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Access to new medicines in Europe:

technical review of policy initiatives and opportunities for collaboration and research

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ABSTRACT

This report, with a focus on sustainable access to new medicines, reviews policies that affect medicines throughout their lifecycle (from research and development to disinvestment), examining the current evidence base across Europe. While many European countries have not traditionally required active priority-setting for access to medicines, appraising new medicines using pharmacoeconomics is increasingly seen as critical in order to improve efficiency in spending while maintaining an appropriate balance between access and cost–effectiveness. The study features findings from 27 countries and explores different ways that health authorities in European countries are dealing with high spending on new medicines, including methods such as restrictive treatment guidelines, target levels for use of generics, and limitations on the use of particularly expensive drugs. It also outlines possible policy directions and choices that may help governments to reduce high prices when introducing new drugs.

Keywords

DRUG COMMITTEE
DRUG COSTS
DRUG INDUSTRY
FEES, PHARMACEUTICAL
HEALTH POLICY
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List of abbreviations

AMD	age-related macular degeneration
AGENAS	National Agency for Regional Health Services (Agenzia Nazionale per i Servizi Sanitari Regionali – Italy)
AIFA	Italian Medicines Agency
ARB	angiotensin receptor blocker
ASMR	improvement of medical benefit assessment (Amélioration du Service Médical Rendu – France)
ATC	Anatomical Therapeutic Chemical (classification)
CAST	Centre for Applied Health Services Research (Denmark)
CEB	Basel Institute for Clinical Epidemiology (Switzerland)
CEESP	Commission for Medical Evaluation and Public Health (France)
CEM	Medical Expertise Unit (Cellule d'expertise médicale – Luxembourg)
CEPS	Pricing Committee (France)
CHTE	Centre for Health Technology Evaluation
CPG	clinical practice guideline
CTI	Commission for Technology and Innovation
DAHTA	Agency for Health Technology Assessment (Germany)
DECIDE	Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence
DMARD	disease-modifying antirheumatic drugs
DPP	dipeptidyl peptidase inhibitor
DRG	diagnosis-related group
DTC	drug and therapeutics committee
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EML	essential medicines list
EOPYY	National Organization for Health Services Provision (Greece)
EPIRARE	European Platform for Rare Diseases Registry
ERP	external reference pricing
ETH	Swiss Federal Institute of Technology
EU	European Union
EUCERD	European Union Committee of Experts on Rare Diseases
EUnetHTA	European Network for Health Technology Assessment
EuroScan	International Information Network on New and Emerging Health Technologies
FDA	Food and Drug Administration (United States of America)
FIMEA	Finnish Medicines Agency
FOPH	Federal Office of Public Health (Switzerland)
GDP	gross domestic product
GLP-1	glucagon-like peptide-1
GP	general practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	glycated haemoglobin

HCV	hepatitis C virus
HEK	Pharmaceutical Evaluation Board (Heilmittel-Evaluierungs-Kommission – Austria)
HER2	human epidermal receptor 2
HPIU	Health Project Implementation Unit (Armenia)
HSRP	Health Services Research and Policy (United Kingdom)
HTA	health technology assessment
HunHTA	Hungarian Office for Health Technology Assessment
ICER	incremental cost–effectiveness ratio
IER	Institute for Economic Research (Inštitut Za Ekonomska Raziskovanja – Slovenia)
INAHTA	International Network of Agencies for Health Technology Assessment
ISPM	Institute of Social and Preventive Medicine (Switzerland)
IT	information technology
KRIS	Coordination Council for the Deployment of Hospital Medicine (Denmark)
LBI-HTA	Ludwig Boltzmann Institute for Health Technology Assessment (Austria)
LSE	London School of Economics and Political Science (United Kingdom)
MCDA	multicriteria decision analysis
MEA	managed-entry agreement
MEM	Institute for Evaluative Research in Orthopaedics (Switzerland)
MoCA-OMP	Mechanism of Coordinated Access to Orphan Medicinal Products
MTRG	Medical Technology Research Group (United Kingdom)
NCD	noncommunicable disease
NHS	National Health Service (United Kingdom)
NHSC	National Horizon Scanning Centre
NICE	National Institute for Health and Care Excellence (United Kingdom)
NIHR	National Institute for Health Research
NOKC	Norwegian Knowledge Centre for the Health Services (Nasjonalt Kunnskapssenter for Helsetjenesten)
NoMA	Norwegian Medicines Agency
NPH	neutral protamine Hagedorn (insulin)
NVD	National Health Service (Nacionlais Veselbas Dienests – Latvia)
OECD	Organisation for Economic Co-operation and Development
OMP	orphan medicinal product
PARENT	Patient Registries Initiative
PHIS	Pharmaceutical Health Information System (project)
PML	progressive multifocal leukoencephalopathy
PPRI	Pharmaceutical Pricing and Reimbursement Information Network
PPRS	Pharmaceutical Price Regulation Scheme (United Kingdom)
PVA	price–volume agreement
QALY	quality-adjusted life-year
RGO	Advisory Committee on Health Research (Netherlands)
RZZO	Serbian Health Insurance Fund
SAGEM	Directorate General of Health Research (Turkey)
SEED	Shaping European Early Dialogues
SGLT2	sodium glucose co-transporter 2
SMC	Scottish Medicines Consortium
SNHTA	Swiss Network for Health Technology Assessment

TAR	Technology assessment review
TLV	Dental and Pharmaceutical Benefits Agency (Tandvårds och läkemedelsförmånsverket – Sweden)
TNF	tumour necrosis factor
TPH	Tropical and Public Health Institute (Switzerland)
TVF	Transparent Value Framework
UNIL	University of Lausanne
UVT	Health Technology Assessment Unit (Unità di Valutazione delle Tecnologie – Italy)
VBP	value-based pricing
ZHAW	Zurich University of Applied Sciences (Switzerland)
ZINL	Care Institute Netherlands (Zorginstituut Nederland)

Glossary

Access	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 health care facilities, transportation, hours of operation and cost of care. Barriers to access can be financial (insufficient monetary resources), geographical (distance to providers), organizational (lack of available providers) and sociological (such as discrimination or language barriers). Efforts to improve access often focus on providing or improving health coverage.
Biological medicines	These are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules, such as human insulin or erythropoietin, or complex molecules, such as monoclonal antibodies.
Biosimilar medicines	A similar biological or "biosimilar" medicine is a biological medicine that is similar to another biological medicine that has already been authorized for use. Biosimilars can only be authorized 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 authorized for at least 10 years before a similar biological medicine can be made available by another company.
Diagnosis-related group (DRG)	The DRG is a classification system of hospital cases used to pay hospital services, regardless of the cost to the hospital to provide services. The system is based not on the severity of the disease but on the amount of resources consumed. It categorizes illness by diagnosis and treatment. Specific software groups patients into "homogeneous groups" on the basis of diagnosis at discharge (coded by the International Classification of Diseases) and modified by the presence of a surgical procedure, patient age, presence or absence of significant comorbidities or complications and other relevant criteria.
Discount	This is a price reduction granted to specified purchasers under specific conditions prior to purchase.
Economics, health economics	This is the study of how scarce resources are allocated among alternative uses for the care of sickness and the promotion, maintenance and

	improvement of health, including the study of how health care and health-related services, their costs and benefits, and health itself are distributed among individuals and groups in society. Related to pharmaceutical policies, it includes coverage, funding and reimbursement systems; patient co-payment including tier levels; positive and negative financial incentives for physicians and rebate schemes for overprescribing of agreed medicines; and pricing policies.
Education	Education is defined as organized and sustained communication designed to bring about learning. In the field of pharmaceutical policies, educational activities can be directed at physicians (such as quality circles, prescription monitoring) or at patients (such as disseminating of prescribing guidance, public campaigns).
External reference pricing (ERP)	ERP is the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country.
Forecasting	This is evidence-based expectations on sales, budget requirements, demand, projected health gain/outcome and similar.
Grading of Recommendations Assessment, Development and Evaluation (GRADE)	GRADE is a systematic and transparent approach for grading the quality evidence and the strength of recommendations in guideline development. The GRADE approach was developed by the GRADE Working Group in 2000 (with over 200 contributors, including methodologists and clinicians) and is continually refined. It is widely used by international and national health organizations, specialized medical bodies and other health-related organizations.
Health technology assessment (HTA) (definition courtesy of the European Network for Health Technology Assessment)	Health technology is the application of scientific knowledge in health care and prevention. HTA is a multidisciplinary process that summarizes 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. Despite its policy goals, HTA must always be firmly rooted in research and the scientific method. Examples of health technology include: • diagnostic and treatment methods • medical equipment • pharmaceuticals • rehabilitation and prevention methods • organizational and supportive systems within which health care is provided.

High-cost medicines	The concept of “high-cost”, “high-priced” or “premium-priced” medicines has not yet been clearly defined internationally. The high price itself might not be the decisive criterion: other determining factors may include use of or demand for the product, resulting in high costs for the treatment of the patient. A broad definition of a new premium-priced medicine is one whose acquisition cost is greater than €10 000 per patient for a yearly therapy for the public payer and which is replacing an existing medicine (whose costs public payers were already paying).
Horizon scanning	This is a systematic examination of information to identify potential threats, risks, emerging issues and opportunities, allowing for better preparedness and the incorporation of mitigation and exploitation into the policy-making process.
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. Examples of benefits in the socioeconomic domain include a medicine that would prevent (expensive) hospital admissions or enable patients to work.
Inpatient care/ hospital care	This refers to residential care facilities or establishments that are classified according to their focus of care under the ambulatory care industry but perform inpatient care as a secondary activity. It should be noted that the term “inpatient” used in the Organisation for Economic Co-operation and Development’s system of health accounts has a wider meaning than that used in some national reporting systems, where this term is limited to inpatient care in hospitals. Included are services delivered to inpatients in prison and army hospitals, tuberculosis hospitals and sanatoria. Inpatient care includes accommodation provided in combination with medical treatment when the latter is the predominant activity provided during the stay as an inpatient.
Interface management	These are mechanisms of cooperation between the hospital and outpatient sectors. In the pharmaceutical systems of several countries provision of medicines in the out- and inpatient sectors is realized by different actors following different pharmaceutical policies. Interface management measures increase a seamless treatment with medicines across sectors, ensuring continuation of care according to the patient’s needs and an efficient use of resources in health care systems.

	Similar terms include continuity of care, seamless care, integrated care (comprehensive care, transmural care).
Managed-entry agreement (MEA)	An MEA is an arrangement between a manufacturer and payer/provider that enables access to (coverage/reimbursement of) a health technology subject to specified conditions. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximize their effective use or limit their budget impact. Several types of MEA exist: access with evidence development, conditional coverage, conditional treatment continuation, coverage with evidence development, only in research, only with research, outcome guarantees, patient access schemes, pattern or process care, performance-based agreement, performance-based health outcome reimbursement schemes, performance-linked reimbursement, price–volume agreements and risk-sharing schemes.
Medication reconciliation	This is the process of comparing a patient's medication orders to all the medications the patient has been taking. This reconciliation is done to avoid medication errors such as omissions, duplications, dosing errors or medicine interactions.
Orphan medicinal product (OMP)	An OMP is a product intended for the diagnosis, prevention or treatment of a life-threatening, chronically debilitating, seriously debilitating or serious and chronic condition affecting a small number of people, for which it is unlikely – without incentives – that product marketing would generate sufficient return to justify the necessary investment. In the European Union this refers to an indication with a prevalence not exceeding 5 in 10 000 people. This relates to conditions for which there exists no satisfactory authorized method of diagnosis, prevention or treatment; or, if such a method exists, the product must be of significant benefit to those affected.
Outpatient sector/ outpatient care	This refers to the type of health care sector in which outpatient care is provided, in contrast to the hospital (inpatient sector).
Premium price	This is a high price granted to a product – for example, to a medicine to reward its added value.
Price–volume agreement (PVA)	PVAs are agreements that focus on controlling financial expenditure with pharmaceutical companies refunding over-budget situations. A PVA is one form of MEA.
Pricing	This is the act of setting a price for a medicine.
Rebate	A rebate is 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	Reimbursement is coverage of the cost by a third-party payer (such as social health insurance or the national health service).
Sustainability	This is the capacity to meet the needs of the present without compromising the ability to meet future needs.
Value for money	This is a definition of quality that assesses the quality of provision, processes or outcomes against the monetary cost of making the provision, undertaking the process or achieving the outcomes.

Key messages

This report, with a focus on sustainable access to new medicines, reviews policies that affect medicines throughout their lifecycle (from research and development to disinvestment), examining the current evidence base across Europe. While many European countries have not traditionally required active priority-setting for access to medicines, appraising new medicines using pharmacoeconomics is increasingly seen as critical in order to improve efficiency in spending while maintaining an appropriate balance between access and cost–effectiveness. The following are the key messages to be drawn from the respective sections of the report.

Current trends, practices and evidence of pharmaceutical consumption and use in Europe (section 2)

- The current rapid pace of therapeutic innovation, particularly for noncommunicable diseases (NCDs), is extremely positive from a patient perspective.
- At the same time, the introduction of these new products is adding both therapeutic complexity and higher costs, in turn putting increasing pressure on many European health systems.
- To mitigate such pressures and to balance the demand for new medicines and the financial impact of their introduction, further development of systems and processes to optimize the entry of new medicines is necessary across Europe; this applies both in countries with well developed medicine policies and regulation traditions and in those with less mature systems.
- Key steps in these processes should include methods to distinguish and reward meaningful clinical innovation, as well as evaluation mechanisms to assess the benefits in practice of the introduction of the medicines and impacts on health system budgets.

Pre-launch activities – anticipating potential requirements and impact (section 3)

- Pre-launch activities for new medicines can systematically anticipate and prioritize therapeutic innovation with the highest potential for impact on clinical care, the health care system and patient outcomes, preparing the health system for swift access to such innovations. They also help to assess whether to instigate educational and other activities before the launch of a new medicine to enhance appropriate prescribing after the launch. As a result, pre-launch activities assist policy-makers in taking a longer-term strategic approach to the development of their health care systems and to considerations of access to interventions.
- Pre-launch activities assist with prescribing planning, demand assessment and budget estimation to assess the potential impact of new medicines and national guidance on the health economy. There are few public sector examples in the European context to date; however, those that exist show that strategic forecasting of projected use has had an impact on shaping the markets. Potential gains could be made in analysing and forecasting strategic product needs – a new European Union (EU) initiative is piloting this in relation to influenza vaccines and antiviral medicines.
- Transparent methods and systems for evaluating the therapeutic value of new medicines can improve evidence-informed decision-making and better inform the public of benefits and risks related to new treatments.
- Debate is ongoing about whether the regulatory approach to evidence-based medicines can change to adaptive licensing. For some product groups the first step in changing regulation has been taken and products are launched with conditional approval, with limited data on effectiveness and safety. New medicines licensing approaches require careful consideration, particularly in the context of the health systems of the different countries where regulatory decisions will be implemented. They may also require health authorities to be able to implement disinvestment strategies should the

new medicine be shown to have limited value in routine clinical care, since withdrawal of medicines is problematic.

- Adequate assessment of health gains of new medicines versus current treatment requires ongoing physician involvement and education in critical drug evaluation skills, as well as coordination of patient registries.
- Potential ways to expand the benefits from current pre-launch work include greater scrutiny in differentiating innovation and improvements presented by new products in a meaningful way in the context of different health care systems, continued collaboration by payers on standards and criteria for evaluation of benefits and cost–efficiency, transparency and open prioritization with engagement of stakeholders.

Peri-launch activities – pricing and reimbursement methods for in-patent medicines (section 4)

- European countries use a swathe of different methods to set their prices but most still rely on external reference pricing (ERP).
- Consensus is increasing among payers that medicines should be priced according to the added therapeutic value they deliver. Nevertheless, implementing such a value-based pricing (VBP) system is complicated by methodological challenges and data availability.
- Increasingly, countries are using health technology assessment (HTA) to guide their reimbursement decisions. This may be done in conjunction with budget impact analysis. Conducting HTA through multicriteria decision analysis (MCDA) has been proposed as a way to address some of the limitations of current HTA methods.
- Managed-entry agreements (MEAs), rebates, clawbacks and paybacks are widely used tools to generate savings without affecting list prices.
- Achieving fair pricing and ensuring long-term sustainability of health care systems and access for patients is one of the biggest challenges for health and pharmaceutical systems in Europe and worldwide. Industry supports differential pricing with price confidentiality and a modified ERP system to achieve this. Some stakeholders are concerned about price confidentiality; others think it is the only way to grant lower prices to less wealthy countries. Consensus on such issues is unlikely in the immediate future owing to competing stakeholder interests and certain peculiarities of the European pharmaceutical market (such as parallel trade, extensive use of ERP and large disparities between countries in ability to pay).

Post-launch activities: guidelines, formularies and interface management (section 5)

- All activities carried out to address the appropriate and sustainable use of medicines are principally centred on an evidence-based assessment of their risk–benefit profile.
- Clinical guidelines can promote the appropriate use of drugs, provided that their recommendations are explicit; weighted, following a transparent and systematic assessment of the available evidence; and implemented by clinicians.
- Implementation strategies tailored to local contexts and a shared approach with local practitioners should be developed to put recommendations into practice, mainly considering the configuration of health services, available resources and health professionals' skills and attitudes, along with relevant patient perspectives. This can include quality indicators, which should be developed from pre-launch onwards.
- Essential or "wise" medicines lists induce the use of the most effective and safest drugs and help consolidate prescribers' familiarity with them; more inclusive formularies can also define and prioritize the therapeutic context of drug use.
- In many European countries responsibility and funding for medicines used in the outpatient and inpatient sectors are split (for example, social health insurance funds outpatient medicines and medicines used in hospitals are financed from hospital budgets); this dual financing of pharmaceutical systems can incentivize a shift of treatments and patients between sectors.

- The need for improved medicines management at the interface of the outpatient and hospital sectors has increasingly been acknowledged.
- Activities to improve interface management may include initiatives at the micro level (such as hospital discharge programmes) and policies at the macro level (such as joint reimbursement lists and joint drug and therapeutics committees (DTCs)). The latter may include approaches that aim to overcome the challenge of dual funding.

Impact of policies on funding and use of new drugs – some examples (section 6)

New medicines for patients with cancer

- Cancer is one of the most important NCDs. Costs, including the costs of new cancer medicines, however, are rising at an unsustainable rate, threatening continued access to cancer care and other priorities.
- Prices of new cancer drugs have doubled during the past 10 years and are now typically between US$ 6000 and US$ 10 000 per month, often with little relationship between reimbursed costs and associated health benefits.
- Debate is ongoing about whether differences in spend among countries on cancer care actually translate into improved patient outcomes. Key factors affecting differences in outcomes include issues such as lifestyle, late diagnosis and management approaches, particularly for patients aged 65 and over.
- Differences exist in the use of new cancer medicines across Europe: reasons include differences in reimbursement and funding, as well as access to specialist services.
- Potential ways to address these issues include greater scrutiny regarding the costs and cost–effectiveness of new cancer medicines, including agreement on the definition of "meaningful clinical benefits" for given tumours.

Access to tumour necrosis factor (TNF) alpha inhibitors in Europe

- The introduction of TNF alpha inhibitors in the late 1990s represented a breakthrough in the treatment of diseases such as rheumatoid arthritis but, despite their disease-modifying effects, widespread use has been hindered by their relatively high cost and adverse side-effects, leading to reimbursement or usage restrictions in most European countries.
- Substantial variations exist in national guidelines for the treatment of rheumatoid arthritis across Europe.
- Differences in access occur, resulting from variations in availability of rheumatologists and time from symptoms to diagnosis or treatment. Further disparities in access to TNF inhibitors for rheumatoid arthritis patients are associated with countries' socioeconomic development and co-payment levels. The difference in affordability between western Europe and the new EU Member States is explained by the relationships among gross domestic product (GDP), expenditure on health and global drug prices.
- The introduction of biosimilar medicines may reduce costs and increase access to biological products, but experiences with biosimilars are still new. Further experience and evidence of the substitution of biological therapy in practice is required to assess risk and harms.

New therapeutics for hepatitis C

- Access to new innovative medicines and diagnostics is an important element for the control and treatment of hepatitis C infection.
- The prices requested for the new hepatitis C medicines – in particular the direct-acting antivirals as sofosbuvir – are unsustainable for most countries' health budgets. These prices may preclude thousands of patients from benefiting from a curative treatment that might therefore remain accessible only to the most severely ill patients – in many countries they are restricted to hepatic fibrosis F3A4 and early stages are not treated; hence, this transmissible disease will continue to drive new infections.

- Access in high-income countries, like the EU Member States, to innovative treatment products such as anti-infective medicines could be revisited using a new tool – the European Commission (EC) Joint Procurement Agreement – which sets out the modalities under which EU countries can jointly procure medical products.
- Understanding and addressing current challenges regarding hepatitis C medicine are important for the future introduction of new medicines in other areas. With a focus on public health, a dialogue with stakeholders on access to innovation is urgently required.
- Closer collaboration between countries in Europe can foster new achievements. This may be linked, for example, to potential definition of price ceilings, joint or pooled procurement, standard treatment protocols and guidelines, and collaboration on patient registries.

New orphan drugs

- New orphan medicinal products (OMPs) are a challenge to health authorities, in view of the large number of orphan disease areas where there is still unmet need, coupled with the considerable and growing prices requested per patient, which typically exceed average annual acquisition costs of US$ 200 000–500 000 per patient per year.
- Incentives have been offered for pharmaceutical manufacturers to research and develop new OMPs to address identified areas of unmet need. Growing pressure on available resources, as well as some orphan drugs achieving “blockbuster” status (the term for drugs that earn the manufacturer over US$ 1 billion per year in sales), however, means that this practice is now being challenged. This has resulted in some OMPs being denied reimbursement, a growth in MEAs for OMPs to enhance their value and the development of new approaches to valuing orphan drugs, including MCDA tools.
- As no universally accepted metric exists on what currently constitutes a high price for a new OMP or new drug seeking orphan disease status, the use of approaches such as MCDA tools among authorities across Europe will grow. This is mindful of the need to continue to stimulate research into new OMPs to treat rare and high-priority disease areas, to address continuing considerable unmet need balanced against considerable pressure on available resources. In the first instance these resource pressures are likely to lead to more restrictive criteria for granting premium prices for new OMPs and the growth in pan-European patient registries to improve the evidence base. Subsequently, developing more uniform criteria across Europe for valuing new OMPs will be needed.

New drugs for patients with type 2 diabetes

- Type 2 diabetes is a global public health challenge: it is projected that in 2035 over 1 billion people will be affected by or at risk of the disease.
- Nonpharmacological approaches comprising intensive lifestyle interventions – including healthy diet, regular physical activity and avoidance of tobacco and alcohol use – have been shown to prevent or delay the onset of type 2 diabetes and to improve health outcomes in patients who have already developed the disease.
- Lifestyle management and metformin are effective and affordable interventions that can reduce the economic burden of diabetes and reduce mortality. Interventions to improve adherence to these treatment options are required.
- Insufficient evidence is currently available to recommend the most effective medicine to augment therapy once the disease can no longer be controlled with metformin alone. As the disease progresses, initiation of insulin treatment is recommended. Comparative effectiveness and safety research into new therapies is needed to justify the choice of treatment regimens.
- The cost–effectiveness of the available treatment options should be considered when selecting glucose-lowering agents. Less expensive agents should be chosen in resource-poor settings.

Future directions and brief conclusions (section 7)

- Decision-makers are increasingly faced with difficult choices and are required to make informed decisions. This involves greater use of information technology (IT), better steering of medical practitioners to comply with clinical evidence (perhaps through a combination of financial and nonfinancial incentives) and better targeting of national drug policies to those using resources more intensely (multicomorbidity patterns).
- Prioritization processes will increasingly be required for introduction of new medicines and should incorporate principles of collaboration and transparency.
- Cooperation between countries in Europe and stakeholder dialogues on what constitutes a fair reward for industry innovation while still preserving access for patients could be further strengthened. Cooperation between stakeholders should involve better balancing of the value of innovation with equitable, affordable patient access.
- Collaboration among regional or subregional health systems might benefit from including a particular focus on chronic care, specialty medicines and rare diseases.

1. Introduction – background and context

The affordability and financing of new medicines pose challenges to governments worldwide. In Europe, more specifically, in the context of pursuing equitable and comprehensive health care, and against the backdrop of the global economic crisis, ageing populations and the continuing increase in NCDs, the continual introduction of new premium-priced medicines is of especial concern *(1–5)*. This is particularly the case with new premium-priced biological medicines, in view of the appreciable number in development and their envisaged high prices *(2–4; 6–9)*. Decision-makers, including governments and national health insurance providers/payers, are thus forced to take decisions about what new medicines will be included as part of which health care services, and to what extent they will be funded with public funds. Yet for many countries this is a new or emergent area, in which policies are not yet developed and decision-makers remain unsure how to act.

Policy-makers require guidance on how to optimize the entry of new medicines, to ensure the financial sustainability of their health care systems while encouraging the development of new treatments to address areas of unmet clinical need (see section 2) *(5)*. This comes at a time when the response of many European countries to the financial crisis has been to cut their pharmaceutical expenditure by reducing prices paid by governments and insurers/payers for medicines and increasing patient co-payments *(3; 10–12)*. In addition, the contribution of European medicines to global pharmaceutical sales is decreasing. It is anticipated that by 2016 Europe will account for just 18% of global pharmaceutical spending – down from 24% in 2011 – with emerging markets (including Brazil, China, Mexico, South Africa, Rwanda and Thailand) anticipated to account for 30% and the United States of America for 31% *(2; 13)* of market share.

That this is of concern to policy-makers today is evident from the results of a query on high-cost medicines put to the Pharmaceutical Pricing and Reimbursement Information Network (PPRI), hosted by Gesundheit Österreich GmbH, the WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies in Vienna, Austria (see Annex 1 for the questionnaire and full responses). Most notable, perhaps, is that countries are struggling with the overall issue of defining what constitutes a high-cost or premium-priced medicine in their context. Indeed, most respondents reported that they had no specific definition, although they were clearly aware of the issue and concerned about the potential cost burden such medicines carry. Respondents noted that thresholds for what constitutes an innovative advance over existing (lower-cost) therapies are crucial and reported a range of understandings. Also reflected in responses was the fact that, while countries may be concerned with cost issues, specific pricing and reimbursement policies have yet to be thought through in a systematic manner. Most respondents noted that they did not yet have specific policies for the pricing and reimbursement of premium-priced medicines versus other medicines, although several reported that they were working on inpatient policies in particular. Work on MEAs was reported by most countries, again highlighting that cost implications are a major concern. These are important responses, reflecting clearly the need for information and action among policy-makers in Europe. The high response rate to the PPRI query (27 of 42 countries returned answers to the questionnaire) reflects the significance of the issue to decision-makers.

Consequently, in the face of growing resource pressures, transparent systems and processes to facilitate the entry of new medicines and their subsidization in insurance programmes in countries in Europe need to be developed. It is envisaged that this will involve better planning and improved

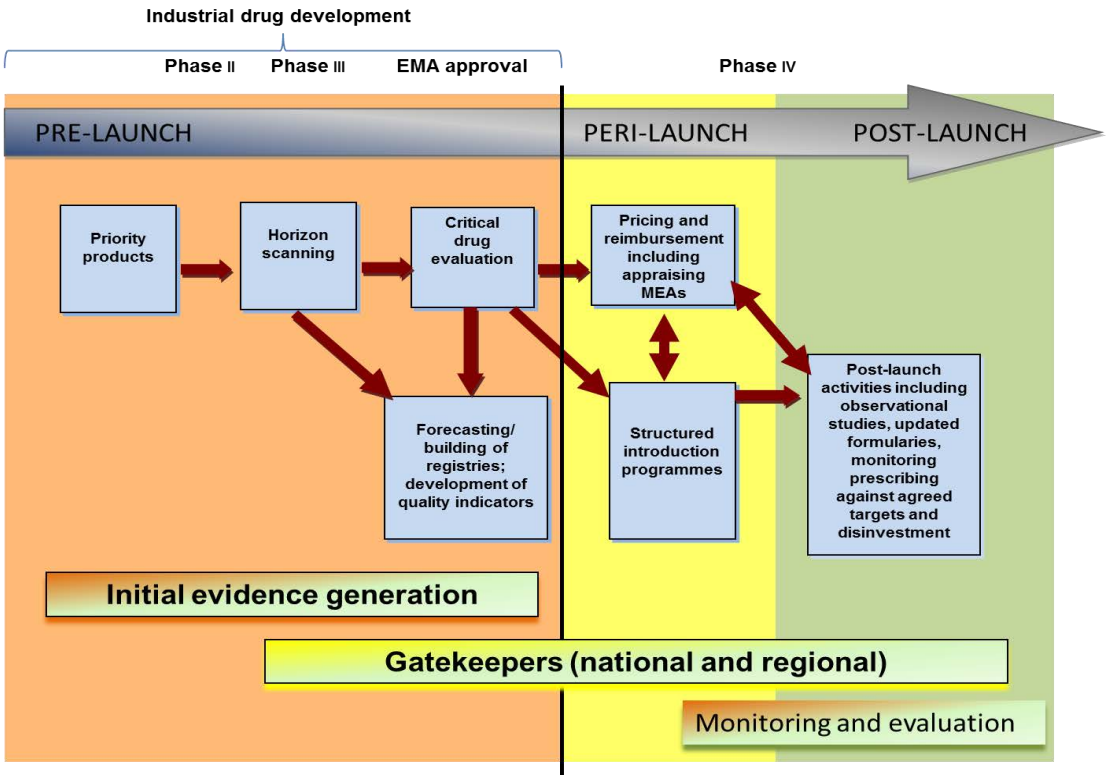
systems – addressing all phases of the product cycle – linking research findings and potential product development closely with access and use scenarios. Thus, governments and insurers or payers could increase opportunities to share their perspectives even before new medicines receive marketing authorization.

It is, therefore, the purpose of this report to review policies and principles for managing the entry (including the financing) of new high-cost or premium-priced medicines in Europe, with two main objectives. The first is to ascertain the quantity of evidence available and to bring together current knowledge and country experiences across the medicines continuum from pre- to peri- to post-launch activities. The second is to explain and summarize this material to provide a resource intended to assist European policy-makers as they attempt to maintain comprehensive and equitable health care systems that are affordable within available resources.

1.1. A framework for locating policy interventions

To help facilitate an informed debate on policies around the introduction of new high-cost medicines, this report offers an overarching framework for locating and examining policy interventions. This is intended to represent where the value of individual patient health outcomes from medicines treatment may be considered carefully through all phases of the product cycle. The cycle begins with pre-launch activities, such as horizon scanning and forecasting; moves into peri-launch activities around the time of product launch, such as HTA, pricing and reimbursement; and continues to post-launch activities, including development of patient registries and monitoring prescribing against agreed guidelines. Fig. 1 shows this continuum, which represents a duration of approximately 9–12 years, depending on the medicinal product.

Fig. 1. Activities to manage the entry of new medicines



Source: adapted from Wettermark et al. *(14);* Malmström et al. *(15)*; Godman et al. *(16)*.

1.1.1. Pre-launch activities

Pre-launch activities (section 3) provide policy-makers with a forward-looking perspective on new medicines in development. This includes a review of their potential specific clinical and treatment outcomes and health system impact (in terms of cost and benefit to patients). Pre-launch activities also anticipate the budget impact of a treatment for its proposed indication, as well as understanding which patients stand to benefit most from the treatment. Governments and payers are thus directly involved as these activities assist them in taking a longer-term strategic approach in development of health care systems and facilitating access to interventions. Pre-launch activities further include horizon scanning (section 3.1) to identify potential new medicines meeting health care priorities and planning for their potential use (section 3.2), including physician and prescriber education; development of patient registries (section 3.3); and demand forecasting. An extensive evaluation of medicines prior to marketing (in some contexts broadly termed "critical drug evaluation") is also part of the pre-launch activities.

1.1.2. Peri-launch activities

Peri-launch activities (section 4) address, among other things, issues of access and affordability. The current thinking in many countries is that there is a need to ensure that prices of medicines reflect their clinical and therapeutic value for patients and society. HTA – with the aim of transparently summarizing information on medical, social, economic and ethical issues related to the use of a product, as well as formulating related patient-focused health policies that achieve best value – is a crucial element of peri-launch activities. Annex 2 gives a summary of national uses of HTA. In addition, various pricing and reimbursement methods and policies are important and generally used during the peri-launch stage.

Many European health systems face significant challenges when deciding whether and how to introduce new expensive therapies. For example, lack of reimbursement of certain expensive therapies limits access; targeting subgroups of patients most likely to benefit from the treatment is more efficient but requires clinical data for these subgroups. In the absence of good clinical data on treatment effectiveness, high patient co-payments or out-of-pocket payments may adversely affect the uptake and use of new medicines. An example of these challenges is the differences across 46 European countries in uptake of treatments for rheumatoid arthritis *(17)*.

Strategies to deal with the high costs of new medicines are many and are examined in detail in section 4.1. They include influencing or managing market entry prices (section 4.1.2) to increase affordability and minimize costs to the health system, as well as regulation of demand – including strategies to reduce adverse drug reactions in potentially more comorbid patients than seen in phase III clinical trials *(15; 18)* – all of which have an influence on pharmaceutical expenditure. Among the main instruments aimed at influencing market entry prices are:

- rate-of-return regulations – an indirect price control mechanism where the manufacturer's contribution to drug development and the economy is considered (section 4.1.2.2);
- ERP – which involves benchmarking proposed prices for new medicines against the prices paid by other payers/countries (section 4.1.2.3);
- cost-plus pricing – whereby retail prices are established by taking into account the production cost of a medicine, with allowance for promotional expenses, the manufacturer's profit margins and profit margins in the supply chain (section 4.1.2.4);

- clinical and cost–effectiveness pricing – which cover different approaches to assessing value, taking into account the drug's cost and clinical effectiveness compared to alternative treatment (section 4.1.2.5);
- VBP – whereby prices are based on a value assessment taking into account a wider range of criteria than cost–effectiveness pricing (section 4.1.2.6).

Reimbursement – coverage of the cost by a third-party payer – is increasingly used in Europe as a way to prioritize access to some medicines (section 4.2). Reimbursement decisions are based on various criteria, which vary across Europe. For new medicines – the focus of this report – decisions on reimbursement are increasingly based on HTA, which may be used in conjunction with budget impact analysis. In addition, MEAs and risk-sharing schemes are also becoming more common. Currently 14 European countries make use of some of these schemes to generate savings without affecting official list prices for these medicines. These agreements are most often confidential and specific to the country context (although this is changing in Germany); the resulting lack of transparency makes cross-national comparison difficult. These agreements are made between the government/payers and the product marketing authorization owner to facilitate early access to new medicines and to reduce uncertainty around the clinical effectiveness, cost–effectiveness and/or budget impact of introducing a new product. They can be divided into access agreements based on financial impact and agreements based on health outcome.

Financial agreements include the following three types:

- price–volume agreements (PVAs) – where an expenditure threshold is set, after which a rebate on the price of all additional doses are triggered;
- discount/rebates – which require full payment of the list price and the subsequent refund of the agreed rebate;
- price/dose/time capping schemes – which establish a cap on either the total treatment cost, the number of doses or the treatment duration, after which the manufacturer assumes all additional treatment costs required to complete the treatment course.

Health outcome-based agreements explicitly link payment to treatment results. The system or insurer agrees to reimburse only for patients obtaining specified outcomes – for example, achieving a desired end-point within a specific time period, of typically 4–12 weeks. Patients who do not meet this threshold receive no or reduced reimbursement, with any difference in payment paid by the manufacturer *(19–21)*. The three types of health outcome-based agreements are:

- payment by result or for performance (also called outcome guarantee or "no cure no pay" agreements) – where a threshold is established demarking whether a treatment was successful or not (if treatment was unsuccessful the manufacturer has to reimburse either the full or partial cost of treatment);
- coverage with evidence development – in instances where evidence is deemed insufficient to make a final reimbursement decision but the competent authority believes it possible to address this data gap, and the manufacturer is asked to collect additional evidence to answer specific questions posed by the authority and possibly to also resubmit a new cost–utility/effectiveness analysis including these real-life data;
- patient registries – to ensure appropriateness in prescribing (monitoring), and to collect data to assess medicines' performance in real life.

Countries are, in the main, using financial agreements. Those using primary PVAs include Belgium, Bulgaria, Estonia, Germany, Hungary, Lithuania, Poland, Portugal and Slovenia, while Catalonia (Spain), France, Italy, Serbia, Sweden and the United Kingdom (England, Wales and Scotland) also use other

financial agreements. In addition, Catalonia, France, Italy and the United Kingdom use results/impact-based agreements. MEAs are an option that can be considered by national governments in providing and targeting access to new medicines. Not all countries in Europe currently use MEAs, however, and there is still debate around the value and impact of these in Europe and other countries *(15; 19–22)*. While agreements of a financial nature, including setting a ceiling on price and volume, have been used for quite some time, impact/results-based payment is relatively new.

1.1.3. Post-launch activities

Post-launch activities (section 5) include monitoring the effectiveness and safety of new medicines in clinical practice and ensuring that patients with the greatest clinical need and those most likely to benefit from treatment can access the medicine, and include systematic detailed analysis of medicine usage data. Systems that facilitate data management include electronic accessible patient registries that collect key clinical data and e-prescription for reviewing prescribing practices to ensure these are consistent with agreed best practice outlines in guidelines and any prescribing restrictions. Standardizing data requirements and integration of different data sets across the health system, as well as close monitoring and evaluation, can allow for improvements in the use of medicines. Better monitoring after launch can also help to optimize the use of resources by encouraging the rational use of medicines, limiting the impact of inappropriate marketing activities and reducing potential expenditures from line extensions and off-label indications *(15; 18–19; 23–32)*.

1.2. Methodology

Section 1.1 provided a short summary of the different policy tools used around prescription medicines, categorized by the pre-launch, peri-launch and post-launch periods of a medicinal product lifecycle, which together make up the medicines policy continuum (see Fig. 1). This conceptual framework guides the rest of the report in addressing key policy issues in greater detail, and complements the general evidence with five case studies based on particular disease areas.

A variety of sources informed the evidence presented in this report, including the results from a primary research exercise, secondary evidence, a broad-ranging literature review and expert opinion. The primary research and data component, although limited, is based on direct input from decision-makers in European countries. This relates to the PPRI query on high-cost or premium-priced medicines, which was specifically commissioned to inform this report. A detailed questionnaire was developed and issued to all PPRI members – including several outside Europe – to collect primary data (see Annex 1). The survey addressed a number of key questions, including the following:

- Does a country-specific definition of high-cost or premium-priced medicines exist?
- What are the key challenges to the funding of new premium-priced medicines?
- Are there specific pricing policies in the outpatient sector for new premium-priced medicines compared to ordinary medicines?
- Are there specific reimbursement policies in the outpatient sector for new premium-priced medicines compared to ordinary medicines?
- Are there specific pricing policies in the inpatient sector for new premium-priced medicines compared to ordinary medicines?
- Are there specific reimbursement policies in the inpatient sector for new premium-priced medicines compared to ordinary medicines?
- Are there any MEAs for new premium-priced medicines?
- Are further initiatives/policies currently being undertaken to better manage the entry of new premium-priced medicines?

The findings indicated priority issues for national decision-makers – specifically in which areas they required more evidence – and informed the choice of issues covered in the report. The query was handled by Gesundheit Österreich GmbH, the WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, and the results discussed and analysed by all contributors to the report.

With regard to secondary evidence, the report is based on a broad-ranging literature search, primarily in the European context, with the focus on publications made with the past 2–3 years and a selection of best evidence identified. The search was carried out via the most relevant databases in the social and medical sciences in order to identify relevant publications in English (Medline, Scopus), including review articles, policy papers and journal articles published up to July 2014. In addition, a general search of the Internet was undertaken in order to identify relevant policy studies and grey literature, with backward and forward citation searching from references. Given the large number of topics under discussion and the need to cover Europe as a whole (as far as possible), this review by necessity cannot be deemed a systematic one. These broad searches, however, led to the identification of more than 400 potentially relevant publications following an initial screening. The final choice of papers reflects the expert opinion of the contributors. Particular attention was paid to publications with examples that could be used in framing the design and development of policy responses at the national and regional levels. Based on this, technical reports from international organizations, national reports and studies, data and other grey literature were used to complement the literature review of the wider academic and journal literature. In addition, discussions with policy-makers in Europe that took place during the drafting of the report have been reflected in the content.

In addition to examining the policy tools, five illustrative examples are provided as case studies (section 6). The key criterion for selection was that these represent examples of new premium-priced medicines – which carry considerable implications for countries' health budgets because they can be considered either "high volume" for treating many patients or "high cost" because of the price of a single course of treatment – in key disease areas. These areas are: (1) cancer, (2) rheumatoid arthritis, (3) hepatitis C, (4) orphan/rare conditions and (5) diabetes. More specifically:

1. Concern is growing about the high cost of new **cancer** medicines, with limited additional survival benefit in most cases and, in the majority of cases, no cure. "End-of-life" treatments also raise an ethical issue of addressing unmet need at this stage in a person's treatment pathway.
2. New drugs for **rheumatoid arthritis** represent high treatment cost and selective use. One issue is that very soon some of these will be available generically (as biosimilars), which raises a policy question around substitution (on the specific indication during treatment).
3. While new treatments for **hepatitis C** are potentially both very cost-effective (because of the high health gain) and curative (if real-life data can demonstrate this in future), they are extremely expensive and potentially unaffordable, given the size of the affected population.
4. Drugs for **orphan conditions** relate to new very highly priced therapeutics for very small populations; they represent a growing concern as to whether this is the way forward for personalized medicines in the future, such as those based on genetic testing, for example.
5. While the concern surrounding **type 2 diabetes** is less about the individual high cost of medicines, collectively diabetes is an expensive disease. While the cost of diabetes medicines is a fraction of the total costs of treating diabetes (diabetes is a disease of comorbidities and treatment also includes other drugs and therapies such as cardiovascular medicines, for example) it is the case that the cost of new medicines to treat diabetes is growing, augmented by the launch of new therapies.

The introduction and/or management of these medicines will need careful handling to ensure that access and equity are maintained, along with sustainable financing.

It should be noted that the concept of “high-priced” or “premium-priced” medicines has not yet been clearly defined internationally, although a few countries have a definition for high-cost medicines (Annex 1 reflects the PPRI query results in this regard). The high price itself might not be the decisive criterion; other determining factors may include use of or demand for the product, resulting in high costs for the treatment of the patient. For this purposes of this report, a broad definition of a new premium-priced medicine is one whose acquisition cost is greater than €10 000 per patient for a yearly therapy for the public payer and which is replacing an existing medicine (whose costs public payers were already paying).

As a review of existing policies and initiatives, this report necessarily uses technical language and terminology specifically related to medicines policies and strategies. The report is, therefore, accompanied by a glossary of major terms in the medicines policy field. The definitions are based on the terminology work of Gesundheit Österreich GmbH and its glossary, although additional terms were specifically defined for this report.

1.3. Partners contributing to this report

This version of the report was made available to Member States in the WHO European Region at the 64th session of the WHO Regional Committee for Europe in September 2014, and has been reworked and amended on the basis of feedback and further work. The report was overseen by the Pharmaceuticals and Health Technologies programme of the WHO Regional Office for Europe (Division of Health Systems and Public Health), and represents a joint work with the following partners:

- Emilia-Romagna Health and Social Care Agency, WHO Collaborating Centre for Evidence-Based Research Synthesis and Guideline Development (Italy): Giulio Formoso and Nicola Magrini;
- Gesundheit Österreich GmbH, WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies (Austria): Sabine Vogler and Nina Zimmermann;
- Karolinska Institute (Sweden): Brian Godman, Lars Gustafsson, Irene Eriksson, Eva Andersén Karlsson and Rickard Malmström;
- LSE Health, London School of Economics and Political Science, WHO Collaborating Centre for Health Policy and Pharmaceutical Economics (United Kingdom): Alessandra Ferrario, Mari Lundeby Grepstad and Panos Kanavos;
- Organisation for Economic Co-operation and Development (OECD) (France): Valérie Paris and Annalisa Belloni;
- WHO Regional Office for Europe (Denmark): Hanne Bak Pedersen, Govin Permanand and Allison Colbert;
- WHO headquarters (Switzerland): Jane Robertson;
- Government of Norway (Directorate of Health): Øyvind Melien and Bengt Skotheim.

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2. Current trends, practices and evidence of pharmaceutical consumption and use in Europe

As pharmaceutical expenditure continues to rise and expensive new treatments come to market, policy-makers increasingly have to consider the impacts on health systems and the cost of care as they decide whether or not to finance new treatments from public funds. It is very likely that willingness to pay will vary across Europe – and even more so beyond Europe – resulting in differences in access and outcomes.

2.1. Trends in the burden of disease and medical product research

Questions around burdens of disease, currently available treatments and assessment of need are critical for decision-makers. The investment of pharmaceutical manufacturers into research and development for NCDs is consistent with the fact that NCDs are now collectively the leading cause of death in Europe; these are often chronic illnesses that require lifelong courses of treatment. Other priority medicine needs, however, are not being addressed. For example, research and development into new antibiotics related to the need to combat antimicrobial resistance is essential, but the smaller market share and comparative lack of economic return make it unattractive for companies to invest their research efforts in this direction. In this regard, the private sector has considerable say over the research agenda and which products are brought to market, yet the market for purchasing and reimbursing these medicines is mostly the public sector. The continuing increase in new high-priced medicines, a growing number of which may offer only marginal advances over existing therapies (especially in the area of chronic diseases), is in part a result of this. For policy-makers, therefore, improved guidance on medical product research efforts is required to ensure that other priority areas are addressed and to better match the trends in burden of disease (see also section 2.2).

To this end, WHO produced a report on priority medicines for Europe and the world in 2004, commissioned by the government of the Netherlands. In 2013 the EC requested an update of the report as a resource to be used in planning the Horizon 2020 combined research programme for the EU *(1)*. The primary audiences for the 2013 update are decision-makers working in the EC, European Parliament and Council of the EU, who are responsible for defining research priorities linked to the Horizon 2020 programme, and national governments. A priority list of 24 diseases, disease groups and risk factors was developed. This includes:

- a preliminary list based on burden of disease and mortality:
    - ischaemic heart disease, diabetes, cancer, stroke, HIV/AIDS, tuberculosis, malaria, Alzheimer's disease and other dementias, osteoarthritis, chronic obstructive pulmonary disease, alcohol use disorders (alcoholic liver diseases and alcohol dependency), hearing loss, depression, diarrhoeal diseases, lower respiratory infections, neonatal conditions and low back pain;
- a preliminary list based on projections:
    - antimicrobial resistance, pandemic influenza;
- a preliminary list based on social solidarity:
    - rare diseases, postpartum haemorrhage and maternal mortality, neglected tropical diseases;
- a preliminary list based on risk factors:
    - smoking, obesity.

It is worth highlighting that published studies have shown a greater correlation between the burden of disease in Europe (as measured in disability-adjusted life-years) and the products receiving marketing authorization via the EU centralized procedure between 1995 and 2009 than is seen in low- and middle-income countries and worldwide *(1)*.

In-depth analysis of the 24 areas identified led to the development of a priority list of medicines for Europe, with "priority medicines" defined as medicines needed to meet the future priority health care needs of the European population *(1)*. These are needed to address the following treatment gaps:

- Gap 1: treatments exist but will soon become ineffective. New treatments are needed to address, for instance, increasing antibiotic resistance; new types of vaccine are needed to address future pandemics.
- Gap 2: treatments exist but the pharmaceutical delivery mechanism or formulation is not appropriate for the target population. New treatments are needed to deal with ischaemic heart disease, HIV/AIDS, cancer, depression, diabetes, pneumonia, diarrhoeal diseases and neonatal diseases and conditions, malaria, tuberculosis, neglected tropical diseases and postpartum haemorrhage and maternal mortality.
- Gap 3: treatments do not exist or are not sufficiently effective. New treatments are needed for acute stroke, osteoarthritis, Alzheimer's disease and other dementias, chronic obstructive pulmonary disease, hearing loss, low back pain and rare (including orphan) diseases.
- Gap 4: global risk factors exist with no or insufficient pharmaceutical treatment. These include tobacco use cessation, obesity and alcohol-related diseases (including liver cirrhosis).

Pharmaceutical innovation is seen as one of the critical approaches to address these gaps. The authors of the study, however, note the need to overcome some general barriers to innovation – such as a high degree of private sector research – in order to further stimulate the development of new medicines in these areas. This includes the possibility of public funding of research into new highly innovative products that offer significant health gain and are therefore priced at a premium in priority areas identified by health authorities. At the same time, countries need to anticipate and prepare for the launch of – potentially many – new premium-priced medicines and to consider policy options available for including these in public health budgets.

In the EU the Innovative Medicines Initiative, "Europe's largest public–private initiative aiming to speed up the development of better and safer medicines for patients", aims to promote innovation by fostering collaboration between industry, academic research, hospitals, regulatory authorities and select patient organizations. The Innovative Medicines Initiative is a partnership between the EU and the European pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA), which acts on behalf of the research-based industry.

Improving planning by health authorities to manage better the entry of new medicines, coupled with analysis of ways to release resources from existing medicines without compromising care, is one potential method to address this issue. It is also a challenge, given inefficiencies resulting from resource constraints coupled with a lack of appropriate use of medicines. In addition, continued studies are most often needed to reduce uncertainty concerning the effectiveness and safety of new premium-priced medicines, while measuring and comparing the effects of medicines in real-life settings. This is especially the case given the differences that can exist between the characteristics of patients seen in clinical practice and those enrolled into randomized clinical trials *(2–4)*, which have resulted in additional evidence requirements from reimbursement and HTA bodies (see section 2.3).

New approaches to pricing and reimbursement may also be needed. This could include a number of considerations – for example:

- developments in how health gains and innovation are valued;
- impact assessment and further appraisal and development of MEAs to enhance access to new medicines that address priority areas efficiently *(1)*, although the evidence base surrounding effectiveness needs further development and concerns with current MEAs should be addressed *(5)*;
- the potential for differential or GDP-based pricing linked to issues such as affordability.

Another consideration relates to a general improvement in the use and availability of electronic health records and patient record linkage schemes in order to assess the effectiveness and side-effects of current and new treatments to ensure that future decisions are better informed. Such improvement is currently occurring in Italy and Sweden *(6–13)*. The rise in pharmacogenomics to verify impact/health outcome will also help with greater targeting of treatment, as well as reducing numbers needed to treat and increasing numbers needed to harm *(14)*, although of course there are considerable cost implications here as well.

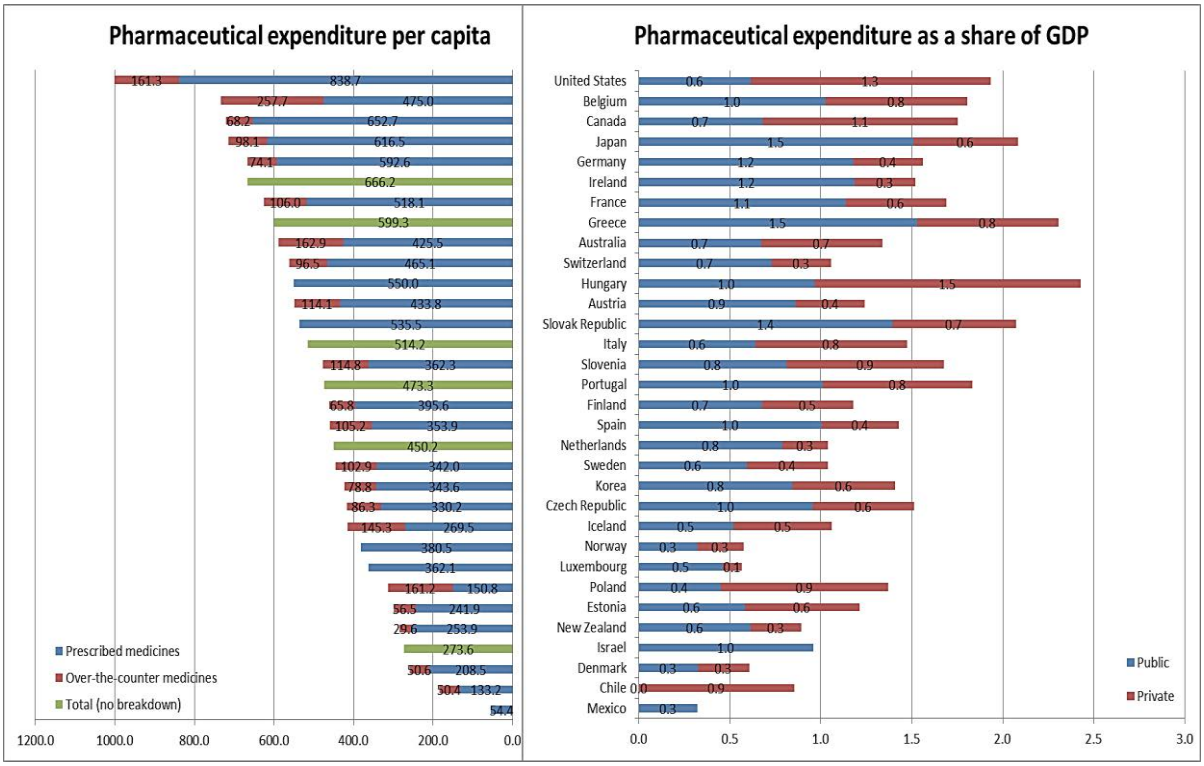
One further consideration is that overall efforts to increase transparency in the regulatory and reimbursement decision-making process are also required. This will be helpful from a public health perspective in order to be able to make and balance choices. Ways to facilitate a public dialogue based on transparency will be crucial in future, in what can be termed something of "an era of uncertainty".

2.2. Trends in pharmaceutical expenditure in the context of new medicines

Pharmaceutical expenditure has risen rapidly in recent years, growing on average more than 3.5% per year between 2000 and 2009 among OECD countries *(15–17)*. Overall, among OECD countries it averaged 18–19% of total health care expenditure in 2009, with similar averages across Europe *(16)*. This growth rate has resulted in pharmaceutical expenditure typically making up the largest cost component in ambulatory care across Europe *(18–21)*. More recently, 2009–2013 saw a fall in pharmaceutical expenditure in some European countries as a result of the global financial and economic crisis – for example, through specific policy interventions as in Greece, Iceland and Portugal – but in several others its growth remained constant *(17; 22)*. In 2011 average pharmaceutical expenditure per capita in OECD countries was US$ 483, and as a share of GDP it accounted for an average of 1.5% (see Fig. 2).

The financial and economic crises have led many countries to make cuts in health care budgets, including price cuts for pharmaceuticals, which was the response of many European countries *(17; 22–24)*. In some countries, however, pharmaceutical expenditure has also been reduced though proactive ways of bringing efficiency into the sector, including various cost-containment strategies; more careful selection of medicines including greater use of generics; more effective purchasing and supply chain management; and measures to manage use of medicines better. In the two years following 2009 average growth rates for pharmaceutical expenditure among OECD countries fell by 0.9%, with the reduction steepest in those countries hardest hit by the financial and economic crisis – for example, in Greece pharmaceutical spending per capita decreased by 10% in both 2010 and 2011 *(17)*. Estonia (−7.2%), Portugal (−5.9%), Iceland (−4.7%) and Ireland (−4.4%) also saw reductions in pharmaceutical expenditure between 2009 and 2011, while in France (−0.6%) and Germany (−0.7%) the drop was less steep *(25)*. It is clear, however, that the crisis has forced countries to revisit their pharmaceutical expenditure and, in some cases, to rethink how to improve efficiency as well as focus more on appropriate use of medicines.

Fig. 2. Expenditure on pharmaceuticals per capita and as a share of GDP, 2012 (or nearest year)



Source: OECD *(17)*.

2.2.1. Measures to reduce pharmaceutical spending

Strategies to contain the growth rate of pharmaceutical expenditure have included national and global (and supranational in the case of the EU) initiatives, many of which are linked to the international development agenda. Global initiatives have focused on promoting access to products that would otherwise be unaffordable – such as new medicines – and prioritizing products that have a major public health impact – such as medicines for tuberculosis, HIV/AIDS and malaria and specific products for maternal and child health. National initiatives have included the introduction or revision of internal and ERP systems (refining or lowering reimbursement rates or ceilings); compulsory rebates; category management of public procurement, including centralized procurement of specific products; reductions in pharmacy margins; increases in patient co-payment levels; and encouraging greater use of low-cost generics and biosimilars *(23–34)*. One policy area where there remains considerable room for improvement is the use of generic medicines, through which potential savings can be used to improve access to innovative medicines.

Measures to reduce spending may include the development and implementation of evidence-based formularies. By creating a system of restrictive criteria for these for certain medicines, the quality of prescribing and its cost–effectiveness can be improved. Formularies could ideally incorporate only a limited number of medicines, catering for the majority of patients' needs in ambulatory care *(35; 36)*. The majority of medicines in these formularies tend be older because of the greater level of published data on these. As a result, conserving pharmaceutical costs without compromising care is crucial *(19; 35–38)*. A limited prescribing formulary also enhances physicians' familiarity with the medicines they prescribe, thereby potentially reducing adverse drug reactions and drug–drug interactions *(14; 35; 39)*. Adverse drug reactions account for between 5% and 10% of all acute internal medicine-related hospital

admissions across continents including Europe. The costs of adverse events due to medicines are estimated at US$ 177 billion per year in the United States alone; similar patterns probably exist in Europe *(36)*. This was the philosophy behind the generation of the "wise list" in the Stockholm Metropolitan Healthcare Region (see section 5.1.4).

Countries in Europe use the various policies in significantly different ways. It is important to focus on measures that assist in maintaining the European ideals of comprehensive and equitable health care, despite continued pressure such as that from ageing populations, while supporting the launch of new valued premium-priced medicines.

2.2.2. Premium-priced medicines

Controlling pharmaceutical expenditure is likely to remain a policy priority in European countries for the foreseeable future – for example, recommendations were made to three EU countries regarding pharmaceutical expenditure and fiscal sustainability by the 2013 European Semester (the EU's annual cycle of economic policy guidance and surveillance). Further initiatives are needed, however, to maintain the general European commitment to solidarity around health care – including universal health coverage – ensuring better access to, and availability and affordability of, effective medicines, while at the same time encouraging pharmaceutical research in Europe. This is particularly the case given the number of new premium-priced medicines being launched and the number of molecules in clinical development. Recent analyses suggest that over 1000 products are in development across all disease areas, 42% of which are biological products; these are typically priced at €10 000–100 000 per patient per year or more *(22; 40–44)* (see Table 1). This increases to over 16 000 when all registered pipeline products are included, with over 6300 pipeline products for treating patients with cancer *(45)*. With some countries already facing difficulties in funding new premium-priced medicines, continued pressures on resources mean the situation can only worsen unless addressed proactively *(2; 46–7)*.

Table 1. Summary of new medicines in development/pipeline among the NASDAQ group of companies, May 2012

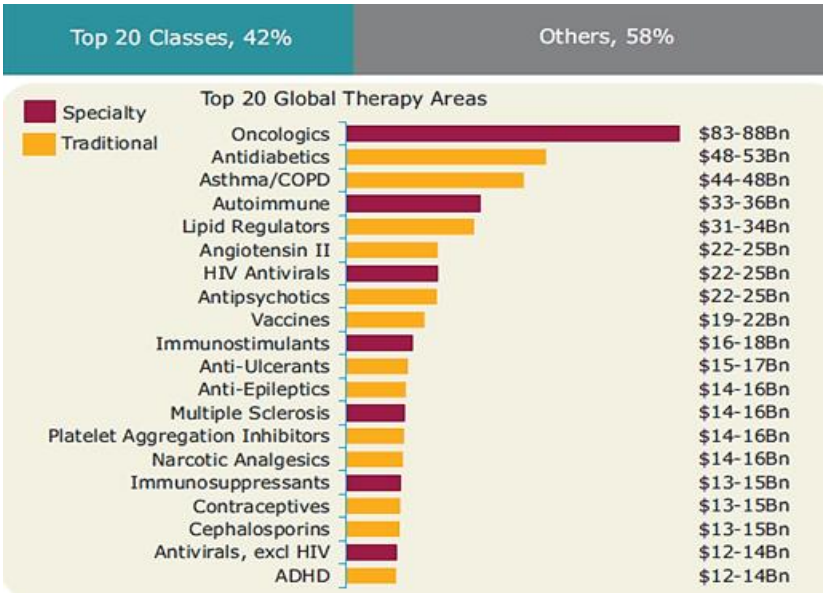
Disease area	Number of products
Oncology and immunomodulators	587
Systemic anti-infectives	220
Central nervous system	194
Cardiovascular	88
Musculoskeletal	60
Blood	55
Endocrine	47
Genitourinary	42
Others	104

Source: EvaluatePharma *(44)*.

It has recently been estimated that this will translate into over 130 new market entrants in Europe between 2014 and 2016 *(48)*, assuming that all are approved by the European Medicines Agency (EMA). At the global level, the IMS Institute for Healthcare Informatics projects that by 2016 spending globally will be focused on NCDs *(49)*. Fig. 3 shows the outlook for spending by disease area and Table 2 gives a list of the number of EMA recommendations for marketing authorization from 2010 to 2014 *(50)*. This indicates a potential continued increase in the number of new products being marketed.

Concerns about the numbers of new products have resulted in initiatives in a number of European countries to manage their market entry better. This includes pre-launch activities such as horizon scanning and estimating likely budget impact and resource needs, as well as peri-launch activities including systematic assessment of the relative benefits, harms and costs of the new medicines; development of clinical guidelines for their use in practice; and pricing and reimbursement deliberations *(2; 47; 51–56)* (see Fig. 1 in section 1.1). Pricing discussions increasingly include the consideration and use of risk-sharing arrangements or MEAs to facilitate inclusion of these medicines (including new orphan drugs – see section 6.4) in reimbursement programmes *(5; 6; 22; 57–58)*.

Fig. 3. Global project spending on medicines by 2016



Source: IMS Institute for Healthcare Informatics *(49)*.

Table 2. Number of new medicines with EMA recommendations for marketing authorization, 2010–2014

Year	Number of new medicines
2010	15
2011	25
2012	35
2013	81
2014 (to end of June)	39

Source: EMA *(50)*.

Measures to optimize the use of new medicines after launch include increasing critical drug evaluation skills and other educational approaches among prescribers, instigating prescribing restrictions in certain situations and other approaches including financial incentives for physicians and variable patient co-payments *(2; 35–36; 47; 59–60)*. Restricting prescribing to target eligible subpopulations most likely to benefit from treatment is increasingly possible across Europe with the growing use of sophisticated IT systems, including e-prescribing and electronic health records *(2; 7; 9; 10; 61)*. Such approaches are favoured by stakeholders from government authorities and insurance companies in preference to increasing private insurance or co-payments *(62)*.

Post-launch activities also include assessing the effectiveness and safety of new medicines in routine clinical practice. Generally, the effectiveness and safety data found through randomized clinical trials may not always match that found in routine clinical practice because phase III clinical trials are conducted under ideal and highly controlled conditions to seek high internal validity. This can lead to differences from their subsequent use in clinical practice: typically, phase III clinical trials do not include treatment preferences and/or multimodal treatment programmes, and they may also include a placebo group *(2; 47; 60; 63)*. As such, specific tools and measures are required to monitor the impact of medicine treatment after launch. This includes using disease-specific patient registries to monitor health outcomes related to medicines treatment, as well as monitoring prescribing against agreed guidelines or quality targets to foster appropriate use of medicines *(2; 10; 47; 64)*. This may include several strategies – for example, financial incentives to facilitate monitoring, reporting and follow-up; prescribing restrictions; and education directed towards the medical profession to improve their critical drug evaluation skills *(2; 36; 47; 60)*.

2.3. Trends in estimating value of new medicines in Europe and determination of product prices

A number of different approaches have been employed across Europe to assess the value of new premium-priced drugs. Some countries (including Austria, France and Germany) agree upon reimbursement rates based on established criteria to compare the health gain from a new product to current standards of care *(18; 20; 65–67)*. Many countries across Europe employ methods and principles of HTA to assess the innovation and added value of a medicine (see Annex 2). These methods include clinical benefit assessment (for example, in France and Germany) or clinical and economic assessment (for example, in England, Hungary, the Netherlands, Poland, Scotland and Sweden, and in France since 2013 for certain products, among others).

Economic inputs to HTA typically include an analysis of cost–effectiveness or cost–utility, such as the incremental cost–effectiveness ratio (ICER): the cost per quality-adjusted life-year (QALY) of the new medicine compared to current standards of care *(2; 65; 68–69)*. While such approaches to economic evaluation are widespread, none is without limitations; in particular, the need for reliable data sources to deliver reasonable advice to decision-makers. Some of these countries have explicit acceptability thresholds for cost per QALY – such as England, Ireland, the Netherlands, Slovakia and Scotland – although at present this approach is only employed in a minority of European countries *(65)*. Other countries (such as Norway and Sweden) adopt more flexible approaches that include issues such as disease severity and unmet need among their decision-making criteria *(2; 65; 69)*.

Whichever method is employed, reimbursement authorities across Europe increasingly require manufacturers to demonstrate meaningful improvements in the efficacy and/or safety of new medicines in all or specific subpopulations of patients in order to justify premium prices. Increasingly, effectiveness data obtained from real-life settings are required to make a final coverage decision, through coverage with evidence development schemes. Such a demonstration of incremental cost–effectiveness may become more difficult as the availability of generic alternatives to effective standard medicines – including the emergence of biosimilars – increases *(22; 47–48; 70–71)*. An example comes from France, where a recent review points to only a limited number of new medicines being considered truly innovative (that is, offering a real therapeutic advance) (see Table 3).

Table 3. *Prescrire* ratings of the level of innovation of new drugs

***Prescrire* ratings**[a]	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**
Innovative drug/real therapeutic advance	0	1	2	3	0	0	1	0	1[a]
Offers an advantage over current standards	6	4	8	14	6	3	3	3	3[b]
Possibly helpful	12	20	31	27	25	14	22	13	14
Minimal clinical advantage/nothing new to existing standards	41	38	69	79	57	62	49	53	42
Not acceptable – including safety concerns	7	19	17	15	23	19	19	16	15[c]
Judgement reserved – usually because of insufficient data from clinical trials	4	2	8	3	9	6	3	7	7[d]
Total	**70**	**84**	**135**	**141**	**120**	**104**	**97**	**92**	**82**

[a] The drug was boceprevir in chronic hepatitis C (Prescrire Int n° 126).

[b] The drugs were:

- abiraterone in prostate cancer after failure of other treatments (Prescrire Int n° 128);
- telaprevir in chronic hepatitis C (Prescrire Int n° 126);
- trastuzumab as adjuvant therapy for breast cancer after more follow-up (Prescrire Int n° 133).

[c] The drugs were:

- asenapine in manic episodes in bipolar disorder (Prescrire Int n° 131);
- bevacizumab in metastatic breast cancer in combination with capecitabine (Rev Prescrire n° 340);
- bevacizumab in advanced ovarian cancer (Rev Prescrire n° 348);
- domperidone in gastrointestinal disturbances (Rev Prescrire n° 340);
- fluticasone in atopic dermatitis in infants 3 months of age and older (Prescrire Int n° 129);
- insulin detemir in combination with liraglutide in type 2 diabetes (Rev Prescrire n° 348);
- ivabradine in heart failure (Rev Prescrire n° 348);
- linagliptin in type 2 diabetes (Rev Prescrire n° 347);
- pirfenidone in mild to moderate idiopathic pulmonary fibrosis (Rev Prescrire n° 350);
- roflumilast in severe chronic obstructive pulmonary disease (Prescrire Int n° 134);
- saxagliptin in type 2 diabetes in combination with insulin (Rev Prescrire n° 349);
- the saxagliptin + metformin combination in type 2 diabetes (Rev Prescrire n° 349);
- sildenafil in pulmonary arterial hypertension in children (Prescrire Int n° 129);
- vandetanib in medullary thyroid cancer (Prescrire Int n° 131);

- vernakalant in atrial fibrillation (Prescrire Int n° 127).

[d] The drugs were:
- carglumic acid for organic acidaemia in neonates and infants (Rev Prescrire n° 349);
- brentuximab vedotin in Hodgkin's lymphoma or systemic anaplastic large cell lymphoma (Rev Prescrire n° 349);
- ipilimumab in metastatic melanoma (Prescrire Int n° 128);
- mexiletine in myotonic syndromes (Rev Prescrire n° 344);
- ranibizumab in retinal vein occlusion (Prescrire Int n° 130);
- tafamidis in transthyretin amyloidosis (Rev Prescrire n° 349);
- vemurafenib in metastatic melanoma (Prescrire Int n° 133).

Source: *Prescrire Int*. *(72).*

Alongside this, increasing debate is likely among European countries about whether new medicines in patient populations with high clinical need – such as those with cancer or orphan diseases – should continue to have preferential pricing and reimbursement considerations. This is particularly relevant given the high requested prices for some new cancer and orphan medicines, often with only limited health gain *(43; 73–77)*, coupled with the growing prevalence and cost of treating patients with cancer *(73)*. Increasing concerns with the value and overall costs of such medicines mean that changes are starting to be made, but they need to be balanced against providing incentives for companies to address current areas of unmet medical need *(1)*. These concerns are leading to:

- refusal of reimbursement for new orphan medicines owing to concerns about their value;
- growth in MEAs to manage better the uncertainty surrounding their introduction;
- proposals for pricing of new cancer medicines;
- development of formal systems to provide a common and consistent framework by which European health authorities can improve their assessment of the value of new orphan medicines across a wider range of conditions, including the Transparent Value Framework (TVF) *(5; 43; 47; 58; 78–80)*.

Consequently, any clinical evidence generated for new medicines needs to take account of the requirements of reimbursement and HTA agencies, which differ from those of regulatory agencies such as EMA (see Box 1).

Box 1. Additional evidence required by reimbursement and HTA agencies

Reimbursement and HTA agencies require further clinical evidence, including data on:

- improvement in patient-relevant outcomes, such as quality of life, in addition to improvements in clinically defined end-points – in some cases they may also be interested in wider impacts, such as those on caregivers' quality of life and on the social care system and/or the economy;
- longer-term clinical outcomes than are often required for regulatory review to reflect the clinical course of disease – this often requires modelling of benefits and outcomes beyond the clinical trial data;
- applicability of the data from the trial populations to the patients likely to receive the drug, under the care of "typical" clinicians, in the health system for which the coverage body is responsible;
- costs to the system, budget impact, cost–effectiveness, and/or value for money;
- performance in these regards in comparison with the most appropriate comparator for the health system for which the coverage body is responsible – that is, the treatment that patients would receive in the absence of the drug in question – which will normally involve comparison with another active treatment (rather than placebo), although the actual treatment comparator may vary among health care systems according to prevailing clinical practice and the requested place of the therapy in clinical practice.

Source: Henshall et al. *(81)*.

In some circumstances reimbursement bodies or insurers, as well as HTA bodies, may also ask for information on the patient subgroups for which the new medicine provides most benefit. This is likely to increase with improvements in pharmacogenomics and other areas.

As a result, pharmaceutical manufacturers are increasingly advised to take advantage of opportunities to interact with individual reimbursement agencies or HTA bodies and/or initiatives to coordinate HTA activity. This may help ensure that any future guidance and procedures take account of their perspectives and that manufacturers have an opportunity to discuss with reimbursement and HTA

bodies how particular aspects of the guidance or procedures may apply to their specific products as they refine their phase III studies and collate evidence *(47; 60; 81)*.

2.4. Current and future developments aimed at improving access to and appropriate use of medicines

As individual countries consider appropriate use of HTA methodologies in their jurisdictions – and introduce further measures to optimize the use of available resources or pharmaceutical expenditure (see section 5) – several international and supranational initiatives throughout Europe are also seeking to promote access to and appropriate use of new medicines. Several key recent and ongoing initiatives are described below, including a series of initiatives at the EU level, as well as HTA harmonization efforts such as the European Network for Health Technology Assessment (EUnetHTA). These will be bellwethers for access to new medicines in the future, although a key consideration is the applicability of such initiatives and their findings to countries outside the EU or EUnetHTA, particularly European states with emerging HTA initiatives (see Annex 2).

The EU has intensified its focus on the pharmaceutical industry in recent years, particularly since a 2000 report raised concerns about the current and future competitiveness of the European market *(82)*. In response, the EC formed the High Level Group on Innovation and the Provision of Medicines, then called "G-10 Medicines", to consider innovation, provision of medicines to patients and competition and regulation in the European market structure *(83)*. Subsequent to the final G-10 Medicines communications in 2003, the EU organized the Pharmaceutical Forum from 2005 to 2008 as a platform for Member States and health care stakeholders to discuss public health and policy solutions around pricing and reimbursement, relative effectiveness and disseminating information to patients *(84)*. The resulting recommendations went to the Member States and the EC for consideration, and in 2010 the EU launched the platform on access to medicines in Europe. This includes pricing and reimbursement authorities from EU and European Free Trade Association countries, as well as representatives from stakeholder organizations, and to date has launched projects on the following issues:

- a mechanism of coordinated access to OMPs
- capacity-building on MEAs for innovative medicines
- facilitating the supply of medicinal products in small markets
- promoting good governance for nonprescription drugs
- market access for biosimilars *(34; 85)*.

In addition to these internally focused initiatives, on 20 March 2014 the EU Global Health Policy Forum focused its agenda on access to medicines, primarily concerned with developing countries *(86)*.

In parallel to these initiatives on innovation and reimbursement, EUnetHTA was created in 2004 to assist with harmonization and information-sharing through a series of collaborations and joint actions. Current participants include 51 HTA organizations and health ministries from all EU Member States plus Norway and Switzerland *(87)*. Additional international HTA initiatives include the International Network of Agencies for Health Technology Assessment, Health Technology Assessment International, the International Information Network on New and Emerging Health Technologies (EuroScan) and the Cochrane Collaboration. By cooperating in any of these international or supranational initiatives, European Member States indicate a desire for shared learning and efficiency in improving access to and appropriate use of pharmaceuticals.

On a more direct patient care level, a number of initiatives around Europe aim to integrate pharmaceutical access and use across the continuum of care, such as interface management between hospital and ambulatory care. Such initiatives include joint agreements on suggested treatment approaches in an attempt to curb the considerable influence of hospital prescribing on ambulatory care costs *(36; 88)*. These will increasingly include new biological medicines, which are already a particular focus in Scotland, Spain (Catalonia) and Sweden, with continued growth expected across Europe. The various activities can be consolidated into the proposed framework for locating and examining policy interventions (see section 1.1), which will be elaborated throughout the remainder of the report.

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3. Pre-launch activities – anticipating potential requirements and impact

Pre-launch activities undertaken on behalf of decision-makers can be used to anticipate and prioritize therapeutic innovation with the highest potential for impact on clinical care, the health care system and patient outcomes. They can assist in prescribing planning, demand assessment and budget estimation to assess the potential impact of new medicines and national guidance on the health economy.

A number of pre-launch activities are carried out to facilitate the introduction of new medical products. These include horizon scanning: detecting emerging new health technologies well before they are launched (for example, 1–3 years before likely regulatory approval such as EMA approval) *(1–3)*; developing documentation on risk and benefits to meet evidentiary requirements for assessments of the clinical value of the medicine (evidence-based medicine); early dialogue between key stakeholder groups; and the development of quality indicators, where pertinent and possible *(4–5)*. Some HTA activities also occur before launch, but HTA is an ongoing activity mostly undertaken in the peri-launch phase. Systematic assessments of documentation prior to marketing assist in preparing for the introduction of new medicinal products to the health system – they are useful for balancing risk and benefit and assessing value to the individual and society, as well as setting price and reimbursement levels.

Medicines development is no longer a linear process; instead, many partners are engaged at different stages to ensure early access to promising new products. The global medicines regulatory environment is also changing: balancing the risk and benefits of new medicines is considered differently depending on the context, and evidentiary requirements change over time. Some new products enter the market with an EU conditional approval or approval under exceptional circumstances. These regulatory instruments may open markets without having exhaustive evidence available at the time of introduction; these approvals are subject to further work being undertaken to substantiate the value of the product once in use. For example, coverage with evidence schemes were introduced in the Netherlands for enzyme replacement therapy for the symptomatic treatment of Fabry disease and for alglucosidase alfa to treat Pompe disease. The clinical data continued to show limited value. Consequently, the Dutch Healthcare Insurance Board argued against continued reimbursement, but the draft advice was leaked prior to its official release, leading to vocal opposition and pressure on the ministry of health to ignore it *(6)*.

Nevertheless, recognizing uncertainty, these kinds of approach make use of stepwise learning about new medicines, and adaptive licensing may become the next step in medicines approval. While implementation of adaptive licensing will provide earlier access to new medicines, however, it will require systems geared to respond to findings, including negative findings, for their continued credibility and acceptance. This may require several regulatory steps and interventions; many regulatory systems do not currently operate in this way and adaptations will be required. Delisting, if new medicines provide little value at the requested prices – as seen with the examples of Fabry and Pompe disease in the Netherlands – is currently not a widespread option.

3.1. Horizon scanning

A number of activities are undertaken across Europe to provide health authorities and health insurance companies with time to plan their activities better to optimize the use of new premium-priced medicines and other health technologies. Horizon scanning is one such process, which – although this can vary – generally includes identifying new medicines with imminent expected marketing authorization or new uses of existing medicines; estimating and prioritizing their potential impact on patient care, costs, society and the health care system; and disseminating and updating this information as needed *(1–2; 7–9)*.

Horizon scanning is important in forecasting and for future planning as new health technologies may have an appreciable budget impact. It also plays a role in initiating further studies – such as those related to safety concerns *(5; 7; 10)* – and in forecasting future best practice. For example, in a hospital it is clearly interesting to predict changes in practice and also simply to ensure that up-to-date health care is delivered. In addition, horizon scanning helps to estimate the likely budget impact of a treatment within its proposed indication, and is a means to understand which patients are most eligible within the indication. These pre-launch assessments are typically undertaken up to three years before launch *(1–2; 8; 11–12)*. They usually incorporate a limited number of phase II study results for new medicines and sometimes interim phase II results presented at conferences, balancing timeliness with accuracy.

Only limited data are typically available on the potential budget impact of new technologies before launch, and assessment of value or comparative cost–effectiveness is not yet systematically performed in Europe *(7)*, but providing policy-makers with comparative and timely evaluations of new medicines is crucial. Here, additional activities with the help of expert groups can be useful. Using a proactive approach to the introduction of new medicines before launch, health systems are better able to prioritize their planning of investments in staff, skills, training and guideline development so that the best use of medicines offering clinical benefits can be prioritized and facilitated. On the other hand, seeking to limit the use of new premium-priced products with limited or no apparent value versus current standards would also be important *(5; 10)*.

Existing programmes may have different goals and use different methods to identify and assess emerging health technologies, but there is consensus on the general scanning process among the major health care horizon scanning programmes *(3; 13)*. As such, most horizon scanning bodies share experience through EuroScan, a collaborative network of member agencies for exchange of information on emerging new medicines, procedures, programmes and settings in health care, with the long-term aim of sharing applied methods, information and evidence on new and emerging health technologies. EuroScan maintains a tool kit for identification and assessment of emerging health technologies *(14)* and evaluates the sources of information used; members have similar processes that consist of a series of phases – such as identification, filtering, prioritization and assessment *(3; 8–9; 13; 15)*. Through this collaboration, EuroScan has been effective in reducing duplication *(9; 13)*.

EuroScan has a number of members from 13 European and several non-European countries. Member agencies are typically funded from public sources and exchange information on important emerging new drugs, devices, procedures, programmes and settings in health care *(9)*. Their main aims are to prepare health services for decisions on coverage, financing or reimbursement of new technologies and secondary research strategies (such as HTAs and systematic reviews). The main differences between agencies lie in their customer bases, the types of technology covered and data sources used

(1). Customers for reports range from national government health departments and ministers (or regional counterparts) to hospitals, insurance or reimbursement organizations, health care professionals, medical advisers and clinical experts *(1; 13)*. Agencies also differ greatly in how they provide information to key stakeholders: some make their early assessments publicly available and others keep all information as internal confidential documents distributed only to particular target groups *(1; 13; 16)*. Data sources include pharmaceutical companies, financial analysis companies, international scientific societies, meetings (including conference abstracts), documents and websites produced by regulatory agencies, health information websites, medical–scientific literature, experts in their field and pharmaceutical companies' press releases *(1; 7)*.

Italy is one country with substantial experience in horizon scanning; it employs the following key criteria to prioritize topics for evaluation, which cover possible budget impact as well as likely health benefit:

- burden of the specific disease;
- potential efficacy, safety and compliance of the emerging drug compared to available treatments;
- potential social, economic and organizational impact of the new medicine on the Italian national health service;
- possible market authorization date by EMA.

Subsequently, the Italian Horizon Scanning Project researches and appraises the epidemiology of the disease, the potential organizational and social consequences of the emerging medicine and potential economic aspects (direct costs, availability) to provide further direction to the regions for planning purposes *(2)*. The Project provides national and regions payers with three different reports, issued 36, 18 and 12 months before possible European market access via EMA (see Table 4).

Table 4. Details of the three reports issued by the Italian Horizon Scanning Project

Time before potential EMA approval	Report content/objective
36 months	• This report contains information on the mechanism of action of emerging drugs, phase II trial data and the indications of ongoing phase III trials. • All information is recorded in national and international clinical trial registries. • The report provides the Italian Medicines Agency with information on the development plans of emerging drugs.
18 months	• This report assesses available results of the first phase III completed trials. • It enables the identification and prioritization of emerging medicines likely to have a clinical and economic impact on the Italian health service. • It is primarily utilized by the regions for internal purposes.
12 months (new product information report)	• This report critically assesses and reports on available data on efficacy and safety of the new medicine versus current standards, its possible advantages over existing treatments (level of innovation), its possible place in therapy, estimated direct costs and information on other potentially relevant indications in development or on competitors in development for the same indication. • Any changes in the prescription details can also be assessed by using historical prescription data on available treatments and by defining the target population according to the inclusion/exclusion criteria and the results of the trial(s). • As a result, this report improves planning and helps optimize the most appropriate use of resources, as well as helping the Italian Medicines Agency decide on the level of reimbursement of a new drug and possible limitations in its prescription.

Source: Joppi et al. *(2)*.

The Scottish Medicines Consortium (SMC), on the other hand, appraises potential new medicines only around 6–18 months before their likely launch, and produces a confidential annual report for health board financial officers to help with their planning *(1)*.

England has more than a decade of experience in horizon scanning. The National Horizon Scanning Centre informs the future work programme of the National Institute for Health and Care Excellence (NICE) and provides key policy-makers with advance notice 2–3 years before launch on the English health service. More than 1000 cases have been entered into the horizon scanning process for NICE appraisals or for consideration by the National Horizon Scanning Centre's other customers. A retrospective review showed a positive predictive value but also highlighted the importance of tightening filtering criteria for increased efficiency *(3)*.

Some horizon scanning units in Europe focus on specific disease areas, such as the Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA) for cancer drugs in Austria, where the adoption and availability of new cancer drugs is among the highest in Europe *(8)*. This may be facilitated by different reimbursement and funding mechanisms for hospital and ambulatory care drugs, as the Main Association of Austrian Social Health Insurance Institutions only assesses reimbursement levels and associated prices for new drugs in ambulatory care *(17)*. This has driven companies preferentially to launch new high-priced speciality drugs in hospitals if they are worried about potential reimbursed prices in ambulatory care, given the strict pricing formula used. LBI-HTA was commissioned in 2007 by regional hospital cooperations and the ministry of health to establish a horizon scanning system in oncology in Austria. The objective was to facilitate the evidence-based use of anticancer therapies and to estimate their potential financial implications to better inform decision-makers *(8)*. The LBI-HTA website provides free access to their new cancer medicines assessments *(18)*, and LBI-HTA and the Italian Horizon Scanning Project collaborate closely.

Seven criteria were initially identified and agreed upon to prioritize new oncology drugs for assessment by LBI-HTA. These were subsequently refined following further discussions with key stakeholder groups to become *(8)*:

- the number of patients eligible for the drug under consideration
- the intended use of the new therapy – add-on or replacement
- the estimated impact on health benefit
- the estimated impact on financial resources
- the potential for off-label use
- overall score.

The dissemination reports produced by LBI-HTA are typically 12–14 pages long and written in English. They contain details of the company or developer, brand name or generic name, mode of action, dosage(s), indication, EMA or Food and Drug Administration (FDA) licensing status, current treatment options for the cancer and disease state in question, available evidence, estimates of costs and budget impact, any ongoing trials and a commentary section.

In terms of horizon scanning for disinvestment, little experience of identification of potentially obsolete technologies or technologies of limited value is available, and further research is required to determine the best search strategies and sources to be used for identification of potentially obsolete, ineffective, inefficient or harmful health technologies. This would build on activities that have already taken place in France, Sweden and the United Kingdom *(19–22)*. In cases where new technologies are subject to HTA (later along the product lifecycle), by rendering a new technology clinically cost-

effective for a particular pathway, HTA recommends a new technology over the older one, making the latter obsolete. As such, HTA – to the extent that it is taking place – makes recommendations about disinvestment based on clinical and cost–effectiveness analysis. Positive framing of disinvestment as a priority-setting for reallocation with the aim of modernizing health care is important. It is a shared responsibility between clinicians, health policy-makers and the public.

3.2. Forecasting, budget impact and critical drug evaluation

Forecasting of medicines use and expenditure is needed to improve planning for resource allocation and to prepare health authorities and health insurance agencies for new – potentially high-expenditure – interventions to promote their rational introduction. Forecasting demand is also useful in shaping supply chain capacity and is important for planning procurement, including for tenders.

Forecasting pharmaceutical use and expenditure patterns is a complex undertaking *(1; 7; 23)*. It can have a strategic impact, however, if the forecasts are reliable and updated regularly so that stakeholders can use them effectively for planning purposes. Factors that drive pharmaceutical expenditure can be divided into those that affect price, volume or both. These include more prescribers and longer duration of therapy, and changes in usage patterns that emphasize newer, more expensive agents over older, less expensive yet perhaps equally effective alternatives *(1; 7; 20)*.

Only a limited numbers of studies on forecasting have been published to date, but this is an area of increasing focus *(7; 23)*. At the global level, strategic demand forecasting has been a major driver in accelerating access to certain new products in low-income countries. One example is the accelerated vaccine introduction initiative, which was launched by GAVI, the Vaccine Alliance, in January 2009 to achieve two core goals:

- to broaden and speed up access to rotavirus and pneumococcal vaccines;
- to create a platform for introducing other new vaccines, such as meningococcal type A, human papillomavirus, typhoid, Japanese encephalitis and rubella *(24)*.

Within the EU an initiative for joint procurement of pandemic influenza vaccine and antiviral medications based on future forecasts is also now in place *(25)*. This new voluntary collaboration aims to improve solidarity between participating EU Member States by guaranteeing a minimum level of equitable access to pandemic influenza vaccines and improving Member States' purchasing power. As this initiative progresses it could be expanded to cover other strategic products to match forecasted demand and production capacity better and to increase access to strategic, essential new medicines.

Overall, few cross-national examples exist where strategic forecasting has been a major driver in shaping the market, and none currently apply to the European context. Examples are available, however, at the national level. In Sweden a forecasting model has been developed with longitudinal trends in drug expenditure *(7)*; this is linked to national and regional health system planning in Sweden but could be linked to broader initiatives across Europe. With the model, linear regression analyses are applied to aggregate sales data from the National Corporation of Swedish Pharmacies on hospital sales and dispensed drugs in ambulatory care, including both reimbursed expenditure and patient co-payments. Annual expenditures and volumes for all pharmacological groups at the third Anatomical Therapeutic Chemical (ATC) classification level are included in the analysis, with volumes measured in defined daily doses. A linear regression model is applied to each time series and crude predictions for the coming two years are based on linear extrapolation. These predictions are subsequently adjusted for factors likely to increase or decrease future use and expenditure, such as patent expiries, probable

new drugs or new guidelines from national or regional bodies. No specific adjustments are made in the model for ageing of the population, population growth and financial incentives for drug prescribing since these changes are already covered by the original trends.

A key strategy to increase the robustness of the resulting forecasts is the involvement of disease area experts. All the information collected is discussed and prioritized in consultation with 23 expert groups, who cover different diseases of organ systems such as cardiovascular, gastrointestinal and neurological disorders. The forecasting models are subsequently scrutinized and modified after both input from joint workshops with expert groups and final input and comments from the main authors, who typically have extensive clinical pharmacological and/or pharmacotherapeutic knowledge *(7)*. Overall, forecasting of drug use and expenditure in this model incorporates horizon scanning and forecasting activities, combined with critical drug evaluation. Strong conflict of interest statements from those involved are also given. Such initiatives should help reduce the prescribing of drugs beyond suggested patients and indications, which can be a problem in some countries *(26–29)*. A recent internal assessment showed that predictions had been adequate overall, giving good guidance. Miscalculations have occurred, however, in some therapeutic areas because of uncertainties surrounding, for instance, the time of patent expiries and unexpected reimbursement restrictions instigated by the national reimbursement agency.

Critical drug evaluation before launch is also an essential component of planning to optimize the use of new premium-priced medicines after launch. This builds on horizon scanning, budgeting and forecasting activities. Ideally, it should be undertaken by clinical experts coupled with pharmacologists and clinical pharmacists. Strict declaration of interest criteria should again be applied to all experts involved, including reporting on any contact with the pharmaceutical industry, to enhance the credibility of subsequent deliberations *(20; 30–31)*. Critical drug evaluation should include clear guidelines on potential criteria for medicine use after launch, as well as the need for information and education campaigns for key stakeholder groups. The deliberations could also inform potential quality indicators and the development of post-launch registries to monitor medicine use against agreed guidance and indicators and to collect data on the effectiveness and safety of the new medicine in routine clinical practice (see section 5.1) *(4–5; 10; 31–32)*.

New oral anticoagulants, such as dabigatran, are an example of this comprehensive approach. They showed promise in stroke prevention and atrial fibrillation, but concerns arose about their use in older adults, particularly those with poor renal function, since there are variable drug concentrations, no known antidote and dependence on renal elimination *(10; 32–33)*. Older adults with poor renal function were likely to be the principal cohort for treatment in clinical practice *(34–35)*. As a result, there is greater potential for excessive bleeding that is difficult to handle (which happened in practice), especially with no known antidote and no commercially available method to monitor blood levels when the medicine was launched. These concerns led to comprehensive educational campaigns conducted by a number of health authorities across Europe and New Zealand, as well as prescribing restrictions applied at launch *(10; 32)*. Further educational programmes are also being planned where there are ongoing concerns with prescribing, including contraindications *(32; 36)*.

3.3. Physician education and patient registries to optimize use of new medicines

Pre-launch educational activities (during phase III and EMA approval – see Fig. 1 in section 1.1) begin with educating physicians concerning the effectiveness and/or safety of new drugs; they continue during and after the launch in recognition of the considerable resources that pharmaceutical companies spend on marketing activities *(36–37)*, which commence pre-launch. Here, a crucial question remains who will undertake such campaigns, as company-based detailing needs to be matched by academic detailing and activities by other actors such as Bandolier in the United Kingdom, Prescrire in France or the Janus information system in the Stockholm Metropolitan Healthcare Region. Improved education activities are required to provide physicians with critical drug evaluation skills and training in the benefits and risks of new treatment options so that they can assess adequately the health gains of new medicines versus current treatments *(31–32; 38)*.

It is acknowledged that launching a new pharmaceutical product requires considerable planning. As a result, pharmaceutical company activities usually start early and include identifying key opinion leaders associated with the new medicine at least 24 months prior to the likely launch date. Early interactions with key opinion leaders include informing them about the science behind the new medicine, ongoing clinical trials and timelines, as well as the findings of studies already made public through conference presentations and early publications. Pre-launch educational activities also include presentations of key findings at advisory boards and clinical investigator meetings, with the aim of sharing relevant data and continuing to foster relationships.

Closer to the launch, activities with key opinion leaders increasingly focus on the new medicine itself, including informing them about compound-specific attributes. External educational activities include continued presentations at congresses and advisory boards and seeking publication of clinical trial data *(38)*. Early pre-launch phase activities include traditional marketing activities involving key opinion leaders and others to enhance the interest of potential prescribers in the new medicine. These coordinated activities by pharmaceutical companies also take account of growing work in early planning by health authorities, which is increasingly taking place to help optimize the use of new medicines after launch. Examples of such pre-launch educational activities include those undertaken by the Stockholm Metropolitan Healthcare Region (see Box 2) in recognition of the potential safety concerns over dabigatran *(10; 32)*.

To complement this pre-launch work, educational activities undertaken by health authorities after the launch range from distribution of printed material to intensive strategies including using professional medical networks to pursue academic detailing, continuous medical education and monitoring of prescribing habits *(10; 30–31; 39)*; nevertheless, this remains an area where more can be done. Examples of printed materials include local, regional and national formularies, guidance and guidelines, including those from DTCs *(10; 30)*. Financial incentives for physicians (payment for performance) if they achieve agreed prescribing and quality targets can also be used *(10; 40)*, but it is recognized that payment for performance initiatives have a variable impact *(41)*.

Box 2. Educational activities undertaken by the Stockholm Metropolitan Healthcare Region prior to the launch of dabigatran

Pre-launch educational activities by the DTC with general practitioners (GPs), hospital specialists and clinical pharmacologists included:

- systematic and long-term involvement of medical and scientific expertise in the development of guidelines and advice for patients and prescribers through the regional DTC, supported by clinical pharmacologists;
- extensive pre-launch activities with key messages broadcast to both the public and prescribers through websites of the DTC and the Swedish Medical Journal;
- an appreciable number of pre-launch meetings and training sessions with all major physician groups around the key issues and concerns with dabigatran and its likely place in care;
- production of educational folders regarding dabigatran, slide kits, published articles and data on the Janus website, as well as published information for patients;
- forecasting of the potential use and budget impact in 2011 and 2012 ahead of the launch (and subsequent monitoring of this in practice).

The potential to use patient registries will grow across Europe in view of the growth in MEAs (see section 4.2.3) and the increasing need to monitor the safety and effectiveness of new premium-priced drugs in practice by both researchers and health authorities. This is especially the case where concerns exist about their perceived value and/or safety, based on clinical trial results. It is recognized, however, that a number of considerations need to be addressed when authorities are planning patient registries before launch. These include the following *(10)*:

- funding:
  - explicit and transparent funding arrangements should be agreed before initiation;
  - feasibility for joint arrangements between health authorities and commercial organizations should be investigated, as with the registry for natalizumab in France (see details below) and the registries in Italy through the Italian Medicines Agency;
  - funding arrangements need to be transparent;
- legal considerations: compliance is required with current regulations and legal requirements in each country (including data confidentiality);
- ownership: a priori agreement regarding ownership should be in place;
- endorsement: any registry instigated should be endorsed by leading research groups or scientific societies, authorities and patient groups;
- linkage: how any proposed new registry will be linked to other existing databases and the activities of research groups to enhance the output should be established;
- timing:
  - sufficient time should be made available to develop “user-friendly” registries that will fully capture all the patient variables of interest and satisfy the interests of all key stakeholder groups;
  - data functionality of patient registries needs to be considered early pre-launch, and time given to recruit personnel competent in computer science and knowledgeable in the major medical issues for the disease area;
  - this will facilitate the development of user-friendly screens; data entry systems should be incorporated that help to detect errors early and rectify them quickly.

Monitoring of the use of new medicines against agreed guidance and any agreed indicators after launch will also increase, thanks to clinical and research interests in how new treatment principles

work in practice *(4–5)*. Another important driver is budget impact concerns: this can form part of any agreed risk-sharing agreements or MEAs (see section 4.2.3).

Data from post-launch registries and other studies can range from simple aggregated descriptive drug statistics to more sophisticated comparative effectiveness and outcome studies. Opportunities for sophisticated outcome studies will increase with the availability of encrypted patient identifiers, and such studies will also facilitate research into the prevalence and incidence of medicine use for given patient populations. Opportunities for observational comparative studies also depend on the IT infrastructure within countries.

Patient-level data can be used to assess the appropriateness of new medicine prescribing – the extent to which prescriptions correspond to the labelled or reimbursed indication and the need to avoid under- or overdosing. They may also be used to assess the safety and effectiveness of new medicines in routine clinical care *(42)*. In such studies relevant patient characteristics – such as age, gender, comorbidity, disease status, concomitant drug therapy and dosing regimen – may be analysed for all or a for selected sample of patients and compared with those initiated on other drugs (see Table 5).

Table 5. Examples of registry and database studies across Europe

Country/region	Details
Italy (Emilia-Romagna) and Sweden *(43)*	The study evaluated how the marketing authorization and reimbursement of dronedarone affected the prescribing of other antiarrhythmic medicines in Sweden and Emilia-Romagna (Italy). In Emilia-Romagna overall consumption of antiarrhythmics was six times as high as in Sweden, but overall, while clinical guidelines placed dronedarone among first-choice treatments for atrial fibrillation, amiodarone prescribing was not affected in either country by the entry of dronedarone. This was probably the result of a cautious approach by clinicians in line with regulatory recommendations and safety warnings.
Finland (prescription register) *(44)*	An analysis of a cohort of patients aged ≥18 years who were prescribed statins for the first time showed that: • underdosing at initiation was common, even among patients with a high cardiovascular risk; • a considerable proportion of patients initiated on statin therapy with less potent doses remained at the initial dose after one year.
Italy (GISEA registry) *(45)*	The objective of the study was to evaluate four-year retention rates of TNF alpha inhibitors adalimumab, etanercept and infliximab among patients with longstanding rheumatoid arthritis using the GISEA registry. Persistence over the four years was lower than 50%; etanercept had the best retention rate. The main positive predictor of adherence was the concomitant use of methotrexate. The study provides further evidence that the real-life treatment of patients with rheumatoid arthritis may differ from that in randomized controlled trials.
Italy (Psocare) – biologicals *(46–47)*	The study involved 140 reference centres throughout Italy, with mandatory data entry on all patients treated with either conventional or new biological systemic psoriasis therapies. It was established by the Italian Medicines Agency in collaboration with the Italian Dermatological Societies and the Study Centre of the Italian Group for Epidemiologic Research in Dermatology. By March 2008 it had already collected data from over 12 000 psoriasis patients, almost half of whom were treated with a biological drug.

Country/region	Details
Sweden – ARTIS study group *(48)*	The study's objective was to investigate the effectiveness and safety of TNFs in treating patients with rheumatoid arthritis. The study group was organized across all rheumatological clinics in Sweden and involved both researchers and clinicians, with high patient involvement in data catchment. In one recent study involving 10 878 rheumatoid arthritis patients treated with TNFs and 42 198 not (with matched controls), the authors concluded that: • rheumatoid arthritis patients treated with biological drugs are not at increased risk of invasive melanoma; • rheumatoid arthritis patients selected for TNF inhibitor treatment are not at increased overall risk for cancer, but have a 50% increased relative risk of invasive melanoma. Given the small increase in absolute risk, these findings do not shift the overall risk–benefit balance of TNF inhibitors used in clinical practice, but might do so in patients at high risk of melanoma for other reasons.
Sweden (PsoReg) *(49–50)*	The PsoReg was formed in Sweden to create a robust, long-term database to analyse the safety and effectiveness of different systemic psoriasis treatment regimens, including newer biological drugs. Designed and managed by health care professionals, PsoReg enrols all psoriasis patients on systemic treatments in Sweden. A web-based design allows real-time pharmacovigilance, enabling the registry to assist clinicians in their day-to-day management of psoriasis patients and health authorities in their decision-making. A recent longitudinal observational study showed that patients with moderate to severe psoriasis do benefit from biological agents in routine clinical practice.
Sweden – Stockholm Metropolitan Healthcare Region *(51)*	Patient-level data in a retrospective study involving 300 randomly selected patients initiated on weight-loss drug treatment (rimonabant or sibutramine) at 15 primary care centres showed that: • few patients continued on the treatment; • 28% of rimonabant patients and 32% of sibutramine patients had a history of depression or previous antidepressant treatment, which is a specific contraindication for rimonabant; • 41% of sibutramine patients had a history of hypertension and/or cardiovascular disease, which is a contraindication for sibutramine; • 36% of patients had no documented weight changes after treatment. These results suggest that weight-loss drug treatment was often initiated upon patient request but had limited clinical benefit.
Spain – Catalonia *(35)*	The recent follow-up of patients in Catalonia (Spain) aged over 80 years showed that 103 were not receiving the recommended dose of dabigatran. In addition: • 17.2% patients with previous ischaemic heart disease and 2.1% of patients with severe renal impairment were prescribed dabigatran although contraindicated; • renal function was not recorded in electronic records during the previous year for 30% of patients, and a large number had been prescribed dosages that were not recommended; • 15 patients on dabigatran and oral verapamil were prescribed doses that were not recommended. These findings suggest that additional activities are still needed to improve the prescribing of dabigatran. They also confirm the growing need to monitor patients prescribed new drugs in clinical practice, especially where there are concerns. The Catalonian study was made possible because the health authority has supported the development and implementation of computerized tools to capture clinical data from ambulatory practices across the region for several years.

The natalizumab registry in France is an example of a patient registry to assess the safety of new medicines once relaunched in clinical practice. Natalizumab became available again in 2006/2007 under strict regulations – as a second-line treatment in patients with multiple sclerosis after beta-interferon – based on evidence of its effectiveness in reducing relapse rates and reducing the

progression of disability *(52–55)*. This followed its initial withdrawal due to the development of progressive multifocal leukoencephalopathy (PML) resulting from reactivation of the JC virus *(53; 55)*. This was a major concern, as PML is a devastating condition whose survivors are left with serious impairment.

In addition to the pharmacovigilance programmes in France and other countries, ongoing programmes are also investigating whether seropositivity for JC virus antibodies will help to predict development of PML accurately to aid risk–benefit discussions between patients and physicians *(53)*. The objective of these is to improve understanding of the potential benefits of natalizumab as a second-line treatment in more severe multiple sclerosis patients and to ascertain the likelihood of patients developing PML if they remain seronegative to JC virus or the possible risks of developing PML if they convert from seronegativity to seropositivity *(52–53)*.

The patient registry's objectives are to:

- determine the risk–benefit ratio of natalizumab in routine clinical care;
- improve early detection of developing PML as a result of natalizumab through intensive clinical vigilance activities in order to minimize morbidity and mortality;
- minimize the risk of PML by treating only patients who are not immunocompromized;
- warn physicians against concurrent use of antineoplastics, immunosuppressants and immunomodulators;
- determine the incidence and risk factors for PML and other serious opportunistic infections, particularly after two or more years of treatment *(52–54)*.

By June 2011 more than 2800 patients had been enrolled and monitored, with most investigators enthusiastic to participate in the French registry. Serious adverse events were observed in 86 cases (65 patients), of which 36 cases led to treatment cessation. Eight cases of PML occurred, with one death and one "preclinical diagnosis"; these were associated with the duration of therapy (over two years), prior use of immunosuppressive agents and JC virus antibodies *(54)*. The efficacy of natalizumab measured in randomized controlled trials has also been confirmed in clinical practice in the more severe multiple sclerosis patients.

Patient registries can also help determine whether prescribing restrictions are being followed after launch, as with prescribing restrictions for dabigatran in Austria and Slovenia, patented statins in Finland and angiotensin receptor blockers (ARBs) and duloxetine in Sweden *(10; 44; 56–57)*. New techniques are also being developed and evaluated to monitor patient care based on extracting prescribing data directly from electronic health records. A recent study undertaken at Karolinska University Hospital, Sweden, showed that it was possible to extract drug therapy data in a hospital setting using the TNF alpha inhibitor infliximab as an example. The authors also showed that a semi-automatic procedure produced an almost complete pattern of demographics, diagnoses and dosages for treatment with infliximab, providing direction for the future *(58)*. The increasing ease of using databases and electronic health record data to research and address important clinical scientific issues around diagnostic procedures and drug therapies should help increase the number of such studies appreciably in the future *(46; 58–60)*.

3.4. References

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4. Peri-launch activities – pricing and reimbursement methods for in-patent medicines

In the process of managing the entry of new medicines on the market, activities surrounding pricing and reimbursement are of major relevance. While marketing authorization has been harmonized in the EU, pharmaceutical pricing and reimbursement are set nationally, although they have to comply with overall EU regulation such as the EU Transparency Directive (Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems). This provides procedural rules (such as the need to justify the competent authority's reasons for its decisions and to offer the opportunity to appeal against the decision).

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 social health insurance or a national health service. In practice, pricing and reimbursement are closely linked, and some European countries have joint procedures for both. The link between pricing and reimbursement is also highlighted by the fact that government policies to regulate the medicine prices usually refer to reimbursable medicines – those eligible for reimbursement by public payers. As a result, although specific policies are typically classified either as pricing policies or as reimbursement policies, any such classification can be challenged.

4.1. Pricing

4.1.1. Balancing health and industrial policy in pharmaceuticals

Pharmaceutical companies with patented drugs face relatively inelastic demand and often little competition, particularly if a new patented product is the first in its class. Price regulation thus provides a policy response to mitigate the effects of monopoly power and inadequate competition in the market. The regulation of pharmaceutical prices, whether directly or indirectly, aims to contain costs from a supply-side perspective. Governments wish to ensure that the price paid by individuals or publicly funded health systems is reasonable, given the perceived value of the drug and existing budget constraints. Pricing and reimbursement agencies aim to secure accessibility and affordability of pharmaceuticals, in addition to minimizing their cost to health systems for their long-term sustainability in the face of growing resource pressures.

A secondary policy objective for a number of national governments is to provide incentives to safeguard research into and development of innovative medicines. Beyond actively engaging in innovation activities, the pharmaceutical industry can be a key pillar of the economy. Many governments – through an active industrial policy – are keen to maintain a favourable environment for companies to operate and contribute to the national economy by incentivizing research, development and manufacturing activities, which in turn can boost economic growth, inward investment, exports and employment *(1)*. This has become known as the pharmaceutical "problem" and represents a potential conflict faced by policy-makers seeking to allocate scarce resources *(2)*. As such, pharmaceutical policy constitutes the area in which health policy becomes intermeshed with industrial policy.

In view of economic globalization and its impact on employment, the pharmaceutical industry is among the sectors that remain a major source of employment in OECD countries *(3)*. According to EFPIA, the pharmaceutical industry employs 700 000 people in the EU directly, with three times more jobs generated downstream *(4)*. In 2012 more than 105 000 people were employed by the industry in Germany, nearly 104 000 people in France and 65 000 people each in the United Kingdom and Switzerland. The total production value of the European pharmaceutical industry for 2012 was estimated at €210 billion; the top five net exporters of drugs were Belgium, Germany, Ireland, Switzerland and the United Kingdom *(4)*.

4.1.2. Entry prices

Pharmaceutical manufacturers have adapted to a number of regulations in different countries, across Europe and beyond, that affect how they are permitted to price their products at launch. A summary of the key mechanisms employed in various European countries is provided in the following sections.

4.1.2.1. Free pricing

Free pricing means that pharmaceutical companies are free to price their products with little or no intervention from regulatory bodies. Until 2011 Germany was one of the few countries in the EU where companies were largely free to set prices. Until the cost-containment regulation reform Act on the Reform of the Market for Medicinal Products was introduced in 2010 and implemented in January 2011, Germany had among the highest drug prices among OECD countries *(5)*. Although subject to indirect regulation through the Pharmaceutical Price Regulation Scheme (PPRS), the United Kingdom is often perceived as operating on the basis of relatively free pricing of innovative drugs *(6; 7)*. As a result, it is often preferred by manufacturers as the country for product launch in Europe; currency fluctuations do, however, have an impact.

4.1.2.2. Rate-of-return regulation

Rate-of-return regulation is an indirect price control mechanism where the manufacturer's contribution to drug development and the economy is considered when determining drug prices *(8)*. The objective is twofold: regulators want to reward innovation, but at the same time they want to ensure that pharmaceutical firms do not make excessive profits. There are, however, negative effects of rate-of-return regulation. The pricing mechanism provides few incentives for cost cutting and efficiency, since increased costs for the manufacturer can be recovered through increased prices, or manufacturers may have a perverse incentive to overinvest in capital or shift production costs in ways that allow for higher drug prices *(8)*.

In the United Kingdom, prices of patented drugs have been regulated through the PPRS (a rate-of-return regulation scheme) since 1957; this consists of pricing agreements between the department of health and the Association of British Pharmaceutical Industries. Pharmaceutical companies are free to set the price for their patented products and originators, but profit – that is, return on capital employed – is controlled by the department of health. In the latest PPRS, the spending level for branded medicines in the United Kingdom from 2011/2012 was capped at £12 billion and is to remain flat for two years, followed by an increase of less than 2% in the following three years *(9; 10)*. Exceeding these rates of return may lead to mandatory paybacks to the government; these are also used in other European countries including Belgium, France and Hungary *(11)*. Expenditure on patented products in the United Kingdom can also be limited by extensive demand-side measures, including high voluntary international nonproprietary name prescribing *(12)*.

4.1.2.3. ERP

ERP (also called international reference pricing and external price referencing) involves benchmarking proposed prices for new pharmaceuticals against the prices paid in other countries. The lowest price, the average or the average of the lowest prices in a basket of selected countries is defined as the reference price. ERP is the most common pricing method used by European countries and is used extensively in all but three EU Member States (Germany, Sweden and the United Kingdom). It is also widely used outside Europe *(13; 14)*.

While ERP may help contain costs by reducing prices, critics are concerned about arbitration of the targeting price, launch delays and the lack of incentives for innovation. Sweden, the United Kingdom and – until recently – Germany are characterized by relatively free pricing mechanisms for pharmaceuticals. This, coupled with their strong local pharmaceutical industries, has often led them to be the first to adopt pharmaceutical innovation *(15)*, although there have been concerns with the rate of adoption of new medicines in the United Kingdom, including new cancer medicines (see Table 13 in section 6.1). Further, in order to hinder low-price spillover through ERP, products are often launched in higher-priced EU markets, which can lead to launch delays and high launch prices in lower-priced EU markets such as Portugal and Spain *(15; 16)* or no launch at all in less wealthy countries. This is not universal, however. For instance, recent measures in Croatia – including restricting medicines to second line, strict control of pharmaceutical company activities, ERP and regulations for lowering the prices of successive generics – resulted in 85 new medicines being added to the reimbursement list between 2009 and 2011, coupled with a deficit reduction *(17–18)*. This was up from 47 new medicines between July 2009 and 2010, with 13 new medicines added to the list of expensive hospital products *(19)*.

ERP is implemented in different ways across Europe. In France it is used at launch only. Through an agreement with the Pharmaceutical Industry Association, the Economic Committee on Health Care Products must accept a list price that is no lower than the lowest price observed in Germany, Italy, Spain and the United Kingdom. Pharmaceuticals are assigned levels of innovation in the so-called improvement of medical benefit assessment (ASMR), which categorizes innovation on a scale including "no or inadequate improvement" (ASMR 5), "minor improvement" (ASMR 4), "modest improvement in efficacy and/or reduction of side-effects" (ASMR 3), "significant improvement in efficacy and/or reduction in side-effects" (ASMR 2) and "major improvement" (ASMR 1). Within this system, and until very recently, ERP was mostly used as a guide for products with an ASMR rating of 1, 2 or 3 *(20)*.

In the Netherlands a maximum wholesale price is set for outpatient drugs based on average prices for similar products in Belgium, France, Germany and the United Kingdom. Prices are reviewed every six months to adjust for price changes in the reference countries and fluctuations in exchange rates *(21)*. In Spain the basket of countries is not specified beforehand but normally constitutes the lowest available price in Eurozone countries. In Austria the average European price (ex-factory and wholesaler) – ideally among at least 50% of EU members – is used to establish the price of new medicines seen to have substantial added benefit compared to existing standards *(22)*.

ERP has come under increased scrutiny in recent years in various international studies. Ruggeri and Nolte *(23)* explored it in a selection of high-income countries in order to inform ongoing discussions on pharmaceutical pricing in the United Kingdom and the forthcoming changes in pricing policies. They concluded that the price in one reference country has only minimal or indirect impact on prices elsewhere, largely because of the diverse ways in which reference pricing is implemented. Similar

conclusions were drawn in an EU report that explored price evolution in ERP systems, finding little evidence to believe that price divergence would be any larger without ERP *(24)*.

4.1.2.4. Cost-plus pricing

Cost-plus pricing is a method whereby retail prices are set by taking into account the production cost of a medicine, an allowance for promotional expenses, the manufacturer's profit margins and charges and profit margins in the supply chain *(25)*. This method is confounded by the problem of transfer pricing *(8)*, however, and is generally not recommended as an overall pharmaceutical pricing policy. Nevertheless, it is used in a number of low- and middle-income countries including China, Vietnam *(26)*, Bangladesh, Indonesia *(27)* and – until 2012 – India *(28)*, particularly for locally produced pharmaceuticals.

Cost-plus is also employed in high-income countries including Slovakia and Australia and, until recently, was in use in several other European countries such as Greece and Spain, but it is usually confined to locally produced pharmaceuticals. The price of pharmaceuticals produced in Greece, for example, was calculated on a cost-plus basis before being compared with the lowest prices of the drugs in the EU *(29)*. Cost-plus pricing was also previously in use for locally produced medicines in Cyprus *(3)* and is still used in Slovakia *(27)*, although here a rigid low ICER for new medicines is set at €18 000 per QALY *(31)*. In Spain cost-plus methods were introduced in 1964 *(24)* and led to Spain's involvement in parallel export of pharmaceuticals *(32–34)*.

4.1.2.5. Clinical and cost–effectiveness pricing

Pricing methods based on value assessments of the medicine may take into account the drug's clinical and cost–effectiveness – or simply its clinical effectiveness – compared to alternative treatments. Differences in methodological preferences, such as costing perspective in value assessments, across and within European countries show that a drug's "value" is highly subjective *(14)*.

Countries employ different approaches to assessing value. While some divide the level of innovation or the therapeutic value into separate categories for use in subsequent price negotiations (including Belgium, France, Germany, Italy and Spain), others use a cost-per-QALY approach (including England, Scotland and Sweden). French health authorities, for example, consider the level of innovation in five ASMR tiers *(20)* (see section 4.1.2.3), which help to determine drug prices during a second stage. Recent developments in France have introduced economic evaluation to the pricing and reimbursement process. Under the 2012 Law for the Financing of Social Security, the French Haute Autorité de Santé (National Authority for Health) was mandated to consider cost–effectiveness in its drug evaluations from October 2013. The changes necessitate mandatory submission of cost–effectiveness analysis by companies applying for reimbursement in ASMR tiers 1–3, but the analysis is not used to make decisions on reimbursement and only features as complementary information for the Economic Committee on Health Care Products, although this may affect drug prices *(35)*.

The newly implemented Act on the Reform of the Market for Medicinal Products in Germany (see section 4.1.2.1) means that companies must demonstrate their drug's additional therapeutic benefit in a structured dossier to be assessed by the Institute of Quality and Efficiency in Health Care. The results of the Institute's assessments are then used in price negotiations between the Federal Association of Statutory Health Insurance Funds and the company concerned, based on the drug's perceived level of additional benefit. Drugs that fail to demonstrate additional benefit are assigned to a reference price group *(5; 36)*. Of the 25 dossiers (excluding orphan drugs) assessed by the Institute up to the end of

2012, 14 contained sufficient data from randomized active-controlled trials investigating patient-relevant outcomes or at least acceptable surrogate measures, while 11 contained insufficient data. Of the 14 drugs with sufficient data, the extent of added benefit was rated as minor in three cases, considerable in eight and nonquantifiable in two; the remaining medicine evaluated showed no added benefit *(36)*.

In Italy the innovation assessment algorithm uses the seriousness of the disease, availability of alternative treatments and therapeutic effect as input variables to generate a therapeutic innovation score classified as “important”, “moderate” or “modest”. Pharmaceuticals are divided into three categories: drugs for fatal or serious conditions that result in permanent disability or hospitalization, that reduce the risk of serious diseases and for nonserious conditions *(37)*. The Italian Medicines Agency has used the innovation assessment algorithm to assess the level of innovation of new drugs *(38)* and as a tool in price negotiations.

4.1.2.6. VBP

VBP sets prices based on a value assessment that takes into consideration a wider range of criteria than clinical cost–effectiveness, including the burden and severity of the disease and long-term benefits of the treatment. Notions of “value-based” have developed over the last two decades, and the term is now broadly understood to mean that activities within the health sector should be oriented, organized or funded to maximize health benefits for patients and societies *(20)*. While VBP outside the health sector refers to the price that reflects the value of the product to the customer (that is, based on their willingness to pay), in most European health systems the customer’s willingness to pay is not relevant to determining the price, as most services are financed by third-party payers. VBP in the health sector is therefore defined in the context of the English health service as: “the price that ensures that the expected health benefits [of a new technology] exceed the health predicted to be displaced elsewhere in the national health service, due to their additional cost” *(39)*. This definition implies the use of cost–effectiveness analysis in decision-making. Others have gone further, linking VBP with HTA and suggesting that VBP consists of negotiating prices for new pharmaceuticals based on the value of the drug for the society as assessed through HTA *(40)*.

By ensuring access to cost-effective drugs today and incentives for manufacturers to invest in cost-effective products for the future *(39)*, VBP seeks to provide a sustainable solution to pharmaceutical price regulation. But while it aims to reward innovation, establishing a clear link between the level of innovation and the price is not straightforward.

Although interest in VBP is growing, its practice in European national health authorities is still limited and little evidence of the risks and benefits exists. In Sweden the national outpatient reimbursement agency, the Dental and Pharmaceutical Benefits Agency (TLV), employs VBP in outpatient reimbursement recommendations and conducts assessments on selected inpatient drugs on behalf of the counties’ health services *(41)*. A flexible threshold for cost per QALY is set, based on three criteria *(17; 20; 42)*:

- the human value principle that guards against discrimination of individuals;
- the need and solidarity principle that gives priority to those with the highest need;
- the cost–effectiveness principle that ensures that the cost of the drug is reasonable from both a clinical and an economic perspective.

Following a public consultation by the department of health in the United Kingdom *(43)*, terms of reference were developed outlining the broad principles on which VBP is likely to be implemented.

According to the plan, NICE is the institution responsible for implementing the changes. In addition to the HTA approach already in place at NICE, the system is meant to account for disease severity and indirect costs (societal costs) *(43–44)*. (While the 2014 PPRS further embeds value assessment and additional initiatives carried out by NICE have been announced, at the time of writing (September 2014) little is known about what the new pricing system will look like in practice.)

Traditionally, new orphan drugs (see section 6.4) at premium prices have faced few reimbursement hurdles, although additional years of market exclusivity have been granted to encourage their development *(45–47)*. But while such orphan drug policies have been essential in incentivizing the development of treatments that would not otherwise have emerged, the weaknesses of the current policy framework need to be addressed: concerns regarding orphan drugs' value and clinical effectiveness – and overall costs – are increasing, especially with some now attaining "blockbuster" status *(45–46)*. Proposed improvements include better data collection and registry initiatives at the EU level *(48)*. The means of value assessment needs to be improved so that it takes into account the unique characteristics of rare diseases. Other proposed criteria to include in assessment of orphan drugs are rarity, disease severity, availability of alternatives and whether the product can be used for more than one indication *(49)*.

In addition, to help European countries in their value assessment of orphan drugs, the TVF was developed as part of the Mechanism of Coordinated Access to Orphan Medicinal Products (MoCA-OMP) in the EU Process on Corporate Social Responsibility in the field of pharmaceuticals *(50–51)*. Use of the TVF enables comparison of therapeutic alternatives with similar framework scores to provide future guidance in pricing and reimbursement negotiations (see Table 6).

Table 6. The TVF to assess the value of orphan drugs

Criterion	Low degree	Medium degree	High degree
Alternatives available	Yes	Yes	No
Unmet need	New medicine does not address unmet need	Major unmet need still exists	No alternatives exist except supportive care and major unmet need exists
(Relative) effectiveness, degree of net benefit relative to alternatives including no treatment	Incremental	Major	Curative
Response rate	<30%	30–60%	>60%
Degree of certainty	Promising but not well documented	Plausible	Unequivocal

Source: EC *(50)*.

While seen as a good start, since its development included all key stakeholder groups, debate is ongoing about the feasibility of implementing the TVF in the decision-making of national reimbursement authorities and further refinement continues.

Other frameworks for the evaluation of drugs that do not fit standard methodologies of HTA have been proposed. Hughes-Wilson and colleagues' *(49)* proposals included 10 criteria by which orphan drugs could be evaluated, indicating price differentials based on baseline measures for each individual criterion. The criteria included rarity of the disease, level of research undertaken, level of uncertainty of effectiveness, manufacturing complexity, follow-up measures (additional benefits and associated

costs), disease severity, available alternative or unmet medical need, level of impact on the condition (disease modification) and whether the drug is used in a single or several indications. Further, in an attempt to manage uncertainties and budget impact, a number of MEAs have been implemented for orphan drugs *(46)* (see section 6.4).

4.1.3. Price revision – mandatory price cuts

In contrast to mechanisms for regulating the entry price of pharmaceuticals, mandatory price cuts aim to revise existing prices in order to contain costs. They aim to reduce drug prices, either on an ad hoc basis as a result of, for example, external economic pressure (such as the financial crisis) or by imposing regular price reviews. While widely used for multiple-source products, price cuts are increasingly used for in-patent drugs, usually when the drug has been on the market for some time or when a therapeutic alternative enters the market.

In Denmark prices for both in-patent and multiple-source products are reviewed fortnightly for this purpose *(52)*; in Croatia this is done yearly *(19; 53)*. A study looking at pharmaceutical policy interventions applied during the financial crisis found price cuts to be an important cost-containment measure between January 2010 and February 2011. During this period, Greece applied quarterly price reviews followed by price cuts and Lithuania imposed price cuts of 10–11% on nonreimbursable medicines. Similar price cuts were enforced in the Czech Republic, Iceland and Portugal. In Italy pharmaceutical companies were given the choice between payback schemes and price cuts and in Spain prices of original drugs and orphan drugs were cut by 7.5% and 4% respectively *(54)*.

4.2. Reimbursement

The primary tool of reimbursement in pharmaceutical policy is a positive list or formulary, which lists new drugs following predefined criteria. Various reimbursement criteria and methods are employed in European countries. The following sections focus on HTAs through the use of economic evidence and through MCDA, MEAs and budget impact assessments.

4.2.1. HTAs through the use of economic evidence

A number of European countries use economic evaluations in their decision-making regarding reimbursement and funding for new drugs *(20; 55)*. HTAs are used in decision-making in a transparent manner to provide evidence-based coverage decisions. These typically take the form of a cost–utility, cost–effectiveness or cost minimization analysis. Various HTA agencies choose to consider different evidence in their analyses, but the types of health outcome considered tend to be similar and they all prefer final end-points rather than surrogate markers *(20)*. An overview of key approaches follows (see Annex 2 for additional information).

The health economic evaluation takes either a societal perspective – taking into account indirect costs of treatment and illnesses (as in the Netherlands, Norway and Sweden) – or a health system perspective, in which only direct costs to the health care system are considered (as in Belgium, England and Scotland). Some countries employ a mix of societal and health system perspectives *(20)*. The Belgian Health Care Knowledge Centre, for example, encourages manufacturers to include a separate analysis in which indirect costs are taken into account if these are considered relevant *(56)*. Little variation exists in the HTA agencies' guidance on the choice of comparator, and relevant comparators are usually the most relevant treatment option within the country *(20)*. In France the drug is assessed

against the cheapest reimbursed treatment used for the indication, while in Norway separate assessments are required when more than one relevant treatment option exists.

A wide range of stakeholders is involved in the HTA process in European countries, including patients and clinicians; this enhances the transparency and trust in decisions made and fosters mutual respect between patients, industry and regulators to help address areas of unmet need, particularlyhigh unmet need *(20; 57)*. One example is SMC in Scotland – a consortium of stakeholders including policy-makers, clinicians, pharmacists, patient representatives and industry representatives. The deliberative process employed by SMC has led to good engagement and a strong relationship with the area DTCs, which implement SMC's decisions in the National Health Service (NHS) in Scotland *(58)*. In Sweden patient representatives sit on the TLV reimbursement board and as members of the Swedish Council on HTA; they are expected to give input on ethical matters and interpretation of study outcomes *(59)*.

Communication between HTA agencies and manufacturers may avoid delays in the appraisal process *(60)*. Efforts such as early and informal dialogue between the Norwegian Medicines Agency and manufacturers to identify relevant comparators *(61)* aim to avoid resubmissions and save resources for both health authorities and the company. In the United Kingdom in 2009 NICE established a fee-for-service scientific advice consultation service to pharmaceutical companies, which includes the supply of written advice *(55)*; 52 formal written advice projects were completed in the first three years of the service *(62)*.

At the European level two initiatives to facilitate early dialogue between regulatory bodies and manufacturers deserve attention. First, EMA issued a press release in 2013 stating that: "A strong interaction between regulators and HTA bodies is critical to enable innovation to reach patients, and ultimately for the benefit of public health" *(63)*. Since 2010 EMA has run a pilot project of parallel scientific advice. The programme allows developers to receive simultaneous feedback from regulators and HTA bodies on their development plans for new drugs. At the time of writing (September 2014), guidance for EMA–HTA parallel scientific advice is still expected to be published in 2014. Second, the Shaping European Early Dialogues (SEED) consortium, led by the French Haute Autorité de Santé (National Authority for Health) and financed by the EC, aims to explore ways of increasing early dialogues between HTA assessors and manufacturers during the product development phase *(64)*.

4.2.1.1. Thresholds for reimbursement

Some HTA authorities employ a fixed and explicit threshold for cost per QALY, such as €45 000 in Ireland, €80 000 (maximum) in the Netherlands, three times GDP per capita in Poland, €18 000 in Slovakia and a range of £20 000–30 000 (€24 300–36 450) in the United Kingdom (with exceptions: see below) *(20; 31; 65)*. Others use variable or no explicit thresholds, such as Norway and Sweden, where the willingness to pay depends on the severity of the disease area and level of unmet need *(17; 62)*. In a pilot study on willingness to pay in Sweden researchers estimated the threshold value for a QALY at €45 000 based on individuals' preferences *(63)*, but for more severe conditions this increased to the region of €100 000. As a result, currently no formal cost-per-QALY threshold appears to exist for new drugs in Sweden.

Without setting explicit thresholds, however, historical data allow for suggestions as to where the line is drawn via a precedent approach, using legal decisions in specific cases to build pressure for moving the threshold up more generally over time. In Belgium it is thought unlikely that the authorities would reimburse new drugs with an additional cost per QALY of €80 000 *(20)*. An €80 000 per QALY threshold

has been reported in the Netherlands *(68)*, but evidence has shown that for orphan drugs much higher ICERs were accepted (although mainly due to public pressure *(45)*). In Norway a notional reference value of no more than 500 000 Norwegian krone (€60 500) per QALY is proposed as a guiding threshold by the Board of Health, which has developed guidelines for health economic evaluations in Norway *(69–70)*, but no formal threshold levels are currently used.

In the United Kingdom scholars suggest that the tipping point for NICE positive recommendations is between £39 000 (€47 385) and £44 000 (€53 460) *(71)*, with no significant changes over time *(72)*. Generally, however, NICE is most likely to recommend treatments with an ICER not higher than £20 000–30 000 *(73)*. Higher ICERs may be accepted for end-of-life therapies if the treatment is indicated for patients with a life expectancy of less than 24 months, sufficient evidence is available to indicate that the treatment will offer a life extension of at least three months and the treatment is licensed or indicated for small patient populations *(74)*. NICE's end-of-life guidance continues to be controversial, since it effectively advises the Institute to deviate from the normal threshold range and value the lives of, for example, patients with terminal cancer more than the lives of patients with chronic, acute and potentially curable diseases *(75)*. An example of the application of this criterion is vemurafenib for the treatment of metastatic melanoma, which was accepted with an ICER between £44 000 and £51 800 (€53 575–63 073) based on the end-of-life criteria *(76)*.

A study analysing all decisions made by NICE up to 2011 found that cost–effectiveness is the most important factor, alone predicting 82% of recommendations analysed *(71)*. Further, NICE's decisions were more likely to be favourable for cancer and musculoskeletal diseases, while respiratory diseases were more likely to be rejected, other things being equal. In Scotland cost-per-QALY considerations also play a major role in SMC's decision on whether to endorse funding for a new medicine in all or a subpopulation of patients *(77)*.

Willingness-to-pay thresholds that have come into use are thought to be mostly arbitrary in nature *(78–79)*. Nevertheless, WHO recommends that where the incremental cost per QALY is less than a country's per capita GDP the technology should invariably be considered cost-effective, while technologies where the incremental cost per QALY is more than three times a country's per capita GDP should not be viewed as cost-effective *(80–81)*. Scholars have pointed out, however, that enforcing a clear-cut willingness-to-pay threshold is unrealistic for two reasons. First, the theoretical ICER threshold cannot be identified in practice because of a lack of information on explicit scientific evidence. Second, even if such a threshold could be identified, other considerations would make its application difficult, such as budgets that cannot be fixed, adjustments for inflation, health maximization not being the only objective equity concern and other parameters of interest or value *(56; 66)*. Furthermore, while defining ICER thresholds based on societal willingness to pay for a QALY is appealing, it is equally difficult thanks to the impossibility of measuring the maximum societal willingness to pay for a generic QALY, since "a QALY gained" is inseparable from any concrete context, depending as it does on the elicitation format and the policy context environment *(68)*. Scholars commenting on the rationale behind the willingness-to-pay threshold in the United Kingdom define three approaches to establishing a cost–effectiveness threshold: inferring thresholds from previous decisions, setting thresholds in order to determine the optimal budget and setting thresholds to exhaust the optimal budget *(73)*. Lacking the mandate to fix the budget, the appropriate model for considering NICE's cost–effectiveness threshold is that of identifying a threshold to exhaust the optimal budget *(82)*.

Structural differences in health care systems also seem to affect the application of willingness-to-pay thresholds. In social health systems there seems to be greater reluctance to define a single threshold value for the ICER since budgets are less defined and fixed than in national health care systems *(68)*.

Countries have sought to find ways of strengthening the QALY as a measure of health outcomes. For example, health authorities in the Netherlands have proposed the use of "proportional shortfalls" to weigh QALYs. These combine two competing principles considered for equity purposes:

- fair innings (everyone should experience the same quantity of healthy life, which implies, for instance, that treatment for children should be prioritized over treatments for old people);
- expected health (priority should be given to treatments expected to provide the highest health benefits to their population targets) *(20)*.

The proportional shortfall for a population target for a treatment is defined as the ratio of the number of QALYs lost in absence of treatment to the number of QALYs this population could expect in absence of the disease. Using the principle of proportional shortfalls to make decisions means giving priority to patients whose QALY gains are higher – an approach that remains highly contested.

Consequently, while economic evaluations are used in national-level decision-making, their effect on the implemented decision on funding and reimbursement in practice may be questioned. For example, TLV in Sweden makes reimbursement recommendations based on cost–utility analysis, but the final decision on whether to fund the new medicine or not lies with the 21 county councils *(66)*. Nevertheless, HTAs and economic evaluations do enhance the decision-making process for whether to endorse funding for new medicines in all or a subpopulation of patients and are endorsed by WHO's suggested pricing strategy document. WHO's recommendations regarding the increasing use of HTA when assessing the value of new medicines for potential reimbursement are as follows *(25)*:

- Countries should use HTA as a tool to support reimbursement decision-making as well as price setting and negotiation.
- Countries should combine HTA with other policies and strategies, particularly within-country reference pricing (by chemical entity, pharmacological class or indication).
- Countries should consider the following actions when using HTA: review the applicability and adaptation of reports from other countries; review reports submitted by pharmaceutical companies; and conduct assessments based on local information and local data. The choice of approach depends on technical capacity and local decision-making structures.
- Countries could take a stepwise approach to develop legislative and technical capacity to take full advantage of the potential utility of HTA in pharmaceutical price setting.
- In establishing the legislative/administrative framework countries should clearly define the roles and responsibilities of decision-makers and other stakeholders, and the process of decision-making.
- Countries should ensure that HTA processes are transparent and that the assessment reports and decisions are made publicly available and effectively disseminated to stakeholders.
- Countries should collaborate to promote exchange of information and develop common requirements for HTA.

4.2.2. HTAs through MCDA

Decision analysis – and MCDA in particular – is widely applied in scientific disciplines and in public services *(83)* in areas such as transport *(84)* to aid decision-making, but has only recently gained attention in health system research. Advocates of MCDA in health resource allocation argue that the priority-setting tools in use today provide only single criterion measures that fail to take into account all relevant criteria simultaneously. MCDA in health care resource allocation is potentially superior to current approaches, allowing for a more comprehensive set of parameters to be taken into account

than just the incremental cost per QALY *(85)*. This can form a more holistic approach to assess the overall value of a medicine, and will involve a wider spectrum of stakeholders with the aim of balancing different, and potentially opposing, interests. The development of the TVF for new orphan medicines (see Table 6) is insufficient on its own and will be developed over time, but is a positive move towards involving all key stakeholder groups.

MCDA methodologies most often follow common stages. After defining a decision context, relevant stakeholders and treatment options, the objectives and criteria that reflect the value associated with the consequences of each option are mapped out. Subsequently, each value associated with the performance of each treatment option is scored against the criteria, followed by a weighting of each of the criteria to reflect their relative importance in the decision. After a weighted sum approach the overall value is derived and sensitivity analysis conducted to test the influence of changes in scores and weights *(83; 85)*. While most proposed MCDA methods in the literature use a weighted sum approach, they may be adapted to more flexible approaches over and above weighting and scoring *(86)*.

MCDA is a tool that allows for a systematic and explicit consideration of multiple factors that influence the decision, through identified criteria that each are assigned a weight in order to make their values and objectives explicit. When criteria and weights are identified based on the decision problem, decision-makers score the performance of the health care intervention under appraisal with regard to each criterion *(87)*. While elements relevant for MCDA are considered in reimbursement decisions in Europe – for example, in the United Kingdom NICE adopts an end-of-life criterion for certain drugs and TLV in Sweden holds equity, need and solidarity as important criteria when giving reimbursement recommendations – MCDA methodologies propose including the parameters in a more formal way.

Among the first attempts at an MCDA approach to reimbursement decisions is the HTA process in the Italian region Lombardia, where the HTA framework incorporates elements from the EUnetHTA core model. These include disease severity, population size, health care goals, efficacy and the quality of the documentation, safety, the financial impact on the health system, the cost–effectiveness and opportunity cost, impact on equity and accessibility, coherence with national and regional planning, pressure from interest groups, historical and political context and system capacity *(88)*. The HTA process in Lombardia is a three-step one. First, the region selects health interventions for appraisal based on applications from stakeholders that include evidence on the impacts of the health technology in eight dimensions (general relevance, safety, efficacy, effectiveness, economic and financial impacts, impacts on equity, social/ethical impacts and organizational impacts) compared to current technologies. Then a full assessment of the prioritized technologies is conducted. Finally, an appraisal of the assessed technologies grounded on the analysis of multiple criteria of each dimension is carried out. The subsequent deliberation guides future investment decisions with new technologies *(88)*. This approach has been used successfully since the end of 2011 to process 26 reported technologies.

4.2.3. MEAs

The aim of MEAs (also called risk-sharing agreements, although only a subset of MEAs includes a true risk-sharing component) is to reduce uncertainty around the clinical effectiveness and/or cost–effectiveness and/or to limit the budget impact of a technology in real life. MEAs are arrangements between a payer and a manufacturer that enable the reimbursement of a health technology, subject to specific conditions *(89)*. These conditions can be either financial or health outcome-based, and different types of MEAs exist for each of these two main groups *(11; 90)*.

Financial agreements include the following types *(11)*:

- PVAs: an expenditure threshold is set after which a rebate on the price of all additional doses is triggered.
- Discount/rebates: discounts are ex-ante price reductions on the list price; rebates are ex-post price reductions requiring full payment of the list price and subsequent refund of the agreed rebate.
- Price/dose/time capping schemes: these establish a cap on the total treatment cost, the number of doses or the treatment duration, after which the manufacturer assumes all additional treatment costs required to complete the treatment course.

Health outcome-based agreements include the following types *(11; 51; 90–91)*:

- Payment by results or for performance (also known as outcome guarantee or "no cure no pay" agreements): this type of agreement establishes a threshold – defined by either a surrogate marker correlating with the final end-point of interest or the end-point of interest itself – demarking whether treatment was either successful or not. If treatment was unsuccessful the manufacturer has to reimburse either the full or part of the cost of treatment, depending on the agreement between payer and manufacturer.
- Coverage with evidence development: when evidence is deemed insufficient to make a final reimbursement decision but the competent authority believes it possible to address this data gap, the manufacturer may be asked to collect additional evidence, to answer specific questions posed by the competent authority and possibly also resubmit a new cost–utility/effectiveness analysis including these real-life data. In the United States this includes other partner stakeholders where coverage with evidence development is increasingly funded by medicare in partnership with the manufacturer, academic centres and similar, such as the National Oncologic PET Registry.
- Registries to ensure appropriateness of prescribing and improving medicines performance in real-life: in case of concern about whether physicians will follow the recommended prescribing indications, registries may be used to monitor prescribing patterns. This is meant to serve as an incentive for physicians to follow guidance and for the pharmaceutical industry not to promote off-indication prescribing, as they may be asked to offer a discount.

A recent report suggests that the most common MEAs among European countries are PVAs (39% of total MEAs), followed by requirements for data collection (29%) and limiting access to eligible patients (13%) *(11)*. Furthermore, conditional continuation (6%) is frequently used in Italy; discounts (5%) are prevalent in Italy and England; and payment-by-results arrangements (5%) are used in Italy and Lithuania. Payment-by-results schemes are also in use in the United Kingdom, including one for bortezomib in patients with multiple myeloma *(90)*. Evidence shows that MEAs are increasingly used in reimbursement decisions for orphan drugs *(46)*. PVAs are widely used in Italy, Lithuania and Portugal, and data collection is a common requirement in the Czech Republic, Italy, the Netherlands and Sweden. Further, Belgium, the Czech Republic and Italy among European countries limit the numbers of eligible patients able to access certain medicines in order to reduce the budget impact and enhance their prescribing in patient populations where their value is greatest and/or reduce potential adverse reactions where they may be widely used *(11; 91)*. Similar activities are also undertaken in Austria and the Republic of Srpska (a semi-autonomous region in Bosnia and Herzegovina) to help contain the cost of new medicines *(22; 92)*. Coverage with evidence development is used more often in the Netherlands and Sweden.

MEAs are often used for high-cost patented drugs for which there is limited evidence of effectiveness in a noncontrolled environment and of their long-term effects. A significant proportion of MEAs (37%) surround antineoplastic and immunomodulating agents *(11)*. An evaluation of all 42 patient access schemes (the designation used for MEAs in the United Kingdom) SMC had engaged up to April 2012

confirmed that most of the schemes focused on antineoplastic products, followed by medicines for musculoskeletal diseases, inflectional diseases, eye diseases and diseases of the central nervous system. While drawing on incentives from both financial and health outcome-based MEAs, most of these patient access schemes were simple finance schemes involving discounts or rebates as opposed to more complex finance schemes involving, for instance, price capping or performance/outcome-based schemes *(93)*.

The burden of managing MEAs relies on the complexity of the agreement; notoriously, payment for performance and coverage with evidence development schemes have been among the most burdensome to implement. Early research findings in 2009 showed that 73% of United Kingdom hospitals did not have the capacity to manage current schemes *(94)*. The administrative burden, lack of communication and concerns with passing on savings were highlighted as key issues with some of the schemes for cancer drugs in the United Kingdom. Meanwhile, some of these agreements have been changed to simple discount schemes, and all new agreements the department of health has engaged since 2011 are either simple discounts or free stock agreements. In this context, greater flexibility around the time limits for processing claims was deemed crucial and good communication between key stakeholders important *(90; 94)*.

An analysis of strengths, weaknesses, opportunities and threats highlighted that among MEAs' strengths is their ability to help address post-licensing uncertainty and to enable access to innovative treatments in a context of uncertainty *(11)*. In general, MEAs offer more flexibility than other pricing methods, and combine both financial and nonfinancial elements to address different issues. Further, MEAs can help increase the evidence base of the therapy in question by agreements such as coverage with evidence development. Pure financial agreements such as price/dose capping and price match help improve the cost–effectiveness of a new intervention. This enables health care payers to control the impact on budgets better, improve use and increase access to medicines. Similarly, MEAs enable manufacturers to obtain reimbursement for drugs that otherwise would be rejected.

Despite these strengths, several weaknesses remain: first, there is little evidence to support the claimed benefits of MEAs in practice and the extent to which some of the challenges involved in MEAs affect the financial outcome. Second, lack of transparency in the agreements implemented, their objectives and evaluation of their impact prevents cross-country learning and limits patients' ability to engage in MEA processes.

The opportunities for MEAs are many. Many countries collect useful data but few leverage this opportunity, and continuity in collecting the data is often lacking. Countries could benefit from increasing efforts to re-evaluate the effectiveness of the drugs, streamline postmarketing studies with data collection requirements as part of MEAs and adaptive licensing, increase transparency in agreements and create formal channels for involvement of patient representatives.

Finally, countries must be cautious not to adopt MEAs as quick fixes or ad hoc solutions that are not integrated into a comprehensive process for introducing new medicines, but should ensure that MEAs are used with long-term perspectives in mind. Health authorities must be careful not to allow for "playing the system". If MEAs are routinely used in countries that employ HTA processes for coverage decisions, manufacturers may have a perverse incentive to offer a price they expect to be rejected. Similarly, the HTA agency would be more likely to reject the price, knowing that a lower price would be proposed as an MEA *(82)*.

A number of MEAs have been concluded for orphan drugs, where the evidence base is severely limited by the small patient population and entry prices are often prohibitively high *(46)*. Expenditure and use of orphan drugs are increasing rapidly *(49)*, enhanced by off-label use *(95–96)*. This is likely to grow, given requested prices and concerns with the potential budget impact of orphan drugs *(51; 96–97)*. A study on MEAs employed on orphan drugs showed that schemes relied on either health outcome-based arrangements or financial arrangements, except in Italy, which employed payment by results as well as price discounts *(46)*. A number of coverage with evidence development schemes were observed in the Netherlands and Sweden, and various patient use and cost caps were observed in Belgium and England.

4.2.3.1. Rebates, clawbacks and paybacks

Rebates, in which manufacturers have to return a part of their revenue to the payer, are often seen as an alternative to decreasing list prices and are widely used across Europe as a tool in cost containment *(55)*. Payback policies are similar to rebates but are only used in relation to specified target budgets. Clawbacks apply to the pharmacy sector and are meant to reduce pharmacy margins by seizing discounts on dispensing fees and passing them on as revenue to the public payer.

In France, the industry pays annual rebates to the French insurance funds *(98)*. As a result of having higher drug prices than many other European countries, Germany introduced major cost-containment regulations in 2010 with the Act on the Reform of the Market for Medicinal Products, aiming to curb expenditure by the statutory health insurance funds *(5)*. The statutory rebates are used for nonreference priced patented drugs. This law requires German manufacturers to pay back a share of the ex-factory price for every package of nonreference priced drugs sold. The level of rebates was raised in 2010 from 6% to 16% *(99)*, including the €700 million already paid at the 6% rate from January to August 2010 *(100)*. This led to slower growth in spending on drug reimbursement for the Gesetzliche Krankenversicherung (Statutory Health Insurance): down to 1% year-on-year growth in 2010, compared to 4.8% year-on-year growth in 2009 *(101)*. According to new legislation, the rebate is expected to be reduced to 7% in 2014 *(102)*.

A payback system is in place in Portugal, whereby the pharmaceutical industry must refund any spending that exceeds the 1.25% of GDP target in 2012 or 2013 *(103)*. In Poland manufacturers are required to payback 50% of the amount exceeding the yearly limit on reimbursement for outpatient drugs *(107)*. Mandatory payback schemes are also used in other European countries including Belgium, France and Hungary.

Clawback systems are in use in several European countries, including Belgium, Germany, Italy, the Netherlands, Spain and the United Kingdom, but the methods vary widely. A flat proportion up to a ceiling per package is used in the Netherlands, while Spain and the United Kingdom have employed a progressive percentage applied to the pharmacy's monthly turnover *(105)*.

4.2.4. Budget impact analysis

Budget impact refers to the total costs incurred by reimbursing and using the medicine in its approved indication; it requires information on the expected consumption volumes. Budget impact may be calculated at the health care system level or in terms of pharmaceutical costs alone, and takes into account the possible reallocation of resources across budgets or sectors of the health system *(106)*. The main reason for carrying out budget impact analysis is to calculate the opportunity cost of using resources in a certain way to assist payers in their decision-making.

While effectiveness, cost–effectiveness and severity of illness are seen as legitimate criteria for resource allocation, less of a consensus exists for the role of budget impact in coverage decisions, despite its widespread use in European reimbursement decisions *(107–108)*. In addition, its relevance has been debated: while some health economists have argued that budget impact analysis undermines cost–effectiveness analysis *(109)*, others have emphasized its need and usefulness for policy-makers *(108)*. Further, the literature on methodologies suggests it is not yet a well established technique, and that budget impact analyses conducted by the pharmaceutical industry appear to be tailored to demonstrate short-term savings *(107)*. Finally, budget impact analysis may be more useful to decision-makers than cost–effectiveness analysis, whose goal it is to reduce variance in health gains rather than maximize health gains subject to a budget constraint.

Despite the scepticism about budget impact analysis, many – if not most – EU countries, including Belgium, the Netherlands, Norway, Poland and Spain, consider budget impact in their deliberations for expensive drugs *(20; 110)*. Manufacturers applying for reimbursement to the Norwegian Medicines Agency are required to include a budget impact analysis with the cost–utility analysis. If total costs exceed "the bagatelle limit" (5 million Norwegian krone in the fifth year after introduction), the final decision is taken in parliament *(111)*. Budget impact also plays an important role in regional decision-making in Denmark and Sweden, alongside considerations of efficacy and safety of the new medicine versus current standards *(112–113)*.

4.2.5. Off-label policies: drug registration versus effectiveness

In most European countries using drugs off-label when a registered product exists is not allowed. In the United Kingdom NICE publishes summaries of the best available evidence for selected unlicensed or off-label medicines on its website *(114)*. The strengths and weaknesses of the relevant evidence are critically reviewed, but the summaries do not constitute formal NICE guidance. A robust evidence base is often insufficient, as national legislation that protects patients from unauthorized drug use generally also protects industrial policies, such as when drug companies do not ask for registration of their drugs for specific indications where this is not commercially convenient.

A relevant example is the off-label use of bevacizumab in age-related macular degeneration (AMD) – this is hindered because a registered drug (ranibizumab) is available, although appreciably more expensive. Head-to-head independent trials demonstrated that bevacizumab is an effective and safe option in AMD *(115)*. This situation causes concerns for health authorities, given the prevalence of AMD (more than 3% of people over 65 are estimated to suffer from it) *(116)*, its clinical consequences (leading to blindness) and its heavy financial burden *(117)* (monthly treatment with ranibizumab costs about 40 times more than with bevacizumab).

In Italy the outcry following a verdict of the Competition Authority in February 2014 around bevacizumab resulted in the Italian Medicines Agency readmitting it as a therapeutic option for AMD. More generally, however, a further result was a change in legislation to allow the off-label use of drugs, provided that strong evidence on their effectiveness and safety is available (Decree Law 36/2014 of 20 March 2014). Specifically, the Authority fined the multinational drug companies commercializing the two drugs €182 million for cartelizing the sales of two major ophthalmic drugs (bevacizumab and ranibizumab) in order to channel demand towards the more expensive of the two *(118)*. Following the case in Italy an investigation started in France, and a law was passed to reallow the use of the less expensive drug *(119)*.

In this example, the different position of the regulatory level – adapting to the policy of drug companies when not registering their products – and the third-party payer comes up clearly. The Emilia-Romagna region in Italy, with a fixed budget to allocate for health care of its citizens, initially took the decision to reimburse the use of bevacizumab in AMD but had to pull back when the drug was definitively excluded from the national off-label list. The region eventually decided to participate as an "offended party" in the trial against the Competition Authority, however, and to follow an evidence-based approach supporting a Cochrane systematic review, which independently assessed the comparative safety of bevacizumab and ranibizumab in AMD *(115)*.

WHO has expressed a clear position regarding off-label uses: the listing of only those drugs that have been registered was challenged in its model essential medicines list (EML), which considers "evidence of efficacy and safety and demonstrable public health importance as the main criteria for inclusion … rather than the indications having been approved by regulatory authorities in national settings" *(120)*. In fact, bevacizumab was included in the EML for the treatment of AMD in April 2013. National drug policies could consider following the WHO position towards the evidence-based (and not registration-based) reimbursement of drugs, in order to facilitate access to effective drugs and affordability of treatments.

4.3. Key considerations in the interplay between pricing and reimbursement

From a pricing perspective, ERP is a widely used method to inform and set prices for in-patent drugs in the majority of European countries (across the EU Member States and beyond). Its strengths include the relative administrative simplicity of applying the method in comparison to, for example, implementing cost–effectiveness pricing or VBP. ERP involves no value judgements and is based on the seemingly appealing concept that no country should pay more than another for the same drug. The way it is applied, however – particularly in the EU – means that ERP does not take into consideration the value a particular drug brings to a society, it ignores affordability issues and does not include a notion of solidarity (for example, lower-income countries paying less than higher-income countries); nor does it consider societal willingness to pay. Finally, because list prices most often do not reflect the actual prices paid by payers, the limited evidence available on the impact of ERP on prices is mostly inconclusive.

Rate-of-return regulation also presents strengths and weaknesses. For example, rate-of-return regulation in the United Kingdom may be attractive from an industry perspective because it allows industry to set the prices of its products freely, and this is very helpful for prices in other settings. Nevertheless, it is doubtful whether this actually means better or faster access for patients, given that launch prices in themselves are not necessarily a predictor of faster access. In the United Kingdom HTA via NICE or SMC is the final arbiter shaping the terms of access. Also on the negative side, rate-of-return regulation is known to be associated with an incentive to overinvest in capacity in order to capitalize on the return on captial employed formula.

Application of cost-plus pricing is very limited in Europe. Some countries used it in the past but its current application seems to be limited to Slovakia. Evidence on the ability of cost-plus pricing to achieve affordable prices is patchy, and its use as an overall pricing policy is not recommended by WHO *(25)*. The motivation behind this decision included the technical and human resource efforts necessary to apply it, the need for sound data that – if missing – might lead to biased prices and potential distortions of formulae to the advantage of the manufacturer. In addition, if applied only to a subset of

medicines and not universally, it could lead to changes in consumption patterns that might not follow rational drug use principles and might also disadvantage local industry *(25)*.

Price cuts are very straightforward to implement and offer a guaranteed and immediate return, which make them particularly useful in periods of economic downturn. They are, however, a blunt instrument as they do not take value into consideration, and if excessively used may provide a disincentive for industry to operate in certain markets.

In contrast to the pricing methods discussed above, cost–effectiveness pricing and VBP explicitly aim to link the price of a new drug to the value it delivers. Countries use different definitions of value and methods to establish a link between the two (see section 4.1.2.6). While VBP may be an appealing concept, which has attracted substantial interest in recent years, its application so far has been limited by methodological and ethical challenges. These include how to define and measure value, but also how to create a link between value and price. Value assessments are also complicated by the paucity of evidence available on effectiveness (as opposed to efficacy) at the time reimbursement decisions need to be taken. Further, external events such as the recent financial crisis have led to the prioritization of short-term fiscal imperatives – for in-patent branded drugs achieved through mandatory price cuts, increased co-payments and higher requirements to obtain reimbursement – over long-term value-based approaches. Nevertheless, a number of countries are implementing some forms of VBP approach when setting their prices (such as allowing price premiums for drugs with an added therapeutic value). Even in the United Kingdom where, on paper, VBP has not yet been introduced, patient access schemes contain elements of VBP. This is likely to lead to ICER pricing (that is, manufacturers will offer a discount just high enough to achieve an ICER within the societal willingness-to-pay threshold considered acceptable in England and Scotland).

Discussions around VBP have also highlighted its conflict with ERP *(20)*. The latter, by construction, promotes uniform or similar prices across countries, whereas VBP essentially promotes differential pricing based on the value a particular drug brings to a society. This is tightly linked with the debate around price transparency and differential pricing as instruments to enable access to new drugs in low- and middle-income countries *(121–124)*. Setting aside judgements about whether differential pricing is desirable or not, implementing differential pricing across countries will require both societal acceptance of cross-subsidizing low- and middle-income countries and confidence that industry will use this tool to offer lower prices to countries that can least afford certain drugs and not to countries with the greater bargaining power. In the EU the combination of ERP with the practice of parallel trade has acted as a deterrent to greater price differentiation between high- and low-income Member States due to the threat of export from low-price to high-price countries. EU Council Regulation 953/2003 to avoid trade diversion into the EU of certain key medicines prevents reimportation into the EU of low-cost HIV/AIDS, tuberculosis, malaria and other medicines to treat diseases affecting predominantly the developing world, but there is no such regulation preventing reimportation from lower-income EU countries to higher-income ones.

Nevertheless, EFPIA will consider differential pricing according to the wealth of different European countries provided certain preconditions are met. The suggested preconditions to enhance access to new medicines through differential pricing where this is practical and such arrangements exist include the following *(122)*:

- Any scheme should be the result of bilateral voluntary arrangements at a national level that protect the confidentiality of any net pricing arrangement.

- International reference pricing schemes should be founded on best practices to ensure consistency.
- Member States should take the necessary steps to ensure that medicines specifically priced for patient groups who would not otherwise be able to afford them are delivered to those patients and are not otherwise diverted.

As personalized medicine gains momentum, there is also discussion around differential pricing across indications *(123; 125)*. Recent evidence from OECD countries suggests that this is not happening yet *(20)*, but from a theoretical VBP perspective it would make sense, although in practice it is likely to be challenging to implement from both an operational and an acceptability perspective.

An evidence-based national reimbursement list is probably the most useful and powerful instrument to ensure monitoring of rational drug use. WHO regularly updates its model EML, which continues to serve as a key decision-making guide, particularly for low- and middle-income countries *(126)*. The same is true for the "wise list" in the Stockholm Metropolitan Healthcare Region, serving a high-income country *(113)*. High adherence rates over 80% to 90% or more are achieved through robust criteria for product selection, involvement of trusted experts and ambulatory care physicians and a comprehensive dissemination programme *(113; 127)* (see section 5.1.4). Because these lists mainly contain patent-expired medicines, however, their usefulness in guiding reimbursement decisions about new patented medicines is more limited.

For new medicines, HTA is increasingly used to guide reimbursement decisions in Europe and worldwide, in line with WHO recommendations (see section 4.2.1). Beyond its use in much of western Europe, Canada and Australia, it is increasingly used in central and eastern European countries, as well as Latin America and East Asia. HTA requires staff with training in health economics to understand and – most importantly – critically evaluate manufacturers' submissions. This can be facilitated by national academic institutions with expertise in HTA, which can serve as external reviewers and train the future generation of HTA assessors. While some countries have more mature systems, the application of HTA for pharmaceutical coverage decisions is still a relatively young discipline. It is also a very dynamic area and the subject of numerous studies striving to advance its methods. MCDA has become the subject of increasing discussion as a method to advance HTA and address some of its limitations. As yet, however, its application in pharmaceutical coverage decisions has been very limited.

Rather than a reimbursement method per se, MEAs are introduced during the HTA process as an instrument to increase access. While they have enabled access to a number of medicines that might otherwise have received negative reimbursement decisions or been subject to reimbursement delays, they present some limitations. A number of these have already been discussed in the literature (free rider problems, distorting prices, management burden and similar), but one issue that has received less attention so far is the impact of price confidentiality on priority-setting and the development of clinical guidelines *(128)*. In settings where the development of clinical guidelines uses the ICER as a priority-setting criterion and the discount-adjusted ICER is publicly known (see section 4.2.1.1), this does not distort priority-setting. But if the ICER is not discount-adjusted, or priority-setting is based on list prices, this can lead to distortions. Even if the discount-adjusted ICER is available, future HTA submission using a confidentially discounted medicine as comparator still faces the issue of not knowing the actual price with which they should compare their product in the HTA submission *(128)*.

Similar issues affect rebates, payback and clawbacks. Even if these are not necessarily confidential, particularly paybacks and clawbacks, their impact on expenditure is unknown at the time reimbursement decisions are made and is therefore not incorporated into the HTA assessment.

Further, clawbacks can be resource-intensive to implement and may need to rely on pharmacists and wholesalers reporting the actual rebates received. It is also suggested that incentivizing lowest cost products may implicitly promote parallel trade *(14)*.

Countries generally use more than one method to inform their pricing and reimbursement negotiations, and in practice there is overlap between different methods. Countries like Belgium and Spain, for instance, use budget impact and HTA criteria, among the others, when making reimbursement decisions. At the same time they also use ERP and elements of VBP in their pricing decisions. The extensive use of ERP has made the industry reluctant to lower list prices to avoid to low-price spillover to other markets. This has several implications. In countries using a relatively explicit willingness-to-pay threshold like the United Kingdom, making a positive recommendation for drugs with an ICER above societal willingness to pay is very unlikely, although it can happen *(51; 129)*. In this context, patient access schemes have served as a tool to obtain lower prices – and therefore lower ICERs – without intervening onlist prices. This obviously distorts ERP practices, which therefore unavoidably rely on unrealistic prices. This is also likely – although it is very difficult to prove due to confidentiality around discounts – to put small and economically less attractive markets in a disadvantaged position, as they will be less able to obtain the same discounts as larger and wealthier countries.

In any event, new models are urgently needed with recent events. These include trastuzumab emtansine which, while increasing median survival by nearly six months in patients with human epidermal receptor 2 (HER2)-positive metastatic breast cancer no longer responding to trastuzumab and a taxane – to be welcomed – currently has an estimated cost of £185 600 per QALY gained *(51; 129)*. Pressure is being put on European governments to fund trastuzumab emtansine, potentially raising the cost-per-QALY threshold for new cancer treatments *(51)* (see section 6.1). New medicines for hepatitis C (such as sofosbuvir), while potentially providing a cure, are also challenging health care systems. In the United States alone it has been estimated that funding all potential patients with sofosbuvir will double annual drug expenditure for a single drug *(130)* (see section 6.3). The funding by NHS England of ivacaftor – a new orphan drug for treating patients with cystic fibrosis who carry the genetic mutation G551D in the cystic fibrosis transmembrane regulator gene – at a cost per QALY between £335 000 (optimistic scenario) and £1 274 000 (conservative scenario) has put pressure on other regions in the United Kingdom and other countries to fund ivacaftor at these levels *(51)*. This potentially again sets a new threshold level for new orphan medicines (see section 6.4). Finally, funding new premium-priced medicines for patients with type 2 diabetes will also be a challenge, given the growing prevalence of type 2 diabetes and obesity *(51; 131)*.

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5. Post-launch activities

5.1. Guidelines and formularies

Evaluation of existing evidence on the risk–benefit profile of medicines is a prerequisite for every activity within health services aimed at promoting the appropriate and efficient use of medicines, on either the supply or the demand side. These activities are carried out by committees defining which medicines can enter formularies, which can participate in tenders for drug procurement (for either inpatient or outpatient use) *(1)* and which should be recommended within clinical practice guidelines (CPGs). Dedicated resources and strong methodological competencies are necessary, considering both clinical expertise and skills in the systematic assessment of the available evidence. In addition, robust conflict of interest criteria need to be ensured. Specific examples of these activities are provided in the following subsections.

5.1.1. CPGs

CPGs are information support tools. They are generally used to facilitate physicians' clinical decisions on the appropriate treatment of a medical condition, but their methodology can be used to promote the appropriate use and introduction of single new drugs and medical technologies. Compliance with CPGs can also serve as a benchmark for appropriate health care *(2)*.

Evidence-based CPGs are meant to promote interventions better supported by evidence with a favourable risk–benefit profile, possibly demonstrated by a number of randomized trials and long-lasting experience in clinical practice (observational data). For these reasons, therapeutic guidelines are (or should be) necessarily cautious with new medicines, when older – and generally less expensive –alternatives are available: the latter have generally been studied more extensively and are better supported by randomized controlled trial or observational data. In addition, when this methodology is used to assess the effectiveness and safety of new single new medicines or other health technologies, an evidence-based comparison with existing alternatives should be provided, if available, so that the added value of the intervention can be appraised and its therapeutic role better defined.

To develop evidence-based CPGs, multidisciplinary panels representing the main stakeholders should make a systematic assessment of the available evidence *(3)* and use a transparent methodology for making recommendations. Methods for deriving CPGs have evolved over the past 20 years. Among these, the Grading of Recommendations Assessment, Development and Evaluation Network (GRADE) approach has gained prominence in the last decade *(4)*, and is currently used by a number of organizations developing guidelines. These include WHO, the Canadian Agency for Drugs and Technology in Health, the United Kingdom's NICE, and the Agency for Healthcare Research and Quality and the Centers for Disease Control and Prevention in the United States. The GRADE methodology is also employed by scientific societies such as the American College of Physicians, the American Thoracic Society and many other groups.

Through a transparent process, the GRADE approach allows guideline panels to assess systematically the quality of evidence, including study design and quality, consistency, precision and generalizability of study results and reporting bias (see Fig. 4). It also allows them to assess the balance between desirable and undesirable effects on the outcomes chosen, taking into account the patients' values and preferences and resource implications (see Fig. 5).

Fig. 4. GRADE quality assessment criteria

Study Design	Quality of Evidence	Lower if	Higher if
Randomized trial ⇒	High	Risk of bias -1 Serious -2 Very serious Inconsistency -1 Serious -2 Very serious Indirectness -1 Serious -2 Very serious Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	Large effect +1 Large +2 Very large Does response +1 Evidence of a gradient All plausible confounding +1 Would reduce a demonstrated effect or +1 Would suggest a spurious effect when results show no effect
	Moderate		
Observational study ⇒	Low		
	Very low		

Source: adapted from Guyatt et al. *(5)*.

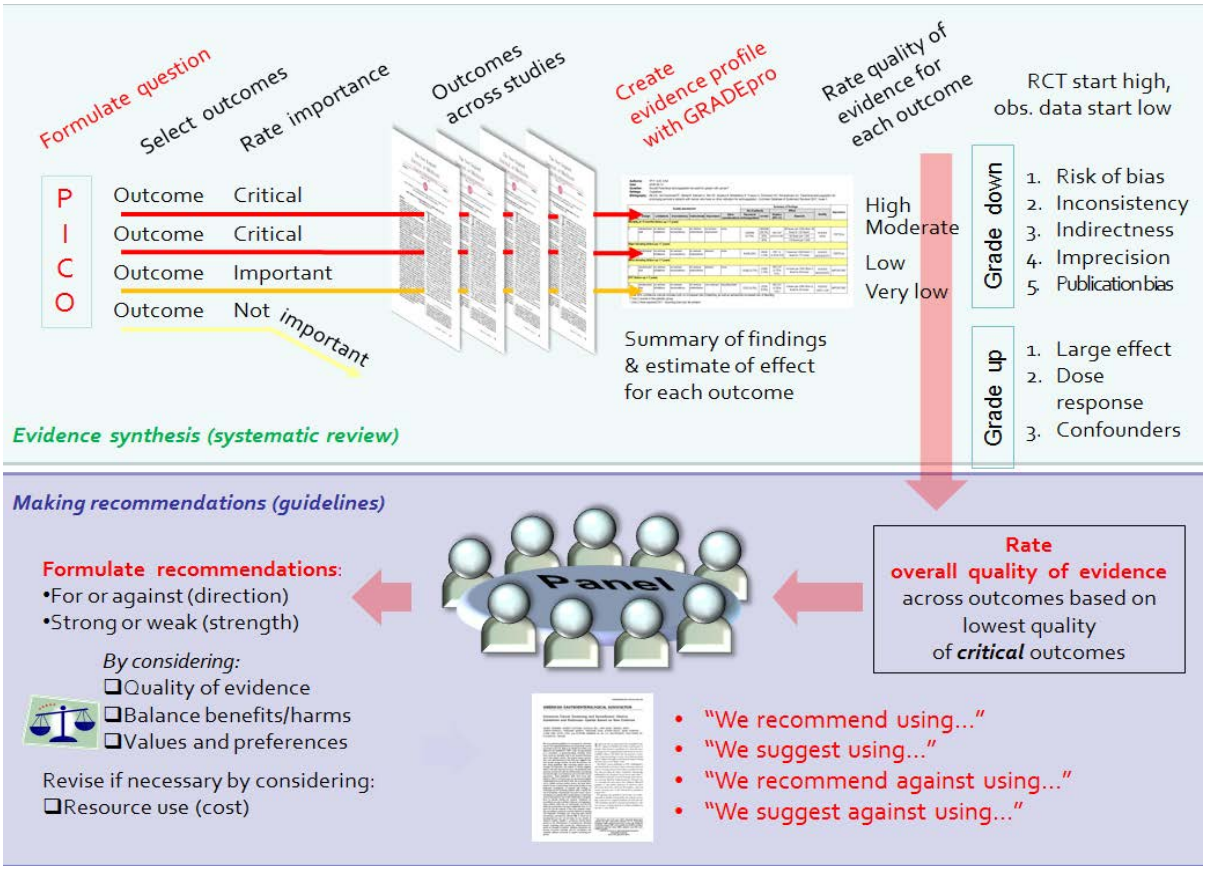
Fig. 5.Determinants of strength of recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted.
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted.
Costs (resource allocation)	The higher the costs of an intervention – that is, the greater resources consumed – the lower the likelihood that a strong recommendation is warranted.

Source: adapted from Guyatt et al. *(6)*.

Panel members can then express their judgement on the strength of recommendations, considering each of those elements (see Fig. 6). Recommendations are categorized as strong (the desirable effects of adherence to a recommendation outweigh the undesirable effects – most of the targeted patients should receive the intervention) and weak (the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but we cannot be confident). They can be either in favour of or against the intervention. Strong recommendations could be used to derive performance indicators. The overall process should be made explicit within the guideline.

Fig. 6. GRADE – the overall framework



Source: McMaster University *(7)*.

The development of CPGs requires dedicated resources and competencies. Some European Member States have organizations that develop national guidelines and recommendations, such as the Haute Autorité de Santé (National Authority for Health) in France, the Agency for Quality in Medicine in Germany, the Scottish Intercollegiate Guidelines Network and NICE in the United Kingdom. At the regional or local level, or in countries with limited capacity where the necessary resources may not be available, a reasonable alternative is to use, adapt or integrate existing national or international guidelines – those produced by the corresponding national authority, a recognized authority from another country or other organization – to the local context *(8)*. This avoids duplication of work, although a multidisciplinary assessment would still be necessary to ensure adaptation to local needs and concerns. Using CPGs to decide on the therapeutic role of a new medicine can have an impact on its reimbursement status (rather than on different management strategies of a disease) and the overall process is generally less burdensome as fewer studies are available to evaluate.

Development or adaptation of CPGs does not guarantee their adoption. An implementation plan should also be developed, considering possible barriers to and facilitators of their use within health services. In this regard, stakeholder involvement from the development phase of the clinical guideline onwards is a key aspect that helps to identify possible implementation barriers and increases ownership among participants *(9)*. Subsequently, a transparent process – as in the GRADE approach – can help ensure acceptance of the recommendations and is ethically desirable: starting from specific questions, clear recommendations should be developed after evaluating the overall risk–benefit profile within the context of implementation. The GRADE approach also addresses conflicts of interest, which is important since in a recent study of 288 panel members taking part in the production of guidelines

for hyperlipidaemia, diabetes or both in Canada and the United States, 52% were found to have conflicts of interest, of which 138 were declared and 12 undeclared *(10)*. Of the 14 guideline panels evaluated, 12 identified chairs, among whom six had financial conflicts of interest. Panel members from government-sponsored guidelines were less likely to have conflicts of interest.

Defining the strength of each recommendation helps with assessment of what could be expected from their implementation, prioritization of the circumstances in which the interventions should be used and derivation of indicators of health care quality. Of course, such a shared and transparent process should be incorporated within clear and usable documents *(11)*.

Expected use of a drug should be related to the strength of recommendations. While the implications of a "strong recommendation" are clear (most of the targeted patients should receive/not receive the intervention, and are actually expected to get/not to get it), the same cannot be said for weak recommendations. For these the elements considered should be as explicit as possible so that their potential range of application can be better defined and eventually monitored. Table 7 shows an example often presented to groups in the Emilia-Romagna Region of Italy for reference regarding what "strong" and "weak" recommendations imply in terms of their subsequent expected use.

Table 7. Strength of recommendations and expected use (GRADE)

Strength	Definition and implications	Expected use
Strong positive	The drugs/interventions should be offered to the vast majority of patients and could be used as an indicator of good quality of care. This does not mean, however, that all patients should receive the treatment.	Almost always
Weak positive	This has a wider range of uncertainty, since it could mean only for a minority of patients (30%) or for a good proportion of them (50–60%). It is necessary to inform patients of the expected benefits and risks (and their magnitude), explore patients' values and discuss potential alternative treatments.	30–60%
Weak negative	The drugs/interventions should be used in selected cases or a defined minority. The decision should go along with detailed information to patients of the benefits and risks (and their magnitude), taking into account patients' values and expectations and discussing potential alternative treatments.	5–30%
Strong negative	This should not be used either routinely or for a subgroup – only in a few selected cases. Its use should be documented, since the benefit/risk balance is negative and potential alternatives are preferable.	Only used in exceptional cases

5.1.2. Example application of the GRADE approach to define drug therapeutic role and use

Use of the GRADE methodology is not limited to the development of national or international guidelines: it can also be applied in a regional or local context to make decisions on the appropriate introduction and use of drugs. A relevant example in this regard is provided by the DTC of Emilia-Romagna, a region in northern Italy, where a specific subgroup was created to address the therapeutic role of cancer drugs. This multidisciplinary group – with representation from oncology, radiation therapy, palliative care, internal medicine, pharmacy and health services management – has been

working to develop evidence-based recommendations by applying the GRADE approach since 2006 *(12)*. The working method has been progressively refined, shortening the time requested for the production of recommendations from 12 to 3–4 months when rapid assessment of specific indications for single drugs is required. This is seen as an acceptable compromise between the need for in-depth analysis that can be shared with the main stakeholders and the need to make rapid decisions to support clinical practice.

The three key phases of the GRADE process (formulating the question and choosing outcomes of interest; evaluating benefits and risks; and defining the strength of recommendations according to the quality and weight of evidence, assessing patients' values and preferences and resource use and feasibility) have been shown to be compatible with such a time frame. The fact that new "innovative" medicines including new cancer drugs often have few studies available to be assessed also makes the time frame feasible. The rapid processes are supported by expert methodologists from the WHO Collaborating Centre for Evidence-Based Research Synthesis and Guideline Development, which is based in the region. Short documents (about 10 pages long) explain the process leading to "graded" recommendations, which are synthesized with clear statements and visual aids. In particular, ratings and votes on the risk–benefit profile are shown (those deemed favourable, uncertain and unfavourable by the panel) and an indicator of the expected applications is defined for each recommendation. Table 8 gives an overview of cancer drugs for which recommendations were issued between July 2009 and January 2014.

Table 8. Cancer drugs with recommendations for use produced in Emilia-Romagna using the GRADE approach

Area (metastatic disease)	Drug	Date of issue
Colon – rectal cancer	Bevacizumab	March 2010
	Cetuximab	March 2010
Breast cancer	Bevacizumab (first line)	July 2011
	Eribuline (third line)	July 2012
	Everolimus (advanced cancer)	September 2013
Renal cancer	Sunitinib	October 2010
	Temsirolimus	October 2010
	Bevacizumab	October 2010
	Sorafenib	October 2010
	Everolimus	October 2010
Lung cancer	Gefitinib (first and second line)	July 2011
	Erlotinib (second line)	July 2011
	Erlotinib (first line)	September 2013
	Bevacizumab	July 2009
	Permetrexed	July 2009
Gastric cancer	Trastuzumab (first line)	July 2011

Area (metastatic disease)	Drug	Date of issue
Urologic neoplasms	Vinflunine (second line)	September 2011
Thyroid cancer	Vandetanib (first line)	December 2013
Chronic myelogenous leukaemia	Nilotinib/dasatinib (first line)	December 2011
Multiple myeloma	Liposomal doxorubicin	October 2010
Idiopathic thrombocytopenic purpura	Romiplostim/eltrombopag	September 2011
Gynaecological cancers	Bevacizumab (first line)	September 2013
Prostate cancer	Abiratenone (second line)	April 2013
	Cabazitaxel (second line)	April 2013
Solid tumours with bone metastases	Denosumab	January 2014
Head and neck cancer	Cetuximab (first line)	February 2012
Malignant melanoma	Ipilimumab (first and second line)	April 2013
	Vemurafenib (first and second line)	April 2013
Myelodysplastic syndrome	Azacitidine (first line)	September 2011
Follicular lymphoma	Ibritumumab tiuxetane	June 2012
Mantle cell lymphoma	Temsirolimus	June 2012

Source: Agenzia sanitaria e sociale regionale – Regione Emilia-Romagna *(13).*

A subset of the Table 8 recommendations was evaluated for the frequency of "strong" and "weak" recommendations. Of 34 recommendations, 20 were graded as weak (evenly split between positive and negative) and 14 strong (2 positive and 12 negative). This suggests that, despite claimed innovations, the clinical benefits to patients of new cancer medicines are often very modest and the evidence base on which to judge them is quite limited. The adoption rate of all 34 recommendations was monitored and was mostly within the range of expected values (see Table 9).

Table 9. Evaluation of adoption rates of a subset of recommendations on cancer drugs

Strength	Expected adoption rate	Number of recommendations formulated	Recommended adoption rate (Number of recommendations)
Strong positive	>60–70%	2	>60% (1) ~70% (1)
Weak positive	30–60%	10	60–70% (1) ~50% (1) ~50% in second line (1) 50–60% (2) 30–50% (2) 20–50% in second line (1) 15–20% in second line (1) 15–20% in third line (1)
Weak negative	5–30%	10[a]	10–20% (4) 5–20% (1)
Strong negative	<5%	12	<5% (12)

[a] For five recommendations it was not possible to define an expected adoption rate.

5.1.3. Implementation of evidence-based information

The relevance of implementation plans is highlighted by many organizations dealing with guideline production *(14–17)*. Nevertheless, data are lacking on implementation activities and their effects on subsequent clinical practice. This kind of information on implementation and evaluation mostly relies on single groups of keen researchers, rather than being part of a continuous evaluation framework.

A recent systematic review addressed the effectiveness of implementation strategies of CPGs for the management of chronic diseases at primary care level in the EU *(18)*. Only a few rigorous studies seem to have assessed this in Europe, with inconsistent results as to which is the most appropriate. Multifaceted strategies may be more likely to be effective, but this conclusion is still not adequately supported by evidence. Table 10 lists the strategies described in the evaluation studies assessed (please refer to the publication for details of the specific studies).

Table 10. Interventions used to enhance the implementation of guidelines in the EU

Implementation strategy	Number of studies
Feedback report	9
Educational materials for GPs	8
Interactive workshops	8
Outreach visits	5
Dissemination of guidelines	3
Formal training	3
Structural interventions	2
Educational materials for patients	2
Small seminars	1
Reminders sent to GPs	1
Computerized decision system	1

Source: adapted from Brusamento et al. *(18)*.

Other systematic reviews – particularly several Cochrane reviews – have examined the impact of activities such as educational outreach visits *(19)* and of audit and feedback *(20)* to support the implementation activities of CPGs and other information material. These interventions require supporting materials that are clear and concise (guidelines, prescribing reports and other information) and specifically targeted at practitioners, and that address known barriers to uptake and acceptability of information *(21)*. Discussion in small groups may facilitate a shared analysis of the therapeutic role of drugs, prescribing data and putting recommendations into practice *(22)*, and may ultimately reduce inappropriate prescribing. In general, the potential of these and other approaches depends on the ability to analyse and address existing barriers in order to define an optimal strategy tailored to local contexts *(23)*. The configuration of health services, available resources and skills, access to resources and attitudes of local practitioners and local opinion leaders are key aspects to consider. It should also be kept in mind that a transparent process, as seen for the GRADE approach, can favour understanding and acceptance of recommendations and identification of appropriate indicators to monitor implementation *(24)*.

It is worth noting that an ongoing European collaborative project called Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence (DECIDE), financed through the EU's Seventh Framework Programme, is specifically aimed at improving the dissemination and uptake of evidence-based recommendations, building on the work of the GRADE Working Group. Through several working packages, the project is developing and evaluating strategies

for disseminating and supporting the uptake of guidelines by the key stakeholders who determine what happens in clinical practice: health care professionals, policy-makers and managers, patients and the general public *(25)*.

5.1.4. Formularies/EMLs

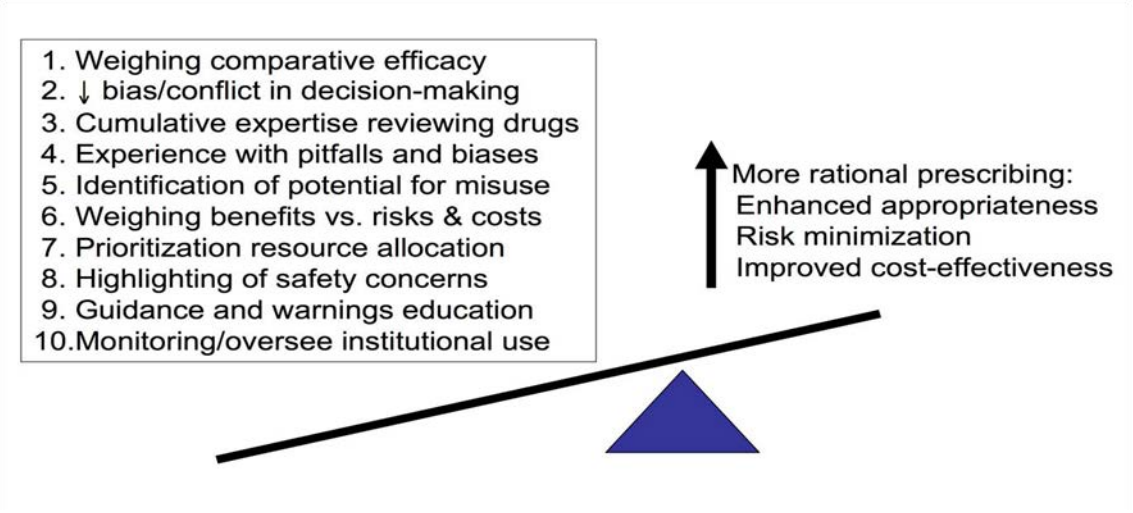
DTCs select medicines to be listed in drug formularies, deciding which can be reimbursed (mostly at the national level), which should be available for local (mostly inpatient) use and which therapeutic role they could have. WHO recommends the establishment of DTCs in hospitals to oversee the selection of drugs, in order to enhance the rational use of medicines and other medication-related activities *(26)*, with scholars providing examples of implementation where activities have been limited *(27)*.

In addition, the WHO model EML is updated and revised every two years and serves as a guide for the development of national and institutional EMLs *(28–29)*, some of which are more inclusive and have a wider range of coverage. Decisions made by DTCs affect drug prescription directly or indirectly. As discussed in a recent study:

> At their best, as vehicles and venues for identifying, weighing, and designating best evidence, formularies can assess, teach, and guide prescribing towards the most appropriate and evidence-based choices, helping to direct use towards the most efficacious, safest, and cost-effective therapies, while serving as a firewall to protect against prescribing overly driven by marketing claims. Through the decision-making activities of the formulary process, knowledge and leverage may be applied to enhance prescribing practices and patient outcomes in ways that go beyond initial regulatory approval and individual prescribers' ability to weigh the role and value of new medications.

Schiff et al. *(30)* (see Fig. 7).

Fig. 7. Leveraging formularies for improved prescribing



Source: Schiff et al. *(30)*.

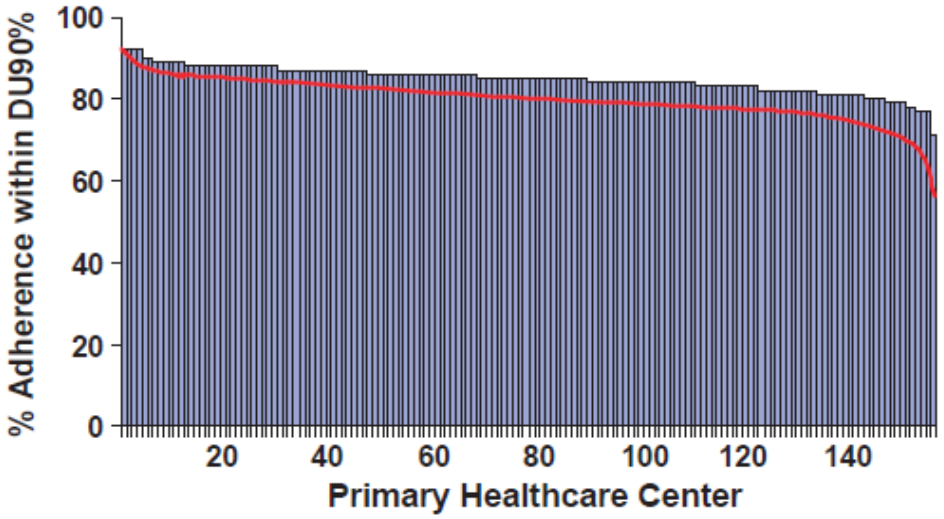
In other words, formularies should not be considered just closed lists of those medicines that can be prescribed or supplied: more "inclusive" formularies can also be used to define and prioritize the therapeutic context of drug use. In addition, in closed formularies decision-makers can restrict choices of medicine to one or two options out of several. To this end, the DTC of the Emilia-Romagna region engaged a few subgroups – in addition to the subgroup on cancer drugs – to address the appropriate

use of medicines in specific clinical areas such as diabetes (incretins), cardiovascular diseases (angiotensin-converting-enzyme inhibitors, sartans, statins), clotting disorders (antithrombotics, new oral anticoagulants) and infectious diseases (in particular hepatitis B and C). Guidelines were produced on each of these topics to define the most appropriate use of these drugs and to make the process leading to specific recommendations more explicit.

Development of EMLs using robust criteria improves physicians' familiarity with drugs with the best defined risk–benefit profile, thereby improving patient outcomes and reducing potential adverse effects. Physicians generally know a number of drugs well, and presenting them with a wide selection runs the risk of increasing unfamiliarity with prescribing choices, potentially leading to underdosing or to an increase in adverse drug reactions and drug–drug interactions. Potentially poorer outcomes can also occur from using new medicines with only limited data or greater uncertainty in patients in routine clinical practice as opposed to well established medicines with proven outcomes and known side-effects *(31)*. Established medicines also tend increasingly to be generics, improving their estimates of cost–effectiveness and reducing budgetary impact, thus helping the cost-effective use of available resources *(32–34)*.

These considerations were behind the generation of the "wise list" in the Stockholm Metropolitan Healthcare Region, which contains approximately 200 drugs, including first- and second-line choices, covering most needs in ambulatory care *(34)*. An additional 100 drugs are included in a separate list but reserved for common needs in specialist and outpatient care. The list was extended to cover the hospital sector in 2009. High adherence rates to this voluntary formulary (see Fig. 8) are enhanced by the involvement of prescribers in the selection process, a comprehensive communication programme including a separate list for both patients and physicians, physician trust in the guidance and regular feedback *(34–35)*. Increased adherence also reduces costs *(36)*.

Fig. 8. Physician adherence rates to the "wise list" in the Stockholm Metropolitan Healthcare Region, 2009



Note: the red line was the adherence rate of the same practices in 2003.

Sources: adapted from Gustafsson et al. *(34)*; Bjorkhem-Bergman et al. *(35).*

Physician trust is enhanced by a comprehensive approach to conflicts of interest, the proven competency of the 23 expert groups developing guidance for each disease area and the training of

expert group personnel in critical drug evaluation skills by clinical pharmacologists working at the Karolinska Institutet, Stockholm, Sweden *(34–35)*. In addition, robust evidence-based principles are promoted for drug selection for both new and established drugs, including cost–effectiveness criteria (see Table 11).

Table 11. Criteria and key questions for drug selection in the "wise list"

Criterion for drug selection	Question typically posed by DTCs in the Stockholm Metropolitan Healthcare Region when reviewing new medicines for possible listing
• Efficacy and safety – these are based on available evidence, preferably including data from randomized controlled trials as the highest level of evidence to answer a series of prespecified questions. • Pharmaceutical suitability – this includes formulations, strengths and pharmacokinetic properties. • Efficiency – this is mainly based on comparative reimbursed prices and the overall budget impact of the medicine compared with alternatives. Use of cost–effectiveness data in decision-making is currently limited in the regions, especially as TLV does not consider the budget impact of drugs in its deliberations. • Experience – this is mainly concerned with drug safety. Recommended medicines should generally have been available for at least two years; however, newer medicines can be included if they have been shown to improve care under evidence-based medicine rules and no major concerns exist with their safety. • Environmental aspects – if medicines are considered similar based on available evidence and are similarly priced, environmental considerations guide choices.	• What was the main scientific question posed? • How was patient selection and diagnosis conducted? • What patients were included in the control groups and what type of study was conducted – e.g. crossover, parallel, placebo controlled, etc.? • Was the study double-blinded, single-blinded, etc.? • How was the randomization conducted? • What about the pharmacokinetics of the new medicine? • Are concomitant medications documented and valid? • Are the drug effects well defined, relevant and reproducible? • Are adverse events well studied and described? • How appropriate was the statistical design and evaluation of the results – was this adequate? • What about measures such as absolute risk reduction – can this be calculated? • Were the conclusions of the studies adequate, doubtful, irrelevant?

Sources: adapted from Gustafsson et al. *(34)*; Godman et al. *(37)*.

5.2. Interface management

Health care and pharmaceutical systems are organized into two distinct sectors: outpatient (ambulatory – in some countries also called the primary care sector) and inpatient (hospital setting). Patients, and their treatments, are shifted between the two sectors as required. Frequent shifting, however, is not desirable, with potential negative effects on health and social outcomes, as well as overall costs *(35; 38–41)*. For instance, it may increase the risk of medication errors and drug–drug interactions. It also carries challenges around the sharing and transfer of patient information and records. For patients themselves, especially if the reasons are not well explained, this can affect their health status and recovery; it can also contribute to their reporting a negative experience with a health system.

5.2.1. Challenge of patients transitioning between care settings

Shifting treatments and patients between sectors is mainly attributable to the different focus of treatment in each sector, since for specific indications either the outpatient or the hospital sector is considered the best point of service, in line with the country-specific understanding of organizing health care. For example, in some countries the hospital is considered the sole point of care for a specific treatment – such as breast cancer treatment – whereas in other countries the same treatment is typically provided in outpatient care *(42–43)*.

In addition, the shift is also incentivized by national organizational structures and funding models. Medicines management in the outpatient and inpatient sectors fall within the remit of different administrations in most European countries. They apply different funding models and even have different payers in some countries, particularly in those countries with a social health insurance system *(44–45)*. This incentivizes (public) providers to shift treatments and patients in order to minimize their own costs. This approach appears rational from an individual payer's perspective, since each purchaser (social health insurance, hospital pharmacy and so on) is responsible for its own budget, but it has negative implications for quality and does not necessarily contribute to overall savings in the health care system *(38–39)*. In fact, it may increase overall costs for the health care system if patients are discharged from hospital on inappropriate premium-priced medicines, with the ambulatory care sector subsequently bearing the costs *(35)*.

New high-cost medicines, owing to their budget impact, are among those most frequently targeted by such shifting efforts. New premium-priced high-cost medicines are often provided to hospitals without any price reduction (although many do have a compulsory discount for hospital-administered drugs compared with their outpatient equivalents). On the other hand, discounts, rebates and similar price reduction arrangements are likely to be granted to hospitals for medicines for which therapeutic alternatives (such as generics) exist and which are of strategic importance – that is, they are typically applied for long-term use in the outpatient sector, such as cardiovascular medicines *(44; 46–48)*. In the outpatient sector, however, high-cost medicines are often covered by discounts, rebates, PVAs and other MEAs between public payers and industry *(49)* (see section 4.2).

5.2.2. Policy options – selected country examples

To address these challenges, a more coordinated approach, an integrative system perspective, different funding models and better cooperation at the interface of outpatient care and hospitals are needed. Such mechanisms of cooperation between the hospital and outpatient sectors are summarized by the term "interface management" *(35; 50)*. Similar notions are seamless care, integrated care (comprehensive care, transmural care) and continuity of care *(51)*.

A number of initiatives and activities can be launched by actors in the system – such as hospitals, GPs and community pharmacies – to improve cooperation at the interface of the outpatient and hospital sectors. A survey on such measures in seven countries (Australia, Canada, Denmark, France, the Netherlands, the United Kingdom and the United States) shows that several activities have been initiated *(38)*. Among the most frequently implemented measures focused on hospital discharge were:

- communication of discharge information to GPs and community pharmacists (for example, sending medication discharge plans to GPs and community pharmacists);
- education and counselling of patients before discharge (for example, predischarge pharmaceutical counselling, proactive programme of discharge);

- education and counselling of patients at and after discharge (for example, community liaison services, home visits by a health visitor 72 hours after discharge, follow-up phone calls by pharmacists two days after discharge);
- so-called "complex interventions" involving patients and health care professionals (a combination of patient education and counselling).

The most frequently reported interventions at admission and discharge were *(38)*:

- a medication liaison service between hospitals and GPs or community pharmacists;
- computer-based interventions (for example, computer-generated medicines lists in hospitals, electronic communication between GPs and local pharmacies to transfer data about prescriptions, a computerized medication reconciliation tool and process redesign involving physicians, pharmacists and nurses).

At the same time, the cost–effectiveness of these interventions has been evaluated only in a few cases *(52)*.

In addressing the issue of shifting patients and treatments among settings – particularly those related to high-cost medicines – individual initiatives (micro level) are not sufficient, and more fundamental changes in the organizational structure and funding models of the pharmaceutical system (macro level) are required. According to a survey of competent authorities for pricing and reimbursement and hospital pharmacists from 27 European countries (25 EU Member States, Norway and Turkey) undertaken in 2011 and repeated in 2012, 17 countries reported interface management activities. Measures included joint reimbursement lists; coordination of hospital drug formularies with lists of recommended medicines in primary care; joint development of recommendations or guidelines; joint and hospital DTCs with a representative from social health insurance; (obligatory) transfer of information on pharmacotherapy between sectors, including IT solutions; patient education and counselling; special funding schemes and financial incentives for cooperation projects; pharmacy liaison services; hospital discharge programmes; and medication reconciliation. These cover measures at both macro and micro levels *(53)*. Considering even more recent developments, including the results of a PPRI query on high-cost medicines (see Annex 1), European countries have opted for the following policies.

5.2.2.1. Joint reimbursement lists and DTCs

The health care system in the United Kingdom is devolved: different systems are in place in England and Wales, Northern Ireland and Scotland. Scotland has a long tradition of an integrated pharmaceutical system; a joint list of recommended medicines for the outpatient sector and hospital care has been present for over 20 years. In the DTCs physicians from both settings are involved in developing joint guidance and guidelines and the formulary guidance applies to both sectors. Nonformulary prescribing has to be justified *(35; 54–55)*. In England discharge notes that follow patients from inpatient care to the community are compulsory.

The Stockholm Metropolitan Healthcare Region also has a joint list for both sectors, which is decided by a joint DTC consisting of experts, clinicians and researchers who cover all major pharmacotherapeutic areas. This "wise list" contains recommendations for medicines. It does not cover all medicines considered reimbursable by the competent federal authority, but a selection; it is updated every year. While the "wise list" was first introduced in 2000, accompanied by a comprehensive communication, monitoring and evaluation process, it was only extended to cover the hospital sector in 2009 (see section 5.1.4 for further details). Other regions in Sweden have similar initiatives but Stockholm's is considered to be the most advanced *(34–35)*.

5.2.2.2. Funding mechanisms

In France outpatient medicines are funded by social health insurance, in principle, while medicines in hospitals are funded from the hospital budget. Lists of medicines from the hospital setting, however, are also funded by the social health insurance. The so-called "supplementary list" contains high-cost medicines, particularly anticancer medicines, blood products, OMPs and some treatments for rheumatoid arthritis. Medicines on this list are excluded from the diagnosis-related group (DRG) funding system applied in hospitals; they are funded on a product-specific basis by the social health insurance a differing rates. If the hospital meets its objectives for the use of these drugs they are 100% reimbursed, according to the "contrat de bon usage" (a good practice agreement between the hospital and its regional health agency), but this can be reduced to 70% if the hospital does not meet its objectives. If the hospital does not have a "contrat de bon usage" with its regional health agency, these drugs are reimbursed at 70%. Another list of "reassigned medicines" may be dispensed to outpatients by hospitals. They are 100% reimbursed by the social health insurance *(56–57)*.

The Netherlands had a similar system from 2006 to 2012. The Dutch Health Care Authority drew up lists of OMPs and of high-cost medicines. One criterion for the list of high-cost medicines was that they amounted to more than 0.5% of the total pharmaceutical expenditure inside hospitals. If used in a hospital setting, the OMPs were 100% and the high-cost medicines were 80% reimbursed by social health insurance. It was argued that the remaining 20% should be paid by the hospitals to incentivize hospitals to use these medicines in an efficient way *(58)*. At the beginning of 2013 this system was abolished, and the use of high-cost medicines by hospitals is now fully reimbursed by the health insurer, as an add-on to a DRG (see Annex 1).

In Norway hospitals pay for specific medicines such as TNF alpha inhibitors (since 2006) and medicines for the treatment of multiple sclerosis (since 2008) that patients need after discharge from hospital *(59–60)*.

In Slovenia high-cost medicines (such as infliximab, rituximab, alemtuzumab and docetaxel) are not part of the hospital budget. The health committee evaluates high-cost medicines on a case-by-case basis and prepares a proposal on whether to finance them for inpatient treatment (covering financing of certain indications for a determined number of patients by a certain scheme in a specific hospital; for example, a university hospital or specialized hospital). The final decision on the financing of high-cost medicines for hospital use is made by agreements between representatives of hospitals, the Health Insurance Institute and the ministry of health. On the basis of these annual agreements, the Health Insurance Institute finances the specific high-cost medicine for a specific hospital *(61)*.

5.2.2.3. Cooperation structures and electronic systems

In Austria, following a legal change, outpatient sickness fund representatives are members of hospital DTCs. Although they have no voting rights, the exchange of information and the learning gained about the positions of actors in the "other" sector was reported to be very valuable to all involved *(62–65)*. A medicines commission was also established in 2014 to decide on the best point of service for high-cost and specialized medicines *(66)*.

In England health economy prescribing committees (or area prescribing and medicines management committees whose "member" organizations are outpatient and hospital care purchasers and providers) can be used as forums to resolve issues around medicines safety and use *(67; 68)*.

In Catalonia (Spain) routine information processing; scorecard evaluation; benchmarking; data diffusion; technical discussions with physicians, pharmacists and hospital managers; follow-up and contracts around the selected indicators of medicine use (indication, selection, duration); bilateral agreements; continuous monitoring; and budget allocation take place. The Catalonian electronic systems permit sharing of clinical data between outpatient and hospital medical records. This allows GPs to request the rationale behind a given prescription from specialists, especially if concerns exist with a recommendation against agreed guidance *(35)*.

5.2.2.4. Growing awareness and challenges

Outside Scotland, a number of policies addressing the challenge of improving medicines management at the interface of outpatient and hospital care have been implemented only in recent years. It appears that awareness of this issue has predominantly been raised during the last decade. This is attributable to the different responsibilities for the settings: in many European countries competent authorities for pharmaceutical pricing and reimbursement policies are responsible for outpatient policies and tend not to be very familiar with the inpatient sector *(44)*. This was highlighted as a result of the PPRI project, which established a network of competent authorities *(45)*. In a subsequent project, the Pharmaceutical Health Information System (PHIS) *(69)* looked at procurement and financing of medicines in European countries, an under-researched topic; this identified the urgent need for interface management, including a need for learning from good practice examples. Two events (a PPRI conference in 2011 and a seminar on interface management in Stockholm in 2012 *(35)*) followed up on this topic and contributed to further awareness-raising.

Several studies have stated that the need for improved interface management has been increasingly understood, but that well documented good practices appear to be limited *(35; 44–45; 47; 53)*. While this continues to be the case, at the same time more and more countries are addressing the issue, taking different approaches. Dual financing is a major barrier for successful interface management. Approaches such as those implemented in Scotland and Stockholm, which aim to address the dual funding logic, are likely to be supportive of improving access to medicines: these no longer incentivize individual payers and procurers to pay attention to the sector for which they are responsible but to look at the impact of their decisions on all sectors *(70)*. Subsequent decisions could be further incorporated into the development of quality indicators for new medicines *(71)*.

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6. Impact of policies on funding and use of new drugs – some examples

To demonstrate the issues covered so far in this report, a select number of practical examples are highlighted in the following sections as case studies. They reflect important areas (in terms of disease burden and cost) where new premium-priced medicines are coming onto the market and policy-makers are faced with difficult choices across the policy intervention continuum: cancer medicines, TNF inhibitors for arthritis, therapeutics for hepatitis C, new orphan drugs and diabetes.

6.1. New medicines for patients with cancer

Cancer is one of the most important and expensive NCDs facing health care systems *(1–2)*. It is a leading cause of death globally, and is currently the second most common cause of death in the EU *(3–5)*. In 2008 in the (then) 27 countries of the EU 2.45 million people were diagnosed with cancer *(6)*.

Two facts appear indisputable for the future. First, more can be done by countries to diagnose and manage most types of cancer, including prevention *(1; 7)*. Second, the cost of cancer care has risen appreciably in recent years, and is projected to increase at an unsustainable rate if left to pharmaceutical companies, with the prices of new cancer medicines increasing up to 10-fold during the past 10 years and likely to continue *(8–9)*. As a result, continued access to cancer care is under threat unless addressed *(1; 9–11)*.

The worldwide cost associated with new cancer cases was estimated at US$ 286 billion in 2009, with medical costs making up more than half of the economic burden *(2)*. It has been suggested that pharmaceuticals currently account for approximately one quarter of total medical costs, although this varies considerably across Europe *(6; 8)*. It is estimated that the number of newly diagnosed cancer patients will grow from 12 million each year worldwide to 20–27 million by 2030 *(11)*. Treatment protocols are likely to become more complex and so is the appreciable cost of new cancer drugs, often with only minor clinical benefits (see Table 12) *(2; 7–8; 10; 12)*. Cancer medicines will also represent a rising proportion of the cancer care budget *(11)*. The cost of cancer care in the United States alone is projected to increase to US$ 173 billion by 2020 *(12)*.

Table 12. Examples of high prices for cancer drugs (acquisition costs) with often limited health gain

Drug	Total drug acquisition costs per patient and estimated increase in survival
Cetuximab	• US$ 80 352 • 1.2 months (non-small cell lung carcinoma)
Bevacizumab	• US$ 90 816 • 1.5 months (metastatic breast cancer – not statistically significant)
Erlotinib	• US$ 15 752 • 10 days (pancreatic cancer)
Sorafenib	• US$ 34 373 • 2.7 months (renal cell carcinoma)

Source: Fojo & Grady *(12).*

Recent assessments show that new medicines to treat patients with cancer cost between US$ 6000 and US$ 10 000 per month, and the relationship between their reimbursed costs and associated health benefit is often limited *(8; 13)*. Of the 12 drugs approved by FDA for various cancer indications in 2012, nine were priced at more than US$ 10 000 per month and only three prolonged survival – two by less than two months *(10)*. In renal cell cancer alone seven targeted therapies were approved in the United States between 2005 and 2012, including sunitinib (2006), everolimus (2009), pazopanib (2009) and axitinib (2012). All improved median progression-free survival in the range of 3–6 months. This was associated, however, with minimal or no impact on overall survival, at a cost of US$ 70 000–140 000 annually *(10)*. Overall, therefore, it is apparent that the cost of new cancer medicines has doubled over the past 10 years without necessarily having a concomitant improvement in survival. Indeed, health gains over the same period have been modest to moderate, despite high prices, and there remains significant unmet medical need in many cancers.

More specifically, prices of new cancer drugs have increased from an average of US$ 5000 per month to more than US$ 10 000 per month over the last 10 years *(13)*. One estimate is that the median monthly price of cancer drugs increased from US$ 1600 in the early 1960s to more than US$ 4000 for new cancer drugs approved between 2000 and 2005 *(14)*. As mentioned, other scholars have suggested that the prices of medicines to treat patients with cancer have increased more than 10-fold in the last 10 years *(8)* (and 20-fold over the past 20 years *(5)*). These high costs are already causing concern among physicians and payers regarding the consequences of limiting access to new cancer medicines, especially given limited rationale for requested prices and often limited health gain *(10; 13)*.

Despite this, requested prices are likely to continue to rise among most new cancer drugs launched for targeted indications, as manufacturers typically seek orphan status and associated high prices *(15–17)*. This is illustrated by trastuzumab emtansine, which costs £90 000 per course at an estimated cost per QALY of up to £185 600 (in patients with HER2-positive metastatic breast cancer no longer responding to initial treatment with trastuzumab and a taxane), despite additional median survival of just under six months *(17)*. This is considerably greater than the cost per course of trastuzumab alone *(16)*, and builds on existing global sales of trastuzumab at 6079 million Swiss francs (£3985 million; €5050 million) in 2013, up from CHIF 5889 million in 2012 *(9; 19)*.

Consequently, the ability for countries – including European countries – to deliver affordable cancer care appears to be at a crossroads *(2)* and the following questions need to be addressed:

- Are there differences in cancer care delivery across Europe? What is the rationale for this and how does it affect patient outcomes, especially given that there may be limited correlation between monies spent on cancer care and mortality rates *(5)*?
- Similarly for new cancer drugs – are there differences in their uptake rates? What is the possible rationale for this, including prices and associated reimbursement, as researchers begin to question cost-per-QALY thresholds, mindful of the need to sustain health care systems in the future *(20)*?
- What are the implications for the future, including potential means to reduce total cancer care costs such as re-examining chemotherapy regimens towards the end of life *(8)*?

The United States is estimated to spend approximately €100 more per citizen than Europe on cancer care *(11)*. Health care costs in Europe are equivalent to €102 per citizen, although these vary widely between countries *(6)*. Debate is ongoing, however, about whether these differences in spending translate into improved patient outcomes. As noted, several European countries – despite lower investment in cancer care than the United States – are achieving comparable or superior outcomes by considering issues such as best practice *(5; 11)*. Overall, there appears to be no correlation between

the number of deaths per 100 000 in a country and spending on cancer per patient in, for instance, solid tumours such as lung, breast, colorectal and prostate cancer *(5)*.

Factors implicated in differences in outcomes from different cancers between countries include issues such as the lateness of diagnosis – incorporating access to screening and diagnostic services – as well as differences in management approaches, particularly for patients aged 65 and older *(5; 21)*. Overall, improved survival appears to be more closely related to issues such as accessibility to services and affordability, as well as factors such as lifestyle, than it is to late diagnosis *(5)*.

It is generally recognized that prevention, screening and early detection, including a reduction in risk factors, can substantially lessen the risk of cancer and reduce rates. Consequently, introducing well coordinated national and regional policies, including prevention, appears to be a beneficial strategy for the future *(1)*. Without such policies the ever-increasing costs of cancer medicines may compromise (universal) access to care in Europe *(1; 8–9)*. Alongside this is the need to resist strategies that distort care provision – for example, taking funds from other cancer services (or other disease areas) without good reason to fund new cancer drugs, especially if these are not seen as cost-effective even when granting a higher cost per QALY than other medicines at the end of life. This was seen recently in the United Kingdom's Cancer Drugs Fund *(1; 7; 22–23).* The additional costs of providing new cancer medicines under the end-of-life criteria were estimated at £549 million per annum between 2009 and 2011 *(20)*, with close to £1 billion invested in the Fund by the end of 2011 *(11)*. Under this scheme about 34 000 patients gained access to high-cost, but not cost-effective, cancer medicines *(11; 23)*.

Several studies have shown appreciable differences in the uptake of new cancer drugs across Europe, as well as between Europe and the United States *(11; 24–26)*. They have also shown Germany and France among the European countries with the highest access to cancer medicines and the United Kingdom among those with the lowest *(24; 26)* (see Table 13).

Table 13. Summary of United Kingdom use of new cancer drugs versus other countries, April 2008 to March 2009

Drug	Launch year	United Kingdom use as a proportion of 10 European countries[a]	United Kingdom use as a proportion of all 14 countries[a]
Bevacizumab	2005	16%	17%
Bortezomib	2004	57%	63%
Cetuximab	2004	82%	102%
Dasatinib	2006	99%	107%
Eroltinib	2005	33%	37%
Lapatinib	2008	24%	25%
Lenalidomide	2007	24%	20%
Nilotinib	2008	58%	66%
Panitumumab	2008	6%	6%
Premetrexed	2004	26%	30%
Sorafenib	2006	20%	23%
Sunitinib	2006	56%	67%
Temsirolimus	2008	25%	25%
Thalidomide	2008	120%	66%
Trabectedin	2008	27%	27%

[a] The European countries in the comparison were Austria, Denmark, France, Germany, Italy, Norway, Spain, Sweden, Switzerland and the United Kingdom (10 in total); other countries were Australia, Canada, New Zealand and the United States.

Source: adapted from Richards *(24)* and Jonsson et al. *(26)*.

Potential reasons for the differences seen include *(3; 11; 25–26)*:

- access to specialist services;
- extent of HTAs for new cancer drugs and their timing, as well as the extent of off-label use;
- available funding for new cancer drugs;
- clinical perceptions and attitudes, including a potential aversion to toxicity among United Kingdom clinicians, which has been seen in other studies.

Other studies have also shown considerable differences in the use of new medicines to treat patients with metastatic renal cell carcinoma *(26)*. One of the principal reasons postulated for variation in use of cancer medicines among European countries is differences in reimbursement and funding, including differences in cost–effectiveness thresholds *(11)*, although this may change with trastuzumab emtansine *(9)*. These issues are resulting in the growth of risk-sharing arrangements or MEAs for new cancer drugs in an attempt to reduce the uncertainty of their value to payers and enhance reimbursement *(3; 27)*.

One suggested way to help curb the unsustainable increase in the costs of cancer care including new medicines is greater use of comparative effectiveness research when reviewing new approaches *(7; 28)*. Such research should include greater scrutiny regarding the clinical value of new cancer medicines and their cost–effectiveness versus current standards *(9; 10; 26)*, as well as greater questioning over the pricing model for new cancer therapies. This builds on current concerns regarding how prices for new medicines are derived and the subsequent implications for sustaining health care systems in Europe *(8–9; 12–13)*, which is associated with the principles for developing guidelines and formularies (see section 5.1). Subsequently, such information should be incorporated into future practice guidelines and recommendations regarding the potential value of new medicines, such as the CPGs and recommendations produced by the DTC of Emilia-Romagna (see section 5.1.2), and a recent partnership among the National Comprehensive Cancer Network, United States Oncology Network and McKesson Specialty Health and United States Oncology and other insurers *(8; 26)*. Such partnerships can be at a national or regional level involving all key stakeholder groups. It is envisaged that such approaches could help reduce the extent of off-label prescribing of new cancer medicines, which has been prevalent in some European countries *(3)*. These deliberations are becoming critical, given potential future cost-per-QALY thresholds: trastuzumab emtansine is being reimbursed at an estimated incremental cost per QALY up to £185 600 (€235 000) *(9; 17)*.

Greater use of patient registries after launch should also enhance the appropriate use of new premium-priced cancer medicines; this may assist countries that have been reluctant in the past to deny potentially life-saving drugs to patients, such as France *(3; 11; 29)*. Alongside this, the extent of chemotherapy given in the last month of life when there may be limited benefit could be reduced *(8)*. Hospice and palliative care are seen as providing better overall care at lower costs than hospital care and should be another consideration. In addition, the patient community could have greater involvement in difficult management decisions, including trade-offs between different approaches *(8; 11)*. This involves providing adequate information to patients to help them make informed decisions, as in the "Choosing wisely" initiative *(28)*, making them more aware of the difficulties of funding decisions and the rationale, building on the pan-Canadian Oncology Drug Review initiative *(30)*, as well as general cost issues if the cost of care will lead to financial hardships for patients and their families (1–2; 31–32).

Future ways to address these issues could also include greater collaboration between European health technology agencies such as EUnetHTA and EMA to improve the availability and relevance of data from

clinical trials when agencies perform HTAs for new cancer medicines *(11)*. This is especially relevant given current concerns with translating, for instance, progression-free survival in solid tumours into robust estimates of improved survival – including the length of survival – for cost–effectiveness evaluations and other considerations *(11; 26)*. Differences in such estimates also influence subsequent calculations of differences in ICERs between current treatments and new cancer medicines – for example, ICER differences between US$ 50 000 and US$ 150 000 were noted for sunitinib by different authors *(26)*. Approaches to improve these estimates will reduce the uncertainty regarding current ICERs and, as a result, potentially aid their usefulness in future reimbursement decisions. HTAs can also highlight alternative treatment approaches with similar effectiveness but lower costs to assist future discussions. For example, Bach et al. compared the efficacy and cost of two anticancer agents – ziv-aflibercept and bevacizumab – in the treatment of metastatic colorectal cancer. After noting that ziv-aflibercept had similar efficacy but was twice the cost of bevacizumab, the authors stated that it would be excluded from their hospital formulary *(10; 31)*. Within a week the manufacturers producing ziv-aflibercept had reduced its price by 50% to facilitate listing.

Key areas for possible collaboration between EUnetHTA and EMA include:

- developing approaches for collection of post-authorization data to support activities of regulatory agencies and HTAs;
- facilitating clinical trial design to enable generation of data relevant for both risk–benefit and relative effectiveness assessments;
- exploring ways of sharing information about OMPs for the common benefit of patients with rare diseases, while ensuring financial sustainability *(11; 16)*.

It is recognized, however, that the prolonged course of cancer disease can slow down clinical research, leading to the shift from hard end-points such as overall survival to soft end-points such as progression-free survival *(3)*. Research into linking progression-free survival with overall survival for given tumours will help to address this slowdown *(10; 26)*.

Finally, potential ways to address the challenges associated with high prices of new cancer medicines, and at times limited health gain versus current standards, could include agreeing among European authorities what is meant by a "meaningful clinical benefit" for a new cancer medicine. Ferguson and colleagues in the United Kingdom suggested that no premium should be paid for a new cancer medicine unless it prolonged survival by at least three months compared with existing standards *(33)*. There were similar timescales for deliberations regarding the value of new medicines at the end of life in the United Kingdom *(20)*. The American Society of Clinical Oncology Cancer Research Committee recently identified an improvement in median overall survival in a range of 2.5–6 months across a range of tumours as the minimum incremental improvement that would define a clinically meaningful outcome for a new cancer medicine (extent would depend on the tumour type) *(34)*. In addition, greater scrutiny of potential prices for new cancer medicines to be reimbursed in Europe, including any MEAs *(9; 27; 28),* especially with standard cancer medicines such as imatinib now available as generics.

These challenges have resulted in Kantarjian and colleagues, as well as others in the United States, suggesting the following when authorities across countries including the United States review the potential prices of new cancer drugs *(10)*:

- US$ 50 000–60 000 per year – more than six months or a third of the usual life expectancy, or improvements in long-term survival of 10% or more;
- less than US$ 30 000 per year – minimally effective drugs that have an overall survival benefit of less than two months or less than 15% of the envisaged patient lifespan;

- US$ 30 000–50 000 – new drugs that have an intermediate benefit between these two bands *(8; 10)*.

The suggestioins of thse authors could act as a basis for deliberations among European countries, taking into account issues of affordability along with competitive bidding, especially where there is similar health gain between different treatment approaches. These deliberations will intensify with an increase in the number of cancer survivors during the next decade due to ageing populations, earlier detection and improved management *(8)*.

6.1.1. References

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6.2. Access to TNF alpha inhibitors in Europe

The introduction of TNF alpha inhibitors in the late 1990s represented a breakthrough in the treatment of diseases such as rheumatoid arthritis, thanks to their ability not only to control inflammation effectively but also to prevent or slow the development of irreversible joint erosion. Despite their disease-modifying effects, widespread use has been hindered by their relatively high cost and adverse side-effects, leading to reimbursement or usage restrictions in most European countries *(1)*.

Disease activity and physical functioning correlate inversely with the number of reimbursed biological disease-modifying antirheumatic drugs (DMARDs) – such as the TNF alpha inhibitors – and barriers to access to these drugs, suggesting that limited access to biological DMARDs leads to poorer health *(2)*. This may undermine the care of specific patient groups denied biological DMARDs known to be effective in treating both moderate and severe rheumatoid arthritis and, in turn, may lead to higher indirect costs of health care and productivity costs due to ill health *(3)*. Studies have shown disparities in access to TNF alpha inhibitors for patients with rheumatoid arthritis across Europe. Inequalities in access to DMARDs are found to be strongest for biological DMARDs *(3)*. Countries in eastern and central Europe are characterized by particularly poor access to these medicines, with barriers including high patient co-payment levels *(2; 4; 5)*.

Substantial variations are present in European national guidelines for the treatment of rheumatoid arthritis. In Belgium, England and Wales, Germany and Sweden it is generally required that treatment needs to fail with two standard DMARDs before biological agents can be used, while France, Greece, Poland and Spain provide biological agents as first-line treatment for early or aggressive disease *(3)*. Reimbursement outcomes and clinical guidelines informed by economic evaluations show that countries have different views of how cost-effective these drugs are. While countries like Norway and Sweden believe TNF alpha inhibitors to be good value for money, other countries such as the United Kingdom have evaluated them less favourably and applied more restricted usage criteria *(1)*. In Poland since 2010 use has been restricted to patients who formally qualify for biological therapy as assessed by the Rheumatology Institute in Warsaw *(3)*. Some countries have employed separate funding for biological medicines – in Slovenia, for example, until 2010 decisions on financing these medicines were taken by special commission at the ministry of health. Since then, biologics have been evaluated by the Health Insurance Institute of Slovenia, together with all other drugs *(3)*. Delays in reimbursement decisions vary from approximately 100 days in Ireland to 300 days in Slovenia and Italy and 400 days in Belgium, which further complicates access to biological drugs.

Further, differences in access result from differences in availability of rheumatologists and time from symptoms to diagnosis or treatment. The number of patients per rheumatologist ranges from fewer than 100 in countries such as France, Hungary and Iceland to more than 600 in countries such as Ireland and Latvia *(1)*. Density of rheumatologists does not, however, appear systematically to influence the uptake of biological drugs: while the United Kingdom has the same density as the Nordic countries, its use of biologics is much lower. In Germany efforts have been made to promote early diagnosis and treatment, resulting in a reduction in mean time from symptoms to first contact with a rheumatologist from 2.0 years in 1994 to 1.1 in 2007 *(1)*.

Restricted dispensing of TNF alpha inhibitors is another important factor affecting access: dispensing through the retail market has a positive impact on access, while dispensing through hospitals may impede access *(6)*. Similar findings were reported in a study in Greece, where access to TNF alpha inhibitors has been hampered by recent cost-containment measures following the economic crisis. Notably, these include limiting dispensing of high-cost medicines such as biological DMARDs to designated pharmacies of the National Organization for Healthcare Provision or the hospitals of the national health system to ensure that use of costly drugs is in line with official treatment guidelines *(7)*.

Finally, the introduction of biosimilars may heavily reduce costs and increase access to biological TNF alpha inhibitors, yet concerns have been raised regarding their clinical use due to the complexity of "copying" biological antibodies *(8)*. Nevertheless, recent events suggest changes in the European biosimilar market: in Norway the national public procurement organization at the hospital level bought biosimilar infliximab at a 39% discount compared to branded Remicade, representing substantial savings for the public health care budget or even lower *(9–10)*. Other European countries are likely to follow suit, especially given the stringent criteria for authorizing biological medicines in Europe *(11)*.

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6.3. New therapeutics for hepatitis C

Hepatitis C virus (HCV) is one of the most widespread transmittable diseases, estimated to affect over 170–185 million people worldwide, and the incidence continues to grow *(1–3)*. HCV prevalence in the general population varies from 0.5% in northern Europe to 5% in southern and eastern Europe *(4)*, ranging from 4% in Italy, 1.9% in Spain, 0.87% in Belgium and 0.84% in France to 0.7% in the United Kingdom and 0.6% in Germany *(5– 6)*. HCV mortality in 2010 was 57 000 in EU countries alone, and is expected to grow in the absence of action *(7)*. HCV is called the silent pandemic because it is one of the most widespread diseases globally, but is surrounded by considerable unawareness among the general public. Even in well organized health systems like those of the United Kingdom and Germany, only 20–40% of infected people are aware of their HCV status.

Until recently, treatment involved a course of pegylated interferon and ribavirin, which caused serious adverse effects in more than 80% of patients, and fewer than 50% were able to finish the course. With new innovative direct-acting antiviral medicines such as sofosbuvir, HCV is increasingly curable – reaching cure rates (defined by sustained virologic response) of 95% or higher *(1; 8)*. These new treatments include options for interferon-free regimens that are shorter and well tolerated. It is anticipated that new fixed-dose combination treatments (such as sofosbuvir and ledipasvir) became available in 2014, potentially reducing treatment to eight weeks with cure rates of more than 92% *(9)*. Because their HCV infection develops slowly, many patients prefer to wait for these more promising

treatments now entering the market (especially as they appear to have higher efficacy in new patients) *(8)*.

The hepatitis C therapeutics market represents one of the most rapidly evolving areas of medicines and commercial development, but is also an area of intense public policy debate and controversy because of the high prices for these new medicines, coupled with high prevalence rates *(10)*. The anti-HCV therapeutics market witnessed growth at a compound annual rate of 2.7% between 2004 and 2011, enhanced by the launch of telaprevir and boceprevir in 2011 *(2; 11)*. Driven by the launch of these premium-priced medicines, however, the market is expected to expand to US$ 14.9 billion by 2018, growing at a compound annual rate of 28.3% per year *(11)* – for example, a 12-week course for sofosbuvir in the United Kingdom costs between £35 908 and £71 816 depending on the genotype *(12)*. In the United States sofosbuvir costs approximately US$ 1000 per tablet, equating to US$ 84 000 for a standard course *(10)*. The current forecast may be an underestimate, since it has been calculated that sales of sofosbuvir could be as high as US$ 250 billion in the United States alone if all patients with HCV were treated with this medicine at current prices *(10)*.

In the past the hepatitis C therapeutics market was dominated worldwide by two companies: MSD and Roche with Pegasys and PegIntron, with sales of HCV therapeutics reaching US$ 2.6 billion in 2011 *(2)*. Research on medicines with new mechanisms of action has resulted in the presentation of new medicines by new companies like Gilead Sciences, Janssen, BMS and AbbVie; this is changing hepatitis C treatment and its costs *(2; 8)*.

The decision-making process for policy-makers regarding these expensive medicines is complex. The new medicines are highly effective and yet at the same time unaffordable if prescribed for all appropriate patients. For example, it is estimated in the United States that treating all HCV patients with sofosbuvir would double the total annual drug budget *(10; 13)*. The current economic difficulties in Europe and elsewhere make this situation challenging. Some health authorities, including those in Europe, are already struggling to fund new premium-priced medicines because of continuing resource pressures *(12; 15)*, which are putting further pressure on the funding of new medicines for HCV.

Generally, most countries find the new HCV medicines unaffordable and therefore limit access, despite patients with high medical need standing to benefit from such treatments (as well as the opportunity cost in the context of health care costs over the patient's lifetime). Pricing and reimbursement consultations are continuing in many European countries, alongside discussion of treatment inclusion criteria, with some countries restricting treatment to F3–F4 stage fibrosis. France raised the matter of access to new HCV-related medicines at the EU Employment, Social Policy, Health and Consumer Affairs Council meeting on 20 June 2014, and 14 countries supported a resolution calling for EU Member States to work together on introduction of the relevant treatments at affordable prices. It is anticipated that the French ministry of health will work on a process for voluntary collaboration between EU Member States to facilitate access to HCV-related innovative medicines. This could build on potential prices as low as US$ 900 per course in Egypt and other developing countries *(10)*.

On 15 September 2014 Gilead Sciences signed licensing agreements with seven Indian generic manufacturers (Cadila, Cipla, Hetero, Mylan, Ranbaxy, Sequent and Strides Arcolab), allowing these companies to manufacture sofosbuvir in India and sell it in 91 low- and middle-income countries. Generic companies pay 7% royalties and are free to set their own prices but have to produce or buy the active pharmaceutical ingredient in India. One company was quoted with an entry price of around

US$ 300. One nongovernmental organization expects entry prices of US$ 400 per 12-week course and in the medium term a reduction to around US$ 135. Nevertheless, these generic products – which may become available within 12–18 months – can only be used in the 91 countries listed, and the agreement only covers four countries in Europe: Kyrgyzstan, Tajikistan, Turkmenistan and Uzbekistan. Countries that are not included can negotiate price or issue compulsory licenses to access the Indian generic versions.

Alongside this, WHO launched HCV treatment guidelines in April 2014; these include recommendations for the use of sofosbuvir and simeprevir (as well as existing pegylated interferon-based regimens). It is expected that the WHO Expert Committee on the Selection and Use of Essential Medicines will review HCV-related medicines during its 2015 meeting. To help countries achieve equitable access to high-quality, effective, affordable and safe hepatitis C treatments, WHO published an analysis of the patent situation for seven new hepatitis treatments in September 2014. The analysis, carried out on behalf of WHO by Thompson Reuters, provides crucial information about the patents themselves and identifies in which countries the medicines are patent protected. This information is vital to inform government policies and actions when selecting and purchasing medicines for their populations. In addition, WHO has invited applications for selected pharmaceutical products to tackle hepatitis C as a coinfection of HIV/AIDS to submit expressions of interest for product evaluation. The list of products for which submissions are sought includes hepatitis C treatments sofosbuvir, simeprevir and ribavirin. Furthermore, WHO is including hepatitis medicines in the Global Price Reporting Mechanism database, which means that prices will be made available in the public domain.

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6.4. New orphan drugs

While new pharmaceuticals are required to address identified areas of unmet need *(1)*, challenges are increasing regarding the future funding of new OMPs – or new drugs in targeted disease areas such as niche cancer populations with orphan status – to address these needs *(2–4)*. EMA identified three criteria for a medicine to qualify for orphan designation. First, it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating. Second, the prevalence of the condition in the EU must not be more than 5 in 10 000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development. Third, no satisfactory method of diagnosis, prevention or treatment of the condition concerned can already be authorized or, if such a method exists, the medicine must be of significant benefit to those affected by the condition *(5)*. The second criterion is also used by a number of European Member States, although some countries have established their own definitions – for example, Sweden and Denmark use a ratio of 1 in 10 000 *(6)*.

Challenges arise from the fact that while individual cases may be few – rare diseases currently number approximately 7000, with some 250 new diseases added annually – they collectively affect some 30–40 million people across the EU *(6–11)*. Over 1000 OMPs have been approved by EMA (as of December 2012) and this number is growing *(11)*; indeed, both EMA and FDA have expedited approval streams for these drugs.

Furthermore, orphan drugs can be appreciably more expensive than other medicines, especially where no other treatments exist *(3; 10; 12)*. They can also be seen as a form of personalized medicine, increasingly representing targeted therapies serving very small populations *(2)*. Consequently, the cost implications are potentially substantial. New orphan drugs are typically priced at US$ 300 000–400 000 per patient per year or more *(3; 13–14)*, although the price is lower for OMPs that are second or later to market *(15)*. Examples of existing orphan drugs include idursulfase (Elaprase), for which the annual medicine cost to treat a 40 kg patient suffering from Hunter syndrome is approximately €500 000 *(3; 6)* (although average annual costs are lower – see Table 14) and galsulfase (Naglazyme), which costs over €1 million per patient per year in France, Germany, Italy and Spain *(15)*.

Overall, the average annual cost of OMPs per patient in France, Germany, Italy, Spain and the United Kingdom is generally over €150 000 *(15)*. Table 14 contains details of eight orphan drugs currently available in ambulatory care costing on average US$ 295 000 per patient per year or more *(3)*, excluding galsulfase because it is much more expensive in general. This includes ivacaftor for managing a subgroup of patients with cystic fibrosis *(13)*. Ivacaftor was granted reimbursement by the NHS Commissioning Board in Englans at a cost per QALY of between £285 000 (€360 000) and £1.077 million (€1.36 million) *(16–18)*. Its pricing strategy of US$ 294 000 (€220 000) per patient per year for life was based on perceived similar prices for other treatments for rare diseases *(3; 13)*; its use is likely to grow in patients with other genotypes, as well including the potential combination with lumacaftor, which will add to the resource pressures *(17–18)*.

Table 14. Eight orphan drugs with average annual costs of US$ 295 000 or more

Orphan drug	Indication	Average annual cost per patient (US$)
Teduglutide (Gattex)	Short bowel syndrome	295 000
Imiglucerase (Cerezyme)	Type 1 Gaucher disease	300 000
Ivacaftor (Kalydeco)	Cystic fibrosis	325 000
Galsulfase (Naglazyme)	Mucopolysaccharidosis VI	441 000
Idursulfase (Elaprase)	Mucopolysaccharidosis I and II	475 000
Eculizumab (Soliris)	Paroxysmal nocturnal hemoglobinuria	486 000
C1 esterase inhibitor (Cinryse)	Hereditary angioedema prophylaxis	487 000
Alglucosidase alfa (Myozyme)	Pompe disease	575 000

Source: Cohen & Felix *(3)*.

No appropriate benchmarks and metrics gauging whether prices for new OMPs are low, high or too high relative to expectations currently appear to be in place *(19)*. Debate around the funding of ivacaftor for patients who carry the genetic mutation G551D in the cystic fibrosis transmembrane regulator gene – at a cost per QALY between £335 000 (optimistic scenario) and £1 274 000 (conservative scenario) – may change this *(17–18)*. It is also generally accepted, however, that development of treatments for conditions carrying high disease severity or with significant unmet medical need is desirable, irrespective of the rarity of the condition *(1; 19)*.

The cost of OMPs is likely to grow as more are launched to address the considerable unmet need *(1; 8–9; 11–12)*. In Europe research and development for rare diseases is encouraged by incentives provided by the EU, such as reduced fees and protection from competition once the medicine is placed on the market; these appear to have boosted the development of new drugs to treat rare diseases *(4; 15)*. Current "push" and "pull" incentives globally include 10 years of market exclusivity in Europe (up to seven years in the United States), tax credits for clinical research (in the United States), protocol assistance, fee reductions from EMA centralized procedures and specific grants for OMP trials *(4; 7–8)*.

In addition, limited patient data have been sufficient to date to secure marketing authorization *(7–8)*: in some cases this has been granted on uncontrolled phase II data, as well as studies involving fewer than 200 patients. Overall, a positive opinion has been given in over 80% of cases of new OMPs submitted to EMA, with only a limited number receiving a negative opinion. The majority of the remainder withdrew orphan status designation, often because companies had not appreciated or fully met the designated OMP criteria *(8; 15)*.

To date, European countries have typically reimbursed new OMPs at high prices even when limited data are available to justify this – few reimbursement hurdles are in place at high requested prices,

compared with other disease areas *(6; 15; 20–22)*. For example, in a survey conducted in 2010, of 22 responding European countries *(6)*:

- five publicly funded access to new orphan products at requested prices;
- eleven stated that access was granted in most cases but could be subject to specific conditions such as the prior approval of the initial prescription from a specialist or other administrative procedures;
- five, including the Baltic countries, stated that access to new OMPs was limited due to budgetary constraints, and in one country public coverage was not guaranteed for expensive new OMPs;
- typically if reimbursed, there is no additional co-payment.

The major reasons given in the survey for not including new OMPs in national formularies or positive lists among European countries included the following *(6)*:

- The new orphan drug has not yet received marketing authorization, although it is being made available to patients via compassionate use or similar programmes – for example, with temporary authorizations for use in France.
- The orphan drug, despite being authorized, is not (yet) available in a country because either no patients have been diagnosed – for example, with Pompe disease in Estonia and Latvia – or commercialization requires administrative clearance by the country's authorities – for example, via price agreements and inclusion in the pharmacy sales list.
- The marketing authorization holder did not apply for reimbursement – for example, with Myozyme (alglucosidase alfa) in Finland.
- Reimbursement was denied by the authorities – for example, for Kuvan in Sweden.
- The reimbursement procedure is pending.

Orphan drugs have been viewed as a good business opportunity by companies, with the potential for exploitation of payers' willingness to accept higher prices for them, which has led some OMPs to reach "blockbuster" status *(20; 23–24)*. This could also lead manufacturers to launch a new drug for an orphan indication first if possible, appreciably enhancing the overall profitability of the new medicine *(23)*.

The reimbursement landscape is changing, however, as seen in an increase in restrictions and greater scrutiny of reimbursement for orphan drugs, including an increase in MEAs for new OMPs *(3; 20–21)*. NICE in the United Kingdom recently reviewed 36 orphan products: 21 were given positive recommendations that included conditional reimbursement and 15 were given negative recommendations (not reimbursed) *(3)*. Ivacaftor would appear to be an exception, as it was reviewed by the NHS Commissioning Board rather than NICE, putting pressure on the other regions in the United Kingdom to fund it, as well as other countries *(18)*. Of 92 OMPs reviewed by the former Dutch Health Insurance Board – now the National Health Care Institute – between 1983 and 2013, 79 were covered, 13 (14%) were denied reimbursement and 22 (24%) of the 79 covered were conditionally reimbursed *(3)*.

These deliberations have been enhanced by the increased burden of orphan drugs on national pharmaceutical budgets due to their requested high prices and an increasing number of patients requiring OMPs *(15)*. A recent study among EU countries suggests that OMP expenditure and use is growing rapidly, particularly for some ATC groups including medicines for cancer. Both expenditure and use have increased rapidly in recent years – expenditure increased from 13% to 28% per annum between 2009 and 2010, while use increased from 7% to 17% *(21)*. This may be facilitated by off-label use, as seen with lidocaine patches, imatinib and modafinil when their prescribing was recently reviewed among programmes for the elderly in the United States *(24)*. Other studies, however, note lower growth rates for OMPs and their contribution to overall pharmaceutical expenditure *(9; 11)*; this

may be due to differences in methodologies. OMPs – such as imatinib – are now also starting to lose their patents *(9)*. In any event, the visibility of OMPs will grow as more premium-priced orphan drugs are launched and more standard drugs lose their patents and become available as low-cost generics or lower-cost biosimilars *(18; 25)*.

Concerns with the increasing number of OMPs and their requested prices (see Table 14), including their individual or cumulative budget impact, have resulted in the development of new approaches to valuing new orphan drugs. This includes multifaceted approaches, especially as new orphan drugs are unlikely to meet cost–effectiveness thresholds where these currently exist *(11; 26–27)*. Such approaches recognize that severe unmet need still persists for many rare diseases; consequently, there is a need to continue to incentivize the development of new OMPs *(1; 12)*. Equally, health systems wish to allow patients with rare diseases equal access to treatment for life-threatening conditions *(1)*. This has to be balanced, however, against issues of affordability and equity (see Box 3) *(3–4; 28)* – that is, whether orphan drugs should continue to be singled out for special status. Such approaches may be seen as giving preferential treatment to the loudest voices among patient advocates, which is not necessarily equitable *(3)*. Others have argued that it is difficult to initiate such discussions before fully discussing issues on what constitutes high prices for OMPs *(19)*.

Box 3. Public preferences regarding orphan drugs

- In a survey of public preferences for medicine prioritization criteria among 4118 adults in the United Kingdom, respondents did not support the special funding status for treatments of rare diseases. They did, however, express a preference for treating diseases where no alternative treatments are available and for treating more severe diseases, even when the costs were higher than current standards, although not when the effectiveness was lower *(4; 29)*.
- A recent survey on orphan diseases among a random sample of 1547 Norwegian citizens showed that, despite strong general support for statements expressing desire for equal treatment rights for patients with rare diseases, there was little evidence of societal preference for rarity if treatment of patients with rare diseases is at the expense of treatment of those with common conditions *(30)*.

Multifaceted models developed to improve the level of decision-making for new premium-priced OMPs include MCDA for valuing new orphan drugs (see section 4.2.2 for further discussion of MCDA). They also include a framework for evaluation based on 10 criteria and three price differential categories (see Table 15) and the TVF, developed by a consultative process through the EU (see Table 16) (see also section 4.1.2.6 for details of these VBP models).

Eight categories were finally chosen in the proposed MCDA framework developed by Sussex and colleagues, given different weightings depending on whether physicians or patients were involved *(27)*. Categories for impact of the rare disease and associated unmet need are:

- availability of effective treatment options or best supportive care in absence of the new medicine;
- disease survival prognosis with current standard of care;
- disease morbidity and patient clinical disability with current standard of care;
- social impact of the disease on patients' and carers' daily lives with current standard of care.

Categories for impact of the new medicine are:

- treatment innovation, defined as the scientific advance of the new treatment together with contribution to patient outcomes;
- evidence of treatment clinical efficacy and patient clinical outcome;

- treatment safety;
- social impact of the treatment on patients' and carers' daily lives.

Hughes-Wilson and colleagues' proposed framework to assist with value considerations for new OMPs contains a number of similar categories to the Sussex and colleagues model (see Table 15).

Table 15. Proposed criteria for the evaluation of orphan drugs and potential parameters

Criterion	Price differential		
	Lower	**Medium**	**Higher**
Rarity	1:2000–1:20 000	1:20 000–1:200 000	Less than 1:200 000
Level of research	Literature review	Building on existing knowledge	Starting research and development in an unknown area
Level of uncertainty surrounding effectiveness	Immature but promising data	Appropriate surrogate end-points	Robust clinical end-points
Manufacturing complexity	Not complex	Moderately complex	Highly complex biological and galenic forms
Follow-up measures (additional benefits/costs)	Moderate to none	Research undertaken to answer specific questions	Safety and efficiency studies undertaken
Characteristics without direct cost impact			
Disease severity	Morbidity	Morbidity/severe invalidity in adulthood	Mortality/severe invalidity as infant
Available alternatives/unmet need	Alternatives with similar characteristics	Alternatives – but offering innovation to future management	No current alternative
Level of impact of the condition/disease modification	Low	Medium	Strong
Use in a unique indication	Existing indications for the same molecule	Potential for multiple indications	Unique indication only

Source: Hughes-Wilson et al. *(11)*.

The development of the TVF among European authorities and groups arose from the challenges posed by the specific nature of OMPs highlighted above *(18; 26)*, including the following:

- Data, information, expertise and knowledge on the therapy or possible alternative or comparative therapies – if available – are often scarce, subsequently limiting evidence on efficacy and (real-life) effectiveness, especially at the time of marketing authorization.
- Registers and registries – if available – are limited in terms of their capacity to produce solid (high-quality) evidence in rare diseases, due in part to their limited number and the limited number of patient entries.
- Limitations in availability of adequate dosages or packages may result in substantial and expensive "waste" when protocols are subsequently adjusted for individual patients.
- The average cost of treatment for common ailments or conditions is around €250 per year. In comparison, the average cost for OMPs is €30 000 per patient per year or higher (as noted earlier, the average annual cost per patient in France, Germany, Italy, Spain and United Kingdom is generally over €150 000, and can amount to hundreds of thousands of euros per year).
- Pressure is placed on health care systems to fund new OMPs even when concerns exist with their value. For example, pressure was put on the ministry of health in the Netherlands to fund alglucosidase alfa to treat Pompe disease at an estimated cost per QALY of €0.3–0.9 million for the classic form and up to €15 million per QALY for the nonclassic form *(22)*.

- Uncertainty remains over the extent of price reductions for existing OMPs when their period of exclusivity finishes.

The deliberations resulted in the development of the TVF (see Table 16) *(18; 26)*. This consists of four elements of value coupled with measures of the extent to which each criterion is met, ranging from "low" to "high". The main intended use of the TVF, as stated in the final report of the Working Group on MoCA-OMP, is in multinational collaborative VBP discussions between reimbursement agencies and pharmaceutical companies. It is recognized that the framework is "indicative, non-prescriptive and non-binding", acknowledging that reimbursement decisions for new OMPs are the responsibility of individual EU Member States.

Table 16. The TVF to assess the value of orphan drugs

Criterion	Low degree	Medium degree	High degree
Alternatives available/ Unmet need	Yes/ New medicine does not address unmet need	Yes/ Major unmet need still exists	No/ No alternatives exist except supportive care and major unmet need exists
(Relative) effectiveness, degree of net benefit relative to alternatives including no treatment	Incremental	Major	Curative
Response rate	<30%	30–60%	>60%
Degree of certainty	Promising but not well documented	Plausible	Unequivocal

Source: Adapted from Godman et al. *(18)* and EC *(26)*.

As shown in Table 16, the TVF has four principal elements. The Working Group on MoCA-OMP defines the first as the degree to which the new OMP addresses the unmet need over existing therapies. It is noted that where no pharmaceutical alternatives exist other nonpharmaceutical treatment can be used as the benchmark. The second element is defined as the net benefit the new OMP provides versus current treatment approaches. Net benefit covers, for example, clinical improvement including improved quality of life measured against the side-effects of the drug. This criterion may be informed by HTAs. The third element will vary, depending on which measure – including surrogate marker and time frame – is used and the available clinical data. It is noted in the final report that response rates will differ for diseases: for enzyme replacement therapies response rates are expected to be higher than for late-stage cancer. The fourth element is defined as the certainty of the claim made by the market authorization holder for the new OMP. The level of evidence may be low when an OMP has conditional approval, but compelling evidence is expected at a later stage *(26)*. Research is ongoing to assess the utility of the TVF in practice and make subsequent recommendations to aid future decision-making, especially given the likely increase in the number of OMPs in the future, including new cancer drugs seeking OMP status, and the likely continuing high prices *(3; 18; 31)*. Such practices could lead to a tightening of the designation of orphan status for new OMPs to continue to command premium prices *(4; 10)*. This could include giving OMP status only to new medicines that truly treat rare, high-priority and serious diseases *(4)*, including those recently identified as priority areas for Europe *(1)*. This may negatively affect future research in this area, however *(19)*.

Future initiatives could also include stimulating further input into patient registries to enable more informed decision-making, given the concerns highlighted above by the Working Group on MoCA-OMP

(24). This builds on four complementary EU initiatives to improve patient registries for rare diseases: the European Platform for Rare Diseases Registry (EPIRARE) project, the Patient Registries Initiative (PARENT) joint action, the European Union Committee of Experts on Rare Diseases (EUCERD) joint action and the International Rare Disease Research Consortium *(19)*. The overall aim of these initiatives is to establish common datasets and quality criteria and to assist further with a political framework for valuing new OMPs. This recognizes that the creation of this evidence base – and the above networks and initiatives – is overdue and that such developments could act as a benchmark or proxy benchmark in future assessments of the value of new OMPs, building on initiatives such as the TVF *(18; 19; 26)*.

As a result, there is a need to continue to stimulate research in these specific disease areas while reducing the potential disincentive for pharmaceutical manufacturers to "salami slice" indications for their new medicines in an attempt to seek orphan status and associated prices *(4)*. This has been the case recently for companies launching new medicines to treat niche targeted cancer patients *(2)*. Others, however, have argued that the more important policy implication is how new OMPs should be valued in the future, including potential reimbursed prices for initial and future indications *(19)*. This includes deliberations concerning the level of evidence necessary to support reimbursement at premium prices, given continual pressure on resources.

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6.5. New drugs for patients with type 2 diabetes

6.5.1. Burden of type 2 diabetes

Diabetes is rapidly becoming a global public health challenge. Its prevalence is increasing and the growing cost of pharmaceuticals is being augmented by the launch of new patented (single-source) products to treat patients with type 2 diabetes, putting added pressure on health care systems. Optimal nonpharmacological management – as well as appropriate use of inexpensive generic medicines to treat patients with type 2 diabetes and potential complications, including generic metformin, statins and renin-angiotensin inhibitor drugs (angiotensin-converting-enzyme inhibitors

and ARBs) – can reduce and prevent the development of complications. As a result, it may reduce the global costs of medicines to treat patients with diabetes, estimated to reach US$48 to 53bn in 2016, with similar figures in 2017 *(1–2)*.

Estimates from the International Diabetes Foundation suggest that over 380 million people are currently living with diabetes and that a further 300 million have impaired glucose tolerance, with increased risk of progressing to diabetes. It is projected that by 2035 nearly 600 million people will have the disease and almost 500 million will be at risk – thus, the population requiring either targeted prevention interventions or diabetes care will exceed 1 billion *(3)*.

Diabetes is subdivided into three main types: type 1 (triggered by an autoimmune destruction of insulin-producing pancreatic beta cells), type 2 (characterized initially by insulin resistance and hyperinsulinaemia and eventually by glucose intolerance, hyperglycaemia and overt diabetes) and gestational diabetes (development of resistance to insulin and subsequent high blood glucose during pregnancy). Type 2 is the most common type (occurring in 85–95% of all diabetes patients) and its prevalence is increasing rapidly *(4)*. Data reported by the International Diabetes Foundation suggest that in the next two decades the global diabetes population will grow appreciably if not addressed, with particularly rapid prevalence increases in Africa (109%), the Middle East and north Africa (96%), south-east Asia (71%), south and central America (60%) and the Western Pacific (46%) *(5)*.

Both genetic and environmental factors contribute to the onset of type 2 diabetes. The recent increase in worldwide prevalence, however, can mainly be attributed to environmental changes *(6)*. While population ageing and increased life expectancy are recognized as contributing factors, type 2 diabetes is no longer considered found exclusively in older populations: the past 20 years have seen a dramatic increase in prevalence in children and adolescents *(7–9)*. Sedentary lifestyles and changing diets have resulted in growing numbers of overweight and obese children and adults *(10)*, which in turn have fuelled the spread of related chronic diseases including diabetes, cardiovascular diseases and cancer. A transgenerational cycle of obesity and diabetes is also affecting rates: it has been shown that exposure to diabetes in utero increases the risk of obesity and type 2 diabetes *(11–12)*. Furthermore, socioeconomically disadvantaged populations often carry a variety of established risk factors (such as health behaviours and obesity) *(13)* and are thus prone to developing diabetes, but are less likely to take control of their health or access services needed for successful disease management *(14–15)*.

Diabetes, including its complications, is one of leading causes of death worldwide, with over 5 million deaths attributable to diabetes in 2013 *(3)*. As its global prevalence increases, so will the number of people with diabetes-related complications. Often remaining undiagnosed in its initial stages, it is estimated that almost half of people living with diabetes are unaware they have it until they develop complications. As the disease advances, its management becomes more complex; for example, the number of pharmacotherapeutic options that can be employed in a multimorbid patient is limited, and more intensive health resource use is required. The most common complications include cardiovascular disease, neuropathy, retinopathy and diabetic kidney disease. The burden of these comorbidities is appreciable: they are the major cause of disability, reduced quality of life and death in diabetes patients.

The costs associated with diabetes comprise the increased use of health services, productivity loss and disability, which can be a considerable burden to the individual, family and society. Today around 11% of total health care spending accounts for treatment of diabetes and its complications and, given the

incidence and prevalence trends, both developed and developing countries will face an inevitable increase in diabetes-related health expenditure *(3)*. This is not evenly distributed in the world: developing countries often allocate much smaller amounts for management of diabetes and its complications (the differences between high- and low-income countries' allocations are 16-fold, on average) *(3)*. Furthermore, people in developing countries often pay a larger proportion of health care costs themselves *(16–19)*. Effective allocation of resources to treat diabetic patients, many of whom live in low- and middle-income countries, is therefore becoming a challenge. This highlights the ever-growing importance of timely prevention, as well as rational approaches to diabetes management using available therapeutic options (including improved adherence to lifestyle and pharmacological interventions), in order to achieve favourable health outcomes and control costs.

6.5.2. Prevention

Diabetes shares a number of modifiable lifestyle risk factors with other chronic diseases, including cancer and cardiovascular diseases, so the value of health and social policies focusing on general health promotion, disease awareness and active interventions is high.

Nonpharmacological approaches comprising intensive lifestyle interventions (such as healthy diet, regular physical activity and avoidance of tobacco and alcohol use) have been shown by meta-analyses and other studies to prevent or delay the onset of type 2 diabetes and to improve health outcomes in patients who have already developed the disease *(20–25)*. The findings of the Diabetes Prevention Programme also showed the benefits of lifestyle modifications and metformin use in prediabetes patients *(25)*. While the impact of pharmacotherapeutic interventions might be limited to the time of exposure, the positive effect of lifestyle changes tends to last, even after the active intervention stage *(20; 26)*.

Health care systems, particularly in low-resource settings, should be realistic about the feasibility of implementing diabetes prevention and screening programmes. If prevention activities are carried out, these should target high-risk individuals. Identifying and informing people about their increased risk for type 2 diabetes are the first steps in encouraging healthy lifestyle changes. Prevention and effective management of diabetes, however, requires close collaboration between patients and health care providers; the effectiveness of lifestyle interventions largely depends on adherence to recommended behavioural changes *(20; 27)*. Close collaboration can also aid in early diagnosis of type 2 diabetes, allowing timely interventions including maintaining blood pressure and blood levels of glucose and lipids close to recommended ranges. Multiple risk-factor intervention is demonstrated to have beneficial effects with respect to vascular complications, as well as on rates of death from any cause and from cardiovascular causes specifically *(28–30)*. These interventions are essential to slow the progression of the disease and help reduce the risk of developing diabetes-related complications.

6.5.3. Treatment options

The landmark UK Prospective Diabetes Study showed the value of metabolic control in recently diagnosed type 2 diabetes patients: if treated, the burden of chronic complications and mortality can be reduced *(31–35)*. The Study provided important information for clinical guidelines for diabetes treatment, which were adopted soon thereafter *(36–37)*.

Improved glucose control can be achieved using both nonpharmacological and pharmacological options. Some patients are able to manage their condition for an extended time period by adhering to a healthy diet and physical activity. If nonpharmacological treatment alone is insufficient for controlling

blood glucose, metformin is recommended as a first-line oral treatment *(36–41)*. Pharmacotherapy, however, should be supported by maintaining a healthy diet, regular physical activity and avoiding use of tobacco and alcohol *(42)*.

Metformin is generally considered weight-neutral and does not increase the risk of hypoglycaemia. It is, however, associated with initial gastrointestinal side-effects and, given its renal elimination, is not recommended in patients with advanced kidney disease owing to the risk of lactic acidosis. Lifestyle management and metformin are inexpensive interventions that can reduce the economic burden of diabetes. Insulin has also been shown effective as a first-line therapy: some studies have demonstrated that aggressive insulin treatment early in the course of the disease can significantly improve outcomes *(43–44)*.

As diabetes is a progressive disease characterized by deteriorating beta-cell function, maintaining normal blood glucose will require augmentation of therapy. Initiation of insulin early in the course of diabetes management is recommended in clinical guidelines *(40–41)*. A combination of insulin and metformin has been demonstrated to be effective in lowering blood glucose while controlling weight *(45)*. Sulfonylureas can also be used as a second-line treatment option, but these are associated with slight weight gain and with a risk of hypoglycaemia and should also be avoided in patients with renal impairment *(46–47)*. These side-effects may limit the use of these drugs in some patients.

The increasing prevalence of type 2 diabetes has stimulated research and development aiming to find further treatment options, with regard to glucose-lowering mechanisms *(48)*. This has resulted in the introduction of a number of new drugs (such as alpha-glucosidase inhibitors, thiazolidinediones, meglitinides, glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase inhibitors (DPPs), sodium glucose co-transporter 2 (SGLT2) inhibitors and new insulins). Development of new potential treatment options (new GLP-1 receptor agonists and SGLT2 inhibitors and drugs with untested mechanisms) is also continuing *(6; 49)*. Given the number of new therapies introduced, selecting the most clinically and cost-effective therapy for blood glucose management in type 2 diabetes has become increasingly complex *(48)*.

Of the alpha-glucosidase inhibitors, only acarbose, miglitol and voglibose are currently available. These drugs delay the absorption of glucose, thus lowering the degree of postprandial hyperglycaemia. In Japan voglibose was approved for treatment of impaired glucose tolerance, becoming the first oral antidiabetic agent to gain approval for this indication *(50)*. While this class of drug is widely used in Asian countries, elsewhere the usage is limited due to low tolerability and limited efficacy.

Thiazolidinediones do not increase the risk of hypoglycaemia and have similar effectiveness in maintaining blood glucose control compared with sulfonylureas, but concerns have been raised over the safety of this class of drug. Troglitazone, the first drug within the class, was withdrawn due to idiosyncratic hepatotoxicity; rosiglitazone was discontinued due to adverse cardiovascular effects; and pioglitazone was recently found to be associated with increased risk of bladder cancer *(51–52)*. Furthermore, thiazolidinediones are associated with a number of other side-effects including increased risk of fractures *(53)*, peripheral oedema *(54)* and weight gain *(52; 55)*. The long-term risk–benefit profile will limit the use of these drugs.

Repaglinide and nateglinide are approved drugs from the meglitinides (glinides) class. Meglitinide was recently approved in Japan, but is not available in Europe or the United States. These drugs exhibit moderate glucose-lowering effects and may be added to metformin therapy for patients with

continued postprandial hyperglycaemia. Drawbacks include side-effects of weight gain and hypoglycaemia, a suboptimal administration regimen and a higher cost compared to other available treatments. Furthermore, the use of these drugs is limited in patients with renal impairment *(56)*.

Among the most recent additions to the diabetes treatment options are new medicines focusing on the incretin system: GLP-1 receptor agonists and DPPs. DPPs provide comparable and GLP-1 receptor agonists superior glycaemic effects compared to other oral antidiabetic drugs, without increasing weight gain and hypoglycaemia *(57)*. Comparisons of the two classes indicate that GLP-1 receptor agonists achieve greater glycated haemoglobin (HbA1c) reductions than DPPs, with an added benefit of weight loss *(58–62)*. Longer follow-up is needed to determine whether either of these incretin-based therapies will result in durable glycaemic control *(63)*. Furthermore, the safety profile has not been conclusively established and the data available to date suggest that these drugs might not be suitable for patients with renal and hepatic impairment. (Exenatide is contraindicated in advanced stages of kidney disease and the safety of liraglutide is not established in chronic kidney disease, although pharmacokinetic studies suggest that drug levels are unaffected as it does not require renal function for clearance *(64)*.) Furthermore, concerns regarding an increased risk of acute pancreatitis remain unresolved *(65)* and both GLP-1 receptor agonists and DPPs may cause malignant transformations in the pancreas *(66)*. Of the two classes, GLP-1 drugs have been received more favourably and may play an important role in the management of diabetes patients.

Liraglutide, a GLP-1 receptor agonist, was also studied for its potential use in treatment of obesity, resulting in the manufacturer filing an application for a regulatory approval for this indication. Should the drug receive regulatory approval, careful consideration should be made regarding its optimal use for the obesity indication. If left uncontrolled, there could be potential for widespread use, with resulting budget implications and a possible increase in unknown adverse medical events.

Another emerging class is SGLT2 inhibitors. In clinical trials these have demonstrated a reduction in blood glucose, body weight and blood pressure. Urinary glucose excretion is, however, associated with increased incidence of urinary and genital tract infections *(67)*. This drug class might also be unsuitable for patients with renal impairment *(68)*. Furthermore, these drugs cause slight increases in low-density and high-density lipoprotein cholesterol *(69–70)*. The limited efficacy, the increase in infections and the potential effect on outcomes for cardiovascular disease might result in limited uptake of these drugs.

Most clinical guidelines currently recommend use of the above new drug classes as third-line therapy *(36–37)*. Once metformin monotherapy alone does not achieve or maintain an HbA1c target, the next step would be to add a second or third oral agent or injectable therapy, such as basal insulin (human insulin or neutral protamine Hagedorn (NPH) insulin, insulin glargine or insulin detemir), and/or GLP-1 receptor agonist. Meta-analyses by a number of national and regional organizations have shown no therapeutic benefit of insulin glargine over other NPH insulins studied when analysing glycaemic control and the frequency and severity of hypoglycaemia together; consequently, long-acting insulins should only be used as second-line therapy *(71–73)*. Being on complex combination therapy, however, might not be practical: it this can lead to side-effects, drug–drug interactions, reduced patient adherence and increased costs.

Furthermore, as diabetes progresses, patients ultimately move towards using insulin to reach target blood glucose levels; hence, earlier introduction of patients to insulins could be advocated. The higher the HbA1c, the more likely insulin will be required. Metformin is often continued when basal insulin is

added, with studies demonstrating less weight gain when the two are used together. Adding either insulin or GLP-1 receptor agonists to the diabetes management regimen requires patient education regarding glucose monitoring, injection technique, storage and safe disposal, and the identification and treatment of hypoglycaemia.

Due to a general lack of comparative effectiveness studies there is not enough evidence at the moment to recommend the most effective augmentation option once the disease can no longer be controlled with metformin alone *(48)*. With the progression of the disease, insulin initiation is recommended because of worsening of HbA1c control. There are concerns around the safety of several new drug classes, adding to the uncertainty over the value of these new drugs. Finally, insufficient data have yet been collected on the longevity of the blood glucose control achieved with the new drugs to fully assess their role and value. A major ongoing comparative effectiveness trial will compare commonly used diabetes drugs head-to-head, when combined with metformin, in terms of glucose-lowering effectiveness and patient-centred outcomes and should provide results to aid clinical decision-making *(74)*. Furthermore, given the growing populations of children and adolescents, as well as elderly patients, affected by type 2 diabetes, clinicians need reliable data on safe and effective treatment options in these age groups. Finally, bariatric surgery might have benefits beyond weight loss and glucose control, such as reduced cardiovascular events and mortality. It was demonstrated that type 2 diabetes often resolves after these procedures and patients are able to stop some, or even all, of their antihyperglycaemic drugs *(75)*.

Given that diabetes is a more heterogenic disease than previously thought, the more recent recommendations advocate personalizing diabetes care *(40; 76)*, but personalized patient-centred diabetes management might be of secondary consideration in low-resource countries. It is therefore essential to develop and adopt rational diabetes treatment options. A recent report by the IMS Institute for Healthcare Informatics suggests that in both high- and low-income countries spending on drugs will continue to increase due to the rising prevalence of diabetes. As mentioned, estimated expenditure on diabetes drugs in 2017 may be over US$ 50 billion, making diabetes the second most expensive disease area *(1)*. As available treatment options continue to change, cost implications of the chosen therapy need to be taken into account, given the ever-increasing prevalence and continuing resource pressures. It must be acknowledged that costs will be a critical issue driving the selection of glucose-lowering agents in many environments, and that less expensive agents should be chosen in resource-limited settings.

6.5.4. Potential policy options

Rational prescribing options include:

- monitoring prescribing patterns to assess whether they are evidence-based (and consistent with local guidelines);
- enhancing the use of generics, particularly in low- and middle-income countries, to manage budget impact;
- investigating liraglutide's new indication for obesity – should the drug be approved, managed introduction is needed.

Education for prescribers and patients should be provided, including academic detailing for prescribers and education on self-management for patients.

Opportunities to develop and implement health policy interventions include:

- defining and implementing evidence-based principles in countries, where possible, and translating this to other contexts and countries (examples of successful diabetes management from resource-rich countries should be translated to developing countries, including benchmarking of countries and identifying the need for intervention);
- developing and implementing policies for rational drug use (including consistency with guidelines) and effective health policies to prevent disease and its progression to complications (WHO aims to stimulate and support the adoption of effective measures for the surveillance, prevention and control of diabetes and its complications, particularly in low- and middle-income countries).

Comparative effectiveness and safety research of new diabetes therapies is needed to justify the choice of treatment regimens. Choosing wisely among the treatment options available is difficult, given the limited number of comparative effectiveness and safety studies conducted in the area. The effectiveness and safety of new drugs should be demonstrated in studies versus current optimal treatment.

6.5.5. References

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7. Future directions and brief conclusions

The current rapid pace of therapeutic innovation, particularly for NCDs, is extremely positive from a patient perspective. At the same time, many of these new products individually and collectively are putting increasing pressure on a number of European health systems, both clinically (in terms of therapeutic complexity) and economically (in terms of cost of treatment and overall health budgets). To mitigate such pressures, further development of systems and processes to optimize the entry of new medicines is necessary across Europe, in countries with well developed medicine policy and regulation traditions and those with less mature systems. Key steps in these processes should include methods to distinguish and reward meaningful and stepwise clinical innovation and evaluation mechanisms for these and other policy interventions.

This report has examined the current evidence base across Europe, evaluating policies that affect medicines throughout their lifecycle (research and development to disinvestment – see Fig. 1 in section 1.1). While many European countries have not traditionally required active priority-setting for access to medicines, medicines policies are increasingly seen as critical in order to improve efficiency in spending, while maintaining an appropriate balance between access and cost–effectiveness. A recent PPRI query (Annex 1) carried out to inform this report, to which 27 countries responded, illustrates some key challenges European health systems face as they set out to develop effective medicines policies:

- balancing the need to provide access to new medicines with budgetary restraints;
- determining the value of new medicines in the face of limited available data and evidence;
- pricing and fair reimbursement of new medicines, particularly in the context of external price referencing policies present in many countries;
- responding to demand for confidential MEAs – a particular issue for public health systems built on transparency as a core value;
- creating mechanisms for reimbursement decision-making at product launch that maintain flexibility as additional data subsequently become available (for example, if a medicine does not meet clinical expectations) or if usage grows unexpectedly;
- managing the growing prevalence of biological therapies for many conditions, including increasing competition from biosimilars.

While not addressing all these challenges, this report has examined policies, tools and activities to facilitate the introduction of new medicines and available evidence of their impact in Europe. The individual chapters have analysed policies, tools and activities employed for medicines before, during and after launch. While many sections contain a summary of key findings, and throughout the report gaps in knowledge and issues for further action are identified, this closing section provides some synoptic conclusions and highlights a number of overarching conclusions and considerations for future directions to ensure appropriate access to innovative medicines.

7.1. Current status

Overall, although many European countries have introduced one or more policies or activities related to priority medicines, few countries engage throughout the medicine's lifecycle to facilitate access to new medicines. In addition, countries vary substantially in how they introduce and finance new medicines. More published evidence is available for EU countries than for newly independent states and Balkan countries regarding these activities and their impact, and it is therefore difficult to assess whether access to new medicines across Europe is generally evidence-based and/or equitable based on

need. What is clear, however, is that stakeholders and decision-makers are increasingly coming to appreciate the extent of the issue and implications carried by the availability of new high-priced medicines.

At the launch of a new medicine limited evidence is usually available on its real-life impact and even fewer studies comparing clinical effectiveness across therapeutic alternatives. Adequate assessment of the health gain of a new medicine would require tools such as head-to-head randomized trials, ongoing physician education including education in critical drug evaluation and coordination of patient registries.

Countries are increasingly using HTA to guide their reimbursement decisions, often in conjunction with budget impact analysis. Many countries acknowledge the limitations of current HTA methods, which experts propose to address at least in part by introducing decision analysis as an element of HTA methodology. Once a health system has determined the clinical value of a product, other economic tools widely employed include MEAs, rebates, clawbacks and paybacks, since these can generate savings when systems and/or manufacturers are unwilling or unable to negotiate list prices down. Legislative tools may be important as well: national legislation should not hinder off-label use of affordable drugs when strong evidence on their effectiveness and safety is available outside their registered indications. Drug policies should follow the position expressed in the WHO EML towards the evidence-based (and not registration-based) reimbursement of drugs.

Consensus is growing among payers that new medicines should be priced and/or reimbursed according to the added therapeutic value they deliver. Some countries have defined clear criteria and processes for medicines value assessment and decision-making, but many others face fragmented decision-making as a result of divisions of authority for various health care services. In particular, although EU countries have implemented many policies and tools in this area, to date few publications evaluate their impact.

Indeed, the balance between ensuring long-term sustainability of health care systems with appropriate access for patients and fair reimbursement for innovation is one of the biggest challenges for systems in Europe and worldwide. For example, some stakeholders advocate price transparency, whereas others maintain that price confidentiality is the only way to ensure affordability of medicines in less wealthy countries. Consensus on issues such as this is unlikely in the immediate future because of competing stakeholder interests and certain peculiarities of the European pharmaceutical market (such as parallel trade, extensive use of ERP and large disparities between countries in ability to pay). It is encouraging, however, that EFPIA is proposing potential ways to assist with access among less-well-off European countries.

Clinical guidelines are an effective tool to promote the appropriate use of new medicines, provided that their recommendations are explicit and stem from a transparent and systematic assessment of available evidence. To effectively translate these recommendations into practice, implementation strategies should be tailored to local contexts and start pre-launch involving clinical experts and strong conflict of interest regulations. They could also include the development of quality indicators starting at pre-launch. Elements that European countries should consider in further developing their clinical guideline systems include a shared approach with local practitioners, the configuration of health services, health professionals' skills and attitudes and available resources.

7.2. Potential future directions

With all these elements in mind, several key themes for future collaboration and research emerge from this review.

7.2.1. Prioritization processes should incorporate principles of collaboration and transparency

Equity in access to medicines continues to be a core value in many European countries, and therefore prioritization may be necessary to preserve this access. New medicines and technologies provide opportunities, but if they have high costs a declining proportion of the population will account for a larger proportion of health care expenditure. A lack of collaborative and transparent policy-making and prioritization runs the risk of unfair and arbitrary treatment decisions and inefficient systems.

Future directions include the following:

- Potential methods to expand current pre-launch value generation and assessment include improved processes to differentiate innovation presented by new products in a meaningful way, effectively placing these benefits in the context of different European health care systems.
- Payer collaboration should continue on evaluation of clinical benefit and cost–effectiveness, potentially expanding the collaborative networks to include European countries outside the EU.
- Since each country faces unique challenges and will require tailored solutions, open prioritization with stakeholder engagement will bring clarity and maximize public acceptance of the value of medicines, particularly when these processes transparently consider patient and societal aspects in order to make sustainable, evidence-informed decisions.
- This must be tempered by realism from companies regarding their pricing approaches, however, given concerns, for instance, with how prices are derived for new cancer medicines.
- National legislation affecting drug use should be tailored to public health needs so that therapeutic decisions are based on the available evidence rather than solely on drug registration.

7.2.2. Cooperation between stakeholders needs to involve better balancing of the value of innovation with equitable, affordable patient access

The current debate on barriers to access for new medicines has focused mainly on how national authorities can effectively use gatekeeping instruments such as HTA. This discussion merits broadening to find consensus on what constitutes a fair reward for industry innovation while still preserving access for patients, highlighted, for instance, by new medicines for cancer, orphan diseases and HCV. While fully acknowledging the need to reward industry for its research and development efforts and the risk companies assume in pursuing innovation, it is also important to ensure that countries do not have to limit access because they cannot afford new medicines that represent a true therapeutic advance. It is also important that industry in turn does not seek to exploit the situation, with cost of goods of small oral molecules as low as 2% of patented prices.

Future directions include the following:

- Research transparency should limit threats of publication bias and facilitate availability of data for HTAs and for evaluation of the added value of medicines by decision-makers and the general public.
- Policy-makers should plan for evaluation of the impact of policy interventions early in the design process, aided by strong research designs and advanced statistical techniques such as experimental or quasi-experimental studies, although observational designs can also be helpful in shedding light on possible effects when more rigorous techniques are not possible.

- Researchers, policy-makers and private stakeholders should cooperate to ensure adequate access to data and reasonable costs, strengthen existing data collection systems and maintain confidentiality and privacy as needed.
- Pharmaceutical companies need to be more transparent in how prices of their new medicines are derived, given current concerns.

7.2.3. Collaboration among regional or subregional health systems could benefit from including a particular focus on chronic care, specialty medicines and rare diseases

Several countries have recently introduced new application and decision processes for specialty medicines in an attempt to better manage pharmaceutical expenditure. Other countries are creating collaboration networks to improve access to new medicines. Such creative strategies and others are needed to achieve sustainability and access to new medicines, wherein many countries can benefit from closer collaboration.

Future directions include the following:

- While many infectious conditions can be effectively treated in an episodic, "clinic"-based system with limited support for medicines management, appropriate use of medicines has become far more challenging with chronic care, where an additional focus on adherence should be employed to obtain the projected impact; greater collaboration between health professionals and pharmaceutical care services are potential activities to consider.
- Closer coordination within and between European health systems should focus on the entire continuum of care including prevention and treatment, particularly for many NCDs, although this may not mitigate the prioritization and value questions discussed above.
- Networks of information exchange for new priority medicines in Europe – including pricing trends, treatment protocols and guidelines, common principles for the registries for patient characterization and effectiveness and similar – can be a solution.
- Emphasis on continuing professional development among physicians to enhance the rational use of medicines, with independent expert groups involved in guidance development building on the success of initiatives among European countries and regions, as in Italy (Emilia-Romagna), Scotland, Spain (Catalonia) and Sweden (Stockholm Metropolitan Healthcare Region). This also includes comprehensive dissemination and follow-up programmes for agreed prescribing guidance and guidelines.

In relation to the above, and as a consideration for the future, it is clear that decision-makers across Europe (and beyond) will increasingly be faced with difficult choices in respect of new pharmaceuticals (and health technologies). As such, they will be required to make informed decisions that balance their duty to maintain health budgets while providing access to the best possible medicines and interventions for their populations. This will in future involve greater use of IT, better steering of medical practitioners to comply with clinical evidence (perhaps through a combination of financial and nonfinancial incentives), potential considerations around task-shifting in the health workforce more generally and better targeting of national drug policies to those using resources more intensely (multicomorbidity patterns).

As mentioned at the outset, this report provides a review of policies and principles around the introduction of new premium-priced medicines (including financing). It does not and cannot cover all the issues in depth. It does, however, aim to provide an informed high-level overview – based on country examples as well as more theoretical and technical material – such that it can act as a resource for policy-makers seeking to understand better the issue at stake and the overarching context. The

report has been through several iterations and an informal two-month consultation period from mid-August to mid-October 2014.

Annex 1

RESULTS OF THE PPRI QUESTIONNAIRE ON NEW HIGH-COST (PREMIUM-PRICED) MEDICINES

The PPRI network consists of 42 countries – 37 European and 5 non-European. Of the 27 countries participating in the questionnaire, Canada was the sole non-European PPRI member country (Table 1).

Table 1. Response rate of European PPRI network participating countries and Canada

PPRI network participating country	Response	PPRI network participating country	Response
Albania	**Y**	Lithuania	N
Austria	**Y**	**Luxemburg**	**Y**
Belgium	**Y**	**Malta**	**Y**
Bulgaria	N	**Netherlands**	**Y**
Canada	**Y**	**Norway**	**Y**
Croatia	**Y**	**Poland**	**Y**
Cyprus	N	Portugal	N
Czech Republic	**Y**	Republic of Moldova	N
Denmark	**Y**	Romania	N
Estonia	**Y**	**Serbia**	**Y**
Finland	**Y**	**Slovakia**	**Y**
France	**Y**	**Slovenia**	**Y**
Germany	N	**Spain**	**Y**
Greece	**Y**	**Sweden**	**Y**
Hungary	**Y**	**Switzerland**	**Y**
Iceland	**Y**	The former Yugoslav Republic of Macedonia	N
Ireland	N	Turkey	N
Italy	**Y**[a]	Ukraine	N
Latvia	**Y**	**United Kingdom**	**Y**

[a] Information provided by a WHO Collaborating Centre based in Italy.

Content of the questionnaire – key questions

- Does a country-specific definition of high-cost or premium-priced medicines exist (Table 2)?
- What are the key challenges to the funding of new premium-priced medicines (Table 3)?
- Are there specific pricing policies in the outpatient sector for new premium-priced medicines compared to ordinary medicines (Table 4)?
- Are there specific reimbursement policies in the outpatient sector for new premium-priced medicines compared to ordinary medicines (Table 5)?
- Are there specific pricing policies in the inpatient sector for new premium-priced medicines compared to ordinary medicines (Table 6)?
- Are there specific reimbursement policies in the inpatient sector for new premium-priced medicines compared to ordinary medicines (Table 7)?
- Are there any MEAs for new premium-priced medicines (Table 8)?
- Are further initiatives/policies currently being undertaken to better manage the entry of new premium-priced medicines (Table 9)?

Table 2. Country-specific definition of high-cost or premium-priced medicines

Country-specific definition	Country
No definition (21)	Belgium, Canada, Croatia, Denmark, Estonia, Finland, Greece, Hungary, Latvia, Luxemburg, Malta, Netherlands,[a] Norway, Poland, Serbia, Slovakia,[a] Slovenia, Spain, Sweden, Switzerland, United Kingdom
Under development (1)	**Austria**: a definition of high-cost and specialized medicines is being developed.
Definition (5)	**Albania**: the definition "the expensive medicines" is used in the reimbursement list.
	Czech Republic: a "highly innovative product" is defined as a medicine containing an active substance, which can be used to treat diseases that – to date – have not responded to other medicines or which represents a promising substantial improvement in treatment but has insufficient amount of data on cost–effectiveness or on results of treatment when used in clinical practice.
	France: no real definition of high-cost or premium-priced medicines exists, but medicines with a *service médical rendu* [health benefit] – those ranked major, important or sometimes even moderate, and with a moderate or higher improvement in actual benefit – can be classified as "innovative". Moreover, a decree published on 2 October 2012 specifies that an HTA should be conducted when the two following conditions are met: • improvement in actual benefit (*amélioration du service médical rendu*) of level III (moderate) up to level I (major); • significant impact on health insurance expenditure, given the price of the product, its impact on the market structure and similar. Although there is no specific rule, the revenue of the product is often taken into account, especially if it is expected to exceed €20 million by the second year of commercialization.
	Iceland: "specialty care high-cost medicines" are defined as medicines that need special care and clinical guidelines and are costly.
	Italy: no specific definition of high-cost or premium-priced medicines is in place. A new algorithm is under development that will provide an assessment of the degree of innovation of new medicines. The 2012 report of the Italian Observatory on the Use of Medicines stated that while a technical and scientific commission of the Italian Medicines Agency (AIFA) had approved criteria of innovation considering only therapeutic improvements in 2007, the new algorithm will consider a more comprehensive evaluation of innovation, also taking "scientific" advances into account.

[a] No specific definition but a list of high-cost medicines is available in the Netherlands (2006–2012) and Slovakia.

Table 3. Key challenges to the sustainable funding and management of new premium-priced medicines

Challenges		Country
Access and funding	Providing access to orphan medicines	Albania, Belgium
	Balancing the need to provide access to new premium-priced medicines (therapeutic innovations) with other budgetary cost pressures/sustainability	Canada, France, Iceland
	Funding/finding new sources of financing/sustainability of expenses for public finance in the context of budgetary cuts (budget restrictions)	Croatia, Czech Republic, France, Italy, Latvia, Malta, Slovenia, Sweden
Value for money	Limited data to indicate whether premium-priced medicines have the desired impact or uncertainties in measuring effectiveness	Canada, Czech Republic, Hungary
	Defining the innovation in terms of added therapeutic value or the costs of treatment – too high compared to the added therapeutic value	Greece, Latvia
	Ensuring that the medicines bill stays within affordable limits and delivers value for money for the NHS	United Kingdom
	Limited data to assess their added value (surrogate outcomes, no relevant improvements in survival, few studies/patients included)	Italy
	The requirement to show an equally high benefit if the additional cost of using a medicine is high (compared to the alternative)	Norway
	The potential for subsequently added indications for premium-priced medicines that expand the market for a medicine without a corresponding price reduction	Canada
Limited choice	No possibility to “switch” to other products in the field of high-cost monopoly products (no competition)	Slovenia
	No option to shift to biosimilars (in Italy, for instance, where their use is recommended for newly treated patients only)	Italy
Prices	Reduction of prices to guarantee access	Spain
	Dependence on prices in the reference countries and nonconsideration of discounts	Switzerland
Limited interface management	Limited coordination between outpatient and inpatient sectors	Austria

Challenges		Country
	Lack of agreement over whether a standard approach to funding of new premium-priced medicines across jurisdictions and across types of medicines (oncology medicines, medicines for rare diseases, etc.) is appropriate and if so, what it would look like	Canada
Others	Unmet medical needs	Belgium
	New biological medicines that contribute significantly to the medicines bill; biosimilars could be an alternative	Belgium, Canada, France
	Lack of agreement over whether a standard approach to funding of new premium-priced medicines across jurisdictions and across the types of medicines (oncology medicines, medicines for rare diseases, etc.) is appropriate and if so what it would look like	Canada

Table 4. Pricing in the outpatient sector

Pricing policy		Country
No difference[a] (25)	Premium-priced medicines are priced according to the ordinary pricing rules.	Albania, Austria, Belgium, Canada, Croatia,[b] Czech Republic, Denmark, Estonia, Finland, Greece, Hungary, Iceland, Italy, Latvia, Luxemburg, Malta, Netherlands, Norway, Poland, Serbia, Slovakia, Slovenia, Spain, Switzerland, United Kingdom
Specific pricing procedures	Pricing schemes for high-cost/innovative medicines should take into account the results of an HTA evaluation by the Commission for Medical Evaluation and Public Health (CEESP). This is a recent process (end of 2012), so only a few reports are yet available. Price–volume agreements are common.	France
	Innovative medicines are priced on the basis of a cost–effectiveness analysis from a broad societal perspective.	Sweden
Local procurement	No specific pricing procedure is in place: pricing is negotiated by AIFA at the national level. Nevertheless, local health authorities may use tendering procedures that allow large rebates through the competitive selection of active pharmaceutical ingredients for use within local health services.	Italy

[a] Or it is not possible to indicate a consistent difference for premium-priced medicines compared to other medicines.

[b] Although high-cost medicines are on the list of hospital medicines.

Table 5. Reimbursement in the outpatient sector

Reimbursement policy	Country
No specific reimbursement policies (20)	Austria, Denmark, Estonia, Finland, France, Greece, Hungary, Italy, Latvia, Luxemburg, Malta, Netherlands, Norway, Poland, Serbia, Slovenia, Spain, Sweden, Switzerland, United Kingdom
Further reimbursement-relevant information	
A committee for premium-priced and/or specialized medicines is established in order to explore best practice in funding/reimbursement models of these medicines.	Austria
When reimbursed, premium-priced medicines are always submitted to a prior authorization process (restriction indication), which determines whether indications/patients are eligible for reimbursement.	Belgium
The reimbursement decision for new premium-priced medicines is taken by each federal provincial territorial government, based on cost–effectiveness and affordability.	Canada
High-cost medicines are on the list of hospital medicines.	Croatia
High-cost medicines tend to be supplied by hospital pharmacies or, in some cases, by private pharmacies following specific agreements with the Italian health service.	Italy
Highly innovative products are not incorporated into any clusters (reference groups) when setting the reimbursement price. This is set by the State Institute for Drug Control, based on the lowest price of the product in the EU. Highly innovative products are provided only in special medical facilities (centres of excellence) under the conditions agreed with insurance funds. During the temporary reimbursement period medical facilities are obliged to gather effectiveness data.	Czech Republic
An extra 5% rebate is applied to high-cost medicines upon inclusion in the positive reimbursement list for one year. In addition, National Organization for Health Services Provision (EOPYY) committees examine whether the patient has the prerequisites for therapy with high-cost medicines.	Greece

Reimbursement policy	Country
Almost all medicines in this group are fully reimbursed but expensive medicines have a different reimbursement policy from other reimbursed medicines. • Specific contracts are set up between the health insurance fund, hospitals and wholesalers. • Patients get these medicines not from private pharmacies but from hospital pharmacies. The mark-up applied to expensive medicines is only the wholesaler's mark-up.	Albania
A new application and decision process for "specialty care high-cost medicines" was introduced in May 2013, with a clinical and economic evaluation undertaken by the Icelandic Medicine Pricing and Reimbursement Committee in cooperation with the University hospital and National Insurance.	Iceland
Price–volume agreements and risk-sharing agreements are common for these types of medicine.	Hungary
In December 2011 specific funding/reimbursement schemes for high-cost/innovative medicines were introduced. Reimbursement is set at a maximum of 20% of the pharmacy retail price if the medicine does not have an official determined price in at least five countries within the EU. "Conditional categorization", a kind of conditional reimbursement, is granted for a period of two years; at least 180 days before the expiry of this period the marketing authorization holder is required to submit a pharmaco-economic analysis and evidence of the medicine's efficacy in clinical practice. Based on these data the Ministry of Health decides on further listing or changes in reimbursements for the medicine. This is the legal framework for conditional categorization.	Slovakia

wTable 6. Pricing in the inpatient sector

Pricing policy		Country
Premium-priced medicines are priced according to the ordinary pricing rules[a] (18)		Austria, Belgium, Croatia, Czech Republic, Estonia, Finland, Greece, Hungary, Iceland, Italy, Latvia, Luxemburg, Malta, Poland, Slovenia, Spain, Switzerland, United Kingdom
No information provided (5)		Albania, Canada, Netherlands, Serbia, Slovakia
Specific procedures	The Danish regions have established the Coordination Council for the Deployment of Hospital Medicine (KRIS), particularly to coordinate the application of cancer medicine. KRIS considers whether a medicine should be recommended as standard treatment; this means that the medicine is implemented as the common medical treatment for a group of patients and is thereby accessible at all attending hospital at procured prices.	Denmark
	A supplementary list outside the DRG system exists for high-cost/innovative medicines. Their official prices are negotiated by the French Pricing Committee (CEPS) and published in the official journal; these prices represent the maximum amount of reimbursement. If the purchasing price is below the maximum level of reimbursement, the difference is shared equally between the hospital and the national health fund. To set the maximum price for high-cost/innovative medicines, CEPS should take into account the results of a CEESP HTA evaluation. This is a recent process (end of 2012), so only a few reports are yet available.	France
	Cooperation between hospitals (health regions), the Norwegian Medicines Agency (NoMA) and the Norwegian Knowledge Centre for Health Services to improve the evaluation of cost–effectiveness of new technology (including medicines) in hospitals was established in 2014. The hospitals and NoMA agree on a selection of medicines to be evaluated by NoMA within 180 days. NoMA then forwards the evaluation reports to the hospitals, which decide whether to start using the medicine. In 2014 the plan is to evaluate at a minimum the five medicines with the highest impact on the budget, which are mostly in cancer treatment.	Norway

Pricing policy		Country
Local procurement	Innovative and high-cost medicines can be purchased directly by the county councils (regions) in discussion with pharmaceutical companies, even though the administration of these medicines does not require a hospital setting.	Sweden
	No specific pricing procedure is in place: pricing is negotiated by AIFA at the national level. Nevertheless, local health authorities may use tendering procedures that allow large rebates through the competitive selection of active pharmaceutical ingredients for use within local health services.	Italy

[a] Or it is not possible to indicate a consistent difference for premium-priced medicines compared to other medicines.

Table 7. Reimbursement in the inpatient sector

Reimbursement policy		Country
No specific reimbursement/funding policies in general[a] (16)		Austria, Denmark, Estonia, Finland, Iceland, Italy, Latvia, Luxemburg, Malta, Norway, Poland, Spain, Sweden, Switzerland, United Kingdom
Funding outside the DRG system (individual product-specific funding)	Premium-priced medicines are always submitted to a prior authorization process (to establish restriction indication/patients eligible for reimbursement).	Belgium
	Some premium-priced medicines are excluded from the hospital lump sum system or receive a separate reimbursement sum.	Austria, Belgium, Estonia, Finland, France
	Reimbursement can be granted via the item-based reimbursement scheme, which includes disease registers.	Hungary
	Some high-cost/innovative oncology medicines can be individually reimbursed (by individual access to the chemotherapy catalogue).	Poland
Special agreements between hospitals and health insurance funds	A supplementary list outside the DRG system for high-cost/innovative medicines exists. Their official prices are negotiated by CEPS and published in the official journal; these prices represent the maximum amount of reimbursement. If the purchasing price is below the maximum level of reimbursement, the difference is shared equally between the hospital and the national health fund.	France
	Medicines are funded via the DRG system. For those cases excluded from the DRG system (including some high-cost medicines such as oncology agents), medicines are funded by EOPYY. Hospitals are subject to National Substance Committee activities in order to achieve lower prices through negotiations with companies.	Greece

Reimbursement policy		Country
	From 2006 to 2013 separate funding was available for high-cost and orphan medicines listed by the Dutch Health Care Authority (NZa) to help hospitals finance them. The hospital received 80% reimbursement from the health insurer for medicines on the NZa list of high-cost medicines; the remaining 20% had to be paid from the hospital's budget. Orphan medicines were 100% funded by social health insurance. Since 2013 the use of high-cost medicines by hospitals is fully reimbursed by the health insurer as an add-on to the DRG system.	Netherlands
	Some medicines are always funded by hospitals (whether administered to an outpatient or in the hospital). This has been the case for TNF alpha inhibitors and multiple sclerosis medicines for some years; in 2014, cancer medicines were transferred to hospital funding.	Norway
	Some high-cost medicines (in a list defined by the Categorization Committee of the Ministry of Health) are not included in DRG funding but are funded separately.	Slovakia
	High-cost medicines are separately financed for hospitals by the health insurance fund.	Slovenia
Special funds	There is a special programme (with funding) for treatment of rare diseases in children.	Latvia
	Two special arrangements are in place: patient access schemes and the Cancer Drugs Fund (with a budget of£200 million/€240 million a year for three years from April 2011) to help patients get the medicines their doctors recommend. This has now been extended for a further two years to March 2016.	United Kingdom
Others	A new application and decision process for "specialty care high-cost medicines" was introduced in May 2013, with a clinical and economic evaluation undertaken by the Icelandic Medicine Pricing and Reimbursement Committee in cooperation with the University hospital and National Insurance.	Iceland
	Risk-sharing agreements have been initiated by hospitals between the social health insurance fund and pharmaceutical companies.	Slovakia

[a] Although specific arrangements are in place for premium-priced medicines (some countries may be listed more than once).

Table 8. MEAs: overview

MEAs	Country
MEAs in the outpatient sector (12)	Belgium,[a] Czech Republic, Estonia, France, Hungary, Italy, Latvia, Malta, Netherlands, Poland, Slovenia, Switzerland
MEAs in the inpatient sector (12)	Belgium,[a] Czech Republic, Hungary, Italy, Latvia, Netherlands, Norway, Poland, Slovakia, Slovenia, Spain, Switzerland, United Kingdom[b]
No (neither in the outpatient nor in the inpatient sector) (6)	Austria, Croatia, Finland, Greece[c], Iceland, Luxemburg
No[a] (5)	Albania, Denmark, Canada, Serbia, Sweden

[a] Contract negotiations between the pharmaceutical company and the reimbursement agency in Belgium

[b] Includes patient access schemes (United Kingdom)

[c] A legal framework was provided in 2014 for the social health insurance fund to allow for MEAs in Greece.

Table 9. Horizon scanning, forecasting and post-launch activities

Country	Pre-launch activities		Post-launch activities
	Horizon scanning	Forecasting	
Belgium	No current activities	No current activities	Monitoring of expenses: monitoring of reimbursement specific expenses reports, audit reports of the social health insurance fund are produced. Education: this includes prescription monitoring and consensus conferences (global evaluation of the medical practice regarding medicines). Engineering: disease management programmes are in place, such as a "cancer plan", "AIDS plan" or "chronic illness plan".
Canada	The Canadian Network for Environmental Scanning in Health identifies and shares information on new and emerging health technologies.	Each jurisdiction requires budget impact analyses as part of their medicines submission process.	The Canadian life and health insurance industry has developed an industry-wide pooling agreement to protect fully insured private drug plans from the full financial impact of high-cost medicines.
Czech Republic	No	No	Information is given to patients about temporary reimbursement. The Ministry of Health is obliged to gather data about the characteristics of patients treated with highly innovative medicines, their diagnosis and previous treatment, the effects of the new treatment and follow-ups on the treatment.
Estonia	No	No	Prescription monitoring is done by health insurance funds.
France	"Narrow horizon scanning" is done by different institutions.	These data are supposed to be included in the application file provided by the manufacturer to CEESP prior to the evaluation.	

Country	Pre-launch activities		Post-launch activities
	Horizon scanning	Forecasting	
Greece	No current activities	No current activities	Specific social health insurance committees examine all new premium-priced medicines regarding the necessity of treatment as well as the response of patients after a period of time. Enforcement: some general prescribing restrictions on high-cost medicines are set during their evaluation for inclusion in the positive list of drugs for reimbursement. Three disease registries are in development (for hepatitis B, chronic myeloid leukaemia and multiple sclerosis).
Hungary	No	No current activities	
Italy	A horizon scanning project is in place in one region (Veneto).		Registries are in place to monitor the use of premium-priced medicines and their effectiveness and safety, and to implement the risk-sharing, cost-sharing and payment-by-results agreements. "Therapeutic plans" are in use: these are forms GPs need to fill in to provide specific information on the correspondence between the patient's clinical situation and the indications of use of medicines. They are often required for prescribing premium-priced medicines, thus limiting their use to specific clinical situations. Local formularies are sometimes used to select medicines with better risk–benefit and cost–benefit profiles. Clinical guidelines are sometimes implemented at the local level to promote the appropriate choice and use of premium-priced drugs. Campaigns promote the use of generic medicines.
Iceland	This is in the process of implementation.	This is in the process of implementation.	

Country	Pre-launch activities		Post-launch activities
	Horizon scanning	Forecasting	
Latvia	No	No	No education or engineering activities are currently undertaken for new medicines. There are pharmaceutical budgets for physicians, with penalties for over-budget situations. Regulations regarding dispensing of medicines are in place for enforcement.
Malta	No	No	No
Norway	This is in the process of implementation (operative from October 2014).		A new system for individual reimbursement is being implemented. A study on switching between the originator's biological medicine and biosimilars is under way.
Slovenia	No	No	Prescribing restrictions, quality circles and auditing are in place.
Switzerland	No	No	No
United Kingdom	UK PharmaScan (horizon scanning database)	No	Guidance, advice and support are available from the National Institute for Health and Care Excellence (NICE) Medicines and Prescribing Centre.

Note: Albania, Austria, Croatia, Denmark, Finland, Luxemburg, Netherlands, Poland, Serbia, Slovakia, Spain and Sweden did not report on this question.

Annex 2

MAIN HTA UNITS AND INITIATIVES ACROSS MEMBER STATES IN THE WHO EUROPEAN REGION

Member State	HTA organization (primarily public sector entities with partners and other organizations)	Organizational mandate (or comments if no public sector HTA entity)	Contact information (useful links)
Albania	No independent public sector HTA entity to date; HTA strategy under development	The Ministry of Health includes a unit for the management of medical devices. A2009health system modernization project included terms of reference to develop an HTA strategy for a broad spectrum of health technology, including drugs and biologics.	• https://www.frameworkcontracts.eu/files/tor/tenders/ToR_HTA%20project%20in%20Albania.pdf • Medical device management contact: Ledina Picari, lpicari@moh.gov.al
Andorra	Caixa Andorrana Seguretat Social (CASS)	The national health system has specific provisions for reimbursement of especially costly drugs, including dialysis, chemotherapy and radiotherapy.	• http://online.cass.ad/documents/534091/553427/DLFE-2264.pdf
Armenia	No independent public sector HTA entity to date; decisions on selection partly covered by the Centre for Procurement and Innovation of the Ministry of Health	The Ministry of Health's Health Project Implementation Unit (HPIU) assesses medical devices for coverage; the Ministry also has a drug policy but limited information on HTA processes. A draft law is pending on drug pricing and importation. Significant capacity is available within the Drug Agency in the areas of rational use and evidence-based medicine, but there is no legal responsibility for the work to be done.	• http://healthpiu.am/index.html • HPIU contact: Armen Karapeyan, akarapetyan@moh.am or Healthpiu@gmail.com • http://www.moh.am/?section=news/open&id=143&nid=2610
Austria	Health Austria (Gesundheit Österreich GmbH – GÖG)	The national research and planning institute for health is an independent private entity but reports to the Federal Minister for Health (BMG). It incorporates the health economics/HTA functionality of the former Austrian Health Institute. Other areas include the Federal Institute for Quality in Health Care and the Fund for a Healthy Austria. It is an EUnetHTA partner.	• http://www.goeg.at/ • Director: Georg Ziniel • Contact: Ingrid Rosian-Schikuta, ingrid.rosian@goeg.at • Ministry HTA contact: Wolfgang Ecker, wolfgang.ecker@bmg.gv.at

Member State	HTA organization (primarily public sector entities with partners and other organizations)	Organizational mandate (or comments if no public sector HTA entity)	Contact information (useful links)
	Ludwig Boltzmann Institute HTA (LBI-HTA)	An academic non-profit-making institute, LBI-HTA's research areas include oncology, health economics and HTA methods and steering instruments, among others. It is an EUnetHTA partner.	• http://hta.lbg.ac.at/page/homepage • Contact: office@hta.lbg.ac.at • Director: Claudia Wild, claudia.wild@hta.lbg.ac.at
	Pharmaceutical Evaluation Board (Heilmittel-Evaluierungs-Kommission – HEK)	HEK evaluates therapeutic benefit based on data submitted by sponsors and recommends reimbursement to the Federation of Austrian Social Insurance Institutions (an EUnetHTA partner), with ultimate decision-making authority from the Federal Ministry of Health, Family and Youth.	• http://www.sozialversicherung.at/portal27/portal/esvportal/content/contentWindow?contentid=10007.683890&action=2&viewmode=content • Current HEK members: http://www.sozialversicherung.at/portal27/portal/esvportal/content/contentWindow?contentid=10007.684193&action=2&viewmode=content
	UMIT – the Health and Life Sciences University	UMIT has a research area focused specifically on health benefits, risk and cost–effectiveness of personalized cancer strategies.	• http://www.umit.at/page.cfm?vpath=departments/public_health/home_d • Department Chair: Uwe Siebert, public-health@umit.at
	Institute of Social Medicine and Epidemiology, University of Graz	The Institute is tasked with studying the distribution and origin of health and disease in a social context, the investigation and development of the health system and the development and evaluation of health promotion and prevention. Reviews are broad but at times include HTA (e.g. mammography).	• http://www.medunigraz.at/sozialmedizin/ • Chair: Wolfgang Freidl, sozmed@medunigraz.at
	Department for Evidence-based Medicine and Clinical Epidemiology, Danube University Krems	The Department aims to support decisions in the Austrian health care system with evidence-based methods, such as meta-analyses and systematic reviews. It also serves as the Austrian branch of the German Cochrane Centre.	• http://www.donau-uni.ac.at/de/department/evidenzbasierteme dizin/index.php • www.cochrane.at • Department Head: Gerald Gartlehner, cochrane@donau-uni.ac.at

Member State	HTA organization (primarily public sector entities with partners and other organizations)	Organizational mandate (or comments if no public sector HTA entity)	Contact information (useful links)
Azerbaijan	No independent public sector HTA entity to date	The Centre for Innovation and Procurement under the Ministry of Health organizes procurement for medicines. The website has a section on medicines and pharmacy, mostly pertaining to regulation, and a portal for drug information aimed at consumers. The Drug Agency is also involved in policies on selection and rational use.	• http://health.gov.az/odenisi_devlet_terefinden.html • http://www.pharma.az/az • http://medportal.az/ • Centre contact: Ramiz Kerimov, kerimov62@hotmail.com
Belarus	No independent public sector HTA entity to date	The Ministry of Health has established a state-owned enterprise (National Centre for Expertise and Testing in Health Care) under the State Scientific Programme on New Technologies, 2011–2015.	• http://rceth.by/ • http://minzdrav.gov.by/en/static/programmes-of-ministry-of-heal/scientic_progr/SSTP_charaterististic1
Belgium	Belgian Health Care Knowledge Centre (KCE)	The federal institution producing studies and reports to advise policy-makers explicitly includes HTA as one of its research domains. It is an EUnetHTA partner.	• https://kce.fgov.be/ • President: Pierre Gillet
	National Institute for Health and Disability Insurance (Institut National d'Assurance Maladie Invalidite – INAMI)	INAMI discusses administrative procedures for registration and reimbursement of medicines, although no explicit HTA process is outlined. It hosts an online tool for price comparison by medical specialty.	• http://www.inami.be/drug/fr/drugs/general-information/refunding/index.htm
	Belgian Centre for Evidence-Based Medicine (CEBAM)	The independent, multidisciplinary and inter-university medical research institute conducts methodological courses, validates CPGs, operates a digital library for health literature and serves as the Belgian branch of the Dutch Cochrane Centre.	• www.cebam.be • Contact: Elizabeth Bosselaers, Elizabeth.Bosselaers@med.kuleuven.be
Bosnia and Herzegovina	Agency for Health Care Quality and Accreditation in the Federation of Bosnia and Herzegovina (Agencija za kvalitet i akreditaciju uzdravstvu u Federaciji Bosne i Hercegovine – AKAZ)	The Ministry of Health-authorized body in the fields of health care quality, safety improvement and accreditation of health care institutions sets accreditation standards and clinical guidelines, but has no apparent HTA authority.	• http://www.akaz.ba/ • Director: Ahmed Novo, anovo@akaz.ba
Bulgaria	National Council on the Pricing and Reimbursement of Medicinal Products (NCPRMP)	A state budget-supported legal entity, comprising a president and six members (doctors, pharmacists, lawyers and economists), NCPRMP's primary mandate appears to be	• http://www.ncpr.bg/en/

Member State	HTA organization (primarily public sector entities with partners and other organizations)	Organizational mandate (or comments if no public sector HTA entity)	Contact information (useful links)
		pricing rather than full HTA. It is an EUnetHTA partner.	
	National Centre of Public Health and Analyses (NCPHA)	An agency within the national health care system, NCPHA is tasked with protecting public health, promoting health and preventing diseases and providing information for health care management. It participates as an EUnetHTA associate partner, particularly with activities related to methodology and dissemination.	• http://ncphp.government.bg/en • Director: Jeni Staykova, j.staykova@ncpha.government.bg • Chief Secretary: Ivan Samardjiev, i.samardjiev@ncpha.government.bg
Croatia	Agency for Quality and Accreditation in Health and Social Care (Agencija za kvalitetu i akreditaciju u zdravstvu i socijalnoj skrbi – AAZ)	Established in 2007, AAZ has explicit authority to carry out consultative HTA (including both clinical and economic evidence) for the Ministry of Health, Croatian Institute of Health Insurance, Croatian Health Insurance Fund, holders of private insurance and hospital management. Its governing council oversees various services, including the Department of Development, Research and Medical Technology. It is an EUnetHTA partner.	• http://www.aaz.hr/hr/procjena-zdravstvenih-tehnologija • President of the Governing Council: Velibor Drakulic • Head of Department of Development, Research and Medical Technology: Mirjana Huić, mirjana.huic@aaz.hr
	Croatian Centre for Global Health (CCGH)	The research centre at the University of Split School of Medicine also serves as the Croatian branch of the Italian Cochrane Centre.	• http://www.mefst.hr/default.aspx?id=140 • http://croatia.cochrane.org/ • Cochrane contact: Dalibora Behmen, dalibora.behmen@mefst.hr
Cyprus	HTA strategy under development	The Ministry of Health Directorate of Pharmaceutical Services handles regulation, pricing and distribution of products reimbursed under the public health system. Audits appear to be based on cost versus clinical evaluation. The Ministry of Health is an EUnetHTA partner.	• http://www.moh.gov.cy/moh/phs/phs.nsf/dmlps13_gr/dmlps13_gr?OpenDocument#
Czech Republic	Institute of Health Economics and Technology Assessment (iHETA)	A nongovernmental, non-profit-making organization, iHETA performs HTA and health economic research and education, in collaboration with health insurance companies, professional societies, government organizations, patient organizations and other companies.	• http://www.iheta.org/o-iheta • Contact: Tomas Dolezal, dolezal@iheta.org

Member State	HTA organization (primarily public sector entities with partners and other organizations)	Organizational mandate (or comments if no public sector HTA entity)	Contact information (useful links)
	Ministry of Health (Ministerstvo Zsravotnictvíeské Republiky)	The Ministry is the decision-making authority for drug procurement; its website includes information on particular products but no explicit HTA process is outlined. It is an EUnetHTA partner.	• http://www.mzcr.cz/
	State Institute for Drug Control (SUKL)	The regulatory agency for drugs and medical devices, SUKL also serves as the decision-making authority regarding pricing and reimbursement, although no explicit HTA process is outlined. It offers scientific and technical consultations to sponsors.	• http://www.sukl.eu/ • Director: Blahuta Zdeněk, Zdenek.Blahuta@sukl.cz
	CzechHTA	A team formed at the Faculty of Biomedical Engineering, Czech Technical University in Prague, CzechHTA focuses on HTA in medical devices.	• http://czechhta.cz/ • Contact: info@fbmi.cvut.cz
Denmark	Coordination Council for the Deployment of Hospital Medicine (Koordineringsrådet for ibrugtagning af sygehusmedicin – KRIS)	KRIS focuses on coordination between the Danish regions on the introduction of new premium-priced medicines at the hospital level.	• http://www.regioner.dk/sundhed/medicin/koordineringsr%C3%A5det+for+ibrugtagning+af+sygehusmedicin+kris • Contact: Ann Vilhelmsen, avi@regioner.dk
	Committee for Use of High-priced Medicines at Hospital Level (Rådet for Anvendelse af Dyr Sygehusmedicin – RADS)	RADS ensures equal access in the Danish regions to premium-priced medicines at the hospital level, develops standard treatment guidelines and negotiates medicine prices through polled procurement for the hospital sector.	• http://www.regioner.dk/sundhed/medicin/r%C3%A5det+for+anvendelse+af+dyr+sygehusmedicin+rads • http://www.amgros.dk/en • Contact: Thomas Birch Andersen, tad@regioner.dk • AMGROS Managing Director: Flemming Sonne, amgros@amgros.dk
	HTA and Health Services Research (HTA-HSR), a department within the Centre for Public Health and Quality (Center Folkesundhed og Kvalitetsudvikling – CFK)	HTA-HSR is a regional initiative on collaboration between the School of Public Health, Aarhus University and Region Midtjylland. It typically performs HTA at the regional or local level but advises on health services research at all levels, including national. It is an EUnetHTA partner.	• http://www.cfk.rm.dk/om+os/in+english/health+technology+assessment+and+health+services+research • Director: Mette Kjølby • Contact: Ulla Tinne Væggemose, Ulla.Vaeggemose@stab.rm.dk

Member State	HTA organization (primarily public sector entities with partners and other organizations)	Organizational mandate (or comments if no public sector HTA entity)	Contact information (useful links)
	Danish Centre for Evaluation Health Technology Assessment (DACEHTA)	The independent state-financed centre to carry out HTA within Denmark's Health and Medicines Authority decided in 2013 to limit HTA activity but to continue participation in EUnetHTA/International Network of Agencies for Health Technology Assessment (INAHTA).	• https://sundhedsstyrelsen.dk/en/health/quality-and-guidelines/centre-for-health-technology-assessment • Contact: Birgitte Holm Petersen, bhp@sst.dk
	National Institute for Municipalities and Regions Analysis and Research (Nationale Institut for Kommuners og Regioners Analyse og Forskning – KORA)	KORA combines the work of three former institutions: the Institute of Local Government Studies, Danish Institute for Health Services Research and Danish Evaluation Institute for Local Government. Most health economics releases pertain to service-level and systems intervention, but reports within the last five years also deal with drug pricing, rheumatoid arthritis biologics, risk-sharing agreements, medicines with limited effect and private–public cooperation on the development and dissemination of health care technology.	• http://www.kora.dk/temaer-paa-tvaers/sundhedsoekonomi/udgivelser-om-sundhedsoekonomi/ • KORA Director: Jan Rose Skaksen • Head of Evaluation and Innovation Programme: Ulf Hjelmar
	Centre for Applied Health Services Research (CAST) at the University of Southern Denmark	A non-profit-making centre financed externally through project work, CAST's research areas include health economics, user involvement and health services, in collaboration with regions in southern Denmark, municipalities, hospitals, patient organizations and the industry. The words "Technology Assessment" were omitted from the Centre's name in 2013 but it retains the acronym CAST.	• http://www.sdu.dk/Om_SDU/Institutter_centre/CAST • Centre Director: Jan Sørensen • Department: Jesper Bo Nielsen
	Rigshospitalet	The Nordic Cochrane Centre is located at Rigshospitalet, which also houses the Hepato-Biliary Group, the Colorectal Cancer Group and the Anaesthesia Group.	• http://www.rigshospitalet.dk/menu/FORSKNING/ • www.cochrane.dk • Cochrane Centre Director: Peter C. Gøtzsche, pcg@cochrane.dk • Contact: Jannie Hedegaard, general@cochrane.dk

Member State	HTA organization (primarily public sector entities with partners and other organizations)	Organizational mandate (or comments if no public sector HTA entity)	Contact information (useful links)
Estonia	Department of Public Health at the University of Tartu	The Department was commissioned by the Ministry of Social Affairs; its results are used by the Estonian Health Insurance Fund on reimbursement decisions and disseminated to medical practices. Its commission runs to May 2015, at which point "It remains to be decided whether future HTA activities will be carried out by a separate governmental agency or commissioned from academia". It is an EUnetHTA partner.	• http://www.arth.ut.ee/en/health-technology-assessment • Head of Unit: Raul Kiivet
Finland	Finnish Office for Health Technology Assessment (FinOHTA)	FinOHTA is the Methods and Assessment Unit of the National Institute for Health and Welfare (an EUnetHTA partner). It also serves as the Finnish branch of the Nordic Cochrane Centre.	• http://www.thl.fi/fi/thl/rakenne/yksikot/menetelmien-ja-kaytantojen-arviointi/terveydenhuollon-menetelmien-arviointi • http://finnishbranch.cochrane.org/ • Head of Unit: Anu Wall, anu.wall@thl.fi • Development Manager: Niina Kovanen, niina.kovanen@thl.fi
	Finnish Medicines Agency (FIMEA)	FIMEA is primarily the regulatory agency but it also produces and collates clinical and economic evaluations and coordinates cooperation. Assessments are used by the Pharmaceuticals Pricing Board, medicines advisory boards and procurement circles of hospital districts, as well as by patients and physicians directly.	• http://www.fimea.fi/development/therapeutic_and_economic_value_of_medicines • Head of Research: Hannes Enlund, hannes.enlund@fimea.fi
	Pharmacoeconomics and Outcomes Research Unit at the University of Eastern Finland (PHORU)	Commissioned by FIMEA to carry out pilot studies of HTA, PHORU's results are used by FIMEA and advisory boards of hospital districts.	• http://www.uef.fi/fi/farmasian-laitos/research/pharmacoeconomics-and-outcome-research • Group leader: Janne Martikainen
France	Committee for Evaluation and Dissemination of Technological Innovations (Comité d'Evaluation et de Diffusion des Innovations Technologiques – CEDIT)	Part of the Assistance Publique Hôpitaux de Paris, CEDIT reviews technologies requested by staff members or affiliates, and generates research topics internally.	• http://cedit.aphp.fr/ • Contact: info.cedit@aphp.fr

Member State	HTA organization (primarily public sector entities with partners and other organizations)	Organizational mandate (or comments if no public sector HTA entity)	Contact information (useful links)
	French National Authority for Health (Haute Autorité de Santé – HAS)	HAS is an independent public body reporting to the government and parliament, tasked with assessment of drugs, medical devices and procedures and publication of guidelines, among other responsibilities. Evaluations are not binding, pending approval by Ministry of Health. It is an EUnetHTA partner.	• http://www.has-sante.fr/portail/jcms/fc_1249926/fr/evaluation-des-technologies-de-sante-et-des-actes • Contact: Jean-Patrick Sales, jp.sales@has-sante.fr
	Centre for Clinical Epidemiology (Centre d'Epidémiologie Clinique), Hôpital Hôtel-Dieu	The Centre serves as the French Cochrane Centre to develop and coordinate systematic reviews and promote the participation of Francophones in evidence-based medicine.	• www.cochrane.fr • Contact: Philippe Ravaud, philippe.ravaud@htd.aphp.fr
Georgia	No independent public sector HTA entity to date	The Ministry of Labour, Health and Social Affairs maintains guidelines for participants in the country's social insurance scheme on numerous topics, some of which involve high-cost pharmaceuticals (e.g. epilepsy and chronic kidney disease). It set up a memorandum of understanding in 2010 with the United Kingdom's National Institute for Health and Care Excellence for strategic and technical expertise and capacity-building.	• http://www.moh.gov.ge/index.php?lang_id=GEO&sec_id=36 • Minister of Health: David Sergienko
Germany	German Agency for Health Technology Assessment (DAHTA) at the German Institute of Medical Documentation and Information	DAHTA was established by parliament with statutory functions to maintain a database on the effectiveness and costs of medical procedures and technologies and to grant research assignments for evaluation of HTA reports. The board of trustees, appointed by the Ministry of Health, selects topics for review. The full database search requires a premium contract; select databases are available for free online searches. It is an EUnetHTA partner.	• http://www.dimdi.de/static/en/hta/dahta/ • Scientific Advisory Board Chair: Monika Lelgemann
	Federal Joint Committee (Gemeinsame Bundesausschuss – G-BA)	The decision-making body of doctors, dentists, psychotherapists, hospitals and health insurance companies in Germany publishes guidelines for particular conditions. Since2011 it has the statutory duty to perform a benefit assessment for all newly approved drugs with new active ingredients immediately after they enter the market, as a basis for determining coverage by statutory health insurance.	• https://www.g-ba.de/ • Contact: info@g-ba.de • Chair: Josef Hecken

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	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen – IQWiG)	IQWiG is an independent scientific institute tasked with producing evidence-based reports on drugs and other services, as well as disseminating online information to the general public. The Drug Assessment Department prepares early benefit assessments, based on sponsor submission to G-BA, as well as reports and rapid reports assessing benefit. It is an EUnetHTA partner.	• https://www.iqwig.de/en/home.2724.html • Institute Director: Jüurgen Windeler • Drug Assessment Department Heads: Thomas Kaiser, Beate Wieseler
	Interdisciplinary Centre for Health Technology Assessment and Public Health at the University of Erlangen-Nürnberg (Medical Valley-EMN)	The Prospective HTA (ProHTA) project is funded by the German Federal Ministry of Education and Research to assess the potential of medical technologies during the conceptual development phase for early assessment of emerging health technologies, with a particular focus on vascular disease and cancer.	• http://www.prohta.de/ • Principal Project Coordinator: Peter Kolominsky-Rabas • Contact: contact@prohta.de
	German Agency for Quality in Medicine (Ärztliches Zentrum für Qualität in der Medizin – ÄZQ)	Founded as a joint institution of the German Medical Association and the National Association of Statutory Health Insurance Physicians, ÄZQ appraises innovations and produces guidelines.	• http://www.aezq.de/aezq/uber • Head of Institute: Christian Thomeczek • Contact: mail@azq.de
	Centre of Competence for Clinical Studies Bremen (Kompetenzzentrum für Klinische Studien Bremen)	The Centre is involved in development and application of methods and models for the planning and evaluation of clinical – or HTA – studies and improvement of general biomedical research.	• http://www.kksweb.uni-bremen.de/ • Director: Werner Brannath
	Federal Association of Regional Health Insurance Funds (AOK Bundesverband)	The Association houses its own research institute, WIdO, to research pharmaceuticals and the hospital sector as a source of information for the entire German health care system.	• http://www.aok-bv.de/aok/english/ • http://www.wido.de/ • WIdO Management: Jürgen Klauber, jurgen.klauber@wido.bv.aok.de
	Research Centre for Biotechnology, Society and Environment (BIOGUM), University of Hamburg	Assigned to the University Senate, the Centre is dedicated to technology assessment and relationships between new technologies and their impact on the environment.	• http://www.uni-hamburg.de/fachbereiche-einrichtungen/biogum/index.html • Director of Medicine Research Group: Regine Kollek, kollek@uni-hamburg.de

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	Centre for Medical Biometry and Medical Informatics (Abteilung fuer Medizinische Biometrie und Statistik), University of Freiburg (Universitaetsklinikum Freiburg)	The Centre supports methods and applied biomedical research, operates the German clinical trials register, an open-access online register for clinical trials conducted in Germany, and serves as the German Cochrane Centre to publish and disseminate systematic reviews of health care interventions.	• http://portal.uni-freiburg.de/imbi/front-page-en • www.cochrane.de • Director: Martin Schumacher, ms@imbi.uni-freiburg.de • Cochrane contact: Gerd Antes, mail@cochrane.de
Greece	National School of Public Health (NSPH)	The Health Economics Department has studied pharmaceutical economics and participates in international collaborations such as EUnetHTA.	• http://www.nsph.gr • Contact: kek@esdy.edu.gr
	Institute of Biomedical Technology (INBIT)	A non-profit-making organization that constitutes an initiative for the advancement of the applied field of biomedical technology in Greece, INBIT's work includes consulting services to hospitals on economics and acceptability of technology investments.	• http://www.inbit.gr/ • Contact: info@inbit.gr
	National Evaluation Centre of Quality and Technology in Health (EKAPTY)	EKAPTY is supervised by the Ministry of Health but not subsidized by the state. It provides services to both the private and public sectors on product/service certification, laboratory quality and digital procurement. Projects include health system procurement reform and cancer technology development, among others.	• http://www.ekapty.gr/ • Board President: Panayiotis Demetriou • Contact: G. Pappous, pappous@ekapty.gr
Hungary	Health Economics and Health Technology Assessment Research Centre; Hungarian Office for Health Technology Assessment (HunHTA), Corvinus University of Budapest	In addition to its education and training mission, HunHTA undertakes EC-funded research in several areas, including HTA, and conducts research work to provide consultation to governmental institutions and private companies.	• http://hecon.uni-corvinus.hu/ • Department Head: László Gulácsi, laszlo.gulacsi@uni-corvinus.hu
	National Institute for Strategic Health Research (ESKI)	ESKI is a subsidiary of the Pharmaceutical and Health Care Quality and Development Institute (GYEMSZI, an EUnetHTA partner). It conducts HTA to assist the National Health Insurance Fund in decision-making.	• http://www.eski.hu/ • Deputy Director: George Surján, surjan.gyorgy@gyemszi.hu • Contact: Marta Pekli, pekli.marta.eski.hu

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	Institute for Health care Quality Improvement and Hospital Engineering (Egészségügyi Minöségfejlesztési és Kórháztechnicai Intézet – EMKI)	EMKI is a subsidiary of the Pharmaceutical and Health Care Quality and Development Institute (GYEMSZI, an EUnetHTA partner). Maintaining HTA reports is one of its clearing house functions, but the National Health Fund develops its own protocols for HTAs.	• http://www.gyemszi.hu/wps/portal/gyemszi/emki/ • CEO: Margitai Barnabás, margitai.barnabas@emki.hu
Iceland	University of Iceland	A participant in EUnetHTA projects along with the Iceland Directorate of Health, the University conducts research and creates guidelines but has no formal HTA process in place.	• http://english.hi.is/school_of_health_sciences/faculty_of_medicine/front_page • Directorate of Health: http://www.landlaeknir.is/
Ireland	Health Information and Quality Authority (HIQA)	Among other authorities, HIQA evaluates the clinical effectiveness and cost–effectiveness of health technologies, including drugs, and provides advice to the Minister and the Health Service Executive. It is an EUnetHTA partner.	• http://hiqa.ie/healthcare/health-technology-assessment • Director of HTA: Máirín Ryan
	National Centre for Pharmacoeconomics (NCPE)	NCPE assesses evidence for the comparative effectiveness and cost–effectiveness of technologies for use by patients in Ireland through assessment of evidence submitted by manufacturers and independent systematic review. Its research also informs national guidelines for HTA.	• http://www.ncpe.ie/ • Director: Michael Barry, mbarry@stjames.ie
Israel	Israeli Centre for Technology Assessment in Health Care (ICTAHC)	ICTAHC is a research centre supporting the Israeli Ministry of Health (Directorate of Technology and Infrastructure) in health policy and decision-making processes of health technologies.	• http://www.gertnerinst.org.il/e/health_policy_e/technology/ • Director: Joshua Shemer • Ministry of Health Medical Device Unit contact: Nadav Sheffer, nadav.sheffer@moh.health.gov.il
Italy	National Agency for Regional Health Services (Agenzia Nazionale per i Servizi Sanitari Regionali – AGENAS)	The public non-profit-making national organization gives technical and operational support to the state and regions through research, monitoring, evaluation, training and innovation. HTA is commissioned by the Ministry of Health. AGENAS also houses the Centre for the Observation of Emerging Technologies for horizon scanning and the regional research, innovation and HTA network to share activities and collaborate with the regional technostructures. It is an	• http://www.agenas.it/ • President: John Arch Bissoni • Innovation, Research and Development Director: Marina Cerbo • Medical Devices and HTA Executive: Laura Velardi • Directorate-General for Medical Devices:

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		EUnetHTA partner.	Marcella Marletta, Segr.DGFDM@sanita.it
	Emilia-Romagna Regional Agency for Health and Social Care (Agenzia Sanitaria e Sociale Regione Emilia-Romagna – ASSR-RER)	ASSR-RER reviews drugs and emerging technologies, including critical evaluation of the evidence, producing independent information on benefits and risks, development of guidelines and guidance and information campaigns and projects to assess the impact of new programmes of information and education about drugs. It is an EUnetHTA partner.	• http://assr.regione.emilia-romagna.it/it • Director: Roberto Grilli, asrdirgen@regione.emilia-romagna.it • Drug assessments: Nicola Magrini, nmagrini@regione.emilia-romagna.it; Anna Maria Marata, amarata@regione.emilia-romagna.it
	Health Technology Assessment Unit (Unità di Valutazione delle Tecnologie – UVT), Agostino Gemelli University Hospital	Full HTA reports are disseminated internally only (within the hospital), although summaries of the reports are available on the Internet. UVT is an EUnetHTA partner.	• https://www.policlinicogemelli.it • Director: Marco Marchetti • Contact: segreteriauvt@rm.unicatt.it
	Italian Medicines Agency (Agenzia Italiana Farmaco – AIFA)	AIFA monitors consumption of pharmaceutical expenditure at national and regional levels and conducts HTA with the National Observatory on the Use of Medicines and in collaboration with other institutions for pricing and reimbursement. It is an EUnetHTA partner.	• http://www.agenziafarmaco.gov.it • Interim Director: Paul Siviero, p.siviero@aifa.gov.it
	Department of Economics, Law and Institutions (Dipartimento di Economia, Diritto e Istituzioni – DEDI), University of Roma Tor Vergata	DEDI's main research topic is design and development of micro and macro health economic evaluations. It has several collaborations with the Ministry of Health, AGENAS, the regions, regulatory agencies and many hospitals.	• http://www.economia.uniroma2.it/dei/default.asp?a=781 • Economic Evaluation and HTA Research Director: Francesco Saverio Mennini

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	Veneto Region, Directorate of Social Health Planning (Regione del Veneto, Direzione Piani e Programmi Socio Sanitari)	A regional programme for research, innovation and HTA was established to facilitate the development and dissemination of a culture of research and innovation, including the evaluation of technology in health care, with a Working Group composed of various professionals. It is an EUnetHTA partner.	• http://www.regione.veneto.it/web/sanita/prihta • Health Councillor: Luke Coletto, assessore.coletto@regione.veneto.it
	Lazio Region – Health Services (Regione Lazio – Sanità)	The Department defines programmes targeted at use of resources for construction operations and health technologies. It uses HTA to assess evidence on new technologies prior to launch and during the entire lifecycle, as well as the consequences of the introduction or exclusion of such technology for the applicant company. It also expresses opinions on the appropriateness of purchases required for local health safeguards, with expertise from the Department of Epidemiology.	• http://www.regione.lazio.it/rl_sanita/ • HTA Manager: Lucrezia Le Rose, llerose@regione.lazio.it
	University of Modena and Reggio Emilia (Università degli Studi di Modena e Reggio Emilia)	The University serves as the Italian Cochrane Centre, working with the Mario Negri Institute for Pharmacological Research in Milan.	• www.cochrane.it • Manager: Roberto D'Amico, roberto.damico@unimore.it
Kazakhstan	Centre of Standardization of the Republican Centre for Health Development (RCHD-CS)	The Centre develops and implements CPGs and protocols and undertakes HTA for the Ministry of Health.	• http://www.rcrz.kz/ • Contact: Temirkhan Kulkhan, kulhan777@mail.ru • Representative to International Society for Pharmacoeconomics and Outcomes Research: Lyazzat Kosherbayeva
Kyrgyzstan	No independent public sector HTA entity to date	The Ministry of Health develops clinical guidelines and protocols and lists possible topics for future guidance via its Centre for Evidence-based Medicine, Centre for Rational Use of Medicines and Department of Drug Provision and Medical Equipment.	• www.pharm.kg • Head of Health Care Management and Drug Policy: Eshhodzhaeva Anarbyubyu Sagynbaevna

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Latvia	National Health Service (Nacionlais Veselbas Dienests – NVD)	NVD assesses each candidate drug based on relative effectiveness and price. Efficacy is compared with other specific drugs (based on scientific studies, as well as national and international treatment guidelines); the price is compared to prices in other EU countries and to the therapeutic benefits of the medication. NVD took over the functions formerly carried out by the Centre of Health Economics and Health Payment Centre and is an EUnetHTA partner.	• http://www.vmnvd.gov.lv/lv/kompensejamie-medikamenti/kompensacijas-kartiba • Director: Māris Taube • Ministry of Health State Agency of Medicines: http://www.zva.gov.lv/?
Lithuania	State Health Care Accreditation Agency of the Ministry of Health (Valstybinė akreditavimo sveikatos priežiūros veiklai tarnyba – VASPVT)	VASPVT was assigned as the competent authority to organize HTA at the national level. The plan is to prepare an HTA strategy for Lithuania (HTA/Innovation Division of Ministry of Health active since January 2014) and to train and supply evidence reports on new and high-cost health technologies, particularly related to medical devices. It is an EUnetHTA partner.	• http://www.vaspvt.gov.lt/ • Temporary Director: Ramunė Vaitkevičienė, ramune.vaitkeviciene@vaspvt.gov.lt • Medical Technologies Division Head: Gintarė Mikšienė, gintare.miksiene@vaspvt.gov.lt
	State Medicines Control Agency (Valstybinė vaistų kontrolės tarnyba – VVKT)	This regulatory agency has no apparent HTA authority but joined EUnetHTA in 2014 to benefit from pooled resources and expertise, which will ensure the quality and transparency of medicines in Lithuania.	• http://www.vvkt.lt/ • Director: Gintautas Barcys • Contact: vvkt@vvkt.lt
Luxembourg	Medical Expertise Unit (Cellule d'expertise médicale – CEM)	CEM is attached administratively to the General Inspectorate of Social Security and tasked with scientific evaluation and recommendations, particularly related to medical devices. Both CEM and the General Inspectorate are EUnetHTA partners.	• http://www.mss.public.lu/acteurs/igss/cem/index.html • Director: Raymond Wagener • Contact: Juergen Hohmann, juergen.hohmann@igss.etat.lu
Malta	Directorate for Pharmaceutical Affairs, Ministry for Health, the Elderly and Community Care (DPA/MHEC)	DPA/MHEC contains a pharmaceutical HTA unit; the government had previously maintained a Directorate for Pharmaceutical Policy and Monitoring. Included among its tasks are analysis of information and evaluation of clinical evidence to draw up prescribing guidelines through the use of international HTA within its Ministry for Social Policy. It is an EUnetHTA partner.	• https://ehealth.gov.mt/HealthPortal/default.aspx • Directorate Contact: dpa.mfh@gov.mt

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Monaco	No independent public sector HTA entity to date	The Ministry of Health has adopted the French activity-based reimbursement system for its hospitals, which carves out payment for expensive medicines, but has no apparent or explicit role for formal HTA.	• http://en.gouv.mc/Government-Institutions/The-Government/Ministry-of-Health-and-Social-Affairs • Ministry of Health Medical Adviser: Daniel Rouison • Contact: afss@gouv.mc
Montenegro	Ministry of Health (Ministarstvo zdravlja)	The Ministry of Health contains a Department of Bioethics and Pharmaceuticals that establishes the national formulary, distinct from the departments of Health Sector Management and Health Economics, but makes no mention of a formal HTA process. Nevertheless, developing such capacities was recognized as a priority in the 2012 national strategic plan.	• http://www.mzdravlja.gov.me/organizacija • Department of Drugs: jasna.sekulic@mzd.gov.me
Netherlands	Health Council of the Netherlands (Gezondheitsraad – GR)	GR is an independent scientific body, tasked with providing public health consultation services for ministries and parliament. The Advisory Committee on Health Research (RGO) provides advice on priorities in health care research, technology development and associated infrastructure.	• http://www.gezondheidsraad.nl/ • RGO Chair: W.A. van Gool • RGO Scientific Secretary: J.N.D. de Neeling, nico.de.neeling@gr.nl
	Care Institute Netherlands (Zorginstituut Nederland – ZINL)	ZINL advises the government on the content and scope of the statutory insured care package via an assessment process that includes stakeholder consultations. Cost–effectiveness is one of the four criteria set by ZINL, which recently published an exploratory report on the practical application of cost–effectiveness in drug assessments. A follow-up report is in preparation for the end of 2014. Its new mandate replaces the former Dutch Health Care Insurance Board. It is an EUnetHTA partner.	• http://www.zorginstituutnederland.nl/ • Board Chair: Arnold Nut Camp • Chairman of Care Package Committee: Bert Boer
	Medical and Health Research Council of the Netherlands (ZonMw)	ZonMW focuses on enhancing quality and innovation in health research and health care and on proactive promotion of knowledge transfer, implementation in the health care system and initiating research of new health-related themes. Publications are only available in Dutch. It has a specific programme studying efficiency in high-cost medicines.	• http://www.zonmw.nl/en/ • Director: Edvard Beem, beem@zonmw.nl • Contact for High-Cost Medicine Efficiency Study: Astrid van Sonsbeek, farmacotherapie@zonmw.nl

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	National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu – RIVM)	RIVM is an independent research body advising the government, health care professionals, municipal health services and the public, including experts on health care and health economics.	• http://www.rivm.nl/ • Chief Science Officer for Health Economics: Johan Polder • Contact: info@rivm.nl
	Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht	The Centre focuses on acquisition and dissemination of knowledge in the field of health sciences and primary care: primary research areas include cardiovascular diseases, infectious diseases, cancer and methodology. It serves as the Dutch Cochrane Centre.	• http://portal.juliuscentrum.nl/ • www.cochrane.nl • Chair: A.W. Hoes, a.w.hoes@umcutrecht.nl • Contact: Rob J.P.M. Scholten, cochrane@umcutrecht.nl
Norway	Norwegian Knowledge Centre for the Health Services (Nasjonalt Kunnskapssenter for Helsetjenesten – NOKC)	NOKC is organized under the Norwegian Directorate of Health but is scientifically and professionally independent, with no authority to develop health policy or responsibility to implement policies. Audience for reviews includes regional health authorities, the Norwegian Directorate of Health, NoMA, the Ministry of Health and Care Services, clinical environments and professional and user interest groups. NOKC conducts health economic evaluations of pharmaceuticals and other medical interventions. It also serves as the Norwegian branch of the Nordic Cochrane Centre and is an EUnetHTA partner.	• http://www.kunnskapssenteret.no/home • www.cochrane.no • Head of Health Economics and Drugs Unit: Marianne Klemp, marianne.klemp@kunnskapssenteret.no • Contact: post@nokc.no • Cochrane contact: Claire Glenton, claire.glenton@kunnskapssenteret.no
	Norwegian Institute of Public Health (Folkehelseinstituttet – FHI)	HTA is linked to the introduction of new vaccines.	• http://www.fhi.no/eway/?pid=240 • Director General: Camilla Stoltenberg
Poland	Agency for Health Technology Assessment in Poland (Agencja Oceny Technologii Medycznych – AOTM)	AOTM is the legal entity tasked with advising the Ministry of Health on all publicly funded health services. Its mandate is specifically to make recommendations on therapeutic drugs programmes (high-cost, innovative drugs) and hospital chemotherapy drugs lists. It is an EUnetHTA partner.	• http://www.aotm.gov.pl/www/index.php • President: Wojciech Matusewicz • Contact: secretariat@aotm.gov.pl • Faculty of HTA: Anna Brzezińska • Contact: Anna Zawada, a.zawada@aotm.gov.pl

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	Central and Eastern European Society of Technology Assessment in Health Care (CEESTAHC)	CEESTAHC develops standards and methods of assessment for drug and non-drug medical technology across central and eastern Europe.	• http://www.ceestahc.org/index.html • President: Magdalena Władysiuk • Contact: Izabela Kukla, sekretariat@ceestahc.org
Portugal	National Authority of Medicines and Health Products (Autoriadade Nacional do Medicamento e Produtos de Saude I.P. – INFARMED)	The regulatory agency for medicines and medical devices also oversees economic evaluation and reimbursement review for these novel technologies on behalf of the national health service. It incorporates cost–effectiveness into its assessment of new pharmaceuticals and participates in EUnetHTA.	• http://www.infarmed.pt/portal/page/portal/INFARMED • President: Eurico Alves Castro • Contact: infarmed@infarmed.pt
	Centre for Studies in Evidence-based Medicine (Centro de Estudos de Medicina Baseada na Evidência – CEMBE)	The research unit at the University of Lisbon's Faculty of Medicine focuses on evidence-based medicine and serves as the Portuguese branch of the Iberoamerican Cochrane Centre.	• www.cembe.org/ • Contact: João Costa, cembe@fm.ul.pt
Republic of Moldova	No independent public sector HTA entity to date	The Ministry of Health maintains clinical guidelines and protocols and coordinates pricing and reimbursement within its Department of Drugs and Medical Devices, but has no apparent or explicit role for formal HTA.	• http://www.ms.gov.md/?q=directia-medicamenete-si-dispozitive-medicale#overlay-context= • Head of Drugs/Medical Devices Department: Ludmila Topchin, ludmila.topchin@ms.gov.md
Romania	National School of Public Health, Management and Professional Development Bucharest (Şcoala Naţională de Sănătate Publică, Management şi Perfecţionare în Domeniul Sanitar Bucureşti – SNSPMPDSB)	The School conducts HTA and other evidence-based medicine and reimbursement research, disseminates results to decision-makers and providers of health care services. It is an EUnetHTA partner.	• http://www.snspms.ro/ • General Director: Cristian Vladescu, cvladescu@snspms.ro • Director, Health Services Research and Evaluation Centre: Mihnea Dosius, mdosius@snspms.ro
Russian Federation	National Research Centre for Public Health	A research institution developing the HTA concept within the Academy of Medical Sciences, its main purpose is implementation of fundamental and applied research in public health roles in health, sociology, medicine, history of medicine and health care, as well as training.	• http://www.nriph.ru/ • Health Economics Commission Chair: Alexander Leonidovich Lindenbraten

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	Autonomous Non-profit-making Organization National Centre for Health Technology Assessment (ANO NCHTA)	Previously known as the Russian National Research Medical University Research Centre for Clinical and Economic Evaluation Pharmacoeconomics, ANO NCHTA is now an independent organization. It develops HTA, decision-making algorithms and similar in collaboration with the territorial health administration bodies of the Russian Federation.	• www.hta-rus.ru • Chair: Vitaly V. Omelyanovsky
San Marino	No independent public sector HTA entity to date; drug decisions overseen by Istituto Sicurezza Sociale (ISS)	New drugs are considered for inclusion in national formulary by the Commission of San Marino, which analyses patterns of consumption and expenditure to highlight items of interest and is meant to represent the best scientific evidence of effectiveness and cost–benefit ratio, but has no explicit HTA authority.	• http://www.iss.sm/on-line/home.html • Health Section Executive: Zanotti Guerrino, guerrino.zanotti@iss.sm
Serbia	Ministry of Health – Committee for HTA, in coordination with the Serbian Health Insurance Fund (RZZO)	The Committee is tasked with monitoring, coordination and harmonization of the development of health care technologies and assessing existing and new health care technologies, creating national guidelines and defining priorities for the procurement of medical equipment. RZZO houses the Expert Subcommittee on Drugs, which justifies placing medicinal products on the list of drugs.	• http://www.zdravlje.gov.rs/ • http://www.rfzo.rs/index.php/organizacija-main-54/komisije-rzzo/komisije1/strucne-podkomisije-rzzo • RZZO Board President: Rajko Kosanović
Slovakia	HTA strategy under development	The Slovak Agency for Health Technology Assessment (SLOVAHTA) was founded in 2010 but has had little influence to date in decision-making processes, with primarily a strong pharmacoeconomic influence on reimbursement. The Ministry of Health is an EUnetHTA partner.	• www.health.gov.sk • Department of National Drug Strategy and Monitoring: Sarka Kovácsová
Slovenia	Institute for Economic Research (Inštitut Za Ekonomska Raziskovanja – IER)	IER conducts economic research in a number of areas, including health care. It is an EUnetHTA associated partner.	• http://www.ier.si/ • Welfare Economics (including health) contact: Nada Stropnik, stropnikn@ier.si
	National Institute of Public Health (Inštitut Za Varovanje Zdravja/Nacionalni Inštitut za Javno Zdravje – IVZ/NIJZ)	IVZ/NIJZ houses the Register of Medicines for Slovenia and represents Slovenia in EUnetHTA projects, but has limited HTA capacity.	• http://www.ivz.si/ • Office of the Director: Sanda Potocnik-Rožič, Sanda.Potocnik-Rozic@nijz.si

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	Agency for Medicinal Products and Medical Devices (Javna agencijo Republike Slovenije za zdravila in medicinske pripomočke – JAZMP)	The regulatory agency for medicines and medical devices also approves pricing for medicines.	• http://www.jazmp.si • Contact: Matej Breznik, info@jazmp.si
Spain	Health Care Technology Evaluation Agency, Madrid (Agencia de Evaluación de Tecnologias Sanitarias Instituto de Salud "Carlos III" – AETS); now known as the Spanish Network for HTA (Agencias y Unidades de Evaluación de Tecnologías – AUnETS)	An integration effort among regional and local agencies, AUnETS's activities include HTA reports, among others (horizon scanning, clinical guidelines, methodology harmonization, registries). An autonomous public institution attached to the Ministry of Health, it serves as the national public research and scientific support organization responsible for promoting biomedical and health science research for the national health service and society in general. Assessments are discretionary – neither mandatory nor binding. It provides HTA reports to the Inter-territorial Council, the ultimate decision-maker for benefit policy. (In addition, many regions have an HTA agency or service responsible for producing information on the efficacy, effectiveness, safety and efficiency of new health technologies.) It is an EUnetHTA partner.	• http://aunets.isciii.es/web/guest/home • Director: Antonio Sarria-Santamera, asarria@isciii.es
	Andalusian Agency for Health Technology Assessment (Agencia de Evaluación de Tecnologías Sanitarias de Andalucía – AETSA)	The regional HTA agency for the Government of Andalusia, integrated with the Ministry of Gender, Health and Social Policy, conducts HTA. Its specific workstream is dedicated to evaluation of high-impact medications. It is an EUnetHTA partner.	• http://www.juntadeandalucia.es/salud/servicios/aetsa/ • Director: Teresa Molina López • Chief of HTA: Carmen Beltrán Calvo • Contact: aetsa.csbs@juntadeandalucia.es
	Agency for Health Care Quality and Assessment of Catalonia (Agència de Qualitat i Avaluació Sanitàries de Catalunya – AQuAS; formerly known as CAHAIQ and CAHTA)	AQuAS is a regional agency with several workstreams, including HTA. The Programme to Support Innovation in the Field of Medicine (Programa d'Innovació i Suport a l'Àmbit del Medicament) subteam works to facilitate the Catalan Health Service's decision-making regarding pharmaceutical services, designing and providing new tools aimed at improving support decisions on financing, purchasing services and evaluation of outcomes (clinical, economic and quality of	• http://aquas.gencat.cat/ca • Director: Josep Maria Argimon i Pallàs, direccio.aquas@gencat.cat • Department of Medical Technologies: Cari Almazán

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		life) related to drug therapy. It is an EUnetHTA partner.	
	Galician Agency for HTA (Axencia de Avaliación de Tecnoloxías Sanitarias de Galicia – AVALIA-T)	AVALIA-T is a regional HTA agency that advises the Department of Health on health technologies for citizens of Galicia. It considers clinical, economic, organizational, social, ethical and legal dimensions. It is an EUnetHTA partner.	• http://www.sergas.es/MostrarContidos_Portais.aspx?IdPaxina=60538 • Director: Marisa López García • Contact: avalia-t@sergas.es
	Department of Pharmacy and Health Products (Dirección General de Farmacia y Productos Sanitarios – DGFPS)	The Department of the Ministry of Health is responsible for pharmaceutical products and is a partner in EUnetHTA projects, but has no apparent HTA authority. Its purpose is to provide health professionals, the scientific community and citizens in general with data concerning the use of pharmaceuticals financed by the national health system and used outside hospitals.	• http://www.msssi.gob.es/profesionales/farmacia/home.htm • DGFPS Director General: Belén Crespo Sánchez-Eznarriaga
	Aragon Health Sciences Institute (Instituto Aragonés de Ciencias de la Salud – IACS)	A regional HTA agency, the Institute is responsible for research and knowledge management in biomedicine and health sciences in the public Aragon health system. Among other activities, the HTA unit prepares reports and provides consultancy on health technologies and clinical management. It is located at the Biomedical Research Centre of Aragon and is an EUnetHTA partner.	• http://www.iacs.aragon.es/awgc/ • Staff directory: http://pruebaslote4.salud.aragon.es/awgc/inicio.estaticas.do?app=/nosotros/quienes-somos&file=directorio.html
	Osteba, Basque Office for Health Technology Assessment	A regional HTA agency, Osteba is dedicated to conducting HTA via literature search, critical reading of research designs, economic evaluation, identification and assessment of emerging and obsolete technologies. It makes recommendations, develops CPGs and includes a unit for comparative effectiveness research, as well as running a dedicated project on emerging technology called SorTek. It is an EUnetHTA partner.	• http://www.osakidetza.euskadi.net/r85-pkoste02/es/ • Head of Service: José Asua Batarrita, jasua@ej-gv.es

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	Evaluation Service of the Canarian Health Service (Servicio de Evaluación del Servicio Canario de Salud – SESCS)	SESCS is a regional HTA agency reporting to the Canarian Health Service and the Ministry of Health, Social Services and Equality. It is an EUnetHTA partner.	• http://www2.gobiernodecanarias.org/sanidad/scs/organica.jsp?idCarpeta=11f7902a-af34-11dd-a7d2-0594d2361b6c • Director/Deputy Minister: Juana María Reyes Melián, direccion.scs@gobiernodecanarias.org
	Spanish Association of Health Technology Assessment (Asociación Española de Evaluación de Tecnologías Sanitarias – AEETS)	AEETS is an interdisciplinary organization of professionals with an interest in HTA, health policy and clinical management. It provides advisory feedback and consulting on the development of records, databases, web platforms, CPGs and HTA reporting for scientific societies and other stakeholders.	• http://www.fgcasal.org/aeets/index.asp • Contact: info@aeets.es
	Hospital de la Santa Creu i Sant Pau	The Iberoamerican Cochrane Centre housed at the Hospital performs research, dissemination and methodological coordination for Spain, Portugal, Andorra and all Spanish-speaking countries.	• http://www.santpau.es/ • www.cochrane.es • Contact: Ivan Solà, cochrane@cochrane.es
Sweden	Swedish Council on Technology Assessment in Health Care (Statens Beredning för Medicinsk Utvärdering – SBU)	An independent national authority, SBU is tasked by the government to assess interventions from a broad perspective: medical, economic, ethical, social. Its decisions are also used by National Board of Health and Welfare, Medical Products Agency, Dental and Pharmaceutical Benefits Agency, professional societies and institutions. It is an EUnetHTA partner.	• http://www.sbu.se/sv/ • Board Chair: Nina Rehnqvist • Scientific Advisory Committee Chair: Kjell Asplund • Alert Advisory Board Chair: Jan-Erik Johansson
	Dental and Pharmaceutical Benefits Board (Tandvårds- Och Läkemedelsförmånsverket – TLV)	TLV decides which medicines and medical devices should be subsidized and included in the reimbursement system. It conducts health economic evaluations of all medical technologies, with a particular focus on high-cost drugs.	• http://www.tlv.se/ • General Director: Sofia Wallström, sofia.wallstrom@tlv.se • Head of Department for New Drugs: Christin Andersson, christin.andersson@tlv.se
	Centre for Medical Technology Assessment (CMT)	An independent research institute within Linkoping University, CMT's aim is to develop methodology, disseminate research findings and assess methods and procedures in the health care sector. Its research is	• http://www.imh.liu.se/halso-och-sjukvardsanalys/cmt/?l=en • Head of Division: Per Carlsson, per.carlsson@liu.se

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		sponsored by local and state health care providers, scientific councils, other national and international research bodies and commercial clients, and includes economic assessments of pharmaceuticals and medical devices.	
Switzerland	Swiss Network for Health Technology Assessment (SNHTA)	SNHTA has over 20 institutional members with an interest in or conducting HTA, and brings together scientific institutions and experts in order to avoid duplication of work. It is an EUnetHTA partner.	• http://www.snhta.ch/ • Co-chairs: Konrade von Bremen, Maya Züllig • Contact: info@snhta.ch • Note: federal administration and university institute members have distinct entries on this stakeholder map; for additional member institutions see: http://www.snhta.ch/about-us/organisation/member-institutions.html?type=%2Fproc%2Fself%2Fenviron
	Federal Office of Public Health (FOPH) Medical Technology Unit	FOPH reviews new procedures for clinical effectiveness, appropriateness and efficiency. It is a partner in INAHTA (representing the interests of Switzerland abroad in all matters relating to health) and a member of SNHTA, along with other FOPH departments: Evaluation Specialist Centre, Drug Unit.	• http://www.bag.admin.ch/ • FOPH Director: Pascal Strupler • Head of Health Policy Directorate: Stefan Spycher
	Institute of Social and Preventive Medicine, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne (UNIL)	The Cochrane Centre for Switzerland is dedicated to research that informs health professionals and policy-makers, training and facilitation in systematic review, dissemination of findings and encouraging participation. It is a university institute member of SNHTA, along with UNIL's Institute of Health Economics and Management.	• www.swiss.cochrane.org • Contact: Bernard Burnand, bernard.burnand@chuv.ch
	TA-SWISS Centre for Technology Assessment, a Centre of Competence of the Swiss Academies of Arts and Sciences	TA-SWISS conducts traditional technology assessments and participative studies in the fields of life science, information society and mobility for biotechnology, medicine and nanotechnology and the communications and IT sector. Recommendations resulting from its projects are used by	• www.ta-swiss.ch • Contact: Sergio Bellucci, sergio.bellucci@ta-swiss.ch • Contact: Adrian Rüegsegger, adrian.rueegsegger@ta-swiss.ch

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		parliament and the Federal Council as an aid to decision-making. It is a member of the European Parliamentary Technology Assessment network and SNHTA.	
	Commission for Technology and Innovation (CTI), Federal Office for Professional Education and Technology	CTI promotes cooperation between universities, schools of technology and private industry in medical device technology. It is a member of SNHTA.	• http://www.kti.admin.ch/?lang=en • President: Walter Steinlin • Contact: Regula Leuenberger, regula.leuenberger@kti.admin.ch • Head of Life Sciences: Beda Stadler • Biotech: Oreste Ghisalba • Life sciences contact: life.sciences@kti.admin.ch
	Division of National Research Programmes, Swiss National Science Foundation (SNSF)	SNSF funds independent basic scientific research, including HTA on biomedical engineering, somatic gene therapy and implants/transplants. It is a member of SNHTA.	• www.snf.ch • Contact: Beat Butz, bbutz@snf.ch • Contact: Christian Mottas, cmottas@snf.ch
	State Secretariat for Education and Research (SERI)	SERI's main mission is to prepare Swiss science and research policies and ensure their implementation. It does not run any HTA projects but is committed to this activity through its research policy and as a member of SNHTA.	• www.sbf.admin.ch • Lead, State Secretary: Mauro Dell'Ambrogio • National Research and Innovation contact: Gregor Haefliger, Gregor.Haefliger@sbfi.admin.ch
	Swiss Federal Institute of Technology Zurich (ETH Zurich)	The Institute of Biomedical Engineering within ETH Zurich has no explicit remit on medical technology assessment and performance evaluation but takes into account related considerations in most projects. It is a member of SNHTA.	• www.biomed.ee.ethz.ch/ • Director: Klaas Paul Prüssmann, pruessmann@biomed.ee.ethz.ch • Contact: Dieter Meier, dieter.meier@biomed.ee.ethz.ch • Contact: Peter Niederer, peter.niederer@biomed.ee.ethz.ch

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	University of Zurich	The Institute of Social and Preventive Medicine (ISPM) and University Hospital (Horten-Zentrum) are both SNHTA members. ISPM conducts research across a variety of fields, such as economic analysis (including methodological development) and diagnostic and therapeutic procedures, focusing on the integration of clinical–therapeutic and economic evidence. Horten-Zentrum focuses on systematic reviews of diagnostic tests or the effectiveness of therapeutic interventions and on disseminating critically appraised scientific work in German.	• http://www.ispm.uzh.ch/index.html • Director: Milo Puhan, milo.puhan@ifspm.uzh.ch • http://www.evimed.ch/ • Contact: Johann Steurer, johann.steurer@usz.ch
	Zurich University of Applied Sciences (ZHAW)	The Winterthur Institute of Health Economics at ZHAW is a member of SNHTA that is focused on HTA, health economic evaluations and health services research, among other areas. It focuses on research and strategic/operational consultancy projects for various public and private health care stakeholders.	• http://www.sml.zhaw.ch/en/management/institutes-Centres/winterthur-institute-of-health-economics/the-institute.html • Directors: Matthias Maurer, matthias.maurer@zhaw.ch; Urs Brügger, urs.bruegger@zhaw.ch
	University of Basel	The Swiss Tropical and Public Health Institute (TPH) and Basel Institute for Clinical Epidemiology (CEB) are both SNHTA members. TPH departments include a medicines research group focused on research and development of “translational gaps” – particularly those affecting resource-limited economies. It was also involved in a project on development of CzechHTA. CEB conducts systematic reviews and HTA, disseminating research results to physicians, institutions and decision-makers.	• http://www.swisstph.ch/ • Medicines Research Department Head: Christian Burri, christian.burri@unibas.ch • http://www.ceb-institute.org/ • Director: Heiner C. Bucher, heiner.bucher@usb.ch
	University of Bern	ISPM, the Institute for Evaluative Research in Orthopaedics (MEM) and University Hospital (Inselspital) are SNHTA members. ISPM conducts HTA and health services research in a number of defined disease areas. MEM is a dedicated academic research institute in the field of HTA, at the interface of economy and delivery of care, and for outcome research in orthopaedics. Inselspital has conducted government HTA registry research such as the SWISSspine	• http://www.ispm.ch/ • Contact: info@ispm.unibe.ch • http://www.memCentre.unibe.ch/iefo/ • Interim Director: Christoph Röder, christoph.roeder@ memCentre.unibe.ch • http://www.insel.ch/ • Director of Research: Matthias Gugger

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		project – a nationwide HTA registry for balloon kyphoplasty.	• Contact: andrea.bigler@insel.ch
Tajikistan	HTA strategy under development	The Ministry of Health includes integration of evidence-based medicine in practice in its national strategy to 2020, and has recently opened the Centre for Evidence-based Medicine at the Tajik State Medical University to advise the Ministry.	• http://www.health.tj/ • Contact: Salim Abdulazizov, abdu_salim@mail.ru
The former Yugoslav Republic of Macedonia	No independent public sector HTA entity to date	The Ministry of Health houses guidelines for the practice of evidence-based medicine in many specialties but has no apparent or explicit role for formal HTA.	• http://zdravstvo.gov.mk/upatstva/
Turkey	Ankara Numune Health Technology Assessment Unit (ANHTA)	The HTA unit within Ankara Numune Training and Research Hospital chooses evaluation topics driven by volume and other priorities. Its reports consider medical, economic, ethical, legal, social and organizational aspects of medical technologies.	• http://www.anhhta.org/ • Director: Rabia Kahveci
	Turkish Evidence-Based Medicine Association (Kanita Dayali Tip Dernegi – KDTD)	KDTD conducts training and collaboration on HTA.	• http://www.kanitadayalitip.org/ • President: Rabia Kahveci, rkahveci@kanitadayalitip.org
	Health Technology Assessment Department, Directorate-General of Health Research, Ministry of Health (SAGEM)	SAGEM is tasked with conducting HTA on drugs, medical devices, procedures and systems, including primary assessment on clinical effectiveness and patient safety, followed by economic and institutional considerations. Topics are usually internally generated by the Subject Election Commission but new topics may be suggested via a form on the SAGEM website.	• http://hta.gov.tr/ • Head of Department: Bilgehan Karadayi, bilgehan.karadayi@saglik.gov.tr

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Turkmenistan	No independent public sector HTA entity to date; HTA strategy under development	The Ministry of Health has held collaborative events with the medical industry on innovation in medical technology but makes no explicit mention of an HTA function.	• http://www.saglykhm.gov.tm/
Ukraine	State Administration of Ukraine on Medical Products	The state enterprise is a member of PPRI. The Ministry of Health also has a Department of Regulatory Policy overseeing the treatment of drugs and products in the health care system.	• http://www.diklz.gov.ua/control/main/uk/index • Director: Michael Frantsovych • Contact: diklz@diklz.gov.ua
	Ukrainian Agency of HTA (UAHTA)	Not yet fully implemented, UAHTA was established in 2013 to register the company "HTA Excellence", develop HTA guidelines and work on training and communications.	• President: Konstantin Kosyachenko • VP: Mykhailo Aristov
United Kingdom	National Institute for Health and Care Excellence (NICE)	NICE reviews clinical and economic evidence, relying particularly on the quality-adjusted life-year (QALY). The Centre for Health Technology Evaluation (CHTE) develops guidance and HTA on the use of new and existing treatments and procedures within the NHS, such as medicines, medical devices, diagnostic techniques and surgical and other interventional procedures. NICE is also responsible for the Patient Access Scheme Liaison Unit, Scientific Advice Programme and NICE Topic Selection Programme. It is an EUnetHTA partner.	• http://www.nice.org.uk/ • Chief Executive: Andrew Dillon • CHTE Director: Carole Longson
	National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre (NETSCC) HTA Programme (formerly NCCHTA)	The Programme funds independent research on the effectiveness, costs and broader impact of health care treatments and tests for those who plan, provide or receive care in the NHS, as both commissioned and researcher-led studies. Audiences include decision-makers in local government, policy-makers (including NICE), researchers, health service professionals, other NIHR stakeholders and the general public. It is an EUnetHTA partner.	• http://www.nets.nihr.ac.uk/programmes/hta • HTA Programme Director: Tom Walley

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	SMC	A consortium of NHS Scotland's 14 health boards, the Consortium assesses all new medicines for their clinical effectiveness and cost–effectiveness and provides advice to NHS boards and their area DTCs across Scotland.	• https://www.scottishmedicines.org.uk/Home • Contact: hcis.smcsecretariat@nhs.net
	National Horizon Scanning Centre (NHSC), Department of Public Health and Epidemiology, University of Birmingham	NHSC aims to supply timely information to key policy- and decision-makers and research funders within the NHS about emerging health technologies (drugs and devices) that may have a significant impact on patients or the provision of health services in the near future.	• http://www.hsc.nihr.ac.uk/ • Director: Claire Packer, c.packer@bham.ac.uk • Contact: nihrhsc@contacts.bham.ac.uk
	Healthcare Improvement Scotland	Scottish Health Technologies Group (SHTG) is an advisory group set up to provide assistance to NHS Scotland boards when considering selected health technologies, excluding medicines that will be reviewed by the SMC.	• http://www.healthcareimprovementscotland.org/home.aspx • SHTG Lead: Susan Myles, susan.myles2@nhs.net
	Oxford University Hospitals NHS Trust	The Trust provides the United Kingdom Cochrane Centre for production, understanding and the use of high-quality research evidence – in particular, systematic reviews – in the evaluation of health and social care.	• http://www.ouh.nhs.uk/ • Board Chair: Fiona Caldicott • Chief Executive: Jonathan Michael
	Wessex Institute, University of Southampton	The Institute provides the NIHR Dissemination Centre to disseminate the results of NIHR research and put them in the context of existing evidence and of the NHS, enhancing awareness and uptake.	• http://www.wiep.southampton.ac.uk/ • Contact: wiep@southampton.ac.uk
	University of Aberdeen	One of nine institutions with a contract as an NIHR technology assessment review (TAR) team to provide evidence to support NICE and other policy customers' health and social care assessment processes.	• http://www.abdn.ac.uk/hsru/research/assessment/knowledge-synthesis/tar/ • Contact: Miriam Brazzelli, m.brazzelli@abdn.ac.uk
	BMJ Technology Assessment Group (TAG)	One of nine institutions with a contract as an NIHR TAR team to provide evidence to support NICE and other policy customers' health and social care assessment processes.	• http://group.bmj.com/products/evidence-centre/bmj-technology-assessment-group • Head of TAG: Steve Edwards • Contact: bmjtag@bmjgroup.com

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	Peninsula College of Medicine and Dentistry (Pen TAG), University of Exeter	One of nine institutions with a contract as an NIHR TAR team to provide evidence to support NICE and other policy customers' health and social care assessment processes.	• http://medicine.exeter.ac.uk/pentag/workstreams/healthtechnologyassessment/ • Workstream Lead: Chris Hyde, c.j.hyde@exeter.ac.uk
	Kleijnen Systematic Reviews	One of nine institutions with a contract as an NIHR TAR team to provide evidence to support NICE and other policy customers' health and social care assessment processes.	• http://www.systematic-reviews.com/ • Director: Jos Kleijnen, jos@systematic-reviews.com
	Liverpool Reviews and Implementation Group (LRiG), University of Liverpool	One of nine institutions with a contract as an NIHR TAR team to provide evidence to support NICE and other policy customers' health and social care assessment processes.	• https://www.liv.ac.uk/psychology-health-and-society/research/liverpool-reviews-and-implementation-group/ • Group Leader: Rumona Dickson, r.dickson@liverpool.ac.uk
	School of Health and Related Research (ScHARR), University of Sheffield	One of nine institutions with a contract as an NIHR TAR team to provide evidence to support NICE and other policy customers' health and social care assessment processes.	• http://www.shef.ac.uk/scharr/sections/heds/collaborations/tag • Contact: scharrtag@sheffield.ac.uk
	Southampton Health Technology Assessment Centre (SHTAC), University of Southampton	One of nine institutions with a contract as an NIHR TAR team to provide evidence to support NICE and other policy customers' health and social care assessment processes.	• http://www.southampton.ac.uk/shtac • Interim Director: Andrew Cook • Contact: shtac@southampton.ac.uk
	Warwick Evidence, University of Warwick	One of nine institutions with a contract as an NIHR TAR team to provide evidence to support NICE and other policy customers' health and social care assessment processes.	• http://www2.warwick.ac.uk/fac/med/about/centres/warwickevidence/ • Contacts: aileen.clarke@warwick.ac.uk; j.h.hyde@warwick.ac.uk
	Centre for Reviews and Dissemination (CRD), University of York	One of nine institutions with a contract as an NIHR TAR team to provide evidence to support NICE and other policy customers' health and social care assessment processes.	• http://www.york.ac.uk/inst/crd/ • Director: Lesley Stewart, lesley.stewart@york.ac.uk
	London School of Economics and Political Science (LSE)	LSE's Medical Technology Research Group (MTRG) research unit concentrates on interdisciplinary and comparative policy research on medical technologies, including the economics of medical technologies – in particular, medicines and medical	• http://www.lse.ac.uk/LSEHealthAndSocialCare/research/LSEHealth/MTRG/home.aspx • MTRG Lead: Panos Kanavos

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		devices.	
	London School of Hygiene and Tropical Medicine (LSHTM)	The research of the Health Services Research and Policy Department (HSRP) at LSHTM primarily includes policy analysis, sociological studies of care and studies of the organization of care versus HTA.	• http://www.lshtm.ac.uk/php/departmentofhealthservicesresearchandpolicy/index.html • HSRP Head: Pauline Allen, Pauline.allen@lshtm.ac.uk
	All Wales Medicines Strategy Group (AWMSG)	The statutory advisory Welsh Assembly-sponsored public body provides advice on medicine management and prescribing to the Welsh Government's Minister for Health and Social Services. It brings together NHS clinicians, pharmacists, health care professionals, academics, health economists, industry representatives and patient advocates for strategic advice on clinical and cost–effectiveness.	• http://www.awmsg.org/ • Contact: awttc@wales.nhs.uk
Uzbekistan	No independent public sector HTA entity to date	The Ministry of Health organizes health services for the population, including needs assessment for pharmaceutical products, but makes no explicit mention of an HTA function.	• http://www.minzdrav.uz/en/about/function.php • Minister: Alimov Anvar Valiyevich • First Deputy Minister: Khudayarov Asilbek Anvarovich (control of quality of medicines and medical equipment) • Deputy Minister: Tillayev Shavkat Hikmatovich (pharmaceuticals)

The WHO Regional Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

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