deductibles decreases with income level and health status. Thus, it appears that deductibles on prescription medicines represent a significant financial burden for low-income individuals and those in poor health, with the potential effect of limiting their access to medicines.

All these cost containment measures and, consequently, the access to medicines, have been diversely affected by the economic crisis, as emerged from the findings of the literature review performed. For example, Leopold et al.⁷¹⁷ studied the impact of the measures implemented during the economic recession on the access to antipsychotic medicines in Finland and Portugal. In April 2009, Finland targeted product prices, implementing a reference price system and delisting brand products with generic therapeutic alternatives on the National Social Security's reimbursement list (which resulted in an overall savings of €109 million). This intervention led to a rapid increase in the proportion of sales of generic antipsychotics, but not to a statistically significant reduction in the overall utilisation, thus likely not posing barriers to antipsychotic medicines access. In contrast, Portugal, whose economy suffered a more pronounced decline leading to a strict three-year public budget savings plan⁷¹⁸, introduced several contemporaneous cost-containment policies. In October 2010, Portugal set the reimbursement rates for antipsychotic medicines to 90% of charges with no indication-specific co-payment exemptions allowed (before this intervention, they

⁷¹⁵ Costa-Font, J., Kanavos, P. and Rovira, J., 2007, *Determinants of out-of-pocket pharmaceutical expenditure and access to drugs in Catalonia*, Applied Economics, 39, p. 541-551.

⁷¹⁶ Kambia-Chopin, B. and Perronnin, M., 2013, *Deductibles and the demand for prescription drugs: evidence from French data*, Irdes Working paper, available at: <http://www.irdes.fr/EspaceAnglais/Publications/WorkingPapers/DT54DeductiblesAndDemandPrescriptionDrugs.pdf>.

⁷¹⁷ Leopold, C. et al., 2014, *Impact of pharmaceutical policy interventions on utilization of antipsychotic medicines in Finland and Portugal in times of economic recession: interrupted time series analyses*, Int J Equity Health, 13, p. 53.

⁷¹⁸ Troika consists of representatives of the European Commission, the European Central Bank and the International Monetary Fund.

were basically dispensed to patients without co-payment). In addition, a television and radio campaign to promote generics was launched and a 6% deduction of the maximum retail price for medicines, that had not already lowered prices earlier, was set. As a result, the generic market share of antipsychotic medicines increased, but there was also an unintended statistically significant decrease of 4.5% in predicted antipsychotic sales, likely due to the higher co-payments incurred by patients after policy changes.

In another study, by Da Costa et al.⁷¹⁹, 375 patients recruited in Portugal via community pharmacies reported the number of prescribed and purchased medicines. Failing to purchase prescription items was identified in 22.8% of patients. Regardless of the underlying condition, the most important reason for this was having spare medicines at home, followed by financial problems. The latter was related to the class of medicines and was also associated with low income (<475€/month).

During the economic crisis, co-payments increased also in Austria, Belgium, France and Iceland, whilst Denmark increased co-payment only with regards to fertility products⁷²⁰. In Spain, the Catalanian government extended existing co-payments for medicines to retired people and increased co-payment rates for people with higher incomes⁷²¹. Also, measures to enforce generic prescribing or dispensing were introduced during the economic crisis in Estonia and Lithuania, whilst other countries had already introduced these measures before the economic crisis⁷²². This included compulsory INN prescribing in Lithuania apart from agreed exemptions. The various measures across Europe have resulted in an increased use of generics among European countries (Table 24⁷²³).

Table 24: Generic share (volume) of reimbursed pharmaceutical market in some European countries

Country	2005	2006	2007	2008	2009	2010	2011	2012	2013
Austria	36.8	39.1	40.2	42.1	43	46.1	46.9	48.5	
Belgium	17	21.3	22.4	23.3	24.7	26.5	27.8	29.9	
Denmark			54.4	55.5	63.5	70.7	72.2	73	
France				20.3	22.9	24.6	23.7	26.8	30.8
Germany	59.3	63.6	67.6	70.8	72.4	73.7	76.3	78.2	
Greece								17.9	19.1
Ireland				16.7	16.8	17.9	17.7	23.2	
Italy	5.7	6.4	8.1	10.7	11.6	13.9	16.2	19.5	20.2
Luxembourg				7.8	9	8.4	8.1	7.8	7.7
Portugal	10.4	12.4	14.9	16.9	20.1	26	30.3	35.3	39
Slovakia	75	73.7	72.5	69.2	68.2	68	68.1	68.9	69.6

⁷¹⁹ Da Costa, F. et al., 2015, *Primary non-adherence in Portugal: findings and implications*, Int J Clin Pharm, 37(4), p. 626–635.

⁷²⁰ Vogler, S. et al., 2011, *Pharmaceutical policies in European countries in response to the global financial crisis*, South Med Rev, 4(2), p. 69–79.

⁷²¹ Rada, A.G., 2012, *New legislation transforms Spain's health system from universal access to one based on employment*, BMJ, 344:e3196.

⁷²² Kheirandish, M., 2015, *A review of pharmaceutical policies in response to economic crises and sanctions*, J Res Pharm Pract, 4(3), p. 115–122.

⁷²³ OECD, *OECD Stat*, 2015, available at: <http://stats.oecd.org>.

Country	2005	2006	2007	2008	2009	2010	2011	2012	2013
Spain	14.1	16.7	20.9	21.8	23.8	27.4	34.2	39.7	
UK	73.6	68.5	70.8	71.5	72.5	73.6	75	80.5	

Source: OECD⁷²⁴.

In Cyprus, in contrast to other EU MS, where everyone is covered through a Beveridge or a Bismarck model, the public healthcare system covers public employees, people with an annual income below a certain threshold and patients suffering from certain chronic diseases, whilst everyone who does not fall within these groups has to rely on the private sector for insurance and treatment. In 2013, Cyprus resorted to the so-called Troika funding resulting from the financial crisis and implemented measures in the pharmaceutical sector in order to decrease costs. For example, a patient co-payment fee per prescription was implemented. As underlined by Petrou et al.⁷²⁵, the introduction of co-payment fees and the reduction of public healthcare coverage may have had an impact on the access to medicines. Furthermore, a shortage of medicines may occur, due to reduced profitability of industry in the private sector after the implementation of price reductions.

6.2.3. Post-launch level

All activities carried out in order to guarantee an appropriate and sustainable use of medicines are based on an evidence-based assessment of their risk-benefit profile. Post-launch activities include all the actions that go from clinical guidelines development and implementation to promotion of the appropriate use of medicines, up to the monitoring of effectiveness and safety in clinical practice (see also Chapter 5.9). All these activities aim to ensure that patients with the greater need can have access to medicines⁷²⁶.

A range of factors, such as a nation's wealth, traditions and political system, influence the manner in which medicines are distributed and sold. As reported by Souliotis et al.⁷²⁷ with respect to biologic disease-modifying anti-rheumatic medicines (among other expensive ones), the barriers that were most often reported with regard to access to pharmaceutical treatment include medicine shortages in hospitals, difficulties in the prescription process and distance from pharmacies. In addition, patient co-payments influence the use of medicines (see Chapter 4.7).

A number of scheduling options for medicines are available, such as prescription-only, pharmacy-only, and OTC. Regulatory authorities in a number of countries have used some or all of these options in their medicine scheduling systems⁷²⁸.

When a new medicine is introduced on the market, it is scheduled for prescription only⁷²⁹. Rescheduling of medicines to pharmacist-only, or OTC, by regulatory authorities is based on criteria including a low risk of side effects, the efficacy of the medicine and the ability of the consumer to take care of his/her own minor ailments or symptoms. Gilbert et al.⁷³⁰

⁷²⁴ OECD, *OECD Stat*, 2015, available at: <http://stats.oecd.org>.

⁷²⁵ Petrou, P. and Vondoros, S., 2015, *Cyprus in crisis: Recent changes in the pharmaceutical market and options for further reforms without sacrificing access to or quality of treatment*, Health Policy, 119(5), p. 563–568.

⁷²⁶ WHO European Office, 2015, *Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research*, WHO: Copenhagen, available at: http://www.euro.who.int/_data/assets/pdf_file/0003/273819/WHO-Medicines-Report-FINAL2015.pdf?ua=1.

⁷²⁷ Souliotis, K., et al., 2014, *Barriers to accessing biologic treatment for rheumatoid arthritis in Greece: the unseen impact of the fiscal crisis--the Health Outcomes Patient Environment (HOPE) study*, Rheumatol Int, 34(1), p. 25–33.

⁷²⁸ Spivey, R., Wertheimer, A. and Rucker, T., 1996, *International pharmaceutical services, the drug industry and pharmacy practice in twenty-three major countries of the World*, Pharmaceutical Products Press: Binghamton.

⁷²⁹ Lowe, N. and Ryan-Wenger, N., 1999, *Over-the-counter medications and self-care*. Nurse Pract, 24, p. 34–44.

⁷³⁰ Gilbert, A., Rao, D. and Quintrell, N., 2006, *A review of pharmaceutical scheduling processes in six and the effect on consumer access to medicines*, IJPP, 14, p. 95–104.

determined how the different scheduling arrangements affect availability of medicines to the public. They revealed that, in countries with a single 'prescription-only' schedule, such as France and the UK, all medicines are treated as if they are in the higher schedule, and direct consumer access to medicines is more restricted than in countries with two pharmacy schedules, 'prescription-only' and 'general sale', such as New Zealand, Australia and Canada. The study provides some support for the view that offering two pharmacy schedules allows greater consumer access to medicines, rather than offering a single schedule.

A comprehensive comparison of consumer access to medicines that have been switched from prescription to non-prescription schedule across six developed countries (i.e. the US, the UK, Australia, Japan, the Netherlands, New Zealand) has also been provided by Gauld et al.⁷³¹. The comparative study showed that the health system in some countries may be unnecessarily burdened by managing conditions that could reasonably be self-managed or pharmacist-managed instead. In fact, the study stresses that, other than switching, other mechanisms, such as widening prescribing rights to non-physician practitioners, may increase consumer access to prescription medicines.

The increasing number of medicines rescheduled from prescription-only to OTC status, as well as the importance of the pharmacist in rationalising medicines' use in a safe and effective manner, have contributed to the development a new role of pharmacies as a first contact point for patients in case of minor ailments. Some countries applied the deregulation of the pharmacy sector with the aim of increasing the accessibility of medicines and to reduce costs by ensuring an equitable distribution of pharmacies across the regions, in particular between urban and rural areas⁷³². However, such a rationale has been contradicted by a comparative analysis performed by Vogler et al.⁷³³. The study aimed to assess the impact of deregulation of the community pharmacy on accessibility of medicines, quality of pharmacy services and costs. They revealed that, following deregulation, several new pharmacies and dispensaries of OTC medicines tended to be established predominantly in urban areas, likely to favour populations with already good levels of accessibility and particularly less vulnerable and less seriously ill patients.

From the demand side, high medicine costs are a major barrier to individuals' access to medicines. From a recent Finnish survey⁷³⁴ examining households' cost-related barriers to the use of health services, prescription medicines and social assistance, it was revealed that barriers were common among respondents having poor health and/or low income. This may create inequities in access to healthcare and prescribed medicines. In fact, below-average income families experienced problems with access twice as often as above-average income families.

In addition to the socio-economic status, some vulnerable groups deserve attention. These include children, pregnant women, elderly people, malnourished people, and people who are ill or immune-compromised⁷³⁵.

⁷³¹ Gauld, N.J., et al., 2014, *Widening Consumer Access to Medicines through Switching Medicines to Non-Prescription: A Six Country Comparison*, PLoS ONE, 9(9):e107726.

⁷³² Gesundheit Österreich GmbH, et al., 2012, *Impact of pharmacy deregulation and regulation in European countries*, Summary report, available at: http://whocc.goeg.at/Literaturliste/Dokumente/BooksReports/GOeG_FP_PharmacyRegulationDeregulation_Summary_March2012.pdf.

⁷³³ Vogler, S., Habimana, K. and Arts, D., 2014, *Does deregulation in community pharmacy impact accessibility of medicines, quality of pharmacy services and costs? Evidence from nine European countries*, Health Policy, 117, p. 311-327.

⁷³⁴ Aaltonen, K., et al., 2015, *Cost-related barriers to use of health services and prescription medicines in Finland: a cross-sectional survey*, Eur J Public Health, 25, p. 368-372.

⁷³⁵ World Health Organization, 2003, *Environmental health in emergencies and disasters: a practical guide*, available at: http://www.who.int/water_sanitation_health/hygiene/emergencies/emergencies2002/en/.

Children have the right to receive medicines that are evaluated with regard to their efficacy and safety⁷³⁶. A systematic literature review performed by Costello et al.⁷³⁷ provided evidence on interventions aiming to improve children's access to medicines in the UK. It showed that access to medicines for children at school improves particularly when teachers are trained by pharmacists. Also, the availability of OTC medicines improves children's access, but improper use of medication, and subsequent side effects or poisoning, could be a problem for children of all ages. Refugees and refugee children are a highly vulnerable group likely to experience significant problems in accessing healthcare and medical treatment, as explored in a cross-sectional study from Alkahtani et al.⁷³⁸. It appears that, in the East Midlands region of England, refugee children, even when having access to primary healthcare, medicines, family doctor, and when registered with a GP, are less likely to receive OTC medicines, especially paracetamol.

Using nationwide data, Jiménez-Rubio and Hernández-Quevedo⁷³⁹ examined whether there are differences in the consumption of medicines between immigrants and the Spanish population. The study showed that the lower consumption of medicines by some immigrant categories, particularly Africans, Europeans and EU individuals, relative to Spaniards is mainly related to variables associated with the specific cost-sharing structure in Spain, such as type of health insurance, activity status and health status.

A major challenge in Europe involves achieving greater treatment coverage for people who inject drugs, especially regarding HIV treatment, integrated HIV-Tuberculosis services, HCV treatment, and opioid substitution therapy. Barriers to HIV and HCV treatments have been assessed in a collaborative project between the EC Directorate of Health and Consumers and the WHO Regional Office for Europe. Particularly, facilitators and barriers to antiretroviral therapy have been qualitatively studied among a sample of HIV positive people who inject drugs in Estonia. Overall, despite relatively good availability of HIV treatment services, the study found there was a delay between diagnosis and HIV treatment. The major reason for such a delay was found in structural and systemic barriers related to treatment access and perceived scarcity of resources, including long queues, waiting times for test results, few specialists, and difficulties with regard to treatment in prisons. In regard to HCV treatment, the study identified structural factors, especially social stigma, housing, criminal behaviour, healthcare systems, and gender as important dimensions in conditioning HCV treatment access. Ethnic minorities and women who inject drugs can face particular challenges when accessing treatment, which include caring responsibilities, lack of engagement with services due to fear of child removal, physical, sexual, emotional and structural violence, and demands of money through sex work. According to the study results, it appears of critical importance that there is social, welfare and psychological support in helping people who inject drugs to effectively access HIV and HCV treatments⁷⁴⁰.

⁷³⁶ Alkahtani, S. et al., 2014, *Access to medicines by child refugees in the East Midlands region of England: a cross sectional study*, BMJ Open, 4:e006421.

⁷³⁷ Costello, I., Wong, I.C. and Nunn, A.J., 2004, *A literature review to identify interventions to improve the use of medicines in children*, Child Care Health Dev, 30, p. 647-665.

⁷³⁸ Alkahtani, S. et al., 2014, *Access to medicines by child refugees in the East Midlands region of England: a cross sectional study*, BMJ Open, 4:e006421.

⁷³⁹ Jiménez-Rubio, D. and Hernández-Quevedo, C., 2010, *Explaining the demand for pharmaceuticals in Spain: are there differences in drug consumption between foreigners and the Spanish population?*, Health Policy, 97, p. 217-224.

⁷⁴⁰ WHO Regional Office for Europe, 2012, *Social contexts of access to treatment and care for HIV, hepatitis C and tuberculosis among people who inject drugs in European cities*, available at: http://www.euro.who.int/_data/assets/pdf_file/0018/183231/Scaling-up-access-to-high-quality-harm-reduction,-treatment-and-care-for-injecting-drug-users-in-the-European-Region-final.pdf?ua=1.

6.2.4. Barriers in specific sub-markets: generic and orphan medicines

Generic medicines play an essential part in treating diseases. They increase accessibility and affordability, stimulate healthy competition with the branded sector, allow savings to national health bills, and enable future long-term savings (Chapter 4.8). The European generic medicines industry, however, faces some challenges, as highlighted by Sheppard et al.⁷⁴¹ in a report for IMS Health. Limitations on pre-empting patent expiration in Europe limits generic medicines production in EU MS that, as a result, tend to import manufactured products from 'non-patent' position countries. Although not a barrier, this does add a further hurdle of complex logistics and discourages the development and production of generic medicines in Europe. Discouragement comes also as a result of increasingly stringent regulations, such as pharmacovigilance requirements and periodic safety updates, and of competitive costs, pricing and tendering.

By overweighing the barriers to generic medicines uptake in Europe, EGA's Health Economics Committee report by Bongers et al.⁷⁴² gives a set of recommendations on how to increase the uptake of generic medicines in Europe and patient access to generic medicines in European Healthcare Systems. Similar to Sheppard et al.⁷⁴³, Bongers et al.⁷⁴⁴ discuss the lack of a clear strategy for developing the role of generic medicines for cost containment by the European government. Continued price linkage after generic market entry represents a significant barrier to the market penetration of generic medicines; this is because of the disharmonised manner of application throughout Europe. As before, both market entry delays and time delays of pricing and reimbursement status after marketing authorisation have significant negative consequences for the generic medicines industry. Lack of incentives for physicians to prescribe generic medicines, economic disincentives for pharmacists to dispense generic medicines, and limited incentives for patients to request generic medicines also contribute to the limited access to generics (see also Chapter 4.8).

Particularly challenging for health authorities is the commercialisation of new orphan medicines. There are several factors that may explain the reason for not including new orphan medicines in national formularies or positive lists among European countries. These factors include a lack of availability of orphan medicines because no patients have been diagnosed, commercialisation requiring administrative permission by the country's authorities, and the lack of marketing authorisation, although these medicines are available to patients via compassionate use or similar programmes. Also, reimbursement denial by the authorities or pending reimbursement procedures may influence orphan medicine availability and accessibility of orphan medicines⁷⁴⁵ (see also Chapter 4.5).

The wide range of pricing and reimbursement policies among EU MS results in considerable differences in orphan medicines access across EU. Eastern European countries have, for instance, fewer possibilities to influence pricing and reimbursement negotiations. In Bulgaria, patients suffering from rare diseases only have access to 16 out of 61 orphan medicines

⁷⁴¹ Sheppard, A., 2009, *Generic medicines: essential contributors to the long-term health of society*, IMS Health, available at: http://www.hup.hr/EasyEdit/UserFiles/Granske_udruge/HUP-UPL/IMS.pdf.

⁷⁴² Bongers, F. and Carradinha, H., 2009, *How to increase patient access to generic medicines in European healthcare systems*, European Generic medicines Association, available at: http://www.egagenerics.com/images/Website/Market_Barriers_Report_FINAL_update_How_to_Increase_Patient_Access_to_Generic_Medicines.pdf.

⁷⁴³ Sheppard, A., 2009, *Generic medicines: essential contributors to the long-term health of society*, IMS Health, available at: http://www.hup.hr/EasyEdit/UserFiles/Granske_udruge/HUP-UPL/IMS.pdf.

⁷⁴⁴ Bongers, F. and Carradinha, H., 2009, *How to increase patient access to generic medicines in European healthcare systems*, European Generic medicines Association, available at: http://www.egagenerics.com/images/Website/Market_Barriers_Report_FINAL_update_How_to_Increase_Patient_Access_to_Generic_Medicines.pdf.

⁷⁴⁵ WHO European Office, 2015, *Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research*, WHO: Copenhagen, available at: http://www.euro.who.int/_data/assets/pdf_file/0003/273819/WHO-Medicines-Report-FINAL2015.pdf?ua=1.

included in the positive drug list, while all the other orphan medicines, being not reimbursed, are virtually inaccessible for patients because of their high price, as reported by Iskrov et al.⁷⁴⁶. The authors identify major barriers and challenges to orphan medicines' access in Eastern European countries. In order to increase Eastern European countries' awareness, specific challenges have been highlighted by the Iskrov et al., including the active introduction of epidemiological registries for rare diseases, fostering research of societal preferences and raising public awareness of rare diseases.

⁷⁴⁶ Iskrov, G., Miteva-Katrandzhieva, T. and Stafanov, R., 2012, *Challenges to orphan drugs access in Eastern Europe: the case of Bulgaria*, Health Policy, 108, p. 10-18.

7. LESSONS LEARNT FROM PREVIOUS EXPERIENCES WITH NEW MEDICINES

KEY FINDINGS

- New models have been successfully introduced across the EU to improve the managed entry of new medicines.
- MCDA frameworks are being developed for new medicines for orphan diseases, given the concerns with existing frameworks to measure value.
- There are new proposals to decouple R&D from the commercialisation/usage of medicines, starting with antibiotics. The objective is to increase the number and affordability of new medicines.
- There are also proposals around consortia either globally, pan-European or with national bodies coming together to increase their negotiating power and affordability of new medicines.

7.1. Experiences with models to optimise managed entry of new medicines

The experiences with forecasting activities, as well as educational and other activities' pre-launch with NOACs, such as dabigatran (Chapter 7.2), demonstrate the viability of the proposed three pillars model to improve the market entry of new medicines (Chapter 5 Figure 3).

Forecasting and BIAs will play an increasing role to enable health authorities to better plan likely expenditure on new medicines in target populations⁷⁴⁷. Alongside this, to improve the planning of potential disinvestment opportunities, as more standard treatments lose their patents and become available either as low-cost generics or biosimilars.

HTA plays a key role in the appraisals and decision-making for new medicines, starting early as part of the evidence generation to help guide future decision-making⁷⁴⁸. This will increasingly include pharmaceutical companies and health authorities entering into dialogue pre-launch when clinical trials are being planned, and as part of adaptive pathways^{749,750}. Such early dialogue approaches, which are already happening, should also help reduce duplication between the requirements of different authorities across Europe^{751,752}.

VBP approaches, as well as MDCA, are being proposed and developed to address concerns with the sensitivity of approaches such as the QALY (Chapter 0 and 5.8). For example, in Scotland, the Patient and Clinical Engagement (PACE) Group has been instigated to help assess the value of new treatments at the end of life and very rare conditions⁷⁵³. The main purpose of PACE is to gather detailed information that allows a fuller discussion on the benefits of a medicine. This includes how the new medicines could impact on the quality of

⁷⁴⁷ Matusewicz, W. et al., 2015, *Improving the managed introduction of new medicines: sharing experiences to aid authorities across Europe*. Expert review of pharmacoeconomics & outcomes research, (5), p. 755-758.

⁷⁴⁸ Ijzerman, M.J. and Steuten, L.M., 2011, *Early assessment of medical technologies to inform product development and market access: a review of methods and applications*, *Applied health economics and health policy*, 9(5), p.331-347.

⁷⁴⁹ Vandenbroeck, P. et al., 2016, *Future scenarios about drug development and drug pricing*. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). KCE Reports 271. D/2016/10.273/59.

⁷⁵⁰ Godman, B. et al., 2015, *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?* Expert review of clinical pharmacology, 8(1), p. 77-94.

⁷⁵¹ Idem.

⁷⁵² Vandenbroeck, P. et al., 2016, *Future scenarios about drug development and drug pricing*. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). KCE Reports 271. D/2016/10.273/59.

⁷⁵³ Scottish Medicines Consortium, 2016, *PACE - medicines for end of life and very rare conditions*, available at: https://www.scottishmedicines.org.uk/Submission_Process/Submission_guidance_and_forms/PACE.

life of patients, especially where this information may not always be fully captured using QALY techniques. Such approaches are likely to grow with ageing populations and the greater prevalence of chronic diseases, such as cancer.

Other proposed approaches include developing specific budgets for high-cost, specialist medicines, including new medicines for patients with cancer, to guarantee available budgets⁷⁵⁴. Such approaches are likely to result in more aggressive scrutiny over the pricing and value of new medicines, as well as ongoing discussions over the price of existing medicines to ensure equitable and comprehensive healthcare^{755,756,757}.

Alternative approaches also include guaranteeing fair and reasonable prices for new medicines. However, this will necessarily include accurate information on actual R&D costs, as well as costs of goods given the concerns with the pricing approaches of, for instance, new medicines for hepatitis C, cancer and orphan diseases (Chapter 4), as well as concerns with the true costs of developing new medicines^{758,759,760}.

Post-launch activities include entering patients onto registries, monitoring prescribing against agreed guidance, including any developed quality indicators, as well as potentially restricting reimbursement of new medicines to defined patient populations where their value is greatest⁷⁶¹. Restricting new medicines to defined populations where their value is greatest will grow as our knowledge of pharmacogenomics grow, i.e. a more personalised approach to healthcare⁷⁶², to reduce the number of patients needed to treat in order to gain a response. A part of these developments is increasing the number of patients needed to treat before side effects are seen. Key issues include assessing the medical, legal, economic, ethical, social and organisational issues associated with personalised medicine, given some of the disappointments to date. The implications for developing and funding new personalised medicines for all key stakeholders, including physicians, patients, payers and pharmaceutical companies, are explored further in the paper by Godman, Finlayson et al. involving health authority personnel from across Europe⁷⁶³.

Typically, stakeholders from academia, government and health authorities/health insurance agencies favour prescribing restrictions of new and expensive medicines post-launch, as opposed to an increased role of the private sector, including increased co-payments, with increasing budgetary pressures⁷⁶⁴.

⁷⁵⁴ Vandenbroeck, P. et al., 2016, *Future scenarios about drug development and drug pricing*. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE), KCE Reports 271. D/2016/10.273/59.

⁷⁵⁵ Godman, B. et al., 2015, *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems? Expert review of clinical pharmacology*, 8(1), p. 77-94.

⁷⁵⁶ Vandenbroeck, P. et al., 2016, *Future scenarios about drug development and drug pricing*. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE), KCE Reports 271. D/2016/10.273/59.

⁷⁵⁷ Godman, B. et al., 2008, *Having your cake and eating it: office of fair trading proposal for funding new drugs to benefit patients and innovative companies*. PharmacoEconomics, 26(2), p. 91-8.

⁷⁵⁸ Avorn, J., 2015, *The \$2.6 billion pill--methodologic and policy considerations*. NEJM, 372(20):1877-9.

⁷⁵⁹ The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. 2013, Blood, 121(22), p. 4439-4442.

⁷⁶⁰ Expert Panel on effective ways of investing in Health (EXPH), 2016, *Report on Access to Health Services in the European Union*, Available at: http://ec.europa.eu/health/expert_panel/opinions/docs/015_access_healthservices_en.pdf.

⁷⁶¹ Godman, B. et al., 2015, *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems? Expert review of clinical pharmacology*, 8(1), p.77-94.

⁷⁶² Godman, B. et al., 2013, *Personalizing health care: feasibility and future implications*, BMC medicine, 11, p. 179.

⁷⁶³ Idem.

⁷⁶⁴ Tordrup, D., Angelis, A. and Kanavos, P., 2013, *Preferences on policy options for ensuring the financial sustainability of health care services in the future: results of a stakeholder survey*, Applied health economics and health policy, 11(6), p. 639-652.

Post-launch activities assessing the effectiveness and safety of new medicines in routine clinical care will grow as part of adaptive pathways approaches, as well as generally among health authorities, as they seek to use available resources wisely.

Post-launch activities also include active disinvestment in redundant technologies to fund more effective and/or more efficient technologies. Disinvestment is outside the scope of this document. However, case histories from across countries, including France, are discussed in a recent paper by Parkinson et al.⁷⁶⁵.

7.2. New oral anticoagulants – example of dabigatran

NOACs showed promise in the prevention of strokes in patients with atrial fibrillation, and are seen as an alternative to warfarin. However, there have been concerns in the elderly with dabigatran, particularly in patients with poor renal function, as there could be a build-up of blood levels. This will increase the risk of bleeding, complicated by no known antidote and no commercially available assay at the time of the launch to measure the blood levels of dabigatran in patients^{766,767}. The potential for dose adjustment and monitoring, particularly in elderly patients with poor renal function, were not being widely communicated by the company ahead of the launch⁷⁶⁸.

The concerns with potential bleeding and death resulted in activities among health authorities across Europe to educate physicians pre-launch about dabigatran. The objective was to reduce unnecessary episodes of patient bleeding and possible deaths post-launch⁷⁶⁹. Some of these activities and their outcomes in terms of reduced or no abnormal bleeding are summarised in Malmstrom et al., Godman et al., Matusiewicz et al. and Sinigoj et al.^{770,771,772,773}.

These and other examples, including new medicines for patients with cancer, demonstrate the need for effective models to optimise the managed entry of new medicines⁷⁷⁴. The alternative is a wasteful use of resources including continuing funding of new high priced medicines with limited health gain. As a result, denying other patients the opportunity to be prescribed more cost-effective medicines within finite budgets.

7.3. New medicines to treat patients with cancer

Initiatives to suggest minimum effectiveness criteria for new medicines to treat patients with cancer to be seen as an advance grew out of payer and physician concerns, given the ever-increasing prices for new cancer medicines within finite resources (Chapter 7.3).

⁷⁶⁵ Parkinson, B. et al., 2015, *Disinvestment and Value-Based Purchasing Strategies for Pharmaceuticals: An International Review*, *PharmacoEconomics*, 33(9), p.905-24.

⁷⁶⁶ Malmstrom, R.E. et al., 2013, *Dabigatran - a case history demonstrating the need for comprehensive approaches to optimize the use of new drugs*, *Frontiers in pharmacology*, 4, p. 39.

⁷⁶⁷ Reilly, P.A. et al., 2014, *The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)*, *Journal of the American College of Cardiology*, 63(4), p.321-328.

⁷⁶⁸ Cohen, D., 2014, *Dabigatran: how the drug company withheld important analyses*, *BMJ*, 349, g4670.

⁷⁶⁹ Malmstrom, R.E. et al., 2013, *Dabigatran - a case history demonstrating the need for comprehensive approaches to optimize the use of new drugs*, *Frontiers in pharmacology*, 4, p. 39.

⁷⁷⁰ Sinigoj, P. et al., 2015, *Dabigatran Concentration: Variability and Potential Bleeding Prediction In "Real-Life" Patients With Atrial Fibrillation. Basic & clinical pharmacology & toxicology*, 117(5), p. 323-329.

⁷⁷¹ Malmstrom, R. et al., 2013, *Dabigatran - a case history demonstrating the need for comprehensive approaches to optimize the use of new drugs*, *Frontiers in pharmacology*, 4, p. 39.

⁷⁷² Godman, B. et al., 2014, *Dabigatran – a continuing exemplar case history demonstrating the need for comprehensive models to optimise the utilization of new drugs*, 5(109), p. 1-11.

⁷⁷³ Matusiewicz, W. et al., 2015, *Improving the managed introduction of new medicines: sharing experiences to aid authorities across Europe. Expert review of pharmacoeconomics & outcomes research*, 15(5), p. 755-758.

⁷⁷⁴ Idem.

It is likely that such initiatives will grow as part of an improved assessment of the value of new cancer medicines, given the concerns that current approaches and systems are unsustainable⁷⁷⁵. This could be part of MCDA approaches (Chapter 5.8).

Other potential approaches include decoupling R&D costs with subsequent commercialisation⁷⁷⁶. This could begin with antibiotics (7.5.1).

7.4. New medicines to treat patients with orphan diseases

MCDA frameworks, such as the TVF, to better assess the price and value of new medicines for orphan diseases (Chapter 4.5, Table 12) grew out of the considerable challenges with the current system across Europe⁷⁷⁷. Similar concerns resulted in the earlier model proposed by Hughes-Wilson et al. (Chapter 4.5, Table 11)⁷⁷⁸.

It is likely these, or modified approaches, will be taken forward by European countries as they struggle to fund all new medicines for orphan diseases. The validity of these models is enhanced by the fact that their generation has involved all key stakeholder groups. This includes the European Working Group on Mechanisms of Co-ordinated Access to Orphan Medicinal Products (MoCA-OMP).

7.5. New medicines for infectious diseases

7.5.1. New antibiotics

The increase in AMR is seen as one of the most critical problems facing healthcare systems worldwide, including European healthcare systems^{779, 780}. Current estimates suggest that AMR infections cause around 50,000 deaths a year in Europe and the US.

However, there needs to be a change in the incentive systems to develop new antibiotics, given their current scarcity and the current poor return-on-investment model^{781,782}. Poor return-on-investment as health authorities will typically look to limit the use of new antibiotics to very defined patient populations for short treatment courses.

These concerns have resulted in proposed new approaches^{783,784}. One suggestion that is gaining credence is the proposal from the UK and others to raise a €1.84 billion fund to tackle antibiotic resistance with projects funded over the next five years⁷⁸⁵. Already,

⁷⁷⁵ Ghinea, N. et al., 2015, *If we don't talk about value, cancer drugs will become terminal for health systems*, available at: <http://theconversation.com/if-we-dont-talk-about-value-cancer-drugs-will-become-terminal-for-health-systems-44072>.

⁷⁷⁶ Vandenbroeck, P. et al., 2016, *Future scenarios about drug development and drug pricing*. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE), KCE Reports 271. D/2016/10.273/59.

⁷⁷⁷ Godman, B. et al., 2015, *Are new models needed to optimize the utilization of new medicines to sustain healthcare systems?* Expert review of clinical pharmacology, 8(1). p. 77-94.

⁷⁷⁸ Wilson, W. et al., 2012, *Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments?* Orphanet journal of rare diseases, 7: 74.

⁷⁷⁹ World Health Organisation, 2001, *WHO global strategy for containment of antimicrobial resistance*, available at: http://www.who.int/csr/resources/publications/drugresist/en/EGlobal_Strat.pdf.

⁷⁸⁰ Hoffman, S.J. and Outtersen, K., 2015, *Introduction: What Will It Take to Address the Global Threat of Antibiotic Resistance?* The Journal of law, medicine & ethics, 43, Suppl 3, p. 6-11.

⁷⁸¹ Brogan, D.M. and Mossialos, E., 2013, *Incentives for new antibiotics: the Options Market for Antibiotics (OMA) model*, Globalization and health, 9, p.58.

⁷⁸² Outtersen, K. et al., 2015, *Repairing the broken market for antibiotic innovation*, Health affairs, 34(2), p. 277-285.

⁷⁸³ Hoffman, S.J. and Outtersen, K., 2015, *Introduction: What Will It Take to Address the Global Threat of Antibiotic Resistance?* The Journal of law, medicine & ethics, 43, Suppl 3, p. 6-11.

⁷⁸⁴ Hoffman, S.J. and Ottersen, T., 2015, *Addressing Antibiotic Resistance Requires Robust International Accountability Mechanisms*, The Journal of law, medicine & ethics, 43, Suppl 3, p. 53-64.

⁷⁸⁵ HM Government, 2015, *Securing new drugs for future generations: The pipeline of antibiotics*, The review on antimicrobial resistance, available at: <http://amr->

GlaxoSmithKline, Johnson & Johnson and Roche are interested, along with a number of private equity investors⁷⁸⁶. There are also initiatives proposed via the government in the Netherlands (Chapter 3.3.2). Such initiatives are likely to grow, alongside moves to improve the appropriate use of antibiotics, given the extent of the problem and its potential impact on morbidity, mortality and costs.

7.5.2. New treatments for infectious diseases such as Hepatitis C virus

The current situation regarding new treatments with HCV, and the different negotiations leading to different prices and uptake patterns (Chapter 4.6.2), needs to be addressed for all European patients to benefit from potentially curative treatments, and not just those in certain stages of the disease and/or certain countries.

Potential programmes across Europe to enhance access to potentially curative treatments could build on the GAVI Accelerated Vaccine Introduction Initiative^{787,788}. However, this requires timely, transparent and accurate information on potential demand and supply forecasting in order to succeed, as well as a body such as WHO Europe or a designated medicines group within the EC to negotiate on behalf of all European countries.

Country negotiations have worked with the manufacturers offering new treatments for hepatitis C at considerably lower prices to lower income, as well as other countries to address unmet need^{789,790,791}.

In the meantime, consortia are developing across countries to negotiate prices better for new medicines through increasing their purchasing power, e.g. Belgium, Luxembourg and the Netherlands⁷⁹². Such approaches, however, need to address issues such as patent protection/IP rights to encourage future innovation⁷⁹³.

[review.org/sites/default/files/SECURING%20NEW%20DRUGS%20FOR%20FUTURE%20GENERATIONS%20FINAL%20WEB_0.pdf](http://www.review.org/sites/default/files/SECURING%20NEW%20DRUGS%20FOR%20FUTURE%20GENERATIONS%20FINAL%20WEB_0.pdf).

⁷⁸⁶ Evans, P., 2015, *Glaxo to boost superbug war chest*, The Sunday Times, available at: <http://www.thesundaytimes.co.uk/sto/business/Industry/article1629956.ece>.

⁷⁸⁷ GAVI Alliance, 2009, *GAVI's Accelerated Vaccine Introduction Initiative*, available at: <http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=0CDIOFjAB&url=http%3A%2F%2Fwww.gavi.org%2Flibrary%2Fpublications%2FGAVI-fact-sheets%2FFactsheet--GAVI-s-Accelerated-Vaccine-Introduction-Initiative%2F&ei=0zxNU-uvD-gw7AbDnoHYDw&usq=AFOjCNFSDuEPimFy3gx9WyHZAOWa5xGLfA&bvm=bv.64764171,d.ZWU2009>.

⁷⁸⁸ GAVI Alliance, 2011, *The GAVI Alliance Vaccine Supply and Procurement Strategy for the period 2011-2015*, available at: <http://www.gavi.org/about/gavis-business-model/vaccine-supply-and-procurement/>.

⁷⁸⁹ Brennan, T. and Shrank, W., 2014, *New expensive treatments for hepatitis C infection*, JAMA, 312(6), p. 593-594.

⁷⁹⁰ Iyengar, S. et al. 2016, *Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis*. PLoS medicine, 13(5):e1002032.

⁷⁹¹ Andrieux-Meyer, I. et al., 2015, *Disparity in market prices for hepatitis C virus direct-acting drugs*. The Lancet Global health 3(11):e676-677.

⁷⁹² Vandenbroeck, P. et al., 2016, *Future scenarios about drug development and drug pricing*. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). KCE Reports 271. D/2016/10.273/59.

⁷⁹³ Hoen, E. and Passarelli, C.A., 2013, *The role of intellectual property rights in treatment access: challenges and solutions*, Current opinion in HIV and AIDS, 8(1), p. 70-74.

8. CONCLUSIONS AND POLICY OPTIONS

Access to healthcare is a fundamental human right. This includes ensuring that all patients receive the right medicine in the right dose at the right time to treat their condition. This also means developing new medicines that will address disease areas and populations, where currently there are no treatments or where current treatments have limited effectiveness and/or appreciable side effects. These objectives need to be balanced against affordability, with pharmaceutical companies typically seeking higher prices for their new medicines. The situation is complicated by the limited economic growth in Europe expected during the coming years.

To improve access to affordable medicines, we present potential policy options for new medicines as well as for existing medicines. These policy options are drawn on best practices and a review of specific measures undertaken and/or implemented in different European countries.

8.1. New medicines

8.1.1. Need to adopt new R&D models and assess the potential of adaptive pathways

It is important to stimulate R&D into medicines that address areas of unmet need. Stimulating R&D can be done by introducing new models, such as pharma-academic partnerships, biotech co-creation and innovation centres.

In addition, potential ways to accelerate the availability and use of new medicines of value in patients need to be explored through initiatives such as adaptive pathways (Chapter 3.3). Inherent to adaptive pathways is a higher degree of uncertainty regarding the safety and effectiveness of a new medicine at the point of authorisation in comparison with traditional licensing. To reduce uncertainty, clear clinical endpoint(s) should be determined. Its real potential, however, has to be shown through studies performed once the medicine is used in clinical practice to ensure current medicines are used wisely to maximise patient benefits. In ensuring real-world effectiveness, observational studies or RCTs should be used in situations where real-life performance is in doubt⁷⁹⁴. Inherent as well is the willingness of pharmaceutical companies to lower prices if the expected benefits, in terms of envisage effectiveness, safety and value, have not been seen in routine clinical practice.

8.1.2. Reduce fragmentation of regulatory agencies and improve coordination regarding licensing and Health Technology Assessment

There is a need to reduce the fragmentation of regulatory agencies and to improve coordination with the goal of faster MA for new medicines. Regulators, HTA bodies and payers should collaborate with the focus on minimising duplications of RCTs and their applications.

Scientific advice and guidance should be given at early stages in the development of new medicines. This should be done in addition to instigating (pilot) approaches (such as conditional approval or adaptive pathways), enhancing early approval for new valued medicines in subpopulations meeting high unmet need⁷⁹⁵.

Regulators should also make every effort to balance risks and rewards. For this goal, attention must be paid to commercially unattractive medicines with a valuable unmet medical need. However, regulators should avoid making any additional requirements for data collection for new medicines as this could result in a decline in productivity of new medicines.

⁷⁹⁴ Eichler, H.G. et al., 2012, *Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval*, Nature, 91(3), p. 426-437.

⁷⁹⁵ Idem.

This means that when RCTs aiming for more subgroups to demonstrate patient benefit are combined with increasing data requirements to demonstrate safety and efficacy, pharmaceutical companies have to collect more data on more patients. The cost incurred, combined with a smaller chance of making a successful medicine, could lead to selective approaches on which medicine is going to be developed⁷⁹⁶. In addition, HTA/payer requirements to assess the potential value of new medicines need to be harmonised to reduce unnecessary data collection and associated costs.

As a result, clinical data requirements for reimbursement considerations for new medicines should be common throughout the EU MS, acknowledging that each country has slightly different systems for assessing subsequent reimbursement. More data collection also means more work for HTA bodies. With the rise in HTAs, the demand for transparency regarding HTA is rising as well. Standardisation of data requirements could decrease the pressure on pharmaceutical companies to deliver data to multiple European HTA agencies. If this process is arranged correctly, this could be a cost saver for governments and manufacturers, and eventually accelerate the timespan in which a pharmaceutical product is developed, reviewed and authorised⁷⁹⁷. However, concerns with the continued use of surrogate markers, where there are issues with translating these into considerations of quality-of-life, morbidity and mortality, also need to be addressed for premium pricing considerations. This is illustrated for instance in the case of new medicines to treat patients with cancer (Chapter 4.4).

8.1.3. Proactively plan for the introduction and utilisation of new medicines

It is recommended to proactively plan for the introduction and utilisation of new medicines through refining strategies based on the three pillars of pre, peri, and post-launch (Chapter 5). This includes proactively identifying and assessing the potential budget impact of new priority medicines, critically assessing their actual level of health gain as well as monitoring their utilisation and performance in routine clinical care.

Other policy options include:

- providing European funding for countries, especially European countries with small populations, to join in and gain from the activities of EuroScan (i.e., horizon scanning activities).
- (co-)funding research activities with pro-active health authorities/health insurance companies in Germany, Italy, Spain and the UK to refine their forecasting models for new medicines. This will lead to the development of predictive models that can be used across Europe to improve the budgeting for new valued medicines.
- development of guidelines for new medicines during the pre-launch phase, including quality indicators where pertinent, and patient registries should be used post-launch.

8.1.4. Critical review the value of new medicines compared to their price

Pharmaceutical companies can assist reimbursement bodies with their assessment of the value of new medicines in all or subgroups of the population by including patient level outcomes in their clinical study designs. This can potentially be combined with adaptive pathways, especially where there is likely to be the need for long-term patient follow-up and/or concerns with the safety of new medicines among more elderly and more comorbid patient populations.

In the case of new cancer medicines, policymakers can critically review their value at requested prices based on, for example, minimum agreed thresholds of effectiveness (e.g.

⁷⁹⁶ PharmaFutures, 2011, *Shared Value: Rebuilding Pharma's Contract with Society*, Pharma Futures 4, available at: <http://apps.who.int/medicinedocs/en/d/Js20198en/>.

⁷⁹⁷ Idem.

median improved survival of 3 to 6 months versus current standards). Such a step would recognise limited survival improvements with most new cancer medicines.

In the case of new medicines for orphan diseases, formal approaches to their pricing should be used, given the escalating prices (e.g. ERT and ivacaftor at a cost per QALY of €360,000 to €1.36 million). These cases raise concerns with their potential budget impact as more new products are launched. Such approaches include refining the TVF, which is currently being researched in Europe, is one way forward in the future.

In addition, a review of MEAs for new medicines, especially around administrative issues associated with their implementation and follow-up, should be expanded. There also needs to be greater evaluation and publication of current MEAs across Europe given the current scarcity of analyses.

8.1.5. Adopt new approaches to the pricing of new medicines for prevalent diseases

Potential approaches to the pricing of new medicines in general could be a mixture of approaches used in Austria combined with incremental cost per QALY thresholds seen in Poland, Slovakia and Slovenia, and proposed in the UK, especially where available resources for new medicines are an issue. Higher threshold levels for funding new medicines can be considered where resources are currently more plentiful, e.g. Sweden.

European countries could form consortia, as well as other mechanisms, to enhance the opportunity for lower prices for new medicines, especially for prevalent diseases, building on the experiences with new medicines for HCV in some European countries. This includes building on the GAVI experience with new vaccines, as well as the experiences in Belgium, Luxembourg and the Netherlands, particularly with new medicines for orphan diseases.

8.2. Existing medicines

8.2.1. Ensure rapid access to good quality generics

An activity that can be undertaken with regard to existing medicines concerns ensuring rapid access to good-quality generics. The market entry of good-quality generics could be accelerated by reviewing internal processes of countries where there is a concern with delays and aligning them to EU countries where there is faster access.

8.2.2. Scrutinise the mark-ups for medicines in the distribution chain

The mark-ups for medicines in the distribution chain for both wholesalers and pharmacies should be continuously scrutinised given their impact on the final prices charged to health authorities. This is especially important, as wholesaler margins have been as high as 24% of the pharmacy retail price, and pharmacy mark-ups as high as 50%. This applies to all aspects of the distribution chain, including the need for cold storage to transport medicines.

8.2.3. Explore strategies to lower the price of generics

Potential tendering opportunities could be explored, especially when multiple sources for the same medicine are available, building on examples in Germany, the Netherlands and Sweden. Other strategies include aggressive prescriptive pricing building on the Step approach for generic pricing in Norway, and compulsory or voluntary INN prescribing, with the pharmacist only reimbursing the cost of the cheapest referenced priced generic.

8.2.4. Address co-payments where there is a concern

Issues of co-payments and their influence on medication adherence and availability should be proactively addressed where this is a concern with attaining good health, especially following the economic crisis. One approach to high co-payments is lowering the prices of

medicines to increase their affordability to both the government/health insurance company and patients.

In addition, there is a need to review strategies to enhance the prescribing of generics and biosimilars, including addressing any concerns/misconceptions where these still occur. The outcome includes strategies to enhance the prescribing of generics versus originators (brand) or patented medicines in a class or related class without compromising (quality of) care. The savings can be substantial, helping to fund new medicines as well as reduce patient co-payments where this is a concern.

8.3. Final reflection

While all the activities described above can contribute greatly to the goal of effective care within limited healthcare budgets, a critical perspective is important in interpreting this report. The fact is, as shown in the report, that present pharmaceutical R&D produces few new, innovative medicines for diseases with a high unmet medical need. Systems to evaluate each medicine, including existing medicines, are essential to identify these high-priority medicines. The goal of an effective and efficient healthcare system can only be met by full information on the effectiveness and cost-effectiveness of each medicine and processes in place that optimise available budgets. HTA and its related activities, including pharmaceutical regulation, can help furnish this information. HTA includes collecting information that is considered meaningful, relevant and plausible to all stakeholders, including the public and by explicating their values. By taking such an integrative perspective towards HTA, it becomes evident that it can unlock the real value of health technology for a society.

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ISBN 978-92-846-0180-6 (paper)
ISBN 978-92-846-0181-3 (pdf)

doi:10.2861/111626 (paper)
doi:10.2861/303636 (pdf)

