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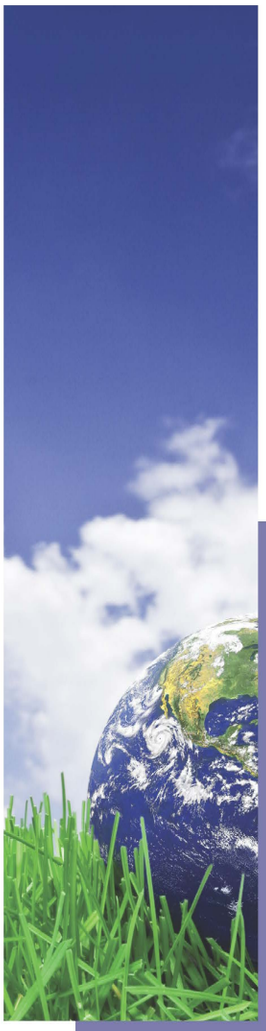
ECONOMIC AND SCIENTIFIC POLICY



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Towards a Harmonised EU Assessment of the Added Therapeutic Value of Medicines

Study for the ENVI Committee

EN

2015

Towards a Harmonised EU Assessment of the Added Therapeutic Value of Medicines

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Towards a Harmonised EU Assessment of the Added Therapeutic Value of Medicines

STUDY

Abstract

This study, produced for the ENVI Committee by Policy Department A, investigates the possibility of a harmonised EU approach concerning the assessment of the added therapeutic value (ATV) of medicinal products. It reviews the current EU legal and policy framework and looks at the state-of-play within all 28 Member States. In addition, it presents the results of an in-depth analysis on the use of ATV in six selected EU countries. The study closes with policy recommendations on how a possible European harmonisation of the ATV assessment might be taken forward within the current legal framework.

IP/A/ENVI/2014-17 June 2015

PE 542.219 EN

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

AUTHORS

Dr VAN WILDER Philippe, Vrije Universiteit Brussel and SMART&BI
Ms MABILIA Valentina, Milieu Ltd
Ms KUIPERS CAVACO Yoline, Milieu Ltd
Ms MCGUINN Jennifer, Milieu Ltd Research and coordination

RESPONSIBLE ADMINISTRATOR

Dr TEJEDOR DEL REAL Purificacion

Editorial Assistant
Karine GAUFILLET

LINGUISTIC VERSIONS

Original: EN

ABOUT THE EDITOR

Policy departments provide in-house and external expertise to support EP committees and other parliamentary bodies in shaping legislation and exercising democratic scrutiny over EU internal policies.

To contact Policy Department A or to subscribe to its newsletter please write to:
Policy Department A: Economic and Scientific Policy
European Parliament
B-1047 Brussels
E-mail: Poldep-Economy-Science@ep.europa.eu

Manuscript completed in May 2015

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LIST OF ABBREVIATIONS

AGES *Agentur für Gesundheit und Ernährungssicherheit GmbH* (Austrian Medicines and Medical Devices Agency)

AIFA *Agenzia Italiana del Farmaco* (Italian Medicines Agency)

ANSM *Agence National de Sécurité du Médicament et des produits de Santé* (French National Drug Safety Agency)

ASMR *Amélioration du service médical rendu* (added therapeutic value)

ATC Anatomical Therapeutic Chemical

ATV Added Therapeutic Value

BASG *Bundesamt für Sicherheit im Gesundheitswesen* (Austrian Federal Office for Safety in Health Care)

CEEPS *Commission d'évaluation économique et de santé publique* (French Committee on Economic Evaluation and Public Health)

CEPS *Comité Économique des Produits de Santé* (French Economic Committee on Healthcare Products)

CHMP Committee for Medicinal Products for Human Use

CNAMTS *Caisse nationale d'assurance maladie des travailleurs salariés* (National Sickness Insurance Fund for Employees)

CPR Pricing and Reimbursement Committee (Italy)

CTS Technical and Scientific Committee (Italy)

EBM Evidence Based Medicine

EK *Erstattungskodex* (Austrian Reimbursement Code)

EMA European Medicines Agency

EPAR European Public Assessment Report

EU European Union

EUnetHTA European Network for Health Technology Assessment (EU Joint Action)

HAS *Haute Autorité de Santé* (French National Health Authority)

HCSA Health Care Surveillance Authority (Slovakia)

HEK *Heilmittel-Evaluierungs-Kommission* (Austrian Pharmaceutical Evaluation Board)

HLPF High Level Pharmaceutical Forum

HTA Health Technology Assessment

HVB *Hauptverband der Sozialversicherungsträger* (Federation of Austrian Social Insurance Institutions)

ICER Incremental Cost-Effectiveness Ratio

ICUR Incremental Cost-Utility Ratio

ICH International Conference on Harmonisation

IGAS *Inspection Générale des Affaires Sociales* (French General Inspectorate of Social Affairs)

ISS *Istituto Superiore di Sanitá* (Italian High Institute of Health)

ITR *Index Thérapeutique Relatif unique* (French Single Relative Therapeutic Index)

LY Life Year

LYG Life Years Gained

MPA Medical Products Agency (Sweden)

MS Member States

NICE National Institute for Clinical Excellence

QALY Quality Adjusted Life Years

R&D Research and Development

REA Relative Efficacy/Effectiveness Assessment

SBU *Statens Beredning för Medicinsk Utvärdering* (Swedish Council on Technology Assessment in Health Care)

SHI Social Health Insurance (Slovakia)

SIDC State Institute for Drug Control (Slovakia)

SKL *Sveriges Kommuner och Landsting* (Swedish Association of Local Authorities and Regions)

TFEU Treaty on the Functioning of the European Union

TLV *Tandvårds- och Läkemedelsförmånsverket* (Swedish Dental and Pharmaceutical Benefits Agency)

UNCAM *Union nationale des caisses d'assurance maladie* (French National Union of health insurances)

WHO World Health Organisation

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EXECUTIVE SUMMARY

Aim

The present study was undertaken upon request of the Committee on Environment, Public Health and Food Safety (ENVI) of the European Parliament. The aim is to investigate the feasibility and opportunity of introducing a harmonised EU approach concerning the assessment of the **added therapeutic value (ATV)** of medicines in the European Union.

Background

The concept of ATV has been proposed in several instances as a way to measure the therapeutic advantages of new medicinal products[1]. While there is no universally agreed definition, in this paper we understand the added therapeutic value of medicinal products as the incremental "therapeutic value" brought by a new drug or intervention compared with the best available treatment options already on the market. The therapeutic value can be defined in terms of positive patient-relevant endpoints and relevant levels of effectiveness, efficacy and safety[2,3]. Furthermore, we understand **Relative Efficacy/Effectiveness Assessments (REA)**[4,5] to be the main tools used to estimate ATV.

REAs are often conducted as part of a broader range of analysis called **Health Technology Assessment (HTA)**, which encompasses a systematic evaluation of the wider issues related to the introduction of a new medicine. This includes economic elements like cost-effectiveness and the impact on a healthcare budget as well as sociological and ethical effects such as the prevalence of the disease or its impact on a particular sub-group of patients.

While the assessment of ATV could theoretically happen prior to the authorised entry of the medicine onto the market (**marketing authorisation phase**), in Europe it is conducted mainly by national authorities in charge of determining the pricing and reimbursement status of a new medicine (**pricing and reimbursement phase**).

Added therapeutic value of medicines in Europe

The current EU legal framework (see section 2.1) does not preclude single Member States from releasing marketing authorisations valid at national level, but it creates several routes for manufacturers to secure an EU-wide marketing authorisation. The most important of these is the "**centralised authorisation procedure**", which allows for a single marketing authorisation of a new medicinal product that is valid in all EU countries and Iceland, Liechtenstein and Norway.

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1 International Society of Drug Bulletins (ISDB): ISDB Declaration on therapeutic advance in the use of medicines, Paris 15-16 November 2001. http://www.isdbweb.org/documents/uploads/Declaration/ISDB-decl-english.pdf (accessed March 2015).

2 Speech by Beate Wieseler, Deputy Head of the Drug Assessment Department, 2011, IQWiG: *How, and on whose behalf, should the "added therapeutic value" of a new drug be assessed?*, Pilule d-Or Prescrire.

3 International Society of Drug Bulletins (ISDB): ISDB Declaration on therapeutic advance in the use of medicines, Paris 15-16 November 2001.

4 High Level Pharmaceutical Forum, core principles on relative effectiveness, available at: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea_principles_en.pdf (accessed March 2015).

5 Eichler et al., 2010, *Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers*, Nature Reviews, Drug Discovery, Volume 9, Paris.

The centralised procedure is compulsory for medicinal products manufactured using biotechnological processes, for orphan medicinal products[6] and for human products containing a new active substance (not authorised in the EU before May 2004) that are intended for the treatment of specific diseases such as diabetes and cancer. For other medicines, companies may opt for using the centralised marketing authorisation procedure for medicines "*that are a significant therapeutic, scientific or technical innovation, or whose authorisation would be in the interest of public health*"[7].

The European Commission is formally in charge of releasing the marketing authorisation, but the procedure itself is managed by the European Medicines Agency (EMA), which conducts a benefit-risk assessment, balancing desirable and undesirable effects of the new medical product[8]. The three criteria that are used during the assessment are: pharmaceutical quality, safety and efficacy. Market authorisation is granted in case of a positive benefit-risk ratio, meaning that the expected benefits (e.g. efficacy, intended effect) outweigh the risks (e.g. safety concerns, unintended effects) when patients are exposed to the product.

Added therapeutic value is not systematically assessed in this phase, nor are the manufacturers of the new medicine legally required to provide any other kind of comparisons to the prevailing treatment alternatives. In fact, studies have shown that between 1999 and 2005, only 48 % of the approved new medicines were compared with existing medicines at the moment of marketing authorisation[9].

Receiving a marketing authorisation is an essential, but only partial, condition for a new medicine to become available to patients in the EU. About two-thirds of the EU's pharmaceutical expenditure is covered by public payers[10], so the pricing and reimbursement measures adopted by national health authorities have a significant impact on whether most patients will have access to a new medicinal product.

The authorities in charge of awarding a marketing authorisation base their evaluation on the efficacy, safety and pharmaceutical quality of a medicinal product. National authorities in charge of pricing and reimbursement also consider its effectiveness, cost-effectiveness, budgetary impact, the severity of the disease and other factors.

The High Level Pharmaceutical Forum (HLPF), a political platform set up by the European Commission in 2005 for a period of three years, brought together a wide range of stakeholders (including national authorities, patients and physicians associations, organisations and payers) in an effort to take forward pricing and reimbursement policies as well as the assessment of relative effectiveness. The Forum underlined the importance of assessing the Relative Efficacy and Effectiveness of new medicinal products (REA) and endorsed REA's aim to compare healthcare interventions in daily practice and classifying them according to their added therapeutic value. It also recommended that Member States

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6 Medicinal products developed specifically to treat rare medical conditions.

7 http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp

8 European medicines Agency, Overview of the CHMP, web page, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000095.jsp&mid=WC0b01ac0580028c7a (accessed March 2015).

9 Van Lujin, J.C., Gribnau, F.W. & Leufkens, H.G., 2007, *Availability of comparative trials for the assessment of new medicines in the European Union at the moment of marketing authorisation*, British Journal of Clinical Pharmacology, 63(2), p. 159-162.

10 Vogler et al., 2008, PPRI Report. Vienna: Gesundheit Österreich GmbH / Geschäftsbereich ÖBIG.

adopt the endorsed definition of relative efficacy and effectiveness, as the extent to which an intervention does more good than harm compared to one or more alternative, either under ideal circumstances (efficacy) or under the usual circumstance of health care practice (effectiveness). The HLPF clearly distinguished REAs from cost-effectiveness analysis (CEA), endorsing the scientific nature of the former.

While there is no shared definition of ATV, in practice, REAs involve many of the same principles and processes across Member States. Nevertheless, they differ in some key areas, such as selecting which drugs to review, the type and quality of evidence required, and methodological approaches. Many countries publish guidelines outlining their evidence and methodological requirements, but the guidelines often vary in detail and transparency[11].

In this study, a mapping exercise was conducted of all EU Member States, and evidence of some form of ATV assessment being conducted was found in 26 countries[12]. Six Member States were the subject of in-depth studies that investigated the how ATV is assessed and the role it plays in decisions on pricing and reimbursement of medicines.

The measurement of ATV depends on the treatment the new medicine is compared with, and choosing one comparator over another may influence the end results. However, when looking at the definition of comparators used in EU countries, there is relatively little variation (see Chapter 3). Most countries identify "best standard care" as their main comparator of choice, even though some will allow and recommend additional comparisons with the "best possible care", or the "cheapest alternative". The evidence is mainly based on regulatory trials, and as a consequence the comparator used in those trials becomes a common assessment comparator for all countries, independent of the local use of that comparator.

Amongst the six Member States studied in-depth, it was found that REAs are conducted in a relatively similar way. Most countries use comparable data sources and show a similar preference for using clinical end-points (e.g. extending overall survival, disappearance of symptoms, etc.) rather than surrogate end-points (e.g. lower blood pressure). Direct comparisons are also generally favoured, as opposed to indirect ones. REA results, combined with other criteria such as cost-effectiveness, safety, potential impact on the healthcare budget are used by the authorities in charge of the pricing and reimbursement of medicines to make a decision on whether to classify the new medicine as reimbursable, and under which conditions. Some but not all Member States also calculate ATV as a separate parameter as part of this decision-making process.

Inputs from stakeholders are generally considered throughout the pricing and reimbursement processes in all Member States[13]. Industry representatives are often called to provide data and to participate in general consultations and in some cases industry associations act as a non-voting member in reimbursement committees. Practitioners and pharmacists are often involved as experts. The views of patients' organisations are presented during hearings or discussions at different stages of pricing and reimbursement

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[11] Sorenson, C., 2010, *Use of Comparative Effectiveness Research in Drug Coverage and Pricing Decisions: A Six-Country Comparison*, the Commonwealth Fund, Issues in International Health Policy: 91: 1-14.

[12] Greece and Cyprus being the two countries for which no such evidence was found.

[13] See Sorenson, C., Drummond, M. & Kanavos, P., 2008, *Ensuring value for money in health care – The role of health technology assessment in the European Union*, European Observatory on Health Systems and Policies Observatory Studies Series No. 11.

processes, depending on the country[14]. Yet, these procedures are usually not transparent and patients are generally not aware of the possibility to express their views in HTA/ATV processes[15]. There is room for improvement in the early involvement of stakeholders, particularly with regard to patients' organisations.

Conclusion

Added therapeutic value provides patients and physicians with crucial information on the expected benefits of a new treatment. This type of information is relevant on its own, regardless of economic considerations.

While there are differences in how ATV is assessed and defined across the EU Member States, the underlying principles are not fundamentally incompatible and share the same goals and concepts. Agreeing on a shared definition of ATV is a desirable and logical next step following the HLPF's endorsed definition of relative effectiveness and efficacy. It should be possible for the Member States to agree on a shared definition and assessment methodology, as long as this is based on clinical criteria, rather than social and economic considerations. The HLPF and the Joint Action Program have already paved the way through their achievements in the field of relative efficacy and effectiveness.

A shared definition and methodology to determine ATV would facilitate communication between all stakeholders, allow Member States to build on each other's expertise and make joint assessments easier. Joint assessments, which have already been conducted through HTA Joint Action 1 and 2, tend to have the added benefit of concentrating expertise that is not usually found within a single national agency and, once there is an agreement on their methodology, saving time. Moreover, the existence of a shared methodology would reduce the administrative burden for pharmaceutical manufacturers, who would need to invest fewer resources in tailoring their dossiers to each Member State where they wish to apply for reimbursement. A shared definition would also clarify the expected benefits of new medicinal products, incentivising the production of innovative medicines and hopefully reducing the burden of unmet medical need.

Ideally, ATV should be measured on an ordinal scale, similar to those used in some Member States with solid experience in using ATV, like France, Italy or Germany. This is more sensitive than a categorical scale and suitable for measuring the small incremental benefits that innovative medicines typically deliver. Furthermore, ATV should be measured by a multi-disciplinary team of trained experts (e.g. technology assessors, clinical pharmacologists, experienced clinicians, experts in clinical and observational research, biostatisticians). These assessors should work independently from the committees in charge of determining the price of medicinal products.

Repeated interactions, shared definitions and methodologies would ideally lead to the creation of an international European joint expert committee. Composed of qualified delegates from Member States, this committee would conduct REAs before any pricing and reimbursement procedure is initiated at the national level. Competent authorities at national

[14] For a comparative analysis, see Kleijnen et al., *Relative Effectiveness Assessment (REA) of Pharmaceuticals, background review*, July 2011, available at http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Final%20version%20of%20Background%20Review%20on%20Relative%20Effectiveness%20Assessment%2Bappendix.pdf (last accessed April 2015).

[15] European Patients' Forum, Patient involvement in health technology assessment, http://www.eu-patient.eu/globalassets/projects/hta/epf-report_hta-survey_po.pdf.

level would be able to adopt the resulting joint REA reports, at their discretion, and use them in the national pricing and reimbursement decision-making process. Such a configuration would have the benefit of concentrating the best expertise and reducing administrative burden while respecting the Member States' competence over their healthcare policies.

Whatever the level of harmonisation achieved, the REAs, including the ATV estimation, should be transparent, based on relevant criteria and revisable in case of new evidence. Detailed methodological guidelines should be made publicly available so as to allow appeals on matters of content rather than just form.

When it comes to more complex Health Technology Assessments, including social, ethical and economic considerations, harmonisation is more complex and may be less relevant. Member States may rightfully have different opinions on the weight given to different factors, not to mention the fact that the data itself and the choices in healthcare spending will likely vary from one country to another. Nevertheless, sharing best practices and building staff capacities in this area would certainly help consolidate a discipline that has proved to be a useful tool in making evidence-based policy decisions.

Whatever the level of harmonisation achieved, the pricing and reimbursement decision will remain the full competence of national authorities, following the EU HTA network's vision: "evidence is global, decision is local".

1 INTRODUCTION

1.1 Aim and scope of the study

The following study was undertaken at the request of the Committee on Environment, Public Health and Food Safety (ENVI) of the European Parliament its aim is to investigate the possibility and opportunity of introducing a harmonised EU approach concerning the assessment of the added therapeutic value (ATV) of medicines within the European Union.

The study sets out the general background to ATV and its use by EU Member States, and explains the different stages in the national decision-making process where ATV considerations play a role. Next, it provides a (non-exhaustive) mapping of practices and the current state-of-play in the 28 EU Member States, as well as an in-depth analysis of the use of ATV in six selected countries: Austria, France, Italy, Poland, Slovakia and Sweden. Based on the information and data collected, the final chapter provides legal and policy recommendations for streamlining the various national systems in place for ATV assessment, towards a common EU approach.

1.2 Defining added therapeutic value

The concept of added therapeutic value has been proposed in several instances as a way to measure the therapeutic advantages of new medicinal products compared to existing ones[16]. **Medicinal products** are defined by the European Commission[17] as follows:

(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

There is no universally agreed definition of **added therapeutic value**. In this paper, we understand it to mean the incremental "therapeutic value" brought by a new drug or intervention compared with the best available treatment options already on the market. The therapeutic value can be defined in terms of patient-relevant endpoints and relevant levels of effectiveness, efficacy and safety[18,19]. Furthermore, we understand **Relative Efficacy/Effectiveness Assessments (REA)**[20,21] to be the main tools used to estimate

[16] International Society of Drug Bulletins (ISDB): ISDB Declaration on therapeutic advance in the use of medicines, Paris 15-16 November 2001. http://www.isdbweb.org/documents/uploads/Declaration/ISDB-decl-english.pdf .

[17] Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. Article 1. Published March 31, 2004.

[18] Speech by Beate Wieseler, Deputy Head of the Drug Assessment Department, 2011, IQWiG: *How, and on whose behalf, should the "added therapeutic value" of a new drug be assessed?*, Pilule d-Or Prescrire.

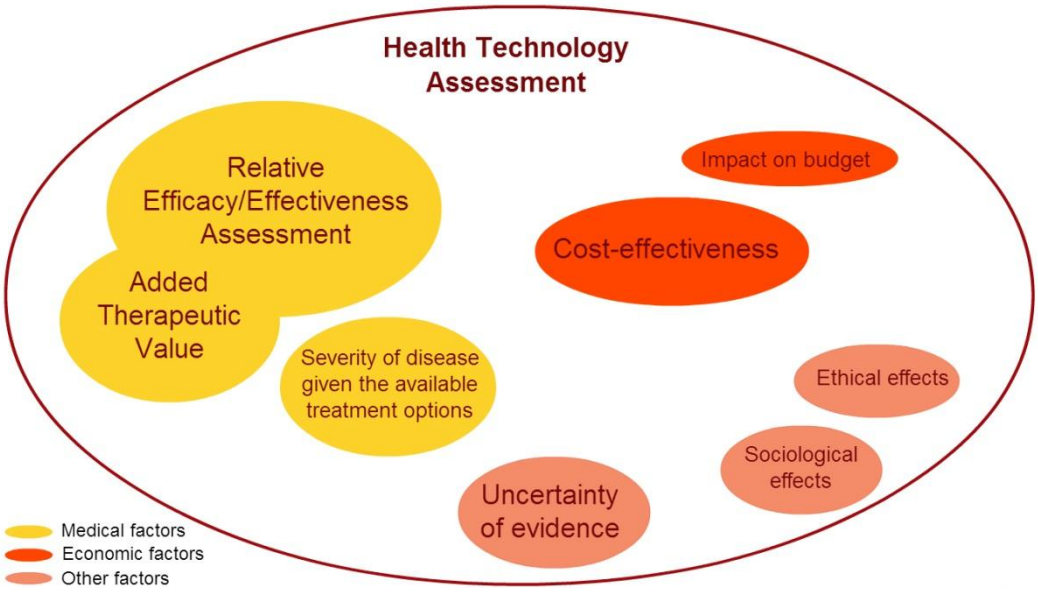
[19] International Society of Drug Bulletins (ISDB): ISDB Declaration on therapeutic advance in the use of medicines, Paris 15-16 November 2001.

[20] High Level Pharmaceutical Forum. Core principles on relative effectiveness, available at: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/rea_principles_en.pdf (accessed March 2015).

added therapeutic value. ATV can be measured in terms of outcomes or indicators that are indirectly relevant for the patient (e.g. lower blood pressure, tumour response), clinical end-points that are directly relevant to the patient (e.g. extending overall survival, disappearance of symptoms, quality adjusted life years gained), or a weighted combination of two or more of these. In practice, it is often expressed on a scale (e.g. low, moderate, significant), or as a categorical concept (i.e. medicine with ATV, medicine with no ATV).

However, the therapeutic value is not the only aspect considered by national authorities when assessing new medicines: its cost, budgetary impact and the quality of evidence used for the ATV assessment are also important considerations. A multi-disciplinary assessment that is often used and referred to is **health technology assessment (HTA)**, which encompasses a systematic evaluation of the wider aspects and issues related to the introduction of a new medicine or drug. HTA is conducted by interdisciplinary groups using analytical frameworks drawing on a variety of methods, with the main purpose of informing technology related policymaking in health care[22,23]. The Relative Efficacy/Effectiveness Assessment and ATV remain the central element of HTA, but cost-effectiveness in particular is seen as an important element to complement the REA. While a full examination of the interactions between HTA factors is outside the scope of this study, the following figure lists the criteria which may be used to evaluate new medicinal products.

Figure 1: Criteria used to evaluate medicinal products



[21] Eichler et al., 2010, *Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers, Nature Reviews*, Drug Discovery, Volume 9, Paris.

[22] International Network of Agencies for Health Technology Assessment (INAHTA). Available at: http://htaglossary.net/HomePage (Accessed March 2015).

[23] Annemans at al., 2011, *Valorising and creating access to innovative medicines in the European Union, Frontiers in pharmacology*, hypothesis and theory article.

In order to provide the context in which the assessment of added therapeutic value occurs, this study will also briefly examine the most important aspects of HTA.

1.3 Timing of the added therapeutic value assessment

The added therapeutic value of new medicinal products can be assessed at different stages during the manufacturing and distribution processes. In broad terms, there are two important moments when the clinical assessment can play a role: prior to the authorised entry of the medicine onto the market (**marketing authorisation phase**); and when the pricing of a new medicine and its reimbursement is determined (**pricing and reimbursement phase**).

In practice however, the ATV assessments (through REA) are often conducted at the stage of pricing and reimbursement of the medicine, rather than prior to its authorised entry onto the market, as further described in chapter 2 and 3.

2 SETTING THE SCENE: ADDED THERAPEUTIC VALUE OF MEDICINES IN EUROPE

This chapter sets out the legal and policy framework that exists within the EU relating to the authorisation of new medicines and the assessment of their added therapeutic value. It then details the two main steps in the marketing process of new medicinal products where ATV could be considered: marketing authorisation and pricing and reimbursement. Finally, the views and roles of the different stakeholders are outlined.

2.1 The EU legal and policy framework

The authorisation of new medicines in Europe for human use (as well as its manufacture and distribution) takes place within the EU legal framework set out by **Directive 2001/83/EC**[24] and **Regulation 726/2004**[25] (both amended by Regulation 1394/2007[26]).

While the Directive does not preclude single Member States from authorising new medicines at national level, it creates several routes for manufacturers to secure an EU wide marketing authorisation. The most important of these is the "**centralised authorisation procedure**", which allows for a single marketing authorisation of a new medicinal product that is valid in all EU countries and Iceland, Liechtenstein and Norway (for more details see section 2.2).

The **European Medicines Agency (EMA)**, created as a result of Regulation 726/2004, manages this centralised procedure. Whenever a new medicine is ready to enter the market, EMA's Committee for Medicinal Products for Human Use (CHMP) conducts a benefit-risk assessment, balancing desirable and undesirable effects[27]. The three criteria on which the assessment is based are: pharmaceutical quality, safety and efficacy.

The current EU legal framework does not require new medicinal products to be compared to the prevailing alternatives. In fact, studies have shown that between 1999 and 2005, only 48 % of the approved new medicines were compared with existing medicines at the time of their marketing authorisation[28].

In cases where a comparison is made between new and existing medicines, the prevailing criterion is not that of an added therapeutic value, but rather that of non-inferiority[29]. Instead of assessing whether a new treatment does more good than harm compared to

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

[25] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 march 20014 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, 30.4.2004, L 136/1.

[26] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, 10.12.2007, L 324/121.

[27] European medicines Agency, Overview of the CHMP, web page, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000095.jsp&mid=WC0b01ac0580028c7a (accessed March 2015).

[28] Van Lujin, J.C., Gribnau, F.W. & Leufkens, H.G., 2007, *Availability of comparative trials for the assessment of new medicines in the European Union at the moment of marketing authorisation*, British Journal of Clinical Pharmacology, 63(2), p. 159-162.

[29] Wieseler, B., 2011, *Comparisons enable better treatment – evaluating therapeutic advances in patients' best interest*, p. 2.

other, already existing and approved intervention alternatives, the EMA uses trials to establish whether a new treatment has more benefits than risks. In case of comparisons with alternatives the principle of non-inferiority sets limits to any difference in clinical effect to ensure the investigational compound is "not unacceptably worse" than the control treatment[30].

For some regulatory tracks, it is expected to find a similar therapeutic value between the investigational compound and the reference product. In the case of generic compounds or biosimilar drugs, their market authorisation is mainly based on trials investigating respectively the bio- or clinical equivalence of the generic/biosimilar compound with the reference product. The pharmacokinetic parameters measured in blood serum or plasma of the generic drug should then be "equivalent" to those of the reference product. Equivalence means that any difference in parameter between the generic and the reference product lies within a range of values which are considered to have no impact on the clinical efficacy and safety. Accordingly, the products that achieve bioequivalence have similar therapeutic value. For biosimilar products, clinical equivalence or non-inferiority is investigated and in case of achieving this equivalence or non-inferiority it is also assumed that both products have similar therapeutic value.

During the pricing and reimbursement phase, the European legal framework does not require an assessment of the added therapeutic values of new medicines. While it is important to note that pricing and reimbursement decisions remain a national competence, some European legislation does apply in terms of procedural obligations:

- the Transparency Directive[31] stipulates that pricing and reimbursement decisions must be taken in a transparent, objective and verifiable way, within strict, stated timelines (maximum of 180 days from submission to decision); and
- the Cross Border Healthcare Directive[32] (Article 15) stipulates that the Union shall support and facilitate cooperation between national authorities or bodies responsible for Health Technology Assessment designated by the Member States.

Recently, the Council of the European Union adopted **Council conclusions on innovation for the benefit of patients**[33], which underlined the importance of HTA as a policy tool to support evidence-based, sustainable and equitable choices in healthcare for the benefit of the patient. It called for further joint work on HTA between Member States and the need to explore opportunities for a cooperative exchange of information between competent bodies.

Strengthening collaboration between national authorities concerning the assessment of new medicines is an issue that was addressed by the **High Level Pharmaceutical Forum**, a political platform set up by the European Commission in 2005 for a period of three years[34]. The purpose of the Forum was to explore solutions to public health considerations regarding

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30 Schumi, J. and Wittes, J., 2011, *Through the looking glass: understanding non-inferiority*, BioMed Central.

31 Directive 89/105/EEC Council Directive of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems, 11.2.89, L 40/8.

32 Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' right in cross-border healthcare, 4.4.2011, L 88/45.

33 Council of the European Union, Council conclusions on innovation for the benefit of patients, Brussels, 1 December 2014.

34 http://ec.europa.eu/enterprise/sectors/healthcare/competitiveness/pharmaceutical-forum/index_en.htm.

pharmaceuticals, while at the same time ensuring the competitiveness of the industry and the sustainability of national healthcare systems. The Forum recommended that Member States regularly exchange information and scientific evidence and that they adopt the working definitions of REA endorsed by the Forum[35].

The Cross Border Healthcare Directive further improved the conditions of information exchange between Member States by creating "a voluntary network connecting national authorities and bodies responsible for health technology assessment"[36], which is now known as the **Health Technology Assessment Network**[37]. To date, all Member States participate in this network, which consists of national authorities responsible for Health Technology Assessment.

Another mechanism that has been put in place by the EU to facilitate cooperation on HTA between Member States is the Joint Action on Health Technology Assessment: **"EUnetHTA"**[38]. The purpose of this programme is three-fold: to develop guidelines for effective joint working models for HTA collaboration, as well as transparent governance tools; to prevent duplication of work between national agencies; and to promote sharing and exchange of HTA information. The network organises "joint assessments" in which two or more HTA organisations come together and prepare shared health technology assessments. Additionally, it has developed and conducted training courses, produced a set of guidelines on conducting REAs, developed a structure for jointly producing and reporting on scientific relative effectiveness information for trans-national use (HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals), written methodological guidelines on issues relevant to REAs[39], and compiled databases on new treatments and their reimbursement status[40], as well as planned and ongoing relevant projects[41].

2.2 Marketing authorisation

As described above, under EU legislation, the marketing authorisation process requires a new medicinal product to have proven efficacy, to be safe, and to fulfil all pharmaceutical quality criteria. The following section sets out in more detail the various steps relevant to the marketing authorisation process and the different aspects that should be taken into account concerning the assessment of the added therapeutic value of new medicinal products.

The **development of a new medicinal product** is a long, complex and costly[42] process; it often takes more than a decade between the synthesis of a new product and its marketing

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[35] High Level Pharmaceutical Forum, 2005 – 2008, Final Conclusions and recommendations, p. 6.

[36] Commission Implementing Decision of 26 June 2013 providing the rules for the establishment, management and transparent functioning of the Network of national authorities or bodies responsible for health technology assessment, (2013/329/EU), 27.6.2013, L 175/71.

[37] European Commission, DG SANTE, web page: Health Technology Assessment Network, Available at: http://ec.europa.eu/health/technology_assessment/policy/network/index_en.htm.

[38] The first EUnetHTA Joint Action ran between 2010-2012 and involved 24 Member States plus Norway and Switzerland. The current EUnetHTA Joint Action (2012-2015), with a total budget of 9,4 million euro, involves all 28 Member States, plus Norway, Switzerland, Turkey and Russia. For more information: http://www.eunethta.eu/.

[39] Available at URL: http://www.eunethta.eu/hta-core-model.

[40] EVIDENT database, available at URL: http://www.eunethta.eu/evident-database.

[41] POP database, available at URL: http://www.eunethta.eu/pop-database.

[42] Morgan, S. et al., *The cost of drug development: a systematic review*, Health Policy 100, 2011, p 4-17.

authorisation[43]. Once a new medicinal product has been produced, it is first tested in non-clinical studies (*in vitro* and *in vivo*) to investigate the medicine's toxicity and pharmacological properties. Next, clinical trials with human beings are conducted. These trials are regulated through Directive 2001/20/EC[44], which incorporates the International Conference on Harmonisation's Guidelines on Good Clinical Practice (ICH E6)[45].

The Directive provides a framework for ensuring patients' safety when being exposed to a new drug: the study protocol must be approved by an independent ethics committee (which consists of both healthcare professionals and non-medical members) and participants must give their informed consent.

Table 1: Phases of clinical testing

Phase I
Tolerability or pharmaco-kinetics as primary indicator in the protocol, independent of the study population and secondary parameters
Phase IIA
Exploratory (non-pivotal) study that has clinical efficacy, Pharmacodynamics or biological activity as primary indicator, conducted in patients or healthy volunteers.
Phase IIB
Definite dose range finding study in patients with efficacy as primary indicator.
Phase IIIA
A pivotal study that is a trial designed & executed to get statistically significant evidence of efficacy and safety as required for regulatory approval.
Phase IIIB
A study started prior to approval and whose primary intention is support of publications rather than registration or label changes. The results are not intended to be included in the submission dossier.
Phase IV
Studies undertaken after a new medicine has obtained a marketing authorisation. Their goals can be to identify less common side effects as well as long term risks and benefits.

[43] European Federation of Pharmaceutical Industries and Associations, 2014, The Pharmaceutical Industry in Figures, Key data.

[44] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, 1.5.2001, L 121/34.

[45] International Conference on Harmonisation, 1995, ICH Harmonised Tripartite Guideline, Good Clinical Practice E6.

Once a medicinal product has successfully gone through the clinical trial period, it may either be required or selected for the **centralised authorisation procedure**, which – if successful – allows the medicinal product to be released in all 28 EU Member States as well as Iceland, Liechtenstein and Norway.

The centralised procedure is compulsory for medicinal products manufactured using biotechnological processes, for orphan medicinal products[46] and for human products containing a new active substance (not authorised in the EU before May 2004) that are intended for the treatment of specific diseases such as diabetes and cancer. For other medicines, companies may opt for using the centralised marketing authorisation procedure for medicines "*that are a significant therapeutic, scientific or technical innovation, or whose authorisation would be in the interest of public health*"[47].

The EMA's Committee for Medicinal Products for Human Use has 210 working days to adopt an opinion on the granting of a marketing authorisation for the new medicine. This opinion is then submitted to the European Commission, which alone has the authority to grant the authorisation. If approved, the document containing the body of evidence analysed by the Committee, called the European Public Assessment Report (EPAR), is made publicly available by the EMA through its website. The EMA publishes monthly reports with the number of submissions handled, the type of submitted product and the outcome of the assessment.

In order to obtain a marketing authorisation for two or more Member States at the same time, manufacturers may also use the **decentralised procedure** or the **mutual-recognition procedure** (unless the new medicine falls within the above mentioned categories for which the centralised procedure is compulsory). They may also choose to apply for a **national authorisation**, which is then limited to a single Member State.

Determining the added therapeutic value of the medicinal product is currently outside of the scope of the marketing authorisation process. The main focus of the benefit-risk analysis is on the safety and efficacy of the product in absolute terms rather than on how it compares to existing treatments. Also the economic aspects of the products (e.g. cost-benefits) are not evaluated at this stage.

At the time of market authorisation the experience with a new product is bound to be limited, and there may therefore still be clinical uncertainty about the incidence and severity of the adverse event profile of a new medicinal product. To ensure safe use for patients exposed to new products, a pharmacovigilance plan is implemented. In each pharmaceutical company a pharmacovigilance officer is responsible of ensuring the appropriate management of safety issues and the collection of spontaneous reports of adverse events, which are then transferred to the regulatory authorities for each marketed product. Moreover, every six months a safety update report (PSUR) is sent to the regulatory authorities, grouping all relevant safety information from the considered time period. If new adverse events or changes in the safety profile are emerging, regulatory authorities may adapt the market authorisation by restricting the access to specific patient populations or even by withdrawing the marketing authorisation if an unacceptable safety risk would arise.

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[46] Orphan medicinal products are developed specifically to treat rare medical conditions.

[47] http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp.

Re-assessment of the benefit-risk ratio takes place at five-year intervals after the medicinal products has been granted access to the market, and includes an assessment of new evidence on efficacy, safety and quality obtained post-approval. As a result of this re-assessment, the product label may remain unchanged, may be modified (e.g. restricting the use to a specific subpopulation), or the product may be withdrawn from the market if the benefit-risk ratio is found to be negative.

2.3 Pricing and reimbursement

The marketing authorisation process described in the previous section is an essential but only partial condition for a new medicinal product to become available to patients. Pricing and reimbursement measures, which are adopted at national level, also have a significant impact, as the access of the product to patients often depends on the reimbursement by a national healthcare system or a social insurance.

The main differences between the marketing authorisation and the reimbursement processes are illustrated in Table 2[48,49].

Table 2: Comparison between the two main phases of medicine approval

	Marketing authorisation application	Pricing and reimbursement decision
Level	EU level; centralised procedure (EU-28, Iceland, Norway and Liechtenstein), or decentralised or mutual-recognition procedure (two or more MS) National level; national authorisation procedure (single MS)	Always at national/local level
Criteria	Based on efficacy, safety and pharmaceutical quality	In addition to efficacy, safety and pharmaceutical quality, based on effectiveness, cost effectiveness, budgetary impact, severity of disease and quality of evidence
Analysis	Analysis of benefit-risk ratio	Analysis of relative effectiveness, added therapeutic value and cost-effectiveness

[48] Van Wilder, P., Dupont, A., 2008, *Introducing Evidence-Based Medicine in Reimbursement Procedures: Does it affect the Outcome?*, Value in Health, Volume 11, Number 4.

[49] Presentation given by Van Wilder P. at the 10th EACPT Congress on Relative Efficacy and Effectiveness assessment on new pharmaceuticals in 3 EU Member States: Belgium, the Netherlands and France, Budapest, 2011.

In contrast to the CHMP-evaluation for centralised marketing authorisation, the pricing and reimbursement evaluation is a national competence. AS such, assessments may differ in scope, objectives, methods and outcomes between EU Member States. A comparative study drug reimbursement in six countries (Sorenson, 2010)[50] found that "*assessments involve many of the same principles and processes across the six countries, but they differ in some key areas, such as selecting which drugs to review, the type and quality of evidence required, and methodological approaches. Many countries publish guidelines outlining their evidence and methodological requirements, but the guidelines often vary in detail and transparency*".

This has been confirmed by the recent survey of 29 jurisdictions by Kleijnen[51] et al: the level of detail and type of content of methodological guidelines varied substantially across these jurisdictions. In addition, as there is no commonly endorsed definition of added therapeutic value of medicinal products, it may be estimated in different ways across countries, ranging from a simple figure to a composed index. This issue will be described further in chapter 3.

During the pricing and reimbursement phase, the direct healthcare costs and, if relevant, the societal costs (e.g. cost of lost working days) are usually considered in a health-economic analysis (e.g. cost-effectiveness). During this phase, the medicinal product is, in general, compared with the alternative that is "most likely to be replaced" on the local market. The medicinal product's incremental cost and incremental effects are estimated and an incremental cost-effectiveness ratio (ICER) is calculated.

The ICER for medicinal products is often expressed in additional cost per additional life year (LY, if the medicinal product has a favourable impact on longevity) or per additional quality adjusted life year (QALY, if the medicinal product affects morbidity). The higher the resulting ICER, the less efficient the medicine will be, as it will take more money to obtain additional gain in LY or QALY. The cost component is particularly important for national authorities, for whom the balance of societal interest and healthcare budgets (affordability and sustainability) is a consideration.

Almost all EU Member States have put in place agencies responsible for conducting HTA of new medicinal products. These agencies may provide input into the assessments conducted during the marketing authorisation, but more often their input feeds into the pricing and reimbursement process. The way in which they relate to the authorities in charge of pricing and reimbursement can vary from one Member State to another[52]. HTA agencies differ in mandate (with or without a formal link to reimbursement), scope (all technologies, only medicinal products, only new products) structure, funding, resources, expertise, applicable methods and procedures. These differences are further detailed in chapters 3 and 4.

In conclusion, even if centrally approved, the market access and uptake of a new medicinal product will vary substantially across Member States. Some of these differences may be due

[50] Sorenson, C., 2010, *Use of Comparative Effectiveness Research in Drug Coverage and Pricing Decisions: A Six-Country Comparison*, the Commonwealth Fund, Issues in International Health Policy: 91: 1-14.

[51] Kleijnen et al, 2012, *Relative Effectiveness Assessment of Pharmaceuticals: Similarities and Differences in 29 jurisdictions*, Value in Health 15, p. 954-960.

[52] Charles River Associates, 2011, *A comparative analysis of the role and impact of Health Technology assessment,* final report, London.

to the different priorities in healthcare, which Member States are entitled to establish independently. Others, however, may arise from the lack of commonality across good practices in the pricing and reimbursement decision-making process. European initiatives like the Health Technology Assessment Network, the High Level Pharmaceutical Forum and EUnetHTA, as described earlier, are necessary to strengthen collaboration in HTA between Member States, and share good practices in order to reduce these differences.

The following section of this study sets out the views of stakeholders, particularly in relation to an EU approach to ATV and HTA, and describes the different roles the stakeholders play in the national pricing and reimbursement processes.

2.4 Stakeholder views and roles

A range of individuals and groups have a stake in the processes concerning the assessment of the added therapeutic value of medicinal products. These include patients' and consumer organisations, HTA agencies and other research bodies, the pharmaceutical industry, health insurance providers and healthcare professionals' organisations. In light of a possible harmonisation of national ATV assessment processes, it is particularly important to define the different views and standpoints of the various stakeholders and actors involved in the process.

The timing of ATV/HTA assessments

Stakeholders have been active in the discussions concerning the role that ATV should play in the decision making and evaluation process of new medicines, particularly with regard to the stage at which ATV should be assessed. Unsurprisingly, the opinions on the issue vary considerably.

NGOs such as the European Public Health Alliance[53] have been putting pressure on policy-makers to ensure that assessments of added therapeutic value are conducted before new medicines are granted a marketing authorisation. Their hope is that national reimbursement agencies would subsequently use these data to make the reimbursement of a new medicine conditional on it having some ATV, thereby making it less profitable for pharmaceutical companies to develop medicines with no ATV[54].

Patients' organisations are supporting this view with regards to orphan medical products, and have put forward proposals for the introduction of a centralised and scientific assessment of ATV by the EU during the market authorisation of new medicinal products. They argue that ATV is best evaluated at a central level, where the scientific expertise is more widely gathered and better accessible. They claim that such an approach would provide efficiencies for national authorities, both in terms of time and money, as they could

[53] The European Public Health Alliance, an organisation that includes health NGOs, patient groups, health professionals and disease groups and advocates for better health of EU citizens.

[54] EPHA, Wemos, Somo and ISDB, September 2014, *Added Therapeutic Value: European citizens should get their money's worth*, Position Paper.

make use of studies already conducted at EU level to support their decisions on pricing and reimbursement[55].

Parts of the scientific community support these views of NGOs and patients' organisations, even going so far as to make the case for ATV being a condition to grant market access. Dr Garattini and Dr Bertele wrote that "*it is unethical to experiment on patients with the sole aim of obtaining a marketing authorisation. New drugs should be required to have some added value (greater efficacy or less toxicity) to current treatments or be cheaper*" [56].

Representatives of the pharmaceutical industry, on the other hand, argue that even new medicines which feature only very small differences when compared with their predecessors, have their value: they may help combating resistant strains of viruses and bacteria, or have a better efficacy for a particular subset of patients[57].

Harmonisation of ATV/HTA processes

In principle, both manufacturers and assessment organisations agree that an EU-wide harmonisation of the relative effectiveness assessment (REA) of new medicines by the national reimbursement decision-makers would be beneficial. They expect that this would limit the costs for the pharmaceutical industry and for the public sector by avoiding the duplication of work, while patients would have access to better quality information about different treatment options[58].

The industry has repeatedly stated that a mutually-agreed definition of medicines' added therapeutic value and a harmonised approach for the assessment of the value of medicines would foster real progress in developing new medicines. An additional benefit would be the avoidance of a needless and potentially dangerous patchwork of different outcomes at national level. Adopting a harmonised approach to assess the value of medicines would not hamper the independent decisions of national authorities, nor substitute the latter. Rather, it would create consistency across assessments, whiles also reducing inequalities among countries in terms of consumer access to medicines and treatments[59].

There appears to be agreement among stakeholder groups that homogeneous HTA or ATV methodologies should be transparent and coordinated, and that these should be accountable to stakeholders' representatives, in particular to those most directly affected by HTA/ATV decisions, i.e. patients and consumers. Some organisations have stressed the

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[55] European Organisation for Rare Diseases (EURORDIS), *EURORDIS Position Paper on the "Centralised procedure for the scientific assessment of the Therapeutic Added Value of Orphan Drugs"*, available at http://www.eurordis.org/sites/default/files/publications/position-paper-EURORDIS-therapeutic-added-value-ODFeb08.pdf (last accessed April 2015).

[56] Garatini, S. & Bertele, V. 2007, *How can we regulate medicines better?,* BMJ 335, p. 803-805.

[57] European Federation of Pharmaceutical Industries and Associations, Recognizing the value of the "me-too" http://www.efpia.eu/blog/125/21/Recognising-the-Value-of-the-Me-Too.

[58] ISPOR 2012 Berlin, How transferable is clinical evidence: does one-size fit all when assessing the relative effectiveness of pharmaceuticals in Europe?

[59] European Federation of Pharmaceutical Industries and Associations, 2014, *Health and growth – Working together for a healthy Europe. A vision towards a life sciences strategy for Europe*, Brussels.

importance of an effective and highly transparent involvement of all interested stakeholders before, during and after the decision-making processes on ATV or HTA[60].

However, some scepticism has been expressed concerning the feasibility and effectiveness of a complete harmonisation of the ATV assessment or HTA processes at EU level. The European Public Health Alliance argues that, while cooperation of experts and exchange of information can be seen as a way to avoid duplication and to facilitate cross-border healthcare delivery, the adoption of a pan-European HTA system might fail to take into account the policy context of each country. It therefore might threaten the individuality of national health systems and their right to choose which technologies and medicines they wish to employ[61].

The common concern of industry, patients' organisations, regulators and HTA agencies about the consequences and effects of fragmented national HTA processes and ATV assessments has led, in recent years, to the development of a number of multi-stakeholder networks and various consultation processes. These aimed to establish an early dialogue among relevant players, enhancing exchange of information and, ultimately, achieving a higher level of convergence among different national processes. The Commission itself, which for a long time has been seeking and supporting the coordination of HTA and ATV practices, launched a public consultation in 2012, to gather information from different parties on how to develop and integrate stakeholder consultations in HTA/ATV activities[62].

Role and involvement of different stakeholders

Inputs from stakeholders are normally considered throughout the HTA/ATV processes in Member States[63]. The industry is often called upon to provide data, industry associations participate in general consultations, practitioners and pharmacists are involved as experts or stakeholders, and the views of patients' organisations are taken into account during hearings or discussions at different stages of pricing and reimbursement processes, depending on the country[64]. These procedures however, are not universally transparent, and patients may not be aware of their right to express their views in HTA/ATV processes.

Early involvement of stakeholders, especially patients' organisations, would allow such organisations to have access to more information on the new treatments. Moreover, it would enable them to provide valuable input and feedback on the real impact of new medicinal products and on the access to value-for-money medicines[65].

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[60] Health First Europe, Editorial of the Honorary President John Bowis, *The EU role in making technology accessible for patients*, 22 September 2014, available at http://www.healthfirsteurope.org/newsroom/246/70/The-EU-role-in-making-technology-accessible-for-patients-by-John-Bowis (last accessed April 2015).

[61] EPHA briefing on Health Technology Assessment (HTA), August 2012.

[62] European Commission, DG Health and Consumers, Report on the public consultation on the modalities of stakeholder consultation in the future Health Technology Assessment Network, December 2012.

[63] See Sorenson, C., Drummond, M. & Kanavos, P., 2008, *Ensuring value for money in health care – The role of health technology assessment in the European Union*, European Observatory on Health Systems and Policies Observatory Studies Series No. 11.

[64] For a comparative analysis, see Kleijnen, S. et al, July 2011, *Relative Effectiveness Assessment (REA) of Pharmaceuticals, background review*, available at http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Final%20version%20of%20Background%20Review%20on%20Relative%20Effectiveness%20Assessment%2Bappendix.pdf (last accessed April 2015).

[65] European Patients' Forum, Patient involvement in health technology assessment, http://www.eu-patient.eu/globalassets/projects/hta/epf-report_hta-survey_po.pdf.

A range of organisations are advocating strongly for the increased involvement of patients, consumers and providers in the decision-making process for pricing and reimbursement, and, more specifically, when it comes to setting priorities on the technologies to be assessed and the methodologies to support decision-making processes. The involvement of patients, consumers and providers could be increased during the adoption of common definitions and best practice principles for HTA/ATV, the identification of unmet medical needs and defining prioritised areas for R&D. Developing relevant information on HTA and ATV, and communicating such information to the general public is also a step where further involvement from patients, consumers and healthcare providers is needed[66].

Two EU initiatives have begun to work towards the integration of this wide range of stakeholders, to facilitate the scientific and technical cooperation among relevant bodies and to allow for an effective exchange of information: the **Health Technology Assessment Network** and the Joint Action on HTA, with **EUnetHTA** as the coordinating organisation. The Joint Action in particular has stressed the need to enable and strengthen the participation and cooperation of any organisation involved in the HTA process. As a result, they established a Stakeholder Forum as a permanent representation of stakeholder views within the EUnetHTA Joint Action[67].

Similarly, the Health Technology Assessment Network has stressed the need to "*facilitate interaction and synergies between the Network and other relevant European networks and bodies, to involve relevant national and regional actors (including HTA statutory bodies, regulators, healthcare providers, payers, patient representatives and research institutes) and to facilitate synergies in all stages of the lifecycle of health technologies"*[68].

Finally, the EMA has emphasised the importance of a continuous and growing involvement of stakeholders, as demonstrated by their decision to start hosting patient groups with the aim to gather their views and try to incorporate them in decision-making processes[69].

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[66] AIM, HOPE, BEUC, CPME, EURORDIS and European Social Insurance Platform, *HTA Position paper of the European organisations of patients, consumers, healthcare providers and payers,* available at http://www.aim-mutual.org/fileadmin/Communication/position_papers/HTA_Position_paper_final_20_March_2013a.pdf (last accessed April 2015). See also Irish Platform for Patients' Organisations, Science and Industry, *Health Technology Assessment in Ireland, where are we now?* Conference Report, 5th April 2011.

[67] See EUnetHTA, *Stakeholder Involvement Policy,* EUnetHTA Joint Action 2010-2012 October 2010, available at https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/EUnetHTA%20JA%20Stakeholder%20Involvement%20Policy.pdf (last accessed April 2015).

[68] EUnetHTA, 29 October 2014, *Strategy for EU cooperation on Health Technology Assessment,* Rome.

[69] See the notes from European Federation of Pharmaceutical Industries and Associations, 12 March 2015, *The EMA at 20: a quality model that deserves to be replicated,* Scrip Regulatory Affairs.

3 OVERVIEW OF THE USE OF ATV IN THE EU-28 DURING PRICING AND REIMBURSEMENT

The following chapter provides an overview of the assessment of the added therapeutic value of new medicines in EU Member States. During this study, only the use of ATV during the pricing and reimbursement process was considered, as no examples were identified of EU Member States assessing the added therapeutic value of new medicines during the market authorisation phase.

3.1 Use of ATV in the 28 EU Member States

A general mapping exercise was conducted to assess the use of ATV by EU Member States. The information was collected through an extensive review of the available literature, in English, comparing ATV assessments between different European countries or providing details on the ATV assessment in a specific Member State. In total, nine relevant studies were identified and used for this exercise:

- Armataki, E., et al, 2014, Health Technology Assessment of Medicines in Greece: Pharmaceutical Industry Executives' Views, International Journal of Technology Assessment in Health Care
- Gulácsi, L. et al, 2014, Health Technology Assessment in Poland, Czech Republic, Hungary, Romania and Bulgaria, European Journal of Health Economics 15, May 2014
- International Society for Pharmacoeconomics and Outcomes Research, Pharmacoeconomic guidelines in Croatia and Baltic countries
- Kanavos, P. and Wouters, O., 2014, Pharmaceutical policies in Cyprus: A Review of the Current System and Future Options, LSE Health, August 2014
- Kleijnen, S. et al, July 2011, Relative Effectiveness Assessment (REA) of Pharmaceuticals, background review
- Kleijnen, S. et al, 2012 Relative Effectiveness Assessment of Pharmaceuticals: Similarities and Differences in 29 jurisdictions, Value in Health
- Le Polain, M. et al, 2010, Les systèmes de remboursement des médicaments: comparaison internationale et recommandations aux décideurs
- Paris, V. and Belloni, A., 2013, Value in Pharmaceutical Pricing, OECD Health Working Papers No. 63
- Wilsdon, T. and Serota, A., 2011, A comparative analysis of the role and impact of Health Technology Assessment, May 2011

Four different aspects of the use of ATV were considered during the mapping exercise:

- With what is the new medicine compared- the alternative treatment that is chosen as a comparator against which the ATV of a new medicine is assessed;

- ATV classifications levels - some Member States use a scale, while others simply assess which products have an added therapeutic value and which ones do not;
- ATV impact on price - where the assessment of ATV has an impact on the pricing of the medicine evaluated, this usually translates into an economic incentive for medicines with significant ATV;
- Assessment of cost-effectiveness - whether or not there is any consideration given to cost-effectiveness, during the pricing and reimbursement decision-making process.

The next table presents the outcomes of the mapping exercise, based on the available literature. Please note that the empty cells indicate that the information could not be identified through the review of relevant literature. Countries have been listed alphabetically according to their geographical name in the original language(s).

Table 3: Overview of the use of ATV in the EU-28

Country	With what is the new medicine compared?	ATV classification levels	ATV impact on price	Assessment of cost effectiveness
Austria	The most similar comparator according to Anatomical Therapeutic Chemical (ATC) level, as long as this is reasonable. This is mostly all pharmaceuticals within a therapeutic class; however, it can also deviate from this	No added benefit (generics), analogous or similar therapeutic benefit, added therapeutic benefit for a subgroup of patients, added therapeutic benefit for the majority of patients, important added benefit for a subgroup of patients, important added benefit for the majority of patients	Medicines with important added benefit (for a majority of a subgroup of patients) are entitled to negotiate a price above the EU average price	Yes
Belgium	Most frequently used pharmaceutical in practice	Class 1: added therapeutic value Class 2: analogous or similar therapeutic value Class 3:	Class 1 drugs are entitled to negotiate a price above the comparator's price.	Only for medicines with added therapeutic value, measured in cost/QALY

Country	With what is the new medicine compared?	ATV classification levels	ATV impact on price	Assessment of cost effectiveness
		generics/copies (same active ingredient)		
Bulgaria [70]				Yes
Croatia[71]	Best standard care[72]	Additional QALYs		Yes[73]
Cyprus[74]	No REA	No REA	No REA	No
Czech Republic [75]	Standard care - product that is the reference product within the relevant reference group	Highly innovative medicinal products	Highly innovative medicinal products are guaranteed reimbursement without having to prove their cost-effectiveness	Yes
Denmark	All relevant comparators	Health gains in natural units	Yes	Yes
Estonia	Best standard care[76]		Yes	Yes

[70] Information on Bulgaria was sourced from Gulácsi, L. et al, 2014, Health Technology Assessment in Poland, Czech Republic, Hungary, Romania and Bulgaria, European Journal of Health Economics 15, May 2014.

[71] Information on Croatia was sourced from International Society for Pharmacoeconomics and Outcomes Research, Pharmacoeconomic guidelines in Croatia and Baltic countries.

[72] Therapies routinely used in the Croatian health system, including technologies regarded as current best practice.

[73] Cost-effectiveness analysis (CEA) or Cost-utility analysis, (CUA), depending on the particularities of the technology being assessed.

[74] Information on Cyprus was sourced from Kanavos, P. & Wouters, O., 2014, Pharmaceutical policies in Cyprus: A Review of the Current System and Future Options, *LSE Health*, August 2014.

[75] Information on the Czech Republic was sourced from Gulácsi, L. et al, 2014, Health Technology Assessment in Poland, Czech Republic, Hungary, Romania and Bulgaria, European Journal of Health Economics 15, May 2014.

[76] Most widely used alternative or current therapy.

Country	With what is the new medicine compared?	ATV classification levels	ATV impact on price	Assessment of cost effectiveness
Finland	Best standard care[77]		Yes	Yes
France	Best standard care[78]	ASMR I: Major improvement, ASMR II: Significant improvement, ASMR III: Modest improvement, ASMR IV: Minor improvement, ASMR V: No improvement.	Medicines with ASMR I to III are entitled to a price premium, determined by the manufacturer and benchmarked to foreign prices. The same applies to medicines with ASMR IV with limited market potential.	Yes
Germany	Best standard care[79]	Considerable additional benefit, Significant additional benefit, Small additional benefit, Additional benefit but not quantifiable, No evidence of additional benefit, Less benefit than comparator.	Medicines with some additional benefit are not clustered in reference price groups and are given a price premium over comparators. The degree of innovation is referred to in the negotiation process.	Yes
Greece				Partially[80]

[77] Most frequently used therapy (relevant therapy with the same indication).

[78] Standard care is defined as the validated care in the field.

[79] This is the term used in Kleijnen, S. et al, July 2011, *Relative Effectiveness Assessment (REA) of Pharmaceuticals, background review*. Whenever a Member State further defined the term, their definition is reported in a footnote.

[80] Greece uses assessments conducted in other EU countries as a basis for decision on reimbursement, according to Armataki, E., et al, 2014, Health Technology Assessment of Medicines in Greece: Pharmaceutical Industry Executives' Views, *International Journal of Technology Assessment in Health Care.*

Country	With what is the new medicine compared?	ATV classification levels	ATV impact on price	Assessment of cost effectiveness
Hungary [81]	Best standard care[82]	Lack of alternative therapies	Sometimes	Cost/QALY
Ireland	Best standard care[83]		Yes	Yes
Italy	Best standard care[84]	Innovation score: Important innovation, moderate innovation, modest innovation, potential innovation	Price advantages for innovative drugs (no formal rule).	Yes
Latvia	Best standard care[85]		Yes	Yes
Lithuania	Best standard care[86]			Yes
Luxem-bourg	Actually reimbursed treatments with the same therapeutic indication		Yes	Yes

[81] Information on Hungary was sourced from Gulácsi, L. et al, 2014, Health Technology Assessment in Poland, Czech Republic, Hungary, Romania and Bulgaria, European Journal of Health Economics 15, May 2014

[82] The main comparator(s) should be the currently accepted standard therapy (therapies) that the new intervention is intended to replace. Selection of any other comparator(s) should be justified. Best standard care is what the clinical guidelines mention as the best available, the best current, a proven, and an established effective treatment.

[83] The preferred comparator for the reference case is 'routine care,' that is, the technology or technologies most widely used in clinical practice in Ireland.

[84] The pharmaceuticals that are used for this indication in practice.

[85] Most commonly used alternative for certain indication.

[86] If the drug belongs to an existing pharmaco-therapeutic group, the comparator should be the most commonly used alternative drug within this group. Otherwise, it should be the most commonly used alternative drug for the indication.

Country	With what is the new medicine compared?	ATV classification levels	ATV impact on price	Assessment of cost effectiveness
Malta	Best standard care, best possible care[87], other medical substances		Yes	Yes
Nether-lands	Best standard care[88]	Annex 1A: similar therapeutic value. Annex 1B: added therapeutic value.	Annex 1B drugs are entitled to a price premium (evidence on Pharmacoeconomics and budget impact required).	Only for medicines with added therapeutic value, cost/QALY
Poland[89]	Best standard care, best possible care[90]		Price premium	Cost/QALY
Portugal	Best standard care, best possible care[91]			Yes
Romania[92]	Active comparator or placebo		Biosimilars are subject to a price cap and can only be sold at a maximum of 80 % of the original International	Yes

[87] Standard care – the medicine assessed is compared with other pharmaceuticals on the Government Formulary List given for the same clinical indication.

[88] Defined as first line treatment according to clinical guidelines and for which the effectiveness is proven. If there is no standard care, the mostly used care is used for comparison.

[89] Information on Poland was sourced from Gulácsi, L. et al, 2014, Health Technology Assessment in Poland, Czech Republic, Hungary, Romania and Bulgaria, European Journal of Health Economics 15, May 2014.

[90] According to Polish HTA guidelines the primary comparator for the assessed intervention must be the so-called existing practice. It is also recommended to perform a comparison with other comparators, i.e. the following technologies: the most frequently used, the cheapest, the most efficient and compliant with the standards and guidelines for clinical management.

[91] Usual care and/or best usual care.

[92] Information on Romania was sourced from Gulácsi, L. et al, 2014, Health Technology Assessment in Poland, Czech Republic, Hungary, Romania and Bulgaria, European Journal of Health Economics 15, May 2014.

Country	With what is the new medicine compared?	ATV classification levels	ATV impact on price	Assessment of cost effectiveness
			Nonproprietary Name price	
Slovakia	Whatever is used in registration trials, best standard care, best possible care		Sometimes	Yes
Slovenia	Whatever is used in registration trials, best standard care[93], best possible care		No	Yes
Spain	Whatever is used in registration trials, best standard care, best possible care[94]	Classification of therapeutic value: Significant, Moderate, Low, No interest.	Price premium of 10-20 % if a drug has a significant or moderate added therapeutic value	Yes
Sweden	Best standard care[95]	Assessment of the number of QALY gained	Price (premium) based on cost-effectiveness ratio.	Cost/QALY
United Kingdom	Best standard care[96]	Assessment of the number of QALY gained	No	Cost/QALY

[93] Standard care as for example indicated in guidelines.

[94] The ideal is to compare with the best standard treatment. If this is not possible/applicable it may be best possible care, what is used in the registration trial or other (pharmaceuticals that belong to the same therapeutic subgroup).

[95] The most cost-effective care, or best standard care.

[96] Relevant comparator technologies are chosen as comparator – usually the treatment(s) used in current clinical practice in the NHS to manage the disease or condition (this may include non-licensed technologies if they are used in current clinical practice); sometimes the comparator is best supportive care, palliative therapy or no intervention.

3.2 Analysis

The measurement of the added therapeutic value of a medicine depends on the treatment to which it is compared, and choosing one comparator over another may influence the end results. That is why the choice of comparator is a crucial aspect of the calculation of ATV. Some countries have guidelines or regulations in place to define the appropriate comparator (e.g. Germany, the United Kingdom and Sweden)[97].

When looking at the definitions employed, there is relatively little variation, even though the same terms may refer to different products. Most countries identified "best standard care" as their main comparator of choice, and defined it as "the treatment(s) used in current clinical practice", "the most frequently (or widely) used therapy", "the validated care in the field", or "the therapy that prescribers would most replace with the proposed pharmaceutical in practice". While one comparator is the minimum required in most countries, many will allow and/or recommend additional comparisons, such as the "best possible care" (under ideal conditions and with no price limitation)[98]. A preferential order in the choice of comparator is not uncommon. For example, in the Netherlands, standard care is preferred, which is defined as first-line treatment according to clinical guidelines and for which the effectiveness is proven. If there is no standard care (according to the definition), the most frequently used care is used for comparison instead[99].

Member States have chosen different ways to measure added therapeutic value. Some countries have adopted a classification which rates the level of ATV. France, for example, classifies new medicines as representing a major improvement, significant improvement, modest improvement, minor improvement or no improvement. Germany, Spain, Italy and Austria follow a similar approach. Other countries have a simple categorical classification system, where a new medicine will be assessed as either having an ATV or not. For instance, in the Netherlands, medicines are classified as either Annex 1A (similar therapeutic value), or Annex 1B (added therapeutic value). Belgium, the Czech Republic and Hungary have a similar system. Finally, Croatia, Sweden and the United Kingdom measure the additional number of Quality-adjusted Life Years gained by the patient in the context of a health-economic analysis.

Once it is estimated, ATV can be used as an explicit or implicit criterion for price regulation or negotiation, or it can be used to inform other decisions. In Germany, for example, medicines with ATV are not clustered in reference price groups and are given a price premium over comparators. Similar implicit or explicit rules are applied in most Member States (Belgium, Denmark, Estonia, Ireland, Spain, France, Italy, Latvia, Luxembourg, Hungary, Malta, the Netherlands, Austria, Poland, Slovakia, Finland and Sweden). In the Czech Republic, medicines with a high ATV are exempt from having to prove their cost-effectiveness. In the UK, where the pricing of medicines is only indirectly regulated through the Pharmaceutical Price Regulation Scheme (PPRS), ATV has no impact on prices.

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[97] Paris, V. & Belloni, A*., 2013, Value in Pharmaceutical Pricing*, OECD Health Working Papers No. 63, p.32-33.

[98] Kleijnen, S. et al, July 2011, *Relative Effectiveness Assessment (REA) of Pharmaceuticals, background review*, p. 43.

[99] Ibid.

Finally, most Member States assess the cost-effectiveness of the new medicine during the pricing and reimbursement process. Some countries consider cost-effectiveness systematically, as is the case in Denmark, Spain, Sweden or the United Kingdom. Others Member States, like Belgium and the Netherlands, only assess the cost-effectiveness of medicines with ATV.

4 IN-DEPTH REVIEW OF ATV PRACTICES IN SELECTED COUNTRIES

This chapter presents the results of an in-depth review of the use of ATV in six EU Member States: France, Italy, Austria, Poland, Slovakia and Sweden. These countries were chosen to ensure a balance in geographical coverage (South-North, East-West) and country size, as well as a mix of Member States with longstanding experience using HTA or REA and Member States that are relatively new to these types of assessment. The latter often results in a difference in the type of assessment systems put in place by countries. Also the final decision-makers differ in these countries (i.e. reimbursement agencies in Austria and Sweden, sections of bodies under the direction of the Ministry of Health in France, Poland, Slovakia and Italy).

France is an interesting case because it recently introduced the analysis of cost-effectiveness (economic considerations of medicines). Austria was selected because it provides an example of a drug reimbursement decision-making process which leads to different outcomes when compared to other countries. Sweden was included as it has a long history of using REA in reimbursement decision-making. In addition, it applies a regional implementation, while other countries implement at national level. Italy is an interesting example of a country assessing purely technological innovations. Poland and Slovakia have a relatively short experience in assessing ATV, but have developed interesting and innovative solutions.

During the first phase of the in-depth review, relevant information was collected through desk research in English as well as national language sources. The national researchers began describing the national marketing authorisation phase and the pricing and reimbursement process. The role of the different actors during these decision-making processes was investigated, as well as the different indicators and criteria used. Next, they provided a detailed overview of the national assessment of the added therapeutic value of a new medicine (type of methodology applied, sources used, providers of data, classification systems, etc.) and the use and role – if any – of HTA in the selected EU Member State. Finally, the researchers investigated whether any economic aspects were considered during the assessment process of new medicinal products and put together an overview of relevant national guidance documents.

Following this first phase, the findings - described in national country reports - were shared with the national HTA experts that take part in the EU joint Action on HTA (EUnetHTA) for review and feedback. The country reports, containing the complete, validated findings of the in-depth research, are described in Annex I- VI of this report.

The following six sections below provide a summary of the most relevant findings. They set out the key data and information collected on the assessment of ATV in the selected countries, as well as any economic considerations of medicinal products that are considered during the pricing and reimbursement phase.

4.1 France

Assessment of the added therapeutic value

In France, the added therapeutic value (*Amélioration du service médical rendu* or ASMR) of medicines is usually assessed during the decision-making process on the pricing and reimbursement of medicines. A fast-track procedure aiming at accelerating the marketing of innovative products can sometimes be used, in which case the assessment of ASMR can begin prior to the marketing authorisation being awarded. All medicinal products which obtain a marketing authorisation are subject to the assessment of ASMR, which is conducted by the Transparency Committee, a group of experts within the French National Health Authority (*Haute Autorité de Santé* – HAS).

The demonstrated added value of a medicinal product is quantified according to the following five levels: ASMR I or major, ASMR II or important, ASMR III or moderate, ASMR IV or minor, ASMR V or absence of added value.

The assessment of the ASMR requires the selection of a relevant comparator. According to the Social Security Code, the ASMR assessment should identify all products of the reference therapeutic class. The evaluated medicine should then be compared with, at least, the most prescribed competitors, as well as with the comparative medicinal product that has the cheapest treatment cost and with the most recent reimbursable product of the same class of medicines[100]. However, in practice, ASMR is not assessed against all medicines or other therapies listed, but against the best available and reimbursed treatment[101]. The selection of the comparator can be based on a range of sources: the suggestions of experts or of the product sponsor, or based on clinical or methodological guidelines[102]. It is also possible to conduct indirect comparisons during the assessment, but this should be based on the National Health Authority guidelines[103].

The ASMR assessment involves an evaluation of multiple sources. The report provided by the pharmaceutical company is one of the main sources of information, complemented by external sources such as clinical guidelines, publications by other HTA organisations, available literature, European and national public assessment reports, as well as unpublished clinical data or confidential information, if relevant[104]. The quality of studies included in the assessment is taken into account, although no classification system to express such quality is used. The replicability of results – from studies or clinical trial – in the French healthcare system always forms part of the evaluation[105].

The level of effectiveness is one of the indicators evaluated during the ASMR. This is generally quantified by looking at the reduction of the absolute risk in terms of morbidity or mortality. The morbidity/mortality criteria that are used to assess the level of effectiveness

[100] Social Security Code, art. R163-18.

[101] Paris, V. & Belloni, A., 2013, *Value in Pharmaceutical Pricing*, OECD Health Working Papers, No. 63, OECD Publishing.

[102] Kleijnen, S. et al, July 2011, *Relative Effectiveness Assessment (REA) of Pharmaceuticals, background review.*

[103] National Health Authority, 2009, *Comparaison indirectes : méthodes et validité*.

[104] Kleijnen, S. et al, July 2011, *Relative Effectiveness Assessment (REA) of Pharmaceuticals, background review.*

[105] Bouvenot, G., 2013, *Le rôle de la Commission de la transparence de la HAS dans la pertinence de l'admission au remboursement des médicaments par l'Assurance maladie*, Regards no 44.

of the medicinal product need to be the best clinically relevant criterion available, which means that[106]:

- Surrogate endpoints[107] are included if no other endpoints are available;
- Generic quality of life end-points are only included as complementary data but disease specific quality of life end-points can be included if the information is validated, and appropriate to the specific disease;
- Safety data and contra-indications are considered; and
- Ease of use is not considered unless it is demonstrated that the ease of use has a clinical impact.

The ASMR has a direct influence on the price of the drug – not, however, on the reimbursement rate. If a product has a high therapeutic value, but a low ASMR, it should be reimbursed by the medical insurance at the same rate as a comparable product, but should not cost the user and the social security system more than the comparable product. An added therapeutic value – even minor - is rewarded by a proportional price premium. This system aims at encouraging innovation, but it is also seen as promoting the development of similar medicines that have an extremely low therapeutic added value compared to existing medicines[108].

Since 2012, the French National Health Authority has been developing a new indicator, the 'Single Relative Therapeutic Index' (*Index Thérapeutique Relatif unique - ITR*). This new index is meant to combine and replace the separate assessment of therapeutic value and ASMR. The five levels defined would inform the decision on pricing and reimbursement. The index is still under discussion but may be implemented in 2016[109].

Reassessments of medicinal products are usually initiated by the National Health Authority. A reassessment of the initial evaluation is compulsory for outpatient drugs after five years in order to maintain the product on the list of reimbursed pharmaceuticals. In addition to this, the reassessment can be initiated at any time if significant new information becomes available.

Assessment of the economic aspects of medicinal products

As described above, the ASMR does not take into account the potential economic impact of a new medicinal product. However, since 2012, a separate cost-benefit analysis (*évaluation medico-économique* or medico-economic evaluation[110]) needs to be conducted for certain categories of drugs. The National Health Authority is responsible for conducting this economic evaluation, which applies to all medicines with a major, important or moderate ASMR, and that are likely to have a significant impact on public health expenditures due to

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[106] Kleijnen, S. et al, July 2011, *Relative Effectiveness Assessment (REA) of Pharmaceuticals, background review.*

[107] A surrogate endpoint is a measure of effect of a specific treatment that may correlate with a real clinical endpoint but does not necessarily have a guaranteed relationship (e.g. lower blood pressure)

[108] Gimbert, V., Benamouzig D., 2014, *Les médicaments et leurs prix: comment les prix sont-ils déterminés?* volet 2, La note d'analyse no 10, Commissariat général à la stratégie et à la prospective.

[109] Dahan, M., 2013, *Révision des critères d'évaluation des produits de santé en vue de leur prise en charge par l'assurance maladie. Analyse de l'Index thérapeutique relatif (ITR) proposé par la HAS*, Inspection Générale des Affaires Sociales, rapport no 2013-099R.

[110] Law on the Funding of Social security 2012, art. 47 enforced by Decree 2012-1116 of 2 October 2012 on medico-economic assessments of the National Health Authority.

their price and/or their potential impact on prescription and use. The assessment is considered irrelevant for unpatented drugs[111].

Whenever a pharmaceutical company submits a request for a medicinal product to be included on the list of reimbursable pharmaceuticals and that medicine is selected for the medico-economic assessment, the company is required to submit the necessary data and information concerning the efficiency of the medicine in question, including a list of medicinal products with which the drug in question should be compared. Next, this data and information is assessed by the economic evaluation service of the National Health Authority, and discussed with the Committee on Economic Evaluation and Public Health (CEESP). This Committee, created in 2008, consists of thirty-three members with different backgrounds: economists, doctors, epidemiologists, public health specialists, human and social sciences specialists, pharmacists, and representatives of patients' associations. The opinion of the CEESP is submitted for consideration to the Economic Committee on Healthcare Products (CEPS), which ultimately decides on the price of the new medicinal product.

The medico-economic assessment is a cost-benefit analysis that compares the evaluated medicine with all existing relevant alternatives in terms of efficiency. In cases where the new medicine is more effective compared to the relevant alternatives on the market ,but also significantly more expensive, the efficiency analysis becomes more difficult. In such situations, the National Health Authority defines a reference value, generally expressed in costs spent per life-year gained, or per healthy life-year gained (QUALY), under which a product is considered efficient[112]. The medico-economic assessment also describes the uncertainty associated with the cost-benefit analysis and the main drivers influencing the results. The medico-economic assessment has a direct influence on the price of the drug, but not on the reimbursement rate.

The practice of medico-economic assessments is still relatively new in France. As of October 2014, the National Health Authority had selected twenty drugs and one medical device eligible for medico-economic assessment. This group of twenty comprised medicines that were potentially expensive and innovative, such as anti-cancer medicines, antiviral drugs (HIV, Hepatitis C), vaccines, and medicines specifically targeting rare diseases[113].

[111] Decision 2013.0111/DC/SEESP of 18 September 2013 of the HAS College on the significant impact on public health expenditures triggering the medico-economic evaluation of products claiming an ASMR I, II, or III: http://www.has-sante.fr/portail/upload/docs/application/pdf/2013-09/c_2013_0111_definition_impact_significatif.pdf.

[112] National Health Authority, *Valeurs de référence pour l'évaluation économique en santé.* Revue de littérature : http://www.has-sante.fr/portail/upload/docs/application/pdf/2014-12/fiche_synthese_vf.pdf.

[113] National Health Authority, interview of Jean-Luc Harousseau, president of the HAS College, October 2014: http://www.has-sante.fr/portail/jcms/r_1502595/fr/evaluation-medico-economique-des-produits-de-sante.

4.2 Italy

Note: Italy is currently reforming its ATV methodology

Assessment of the added therapeutic value

The Italian Medicines' Agency (*Agenzia Italiana del Farmaco*, AIFA) routinely assesses the added therapeutic value of new medical products as part of the pricing and reimbursement decision-making process. However, the Agency's working methods are continuously evolving, and both the assessment of added therapeutic value, and the cost-benefit analysis of medicines, are the object of ongoing reform and reorganisation. This chapter provides a snapshot of the current legal framework and working methods.

While there is no requirement for manufacturers to provide data on the added therapeutic value of their products to obtain a marketing authorisation, such information becomes fundamental when the company wishes for their product to be recognised as "innovative", or included in the list of reimbursable medicines by AIFA[114].

While deciding whether or not a new medicine should be reimbursed by the National Health Service (*Servizio Sanitario Nazionale,* or SSN), AIFA's Technical and Scientific Committee considers whether a product with positive cost effectiveness has:

- proven to be useful for the prevention or treatment of conditions or relevant symptoms for which no effective treatment exists;
- proven to be useful for the prevention or treatment of conditions or relevant symptoms for which current treatments are inadequate; and
- a better cost/benefit ratio compared to existing treatment for the same condition[115].

The first two items are intended to evaluate the added therapeutic value in terms of Relative Efficacy, whereas the third introduces an economic dimension. The failure to fulfil any of the above criteria may mean that the medicine will not be reimbursed, although it may still be considered reimbursable in cases where there are other mitigating factors and its efficacy is not inferior to that of the best standard care[116]. This can be the case for off-patent products, where producers are required to propose a lower price compared to that of the corresponding branded product in order to obtain a positive decision on reimbursement. The impact of cost-effectiveness and therapeutic value on the reimbursement decision was further reinforced by the annual stability law, which provided for their use in a revision of the list of reimbursed medical products[117].

In order to conduct its assessments, AIFA uses data reported by the manufacturer, expert advice and clinical guidelines[118]. Clinical end-points (such as the reduction of mortality or morbidity) are preferred, but validated surrogate end-points can also be used[119].

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[114] AIFA, *Gruppo di Lavoro dull'innovativitá dei farmaci,* 10 July 2007, Criteri per l'attribuzione del grado di innovazione terapeutica dei nuovo farmaci, ed elementi per l'integrazione del dossier per l'ammissione alla rimborsabilitá.

[115] Deliberation of CIPE No. 3/2001 of 1 February 2001.

[116] Ibid. Best Standard care is defined as the treatment used for the same indication in practice.

[117] Italian Stability Law 2015, Law 190, 23 December 2014, art. 585.

[118] Kleijnen, S. et al, July 2011, *Relative Effectiveness Assessment (REA) of Pharmaceuticals, background review*, p. LXIX.

[119] Ibid, p. LXXVIII.

In addition, in 2007 AIFA adopted a method to evaluate the "innovativeness" of medicines, which includes an assessment of added therapeutic value[120]. While this assessment is the subject of on-going reform, it still provides an interesting example of possible ways in which ATV can be incorporated in the pricing and reimbursement process.

The prevalence and severity of the disease are considered as the starting point. Next, the availability of alternative treatments, the added therapeutic value and the efficacy of the medicine are estimated. According to its composite score, the medicine can then be classified as one of the following:

- important innovation;
- moderate innovation;
- modest innovation;
- potential innovation.

Innovative medicines are included in the list of reimbursable medicinal products. The innovative medicines are immediately included in regional formularies and financed through a specific fund[121]. The Stability Law 2015 provided that the marketing authorisation holder of an innovative medicine with an annual sales revenues below EUR 300 million is not required to pay back any excess revenue not covered by the above-mentioned fund. Should its annual sales revenue be over EUR 300 million, the company will only need to reimburse 20 % of the excess revenue. The financial benefits last 36 months. Moreover, the Stability Law 2015 has introduced a 1 billion EUR fund for the acquisition by Regions of innovative medicines for years 2015 and 2016[122].

In addition, AIFA is also responsible for promoting non-profit clinical trials that aim to assess the added therapeutic value of new drugs compared to those already on the market[123]. These studies can be funded through a part of the fund that is subsidised by a 5 % tax on promotional expenses collected from pharmaceutical companies[124].

4.3 Austria

The procedure for medical products to be included in the Reimbursement Code (*Erstattungskodex* or EKO) is set by the Regulation of the Reimbursement Code *(Verordnung Erstattungskodex or* VO EKO*),* published by the Federation of Social Insurances. According to the Code, the decision on whether or not a medical product shall be reimbursed is based on three successive evaluations: the pharmacological, the medical-therapeutic assessment (see section 4.3.1), and the health-economic evaluation (see section 4.3.2).

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[120] AIFA, 10 July 2007,*Gruppo di Lavoro dull'innovativitá dei farmaci, Criteri per l'attribuzione del grado di innovazione terapeutica dei nuovo farmaci, ed elementi per l'integrazione del dossier per l'ammissione alla rimborsabilitá*.

[121] See Law of 29 November 2007, n. 222, Law of 7 August 2012, n.135 as amended and Accordo Stato Regioni 18 November 2010.

[122] Italian Stability Law 2015, Law 190, 23 December 2014, art. 593-598.

[123] Lo Scalzo A. et al, 2009, *Health Systems in Transition, Italy*, Health system review, WHO European Observatory on Health Systems and Policies, Vol. 11, No. 6. Available at: http://www.euro.who.int/__data/assets/pdf_file/0006/87225/E93666.pdf.

[124] Legge 326/2003, Comma 18-19.

For all three evaluations, the applicant has to provide data and information on comparisons with available therapeutic alternatives, taking into account the most frequent indication, the most appropriate medical dose and the most affected groups of patients. The documents provided by the applicant have to correspond to the most up-to-date research. Only data published in peer-reviewed journals or in evaluations of independent institutes and authorities are taken into account, unless otherwise specified[125]. Together with its application, the applicant has to submit a number of additional documents that are listed in an Annex to the Regulation on the Reimbursement Code.

Assessment of the added therapeutic value (pharmacological and medical-therapeutic assessments)

On the basis of documents submitted by the company that has produced the new medicinal product, the Pharmaceutical Evaluation Board (*Heilmittel-Evaluierungs-Kommission* or HEK) will assess if, and for which indications and groups of patients, a significant added therapeutic value of a medicine could be identified and how this can be assessed economically, so that the medicine can be classified as either reimbursable (green box) or reimbursable under certain circumstances (yellow box)[126].

Furthermore, the Price Control Commission (*Preiskommission*) within the Ministry of Health advises the Federation of Social Insurances (*Hauptverband der Sozialversicherungsträger* or HVB) on whether a tendering procedure for substances, or groups of substances, should be introduced, in order to obtain cheaper conditions for the reimbursement of the medicine[127].

The pharmacological assessment defines possible comparators, usually chosen from among medicines with the same ATC (Anatomical Therapeutic Chemical) level that have been listed in the same box (green or yellow). Moreover, it measures the degree of innovation of the new medicinal product on an eight-point scale. The lowest degree of innovation (degree 1) means that the new medical product has "*the same substance, the same strength of substance and the same or similar pharmaceutical form"* as the comparable medical product. The highest degree of innovation (degree 8) is assigned when the new medical product "*allows treating an illness for the first time*"[128].

The medical-therapeutic evaluation defines patient groups that can potentially be treated with the new medical product, considers the therapeutic benefit in comparison with other alternatives, and determines the level of effectiveness and the threshold for data reliability, quality and relevance. The latter is relevant to assess the cost-benefit ratio (see section below on "health-economic assessment").

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[125] VO-EKO § 22. (2).

[126] The dark yellow box contains medicines which are reimbursable only if approved by the chief-and control medical service of the Social Insurance Association. The light yellow box contains medicines which can also be reimbursed if the prescribing physician documents that the prescription is in accordance with the medicine's use.

[127] Allgemeines Sozialversicherungsgesetz (ASVG) (General Social Security Code), BGBl. Nr. 189-1955, § 351 g. (2) available at: https://www.ris.bka.gv.at/GeltendeFassung.wxe?Abfrage=Bundesnormen&Gesetzesnummer=10008147.

[128] Verordnung Erstattungskodex (VO-EKO) (Regulation Reimbursement Code), 2004, § 23. (2), available at: https://www.avsv.at/avi/dokument/binaerdokument_download.pdf?dokid=2004%3D47&dokStat=0&contTyp=application%2Fpdf For a definition of all scale points, see the respective paragraph in the legislation.

Assessment of the economic aspects of medicines (health-economic assessments)

This evaluation assesses the cost-effectiveness of the new medicinal product, based on the medical-therapeutic evaluation (see above). It takes into account the direct costs of the healthcare system, such as expenditure for medical treatments – medicines, medical aid – in both institutional care and rehabilitation measures. Potential costs carried by patients are not taken into account.

Cost-effectiveness is essentially judged as a ratio between the added therapeutic value and the price of a medical product or the cost of treatment with this medical product. In order for medical products to be added to the green box, the ratio has to be "better" than comparable medical products in the green box. This means that it either has to be cheaper than a comparable medical product, or it has to have an added therapeutic value. Furthermore, the price for medical products of all groups has to be below the EU average, if the medical product is to be added to the green group[129]. The HEK publishes some objective and verifiable economic criteria that have to be met so that medical products may be added to the green or yellow box. A document published by the HVB lists these criteria, along with the main legislation on the distribution of reimbursable medical products[130].

The same principle applies for medicinal products to be added to the yellow group. However, if there is no comparable medical product already in existence, a positive cost-benefit ratio for a group of patients needs to be proven. The applicant needs to provide a pharma-economic study to prove the economic benefit in this case[131].

For medical products with an important added therapeutic benefit, there is no threshold for the incremental costs. Poland

4.4 Poland

Assessment of the added therapeutic value

The assessment of the added therapeutic value in Poland is conducted by the Agency for Health Technology Assessment and Tariff System (*Agencja Oceny Technologii Medycznych I Taryfikacji,* AOTMiT), while the decision on pricing and reimbursement is officially made by the Minister of Health. ATV is not assessed separately, but rather as part of the economic assessment on cost-effectiveness. In general, the assessment follows the methodology described in the Guidelines for conducting Health Technology Assessment (HTA)[132]. However from January 1st 2012 it should also be in line with the Act on Reimbursement[133], which sets out some details and additional requirements.

The assessment begins with checking whether the documentation submitted by the applicant meets the minimum requirements enshrined in the relevant Regulation of the

[129] VO-EKO § 25. (2).

[130] Mandlz, Gregor, 2015, *Working Guide Reimbursement Code* (Arbeitsbehelf Erstattungskodex), HVB, available at: https://www.sozialversicherung.at/portal27/portal/esvportal/content/contentWindow?&contentid=10008.555012&action=b&cacheability=PAGE.

[131] VO-EKO § 25. (3).

[132] http://www.aotm.gov.pl/www/index.php?id=765.

[133] Act on reimbursement of medicines, consumption goods for special use and medicinal products, O.J 122 position 696 of 2011 with later amendments.

Minister of Health[134]. This Regulation lays down the rules corresponding to the internationally recognised methodology for assessing medical technologies, adapted to the requirements of the Polish legislation (the Act on Healthcare Benefits[135] and the Act on Reimbursement). The Regulation effectively translates the HTA Guidelines into law, bringing with it a set of advantages and disadvantages. While the strong legal basis, for example, can be seen as an advantage, the lack of flexibility of the rules, can be perceived as a disadvantage. Fulfilment of the methodological requirement depends, among other things, on the availability of data.

Where the documentation submitted deviates from the minimum requirements, the Minister of Health (based on the statement prepared by the Agency) asks for additional information to supplement the application. In this case, the applicant will usually have 14 days to provide the information, a waiting time that is added to the statutory 60-day evaluation period.

The elements verified in the evaluation process include the analytical search strategies, the selection of comparators, evidence from clinical studies, the reliability of data (including calculations and qualitative summaries), the timeliness of costs and other assumptions adopted in the calculations, and the adequacy of the model used in the economic analysis. The results are double-checked by repeating the calculations. In addition, the following elements are summarised:

- the clinical guidelines (preferably on the basis of a systematic review); and
- the reimbursement recommendations issued by foreign HTA agencies, and the reimbursement conditions in other countries

The opinions of medical experts' are included in the assessment process as well as, where possible, the views of the representatives of the patients' organisations invited to present their viewpoint.

In accordance with the Act on Reimbursement, the selection of comparators must reflect the technologies that are currently reimbursed. This is a significant methodological limitation in cases where randomised clinical trials compare a given medical product to products which are not refundable in Poland. In such situations, indirect comparisons should be made with the refundable technologies.

When the clinical analysis does not include randomised trials, the applicant must meet the requirements described in Art. 13, paragraph 3 of the Act on Reimbursement: "the official sales price of the medicine must be calculated in such a way that the cost of using it [...] is not higher than the cost of medical technology [...] financed from public funds so far with the best ratio of therapeutic outcomes to their costs (CER - Cost Effectiveness Ratio)."

Assessment of the economic aspects of medicinal products

The assessment of the economic aspects of medicinal products is carried out in two stages: 1) cost-effectiveness analysis and 2) impact on the payer's budget.

[134] The Regulation of the Minister of Health of 2 April 2012 regarding minimum requirements which have to be fulfilled by the analyses included in the applications for coverage of medicines, medicinal products and nutritional products of special use with reimbursement and for setting their official prices or increasing their official prices, O.J. 12 position 388 of 2012.

[135] Act of 27 August 2004 on healthcare benefits financed from public funds, O.J. 164 item 1027 of 2008.

Cost-effectiveness is calculated according to the HTA guidelines using the Incremental Cost-Utility Ratio (ICUR), the ratio of the additional costs to the quality-adjusted life years (QALY) gained, with the current (reimbursed) clinical practice taken as the baseline. When data to calculate ICUR are missing, an alternative indicator can be used: the Incremental Cost-Effectiveness Ratio (ICER), which is the ratio of the incremental cost to the incremental clinical effects of the new medical technology. Clinical effects needed to calculate ICER should be expressed in terms of life years gained (LYG). According to Polish law, if the cost-effectiveness indicator for the clinical effects expressed as QALY or LYG (i.e. ICUR or ICER, respectively) does not exceed 3 x Gross Domestic Product per capita, the technology is cost-effective and eligible for refund (subject to approval of total costs).

In the case of medicinal products which do not pass this cost-effectiveness test, a so-called "threshold price" is estimated (the price setting ICUR/ICER at the level of 3xGDP per capita threshold), which sets the base for negotiations with the Economic Commission of the Ministry of Health.

The budgetary impact is calculated based on the total increase in expenditure in case of reimbursement of the new technology.

The final adoption of the refund depends on the acceptability of these estimates. The applicant can improve the ICER by offering a confidential "risk-sharing" agreement and proposing a lower implicit price. The final price and risk-sharing instruments are negotiated with the Economic Commission at the Ministry of Health.

4.5 Slovakia

Assessment of the added therapeutic value (effectiveness, safety and importance)

The assessment of added therapeutic value in Slovakia is conducted during the decision-making process on the reimbursement of medicines, by specialised working groups within the Categorisation Committee for Medicinal Products of the Ministry of Health[136].

Firstly, the new medicinal product is assessed according to its therapeutic and anatomic classification. There are 22 specialist working groups for this assessment step, which investigate the effectiveness, safety and importance of the pharmaceutical. The outcomes of the assessment are then submitted to the Categorisation Committee.

Based on the evaluation of the medicine's effectiveness, safety and importance as well as its economic benefits (see next section), the Categorisation Committee determines the therapeutic and social value of the medicinal product. The criteria determining the therapeutic value of a medicine are[137]:

- effectiveness;
- safety;
- cost-effectiveness;

[136] European Observatory on Health Systems and Policies, Szalay, T. et al, 2011, *Slovakia – Health system review,* Health Systems in Transition Vol 13 No.2. Available at: http://www.euro.who.int/__data/assets/pdf_file/0004/140593/e94972.pdf (Accessed April 2015).

[137] Ibid.

- whether it is a first or second option, or adjunctive treatment; and
- Whether it is a causal treatment, prophylaxis, or symptomatic treatment.

The criteria determining the social value of a medicine are[138]:

- severity of the disease;
- impact on society if not treated (e.g. spread of infection);
- social value (e.g. orphan drugs);
- risk of abuse; and
- impact on total costs.

Finally, the Categorisation Committee develops a proposal for inclusion, non-inclusion, exclusion or change of status, in the benefit package. The Committee also prepares proposals for reimbursement levels, co-payment and conditions for reimbursement. For those medicinal products designated as eligible for partial reimbursement, the decision on the specific reimbursement level is based on the following criteria: the therapeutic benefit of the drug, its retail end price, and the reimbursed prices of other products within the same reference category. The recommendations of the Committee can be overruled by the Minister of Health[139,140].

The list of medicinal products that are eligible for reimbursement can include drugs that are reimbursement with restrictions, such as their limited prescription by certain specialists or by certain hospitals.

Assessment of the economic aspects of medicinal products (pharmaco-economic analysis)

The Slovak 363/2011 law states that pharmaco-economics reports are mandatory in the decision-making process on reimbursement of medicinal products. As stated by Decree no. 422/2011, the decisions on drug reimbursement require a pharmaco-economics analysis (cost minimisation, cost-utility analysis or cost- effectiveness analysis), budget impact analysis, and sensitivity analysis. The pharmaco-economic analysis is conducted by a specialist working group which is separate to the one assessing its anatomic and therapeutic value. The discount rate for benefits and costs has been set at 5 %. The threshold that defines whether the product can be considered cost-effective has been defined in Slovak legislation (Act No. 363/2011[141]) as follows:

- Lambda 1: 24 x average monthly salary EUR / QALY
- Lambda 2: 35 x average monthly salary EUR / QALY

For 2015, Lambda 1 is set at EUR 19,776/QALY, while Lambda 2 is set at EUR 28,840/QALY. Medicinal products that have a cost per QALY that is lower than Lambda 1 can be included

[138] Ibid.

[139] Ibid.

[140] Assoc. Prof. Tesar T., 2012, *Health Technology Assessment in reimbursement policy of the Slovak Republic*, Journal of Health Policy & Outcomes Research, ISSN 2299-1247, DOI:10.7365/JHPOR.2012.1.5.

[141] Available at:http://jaspi.justice.gov.sk/jaspiw1/htm_zak/jaspiw_mini_zak_zobraz_clanok1.asp?kotva=k1&skupina=1 (accessed April 2015).

in the reimbursement list. Medicinal products that have a cost per QALY falling between Lambda 1 and Lambda 2 can be included conditionally. Medicinal products that have a cost per QALY higher than Lambda 2 cannot be included in the reimbursement list. These thresholds do not apply to medicinal products for orphan diseases that have a prevalence of less than 1:100,000.

Some highly innovative medicines - where costs exceed the Lambda thresholds but (effective) alternative medicines do not exist on the market - can be covered through Health Insurance Funds. These funds have a legal basis to make exceptions for certain innovative medicines based on specific patient access schemes. Manufacturers of innovative drugs that are not reimbursed through the national list can negotiate such schemes with the health insurance funds by offering price discounts or value limits for reimbursement. It can therefore be stated that the Lambda thresholds are a tool to assess cost-effectiveness rather than a rule to exclude medicines to be eligible for reimbursement.

4.6 Sweden

Note: Sweden is currently reforming its ATV methodology

Health economic assessments of new medicines

The assessment of added therapeutic value in Sweden occurs within the cost-effectiveness analysis for new medicines. The Pharmaceutical Benefits Act of 2002[142] lists cost-effectiveness and marginal benefits as the main criteria for decision-making on reimbursement and pricing. According to section 15 of the Act, 'prescription drugs shall be included on the Pharmaceutical Benefits Scheme and the price for the drug shall be set provided that:

- the costs of using the drug […] appear reasonable from the medical, humanitarian and economic aspects; and
- there are no other available drugs or treatment methods which after overall consideration of the intended effects and harmful effects as referred to in Section 4 of the Medicinal Products Act can be judged as significantly more suitable for the purpose.'

The marginal benefit (the fact that there are no other available medicines that are significantly more suitable) is closely related to the cost-effectiveness. If the marginal benefit is high, the price of the medicine is allowed to be higher, as long as it can still be considered reasonable. However, if the marginal benefit is deemed to be small or null, the medicine might not be reimbursed if the proposed price is too high. The cost-effectiveness and the marginal benefit of a medicine are assessed by comparing it to other treatment options available on the market[143].

In addition, in order to be reimbursed, a medicine should comply with three principles:

- The human value principle, which underlines the equality of care for all individuals. Access to treatment should not be influenced by patient ability, social status, income or age.

[142] Act (2002:160) on Pharmaceutical Benefits, of 11 April 2002.

[143] TLV (2012) Guide for companies when applying for subsidies and pricing for pharmaceutical products.

- The need and solidarity principle: the people with greatest medical needs should be given priority, which means that the severity of the illness is an important indicator in the reimbursement decision. More resources are given to medicines improving the health of people with severe diseases or poorer quality of life, than to medicines improving well-being.
- The cost-effectiveness principle: the cost of a medicine should be reasonable from a medical, humanitarian, and socio-economic perspective. The cost, in particular, should be reasonable in comparison to the achieved health benefits and improved quality of life.

The assessment is based on the documentation provided by the pharmaceutical company. The Dental and Pharmaceutical Benefits Agency (TLV) uses internal expertise to avoid any conflict of interest with industry. The manufacturer's report is frequently supplemented by existing literature, European and national public assessment reports, and, where appropriate, reports from other HTA authorities, unpublished clinical data, or confidential data[144].

Cost effectiveness assessment

Cost effectiveness is evaluated from a societal perspective, which means all the relevant costs and benefits for the treatment and disease must be considered, regardless of who bears the costs – be it the State, the county council, the local authority, or the patient. All the costs associated with using the drug - such as costs for the drug, costs related to visits to the doctor, costs for possible further healthcare measures, and costs due to the side-effects of the drug – are combined and balanced with the benefits of using the drug – effects on health and cost savings. Health benefits are understood as longer life expectancy or a higher health-related quality of life[145], which includes elements such as avoiding surgery or sick leave[146]. The result is expressed in QALYs (Quality Adjusted Life Years), which captures both length of life and quality of life in one measurement. The new medicine is considered cost-effective if the cost per QALY gained is under a certain level.

In the cost-effectiveness assessment, a comparison must be made between the evaluated medicine and the most relevant alternative in Sweden. The comparator can be another pharmaceutical, or a non-pharmaceutical product. The most relevant alternative is that which is most widely used, and it is generally put forward as the appropriate comparator by the pharmaceutical company in its application. If there is no comparator relevant in the Swedish context, the analysis must be supplemented with model calculations. The assessment must include the whole patient population targeted by the medicine. When cost-effectiveness is expected to vary across target population, separate calculations must be made for different target groups (e.g. based on gender, age, degrees of severity of the illness, different risk levels). If clinical tests are not sufficient to cover all target populations, modelling can be used to demonstrate cost-effectiveness in other patient groups[147]. If the patient group is small (orphan or rare diseases) and little data is available, a greater uncertainty is considered acceptable in the cost-effectiveness assessment.

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[144] Kleijnen, S. et al, July 2011, *Relative Effectiveness Assessment (REA) of Pharmaceuticals, background review*.

[145] TLV, 2007, *The Swedish pharmaceutical reimbursement system*.

[146] TLV, 2012, *Guide for companies when applying for subsidies and pricing for pharmaceutical products*.

[147] TLV, 2003, *General guidelines for economic evaluations from the Pharmaceutical Benefits Board* (LFNAR 2003:2).

The timeframe of the cost-effectiveness analysis must cover the period when the main health effects and costs happen; for example, if a treatment affects survival, the assessment should take a lifelong perspective to properly evaluate life years gained. This is done via modelling, as data from clinical trials are not sufficient. For chronic illnesses, cost-effectiveness often varies with age. Consequently, treatment periods of one to five years should be considered at different ages[148].

In the assessment, hard clinical endpoints are preferred; effects on mortality, morbidity, disease specific quality of life are considered. Safety data, contra-indications and ease of use are also taken into account. Surrogate endpoints can be used, but should be complemented with modelling from these endpoints to illustrate the effects on mortality and morbidity. If the treatment mostly affects survival, life years gained should be presented in addition to QALYs. If QALYs cannot be used, cost-benefit analysis with the willingness to pay may be used as a measure of effect. If the drug has the same health effects as the best comparable treatment, a cost comparison can be sufficient.

There is no QALY threshold value under which the medicine is not considered to be cost-efficient. Decisions are made by TLV on a case-by-case basis. The severity of the disease is a critical criterion in the decision: the cost-benefit ratios accepted for medicines treating severe diseases are higher those accepted for treatments for less severe diseases[149].

4.7 Analysis

The selected countries provide an interesting snapshot of possible ways to incorporate the assessment of added therapeutic value in the decision on the pricing and reimbursement of new medicines. While the terminology used is not always the same, the nature of the evaluations the six Member States conduct are strikingly similar: they all try to estimate how a new medicine compares to existing alternatives in terms of its clinical effects, and complement the REA with considerations of social desirability and economic impacts.

All Member States included in our in-depth review conduct REAs, even though in four of the six cases (Italy, Poland, Slovakia and Sweden) these are not considered as stand-alone assessments but rather as factors within a broader assessment, which usually includes some form of pharmaco-economic analysis (with the exception of Italy, where REA is used to calculate an "innovativeness score").

The principles used by the six Member States to estimate the added therapeutic value are also similar. All of them accept comparisons between the new medicines and the 'best standard care', which, in practice, is the reimbursable drug usually prescribed for the same condition. However, the exact definitions of best standard care do vary slightly, which may lead to the selection of different comparators in different countries. This is notably the case for countries where the number of reimbursed medicines is lower: Poland has a specific provision for such a situation and will accept indirect comparisons as a consequence.

In terms of the types of data considered during the assessment, there seems to be a general preference for clinical end-points, even though most countries allow for the possibility of using surrogate end-points when complemented by modelling proves their effects on primary end-points (e.g. in Italy and Sweden). France considers a particularly

[148] Ibid.

[149] Paris, V. & Belloni, A., 2013, *Value in Pharmaceutical Pricing*, OECD Health Working Papers No. 63.

significant wealth of data, including both generic and disease-specific quality of life end-points.

All of the countries use the data submitted by the medicinal product manufacturers as their main basis for REA and other clinical or health-economic assessments, but other sources may also be considered: when necessary, France and Italy will add information from clinical guidelines, expert advice, and, in the case of France, publications by other HTA agencies, literature, EMA reports, published clinical data and confidential data.

In most countries, relative effectiveness will not be the only clinical parameter considered. Efficacy, effectiveness, and safety contribute to the assessments in Italy, Slovakia and France respectively. The quality of these data and the level of evidence is usually taken into account. For example, double-blind, randomised studies on large populations are considered more reliable than smaller, non-randomised trials or simple expert opinions.

The impact of ATV on the final decision is more direct in some cases (in Italy, all medicines with ATV are reimbursed and may have access to financial benefits) and indirect in others (in Sweden and Austria, it is the cost-effectiveness of a medicine that has an effect on its reimbursement status). France appears to be the only country where the existence of ATV has an impact on pricing policies, but not on the reimbursement rate.

Finally, economic considerations are an important part of the reimbursement decision. The decision-makers need to ensure that their citizens have access to the best care possible, while keeping costs for the healthcare system under control, all while keeping incentives for pharmaceutical research and development in place. It is therefore not surprising that all Member States studied evaluate the cost-effectiveness of new medicines and their impact on the healthcare budget. However, the extent and use of these health-economic assessments varies: some countries do not consider societal cost or the cost for the patient (e.g. Austria), while others do (e.g. Sweden). Some countries have set a cost-effectiveness threshold under which the new medicines will not be included among reimbursable drugs (e.g. Slovakia), while most others prefer not to have such a rule in place.

In conclusion, it appears that, despite the differences in terminology, the countries included in our in-depth analysis do conduct similar analyses when it comes to evaluating the added therapeutic value. It would, therefore, not be unreasonable to imagine them sharing a common method in the future. However, the way in which they interpret and use such data, especially when they are considered together with health-economic effects, is more diverse, which would make harmonisation more challenging.

5 RECOMMENDATIONS

This chapter sets out recommendations for action that could be taken to facilitate the development and implementation of a harmonised EU approach concerning the assessment of the added therapeutic value of medicines in Europe. While the Treaty on the Functioning of the European Union (TFEU) gives the EU legislative competences to set high standards of quality and safety for medicinal products[150], Member States are responsible for determining the resources assigned to health services and medical care[151]. In general, in the field of public health, the EU plays a role in supporting, coordinating and supplementing Member State actions[152].

As described in this report, Member States usually assess ATV during the pricing and reimbursement phase, and decisions on the pricing and/or reimbursement of medicinal products are within their purview[153]. Nevertheless, the European Court of Justice has repeatedly clarified that, in exercising this competence, Member States must respect EU law in the public health field as well as other fields, notably competition[154]. Thus, Member States may not undertake pricing/reimbursement policies or practices that unjustifiably distort competition. A distortion of competition may arise, for example, where decisions are based on discriminatory criteria. The Commission has already shown concern about the lack of transparency and the existence of discrimination in this area[155], but a proposal for a directive to improve the transparency of measures to regulate the price of medicinal products and their inclusion in public health insurance systems[156] was withdrawn in March 2015[157].

In light of the current situation and the distribution of legal competences in the field of public health, the following sections set out recommendations focusing on policy-oriented action, targeting both the EU and its Member States.

5.1 Recommendation on the need of ATV as a distinct and specific outcome

Added therapeutic value should be assessed as a distinct outcome of relative efficacy assessments, separately from cost and other economic considerations.

For Member States assessing ATV, it is important to clearly communicate the results of this assessment; for the suffering patient and the prescribing physician ATV illustrates the extent of incremental clinical benefit expected to be provided by a new medicinal product.

[150] Art. 168(4)(c) TFEU. The applicable legislative procedure is the ordinary legislative procedure. The Economic and Social Committee and the Committee of the Regions must be consulted.

[151] Art. 168(7) TFEU.

[152] Art. 2(5) and 6(a) TFEU. The above-mentioned Art. 168(4)(c) TFEU, enabling the EU to set high standards of quality and safety for medicinal products, expressly derogates from these two general provisions.

[153] See Recital 33 and Art. 4(3) of Directive 2001/83/EC. See also Art. 1(2) of Regulation (EC) No 726/2004.

[154] See, for example, case C-372/04, *Watts* [2006] ECR I-4325; case C-169/07, *Hartlauer* [2009] ECR I-1721; case C-531/06, *Commission v Italy* [2009] ECR I-4103; case C-173/09, *Elchinov* [2010] ECR I-8889.

[155] See the competition inquiry into the pharmaceutical sector, at http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/index.html.

[156] COM(2012) 84 final.

[157] See the procedure file at http://www.europarl.europa.eu/oeil/popups/ficheprocedure.do?lang=en&reference=2012/0035(COD)

ATV informs a patient on the expected health impact of a new treatment: extending survival for patients suffering from cancer, delaying irreversible joint damage in patients with rheumatoid arthritis, avoiding retinal damage in patients suffering from diabetes etc. If a medicinal product with ATV, i.e. a product that has a clinically relevant incremental benefit as compared to the alternatives, is not reimbursed, patients are not getting access to optimal treatment. ATV is in fact the first question to be addressed, prior to and separate from the pricing and budget constraints of a medicinal product which will affect its affordability.

5.2 Recommendations on the use of ATV in a reimbursement setting

In the difficult exercise of defining, measuring and estimating ATV, a move towards a joint approach, across Member States and among the various stakeholders, is recommended.

ATV definition and composition

A product has ATV if the incremental health benefit is clinically relevant. To this end, the therapeutic value of a medicinal product should refer to items with clinical relevance such as efficacy, safety and effectiveness. The weighting given to the specific elements will be dependent on the disease characteristics and the available treatment options.

The HLPF made a clear statement on "…the scientific assessment of the relative effectiveness of medicinal products...". The Pharmaceutical Forum also recommended using the same definitions, to agree on best practices for REA and to exchange and communicate on these practices, which will "… ensure a common understanding of the work done at national level and should also ensure medicines receive fast access to market and appropriate reward. It also endorsed "the aim of relative effectiveness assessment to compare healthcare interventions in daily practice and classifying them according to their added therapeutic value".

The HLPF links ATV to timely access for the patient and appropriate reward for the applicant, expecting, in case of a favourable REA outcome, a positive reimbursement decision at an acceptable price versus alternatives.

In times of extensive cross-border healthcare exchange, a common approach towards defining and measuring ATV is beneficial to an efficient and effective uptake of valuable medicinal products. A common approach on ATV, expressed as the level of incremental clinical benefit of a medicinal product compared to its alternatives, will inform physicians and patients about appropriate treatment decisions based on the real clinical value of a product. On the contrary, different ATV definitions and estimates will yield unclear incentives to pharmaceutical R&D, which in turn may affect future clinical development plans.

Defining ATV requires Member States to be explicit on what is meant by therapeutic value. As an example, in Belgium the definition of therapeutic value is mentioned in the legal reimbursement text[158]. Therapeutic value considers five criteria - efficacy, safety, effectiveness, applicability and ease-of-use - and each of these five criteria is defined. The

[158] Royal Decree of December 21st, 2001.

value must relate to the effect of the medicinal product on mortality, morbidity or quality of life. Other Member States use similar criteria but additional criteria may be considered e.g. the Netherlands add 'experience'. As the set of used criteria is not too different, a common set among Member States should be feasible[159], starting from the five mentioned which many Member States already have in common.

ATV measurement scale

The measurement scale for ATV should be harmonised. Preference is given to an ordinal scale.

The existing variability across Member States is illustrated by the implemented measurement scales. The 5-point ordinal scale introduced in Germany following the AMNOG Regulation uses slightly different levels – and level labels - as compared to the well-known French 5-point scale 'Amélioration du Service Médical Rendu'. The Dutch categorical scale considers 'less', 'similar' or 'added' therapeutic value; Belgium considers the latter two categories.

Again, because of the similarities in scale revealed in these examples, evolving towards a common ATV scale should be considered by the competent authorities and by the applicants. The expected benefits of a common scale include enhanced mutual understanding, aligned focus on clinical relevant value items and synergy in the assessment outcome. An ordinal scale is preferred as it is probably more appropriate to disentangle the far more common minor therapeutic improvements provided by innovative medicinal products from the substantial improvements provided by break-through innovative products which occur less frequently.

ATV estimate as the outcome of REA

It is recommended to strengthen further the cooperation between the various competent authorities, EUnetHTA and other stakeholders. The intense and numerous interactions currently happening in the Joint Action programme will help to identify all sources of heterogeneity among the assessors and might facilitate the development of a stepwise approach towards good practices to reduce this variability.

The ATV level given to a new medicinal product is dependent on the product's characteristics relating to the criteria used to estimate ATV. Experience shows that clinical efficacy and effectiveness together with the product's safety profile are probably the factors with most impact on the granted ATV level while less weight is given to differences in convenience or applicability. To reliably estimate the ATV level the assessors will – among others - need to evaluate the results of the performed clinical research studies (efficacy), the results of observational daily practice studies (effectiveness) and the accumulated safety experience (adverse events from clinical studies and from spontaneous post-marketing reporting).

This is probably an area where disagreements between different assessors will emerge.

[159] Annemans, L., et al, 2011, Valorising and creating access to innovative medicines in the European Union, Frontiers in pharmacology, hypothesis and theory article, 2(57): 1-6.

The interpretation of the clinical benefit of the new medicinal product will depend on:

- the assessor's understanding of good clinical and statistical practice;
- the importance given to the primary and secondary end-points;
- the acceptability of surrogate end-points;
- the applicability of indirect treatment comparisons;
- the clinical relevance of a statistical significant difference;
- the uncertainty relating to the incidence of adverse events (which are seldom a primary end-point);
- the possibility to interact with other experts;
- the importance given to patient input; and
- the understanding of the particularities of an R&D programme for orphan diseases etc.

5.3 Recommendations on the organisational assessment level

Assessment by experts versus stakeholders

A multi-disciplinary expert panel instead of a panel of stakeholders should perform the REA. The HLPF made a clear statement on "…the scientific assessment of the relative effectiveness of medicinal products...".

A multi-disciplinary expert panel is best suited to approach the REA-processes in a scientific way. The expertise needed includes in depth knowledge in the following areas: medicine; clinical R&D; clinical pharmacology; biostatistics; epidemiology; niche expertise in specialised medical topics (e.g. auto-immune diseases, oncology…) and in rare diseases and advanced therapies. It is obvious that only a multi-disciplinary team can try to combine various sources of expertise.

A second reason why experts may be preferred to stakeholders is that those experts dealing with the REA should work independently from the financial, budgetary or economical assessments in the reimbursement track.

Assessment by international joint committee of experts

For reasons of local expert resource capacity issues, of the scientific nature of REA and of the similar objectives in REA between Member States, preference is given to an international European joint committee which performs the REA of medicinal products near to market authorisation, prior to local reimbursement submission.

The international expert committee has only REA responsibilities. Such an assessment committee could build on the exchange of expertise and good practices which currently take

place in the European Joint Action[160]. This would bring together the EC, competent Member States and HTA agencies in an effort, among other objectives, to explore the feasibility of joint assessments. International collaboration on REA has already been proposed by other organisations[161] or in the particular area of rare diseases[162].

Uniform REA requirements (e.g. EUnetHTA core template, rapid assessment methodology) would facilitate submission procedures for applicants across the different Member States and avoid substantial redundancy. But much more is needed to develop a common, detailed and documented REA methodology, endorsed by the Member States.

Still, the actual parallel assessment by competent authorities of similar clinical evidence included in the local reimbursement dossiers could favourably be replaced by one joint assessment performed by a team of multi-disciplinary experts in which each Member State delegates staff members, depending on their own local specific expertise (e.g. metabolic rare diseases). Working procedures can be inspired by best practices from selected Member States and by those from regulatory assessment committees such as the CHMP.

A joint and integrated assessment procedure between European MS should not limit the national competence on reimbursement decisions[163]. Each Member State should remain competent to accept or refuse the joint assessment report. The joint assessment report should be available near to the time of market authorisation to be compliant with the timelines for reimbursement and pricing as dictated by the Transparency Directive[164]. A separate local committee will deal with the reimbursement conditions (reimbursement level, price, reimbursement setting). The latter committee performs the appraisal of all relevant criteria and advises the local competent authority.

As the price premium for innovative medicinal products is often linked to proven ATV in the Member States, the committee responsible for the assessment of the ATV should not be responsible for price determination; an international committee of experts who only deal with REA may be more appropriate to resolve this issue.

5.4 Recommendations on transparency and quality assurance of the REA methods and ATV estimation

On the methodological level, the competent authorities should increase their efforts to develop good practices in the field of REA. Authorities and applicants should formally endorse standards for REA. REA methods and REA assessment reports should be made

[160] European Network on health technology assessment (EUnetHTA), 2013, Joint Action 2, 2012-15. Work Package 5. HTA Core model for rapid relative effectiveness assessment of pharmaceuticals. Available at: http://eunethta.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf.

[161] AIM-ESIP-MEDEV Workshop on HTA cooperation in Europe, 30/9/2014, Brussels

[162] Executive Agency for Health and Consumers. Creation of a process for the exchange of knowledge between Member States and European authorities on the scientific assessment of the clinical added value for orphan medicines. EAHC/2010/Health/05 October 2011 Final CAVOD study report.

[163] Annemans, L., et al, 2011, Valorising and creating access to innovative medicines in the European Union, *Frontiers in pharmacology*, hypothesis and theory article, 2(57): 1-6.

[164] Directive 89/105/EEC Council Directive of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems, 11.2.89, L 40/8.

public. The applied assessment process should be compliant with the endorsed assessment standards and should be subject to quality control.

Various authors[165,166], revealed that the local availability of REA guidelines and the information contained in these guidelines on how to perform REA is often limited. The available information relates to the applicable reimbursement procedure and little can be found on good practice methods, even if some Member States encourage the publication of detailed REA methodology. The example of NICE is encouraging in this area: the NICE Guide to Methods of Technology Appraisal[167] is a document describing the key principles of HTA to be applied in NICE appraisals. The series of Technical Support Documents provides complementary information, giving detailed advice on specific methods such as network meta-analyses of regulatory clinical trials.

Evidently, the expert use of specific REA methods will require investments that not all competent authorities can afford. This again reinforces the need for a stronger and synergistic collaboration between competent authorities and HTA agencies in the EU to increase efficiency.

Application of EBM principles may be different between Member States due to variability in the availability and level of specific expertise (medical, clinical R&D, statistical, epidemiological, pharmaceutical…) and necessary resources. Very little is known on the endorsement and implementation of the proposed REA guidelines. There are no systematic reports available on the compliance achieved by the assessment bodies in applying the proposed REA guidelines. Authorities and applicants should formally endorse standards for REA; only in this way will appeals to decisions become possible. Appeal to assessments made by NICE[168] were frequently based on a misinterpretation of clinical (26 %) or cost-effectiveness (18 %) evidence or on lack of transparency (8 %), indicating such issues are real.

The need for transparency in reimbursement decision-making is of utmost importance. The reimbursement criteria used by competent authorities will affect the public resource allocation and the patient access to effective treatments in areas of medical need. To help decision-makers in this critical activity a set of four conditions has been developed in the framework of accountability for reasonableness[169], which includes the following:

- the allocation process should be transparent
- based on relevant criteria
- revisable in case of new evidence
- assurance should be given that the conditions are fulfilled

The main idea behind this framework is that if the set of criteria used in healthcare resource allocation satisfies these four conditions, then policymakers can be held accountable for the

[165] Van Wilder, P.B., Bormans, V.V. & Dupont, A.G., 2013, Relative efficacy and effectiveness assessment of new pharmaceuticals in three EU member states: current practices and outcomes agreement between Belgium, the Netherlands and France, Eur J Clin Pharmacol, 2013 Dec, 69(12), pp. 2037-2044.

[166] Kleijnen, S. et al, 2012, Relative Effectiveness Assessment of Pharmaceuticals: Similarities and Differences in 29 jurisdictions, Value in Health 15.

[167] National Institute for Health and Clinical Excellence, Guide to the methods of technology appraisal, 2008.

[168] Eaton, J., Hubbard, C. & Hawkins, N., 2011, *A review of the NICE appeals process*, In: 14th ISPOR European Congress, Madrid.

[169] Daniels, N., *Accountability for reasonableness*, BMJ 2000; 321: 1300-1.

reasonableness of their decisions. After all, poorly designed or managed HTA processes run the risk of either denying patients an appropriate access to new technologies or of inefficiently allocating resources. Within Europe, the HLPF considered REA as a scientific process. Investigating the scientific nature of REA assessments is of high importance in a context of limited resources and high demands on innovative medicinal products. The challenge is not only about 'value for money' (discriminating a valuable innovation from an invaluable one) but also 'money for value' (sufficiently rewarding valuable innovation) in a context of a strong demand for early access with increased uncertainty about the relative effectiveness.

In this framework of accountability for reasonableness, the condition on transparency and on relevance of criteria asks for competent authorities to be very explicit on evaluation standards, on applied REA methods, on the clinical criteria considered for ATV and on the assessment report including the ATV estimation. The third condition on revisable assessments necessitates updated REA assessments if new trial data become available. The fourth condition asks for mechanisms to be in place that allow independent review of the decisions taken and verify if these are compliant with the allocation process, made explicit by the adopted reimbursement criteria and evaluation methods. Appeal mechanisms to reimbursement evaluations and decisions are often provided by the local legal regulations but appeal on 'content' is only possible if endorsed documented REA guidelines are available. Because of the actual lack of endorsed detailed assessment methods, appeal on content is hardly possible in many Member States.

Evaluation of the performed assessments

On the methodological level, further research is needed to identify factors (besides REA) that may affect the reimbursement decision and to estimate the size of their effect. There is a lack of good quality data linking the reimbursement decision to data on ATV, price, medical need, budget impact and outcomes of cost-effectiveness analyses, such as the ICER. The creation of an accessible (international) database containing the key data of reimbursement dossiers would provide the necessary tool for competent authorities, relevant stakeholders and researchers to regularly review the series of reimbursement decisions and perform more powerful analyses, which may further reduce the unexplained variance in the decision-making. Poland[170] and Belgium[171,172], provided some insight into the relationship between the reimbursement decision and ATV, budget impact and cost-effectiveness; the unexplained variance was still high. Regular statistical review of factors impacting reimbursement decisions is recommended and past decisions should be reconsidered. Such analyses may help to ensure that the reimbursement procedure is in line with the Transparency Directive asking for pricing and reimbursement decisions to be taken in a "… transparent, objective and verifiable way with respect of strict timelines"[173].

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[170] Niewada, M., ISPOR annual European Congress 2011, Madrid.

[171] Van Wilder, P., Zhu, Q. & Veraverbeke, N., 2009, Identifying and rewarding pharmaceutical innovation: Application in an EU member state, *Drug Information Journal*, 2009(44), pp.317-25.

[172] Bormans, V.V., Van Wilder, P.B. & Dupont, A.G., Reimbursement of new pharmaceuticals in Belgium: impact of clinical effectiveness, budget impact and efficiency, ISPOR annual European Congress 2011, Madrid.

[173] Directive 89/105/EEC Council Directive of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems, 11.2.89, L 40/8.

A substantial impact of the "added therapeutic value" on the reimbursement outcome is a clear incentive to develop new effective drugs addressing unmet or partially met medical needs.

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ANNEXES

Annex 1: In-depth country study: France

The French health insurance system is a public insurance system managed by the National Sickness Insurance Fund for Employees (*Caisse nationale d'assurance maladie des travailleurs salariés (CNAMTS)*). Public health insurance is compulsory for employers and workers and can be complemented with private health insurance.

Putting a new medicine on the market requires two different decisions: the **market authorisation**, delivered by the European Medicines Agency if the product goes through the centralised or mutual recognition procedure, or by the French National Agency for Drug Safety (ANSM) if the product goes through the national procedure. Secondly, the decision on **pricing and reimbursement**, is taken by the Ministry responsible for health, after an assessment of the therapeutic value of the medicine by the French National Health Authority (*Haute Autorité de Santé* – HAS). This decision is valid for five years, after which a reassessment is necessary.

Market authorisation

The National Agency for Drug Safety (ANSM) delivers market authorisation through the national procedure, and contributes to the centralised and mutual recognition market authorisation procedures. During the assessment that takes place prior to market authorisation, the ANSM conducts a risk-benefit analysis based on the same criteria as the EU centralised authorisation procedure: quality, safety and efficacy. The new medicinal product should have a risk-benefit (consider benefit-risk) ratio at least equivalent to other comparable products on the market.

In France, the added therapeutic value (ATV) of medicines is usually assessed during the pricing and reimbursement phase of medicinal products. A fast-track procedure aiming at accelerating the marketing of innovative products can sometimes be used. In this case, the ATV assessment can start prior to, or during, the market authorisation procedure, which enables the National Health Authority (HAS) to issue an opinion within a few weeks of the market authorisation being granted.

Pricing and reimbursement

The National Health Authority (HAS) is the centralised body in France responsible for assessing the therapeutic value of medicines and advising the decision-maker on pricing and reimbursement. Inside the HAS, an expert committee, the Transparency Committee, conducts the assessment.

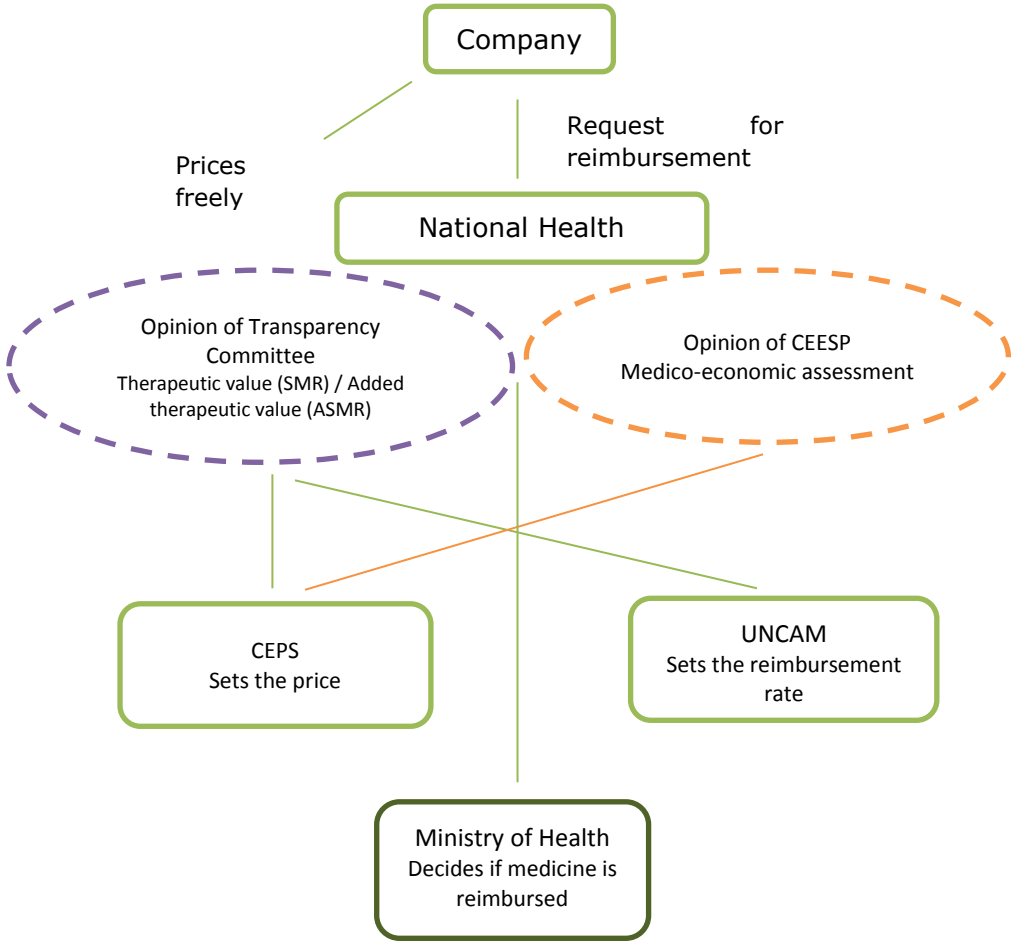
Medicinal products that are eligible for reimbursement are included in lists of reimbursed pharmaceuticals[174] (for outpatient and inpatient medicines) after they have been evaluated by the National Health Authority. When a pharmaceutical company wants a medicine to be reimbursed, the company has to submit a request to the National Health Authority. Upon approval of this request, the Transparency Committee of the National Health Authority

[174] The list is accessible online : http://base-donnees-publique.medicaments.gouv.fr/# Accessed April 2015.

evaluates the therapeutic value and the added therapeutic value of the medicine. Occasionally, the medico-economic efficiency of the medicine is evaluated by the Committee on Economic Evaluation and Public Health (CEESP) of the National Health Authority.

Next, the recommendations based on the outcomes of the assessment are submitted to two separate bodies to determine the price of the medicine and its reimbursement rate. These two bodies are the Economic Committee on Healthcare Products (CEPS), which sets the price of the drug, and the National Union of Health Insurances (UNCAM), which determines the reimbursement rate. The final decision on reimbursement is taken by the Minister in charge of health and social security within 90 days. The pharmaceutical company can appeal the decision made by the Ministry.

Figure 2: Decision making process on pricing and reimbursement of medicines in France



Source: adapted from French Ministry of Social affairs, Health and Gender Equality.

Although the procedure is centralised, main stakeholders are involved in the process through their representation in the Transparency Committee, either as experts or by providing data to inform the Authority's opinion. The Transparency Committee is composed of 26 members representing doctors, pharmacists, and epidemiologists, as well as eight members without voting rights, who represent the General Directorate for Social Security (Ministry), the General Directorate for Health (Ministry) and the General Directorate for Healthcare Services (Ministry), and, finally, representatives from the health insurance funds, the National Agency for Drug Safety (market authorisation authority), and pharmaceutical companies. External experts can be consulted on a needs basis. Optional hearings of patients' associations can also be held by the Committee, but there is, generally, little involvement of patients in France.

Pricing of medicinal products

In France, pricing rules vary depending on how the medicinal product is used (outpatient or inpatient care) and on the status of the evaluated medicine (reimbursable or not, patented or unpatented). Prices of reimbursable medicines are regulated by the public authority (CEPS), after negotiations with the industry. In cases where pharmaceutical companies do not submit a reimbursement request, or where such applications to be included on the reimbursement list are rejected, prices are freely established by pharmacists.

Pricing rules for outpatient medicinal products further vary between patented and unpatented medicines. The price (excluding taxes) of patented medicines is established in agreement with its pharmaceutical producer. Since the 1990s, the general pricing policy for reimbursable medicines is established through three-year agreements, with the pharmaceutical industry setting price negotiation methods with each company, and the renegotiation of prices depending on product sales[175]. The price of patented medicines is based on its added therapeutic value (see section 3.2.3), the projected volume of sales, and the price of comparable medicines in France and other European markets[176]. Since 2003, a new procedure enables pharmaceutical companies to set the prices of innovative medicinal products, provided that it is aligned with prices set in other European markets. The public authority – here, the Economic Committee on Healthcare Products (CEPS) - can oppose the price set by the industry.

Pricing rules are stricter for unpatented medicinal products. The price of off-patent medicines must decrease by 20 % when a comparable generic medicine comes on the market. Generally, since 2014, the price of off-patent medicine must converge towards the price of comparable generics five years after they have been put on the market. The price of generics is calculated from the price of originator products, with an immediate 60 % decrease since 2012, and a possible further decrease of 7 % after eighteen months[177]. Although the CEPS can decide on a smaller price reduction, the general policy guidelines of the Ministry of Health advise to go beyond the 60 % reduction[178]. In parallel, several

[175] Vie Publique.fr, Regulation on pricing and reimbursement rates : http://www.vie-publique.fr/politiques-publiques/politique-medicament/prix-remboursement-regulation-medicament/ Accessed April 2015.

[176] In France, a 'European price' is defined according to prices charged in reference countries: Germany, UK, Spain and Italy.

[177] Gimbert, V., Benamouzig D., 2014, *Les médicaments et leurs prix: comment les prix sont-ils déterminés*? volet 2, La note d'analyse no 10, Commissariat général à la stratégie et à la prospective.

[178] Ministry of Economy and Finance, Ministry of Social Affairs and Health, Ministry of Industry and economic growth, Guidance letter of the Ministers of 2 April 2013: http://www.sante.gouv.fr/IMG/pdf/Lettre_d_orientation_des_ministres_du_2_avril_2013.pdf.

financial incentives for doctors, pharmacists, and users aim at increasing the use of generic medicines.

Prices of inpatient medicinal products have been regulated since 2004; between 1987 and 2004 prices were freely established by each hospital. In particular, prices of medicines available only in hospital pharmacies (and provided to both inpatients and outpatients), high cost medicines, and innovative medicines, are regulated through an agreement between the State and pharmaceutical companies. Pharmaceutical companies must propose a price for validation by the CEPS, which aligns with prices charged in other major European markets, and with prices charged in France for comparable medicinal products. Prices of medicines falling outside these categories are freely established by the companies in question.

Reimbursement of medicinal products

The reimbursement rates of medicinal products in France are based on their therapeutic value (*service médical rendu*), and the severity of the disease they target. Irreplaceable medicines for severe diseases are fully reimbursed (100 %), medicines with high therapeutic values are reimbursed up to 65 %, medicines with moderate therapeutic values up to 30 % and medicines with low therapeutic value up to 15 %[179]. The remaining part is paid by the patient or, in certain cases, by the private complementary insurance. Co-payment exemptions exist for socially disadvantage people (with an annual income of less than EUR 7,083)[180].

Assessment of added therapeutic value

The assessment of medicinal products is based on two main criteria: the therapeutic value (*Service Médical Rendu or SMR*) and the added therapeutic value (*Amélioration du service médical rendu* or ASMR).

Therapeutic value (SMR)

The SMR is an objective criterion that evaluates the value of a medicine without a comparator. It is based on the following five criteria[181]:

- the effectiveness of a drug and its side-effects on patients,
- the stage in the therapeutic strategy at which the drug is used, and the existence of therapeutic alternatives,
- the severity of the disease,
- the characteristics of the drug (preventive, symptomatic or curative), and
- the benefits in terms of public health.

[179] Service-Public.fr, Reimbursement of medicine: http://vosdroits.service-public.fr/particuliers/F21760.xhtml. Accessed April 2015.

[180] Kleijnen, S. et al, July 2011, *Relative Effectiveness Assessment (REA) of Pharmaceuticals, background review*.

[181] Social Security Code, art. R163-18.

The SMR is evaluated for all medicinal products that go through market authorisation. Where relevant, different target populations are considered. The therapeutic value of a medicinal product is defined according to the following scale: major or important therapeutic value, moderate or weak therapeutic value, and insufficient therapeutic value. This classification directly influences the reimbursement rate of the medicinal product (65 %, 30 % or 15 %). Products with insufficient therapeutic value are excluded from the list of reimbursable pharmaceuticals. The SMR does not influence the price of the medicine.

The SMR can be significantly modified when a medicine is reassessed, as new information on effectiveness and side effects can be incorporated at a later stage.

Added therapeutic value (ASMR)

The ASMR compares a medicinal product to other existing medicines, measuring the added value in terms of effectiveness and drug tolerance. The benefit-risk analysis is not part of the analysis as this is conducted by the authority responsible for market authorisation. Unlike the SMR, the ASMR is a relative standard and provides only a snapshot of the added therapeutic value in a given context[182]. Like the SMR, it must be assessed for all medicinal products that gain market authorisation. The demonstrable added value of a medicinal product is quantified according to the following five levels: ASMR I or major, ASMR II or important, ASMR III or moderate, ASMR IV or minor, and ASMR V or absence of added value.

The assessment of the ASMR requires the selection of a relevant comparator. According to the Social Security Code, the ASMR assessment should identify all products of the reference therapeutic class, and the evaluated medicine should, at least, be compared with the most prescribed competitors, as well as with the comparative medicinal product that has the cheapest treatment cost, and with the most recent reimbursable product of the same class of medicines[183]. However, in practice, ASMR is not assessed against all medicines or other therapies listed, but against the best available and reimbursed treatment[184]. The ASMR can change when a medicine is reassessed as new alternatives may have been come on the market in the intervening period.

The comparator can be another medicine or another medical device, or any other non-pharmaceutical product, as long as it used for the same purpose and at the same stage in the treatment as the evaluated drug, and as long as it targets the same population. If such a relevant comparator exists, the medicine that needs to be assessed cannot be evaluated solely against a placebo[185]. The selection of the comparator can be based on a range of sources, such as the suggestion of experts or the product sponsor, or based on clinical or methodological guidelines[186]. It is also possible to conduct indirect comparisons during the assessment, but this should be based on the National Health Authority guidelines[187].

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[182] Bouvenot, G., 2013, Le rôle de la Commission de la transparence de la HAS dans la pertinence de l'admission au remboursement des médicaments par l'Assurance maladie, *Regards* no 44.

[183] Social Security Code, art. R163-18.

[184] Paris, V. & A. Belloni, 2013, Value in Pharmaceutical Pricing, OECD Health Working Papers, No. 63, OECD Publishing.

[185] Bouvenot, G., 2013, Le rôle de la Commission de la transparence de la HAS dans la pertinence de l'admission au remboursement des médicaments par l'Assurance maladie, *Regards* no 44.

[186] Kleijnen, S. et al, July 2011, *Relative Effectiveness Assessment (REA) of Pharmaceuticals, background review*.

[187] National Health Authority, 2009, Comparaison indirectes : méthodes et validité.

The ASMR assessment involves an evaluation of multiple sources. The report provided by the pharmaceutical company is one of the main sources of information, complemented by external sources such as clinical guidelines, publications by other HTA organisations, available literature, European and national public assessment reports, as well as unpublished clinical data or confidential information, where relevant[188]. Data that is provided by the pharmaceutical company responsible for producing the medicinal product is always reviewed according to evidence-based medicine criteria. Moreover, the quality of studies included in the assessment is also considered, although no classification system is used. The replicability of results – from studies or clinical trial – in the French healthcare system always forms part of the evaluation[189]. Where information is not available on the medium and long-term effects of the medicinal product in question, it is not possible to thoroughly assess its added therapeutic value. In this case, the Transparency Committee reaches a decision based on the best interest of the patients[190].

The level of effectiveness is one of the indicators evaluated during the ASMR. This is generally quantified by looking at the reduction of the absolute risk in terms of morbidity or mortality. The morbidity/mortality criteria that are used to assess the level of effectiveness of the medicinal product need to be the best clinically-relevant criteria available, which means that[191]:

- Surrogate endpoints are included if no other endpoints are available;
- Generic quality of life end-points are only included as complementary data, but disease-specific quality of life end-points can be included if information is validated and appropriate to the specific disease;
- Safety data and contra-indications are considered;
- Ease of use is not considered unless it is demonstrated that the ease of use has a clinical impact.

The ASMR has a direct influence on the price of the drug but not, however, on the reimbursement rate. If a product has a high SMR, but a low ASMR, it should be reimbursed by the medical insurance at the same rate as a comparable product, but should not, however, cost the user and the social security more than the comparable product. An added therapeutic value – even minor - is rewarded by price premiums, the potential price rises when the added therapeutic value is higher. This system aims at encouraging innovation, but it is also seen as promoting the development of similar medicines that have an extremely low therapeutic added value compared to existing medicines[192].

Since 2012, the French National Health Authority has been developing a new indicator, the 'Single Relative Therapeutic Index' (*Index Thérapeutique Relatif unique - ITR*). This new index is meant to combine and replace the SMR and ASMR. The five levels defined would

[188] Kleijnen, S. et al, July 2011, *Relative Effectiveness Assessment (REA) of Pharmaceuticals, background review*.

[189] Bouvenot, G., 2013, Le rôle de la Commission de la transparence de la HAS dans la pertinence de l'admission au remboursement des médicaments par l'Assurance maladie, *Regards* no 44.

[190] Ibid.

[191] Kleijnen, S. et al, July 2011, *Relative Effectiveness Assessment (REA) of Pharmaceuticals, background review*.

[192] Gimbert, V., Benamouzig D., 2014, Les médicaments et leurs prix: comment les prix sont-ils déterminés? volet 2, La note d'analyse no 10, Commissariat général à la stratégie et à la prospective.

inform the decision on pricing and reimbursement. The index is still under discussion but may be implemented in 2016[193].

Reassessments

Reassessments of medicinal products are usually initiated by the National Health Authority. A reassessment of the initial evaluation is compulsory for outpatient drugs after five years in order to maintain the product on the list of reimbursed pharmaceuticals. In addition to this, the reassessment can be initiated at any time when significant new information becomes available.

Health Technology Assessments

In addition to the assessment of a single medicine, the National Health Authority conducts health technology assessments (HTA), which are 'systematic evaluations of properties, effects, and/or impacts of healthcare technology. 'These are defined as any intervention that may be used to promote health, to prevent, diagnose or treat disease, or for rehabilitation e.g. medicine, devices, procedures or treatment strategies. They 'address the direct, intended consequences of technologies as well as their indirect, unintended consequences to inform technology-related policymaking in health care'[194].

Health technology assessments (HTA) are conducted in France at the specific request of health authorities or according to the National Health Authority work program. Health technology assessments are usually motivated by a decision to remove drugs from the list of reimbursable pharmaceuticals. In this case, all drugs with the same purpose are assessed at the same time to guarantee the equality of the assessment.

Assessment of the economic aspects of medicinal products

As described above, the SMR and ASMR do not take into account the potential economic impact of a new medicinal product. However, since 2012, a separate cost-benefit analysis needs to be conducted for certain categories of drugs, this is the medico-economic evaluation[195]. The National Health Authority is responsible for conducting this economic evaluation, which applies to all medicines with a major, important, or moderate ASMR, and that are likely to have a significant impact on public health expenditures due to their price or their potential impact on prescription and use. The assessment is considered irrelevant for unpatented drugs[196].

The College of the National Health Authority is responsible for deciding whether a medico-economic assessment is necessary, a decision which is based on the following two criteria:

- The therapeutic added value claimed by the pharmaceutical industry; and

[193] Dahan, M., 2013, Révision des critères d'évaluation des produits de santé en vue de leur prise en charge par l'assurance maladie. Analyse de l'Index thérapeutique relatif (ITR) proposé par la HAS, Inspection Générale des Affaires Sociales, rapport no 2013-099R.

[194] International Network of Agencies for Health Technology Assessment (INAHTA), Glossary, definition of health technologies and health technology assessment: http://inahta.episerverhotell.net/Glossary/.

[195] Law on the Funding of Social security 2012, art. 47 enforced by Decree 2012-1116 of 2 October 2012 on medico-economic assessments of the National Health Authority.

[196] Decision 2013.0111/DC/SEESP of 18 September 2013 of the HAS College on the significant impact on public health expenditures triggering the medico-economic evaluation of products claiming an ASMR I, II, or III: http://www.has-sante.fr/portail/upload/docs/application/pdf/2013-09/c_2013_0111_definition_impact_significatif.pdf.

- The projected turnover (in case of new medicines), including all taxes, after being on the market for two years (with a threshold of EUR 20 million after two years) or the current turnover (in case of reassessment), including all taxes[197].

Whenever a pharmaceutical company submits a request for a medicinal product to be included on the list of reimbursable pharmaceuticals and that medicine is selected for the medico-economic assessment, the company is required to submit the necessary data and information concerning the efficiency of the medicine in question, including a list of medicinal products with which the drug in question should be compared. Next, this data and information is assessed by the economic evaluation service of the National Health Authority, and discussed with the Committee on Economic Evaluation and Public Health (CEESP). This Committee, created in 2008, consists of 33 members with different backgrounds: economists, doctors, epidemiologists, public health specialists, human and social sciences specialists, pharmacists, and representatives of patients' associations. The opinion of the CEESP is submitted for consideration to the Economic Committee on Healthcare Products (CEPS), which ultimately decides on the price of the new medicinal product.

The medico-economic assessment is a cost-benefit analysis that compares the evaluated medicine to all existing relevant alternatives (efficiency). In cases where the new medicine is more effective compared to the relevant alternatives on the market but also significantly more expensive, the efficiency analysis becomes more difficult. If this happens, the National Health Authority defines a reference value, generally expressed in cost per life-year gained, or per healthy life-year gained (QALY), under which a product is considered efficient[198]. The medico-economic assessment also describes the uncertainty associated with the cost-benefit analysis, and the main drivers influencing the results. The medico-economic assessment has a direct influence on the price of the drug but not on the reimbursement rate.

The practice of medico-economic assessments is still relatively new in France. As of October 2014, the National Health Authority had selected twenty drugs and one medical device eligible for the medico-economic assessment. This group of 20 was comprised of medicines that were potentially expensive and innovative, such as anti-cancer medicines, antiviral drugs (HIV, Hepatitis C), vaccines, and medicine for rare diseases[199].

Some elements of the process have been criticised. The comparator is selected by the pharmaceutical company that has manufactured the product in question, which raises suspicions of bias, especially since the choice of the comparator is a crucial factor in the analysis. A recent report by the General Inspectorate of Social Affairs (IGAS)[200] recommends that the choice of the comparator is discussed between the CEEPS and the manufacturer as early in the process as possible. However, according to the National Health Authority, early contacts are established between the Authority and companies, and have proved useful in the collection of meaningful information for the assessment. In addition,

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[197] National Health Authority, interview of Jean-Luc Harousseau, president of the HAS College, October 2014: http://www.has-sante.fr/portail/jcms/r_1502595/fr/evaluation-medico-economique-des-produits-de-sante.

[198] National Health Authority, Valeurs de référence pour l'évaluation économique en santé. Revue de littérature : http://www.has-sante.fr/portail/upload/docs/application/pdf/2014-12/fiche_synthese_vf.pdf.

[199] National Health Authority, interview of Jean-Luc Harousseau, president of the HAS College, October 2014: http://www.has-sante.fr/portail/jcms/r_1502595/fr/evaluation-medico-economique-des-produits-de-sante.

[200] Jeantet, M., Lopez, A., 2014, Evaluation médico-économique en santé, Inspection Générale des Affaires Sociales, rapport no 2014-066R.

the level of detail provided by pharmaceutical companies in their report is considered sufficient[201].

Another flaw of current assessments mentioned in the report by the IGAS is the limitation of the evaluation provided by the CEEPS in relation to the efficiency of the evaluated product. The General Inspectorate of Social Affairs recommends that the analysis be complemented with a comparison of the efficiency of the evaluated product with other products of the same therapeutic class, or with other treatments of the disease.

Thirdly, the report recommends that medico-economic assessments are supplemented by an evaluation of the budgetary impact, as the comparison with a reference value is not sufficient to determine the impact on public expenditures. For instance, low costs per life-year or QALY, can still lead to significant expenses if the drug is used by a large target population. Finally, measures to be taken following the medico-economic assessment, depending on the level of efficiency reached by the product, should be defined to ensure medico-economic assessments have an impact on the pricing decision. Medico-economic assessments are, however, generally seen as necessary additions to the evaluation of the added therapeutic value, and the progress made is perceived very positively.

National guidance documents

The assessments of new medicinal products described in this chapter also aim to support the publication of guidance documents. The National Health Authority produces summaries of the Transparency Committee's assessments and makes these publicly available to inform healthcare professionals about drug prescription[202]. In addition, the Authority publishes factsheets on the use of specific drugs, or categories of drugs, summarising the outcomes of the assessment[203]. Such factsheets are justified by the large target population or the potential risk of misuse. They are meant to help health professionals in defining the stage of the therapeutic strategy at which they should best be used, comparing new medicines to existing alternatives, and the right use of drugs[204]. The National Authority also publishes best practice documents, factsheets and diagnosis protocols in order that health professionals can be informed about drug assessments[205]. The National Health Authority has also published HTA guidelines in 2011[206].

[201] National Health Authority, interview of Jean-Luc Harousseau, president of the HAS College, October 2014: http://www.has-sante.fr/portail/jcms/r_1502595/fr/evaluation-medico-economique-des-produits-de-sante

[202] the Transparency Committee's assessments can be found at : http://www.has-sante.fr/portail/jcms/r_1500918/fr/les-avis-sur-les-medicaments.

[203] Factsheets can be found at : http://www.has-sante.fr/portail/jcms/r_1500923/fr/syntheses-d-avis-et-fiches-bon-usage-sur-les-medicaments?portal=r_1456073.

[204] National Health Authority, Synthèses d'avis et fiches bon usage sur les médicaments: http://www.has-sante.fr/portail/jcms/r_1500923/fr/syntheses-d-avis-et-fiches-bon-usage-sur-les-medicaments?portal=r_1456073 Accessed April 2015.

[205] National Health Authority, Annual activity report 2013.

[206] National Health Authority, 'Les Etudes post inscription sur les technologies de santé (médicaments, dispositifs médicaux et actes). Principes et méthodes', 2011.

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- Agence Nationale de sécurité du médicament et des produits de santé : http://ansm.sante.fr/.
- Vie-publique.fr: http://www.vie-publique.fr/politiques-publiques/politique-medicament/prix-remboursement-regulation-medicament/.

Annex 2: In-depth country study: Italy

The Italian National Health Service (*Servizio Sanitario Nazionale,* or SSN) - established in 1978 on a Beveridge model - is organised in three tiers of responsibilities: the Central Government, 21 Regions, and Local Health Units (*Aziende Sanitarie Locali*, or ASLs). The Central Government is responsible for framing and promulgating laws, financing and setting the budget of the SSN, and allocating budget resources among Regions.

As to pharmaceutical care, essential medicines are fully reimbursed by SSN for all resident citizens for both out-patient and in-patient settings. Over 70 % of pharmaceutical expenditure is publicly funded.

New medicines gain access to the Italian market once they are cleared by the European Medicines Agency (EMA) for those authorised through the centralised procedure, or by the Italian Medicines Agency (AIFA, *Agenzia Italiana del Farmaco*). Except for language requirements, the type of information required by AIFA is almost identical to that required by EMA.

The manufacturer submits a pricing and reimbursement request to AIFA, which will then judge whether the medicinal product will be reimbursed by the SSN, and, if so, initiate pricing negotiations with the manufacturer. The medicine will only be agreed for reimbursement once there is an agreement on price.

The entire pricing and reimbursement process should not last longer than 180 days[207].

Market authorisation

In Italy, the Italian Medicine Agency (AIFA) is responsible for granting national marketing authorisations for new medicinal products for human use. AIFA is a public entity which has been operational since 2004[208]. The national procedure plays a secondary role, since it can only give access to the Italian market, and most medicines are now authorised through the EU centralised procedure, decentralised procedure, and mutual recognition procedure.

The national marketing authorisation procedure begins with the application on the part of the drug manufacturer, who submits a dossier including: the name of the medicinal product, qualitative and quantitative composition, description of manufacturing methods, therapeutic indications, contra-indications and adverse reactions, posology, description of the control methods, results of physic-chemical, biological, microbiological, toxicological and pharmacological tests, as well as clinical trials[209]. In addition, a summary of the product description, labelling and package leaflet are provided in Italian[210].

AIFA's Technical and Scientific Committee (CTS, *Commissione Tecnico Scientifica*), with the assistance of the Italian Institute of Health (ISS, *Istituto Superiore di Sanitá*), then examine the dossier, verifying the quality, safety and efficacy of the new medicine, before producing an evaluation report.

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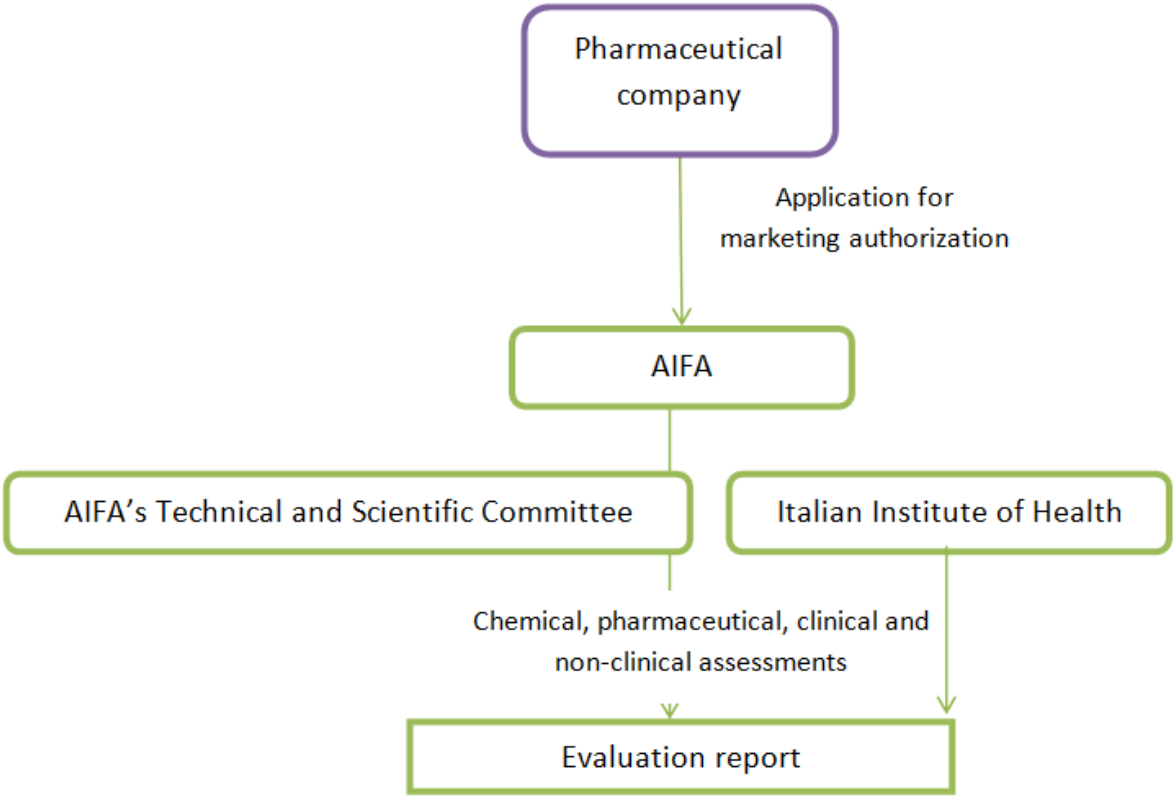
[207] In accordance with Directive 2001/83/EC.

[208] Created by Law 326/2003.

[209] In accordance with Directive 2001/83/EC.

[210] http://www.agenziafarmaco.gov.it/it/content/la-registrazione-dei-farmaci accessed on 22 April 2015.

Figure 3: Marketing Authorisation procedure



Source: adapted from the website of Agenzia Italiana del Farmaco.

Generic medicines[211] are subject to simplified procedures aimed at demonstrating the bio-equivalence with the original medicinal product, which has been authorised in Italy or in the EU for at least eight years[212].

In order to ensure a high level of transparency within the authorisation procedures, AIFA created an online database[213], accessible upon registration, which enables interested parties to follow the status of medicinal products going through the national, decentralised and mutual recognition procedures.

[211] Generic medicines are pharmaceutical products marketed under their chemical name after the expiration of the patent issued for that substance has expired.

[212] in accordance with Legislative Decree n. 219/2006 and Directive 2001/83/EC.

[213] http://www.agenziafarmaco.gov.it/frontend/

Pricing and reimbursement

AIFA is also responsible for the decision-making process on pricing and reimbursement of medicines. After obtaining a marketing authorisation, the manufacturer submits an application, which should include information on the new medicine's efficacy and safety, relative effectiveness, cost-effectiveness, therapeutic class, the proposed price, and potential impact on the budget of the SSN[214]. Once received by AIFA and checked for completion, the dossier is evaluated by the Pricing and Reimbursement Unit and/or by the Pricing and Reimbursement Secretariat, which provides a first assessment with regard to therapy and economic evaluation. AIFA's Technical and Scientific Committee later assesses the application and expresses an opinion with reference to therapy, innovativeness, reimbursement status and classification of the new medicine. New medicines can be classed in one of three ways:

- As a **Class C** medicine, which will not be reimbursed by the SSN and whose price is not negotiated
- As a **Class A** medicine, which is usually a treatment for severe and chronic illnesses and will be totally reimbursed by the SSN
- As a **Class H** medicine, which will be reimbursed by the SSN only when administered by a hospital or clinic[215]

For all reimbursable medicines, AIFA's Pricing and Reimbursement Committee (CPR, *Comitato Prezzi e Rimborso*) will then summon the manufacturer and negotiate a price. The criteria that the Committee takes into account are:

- market potential,
- pricing policy in other countries[216],
- prices of comparable medicines,
- therapeutic value,
- cost-effectiveness ratio,
- innovativeness

In cases where the negotiation process is unsuccessful, the new medicine is then classified as non-reimbursable and its price left to the producer's discretion. If the parties reach an agreement, the Pricing and Reimbursement Committee submits the decision to the AIFA Board. The final decision is published in the Italian Official Journal (*Gazzetta Ufficiale)*[217]*.*

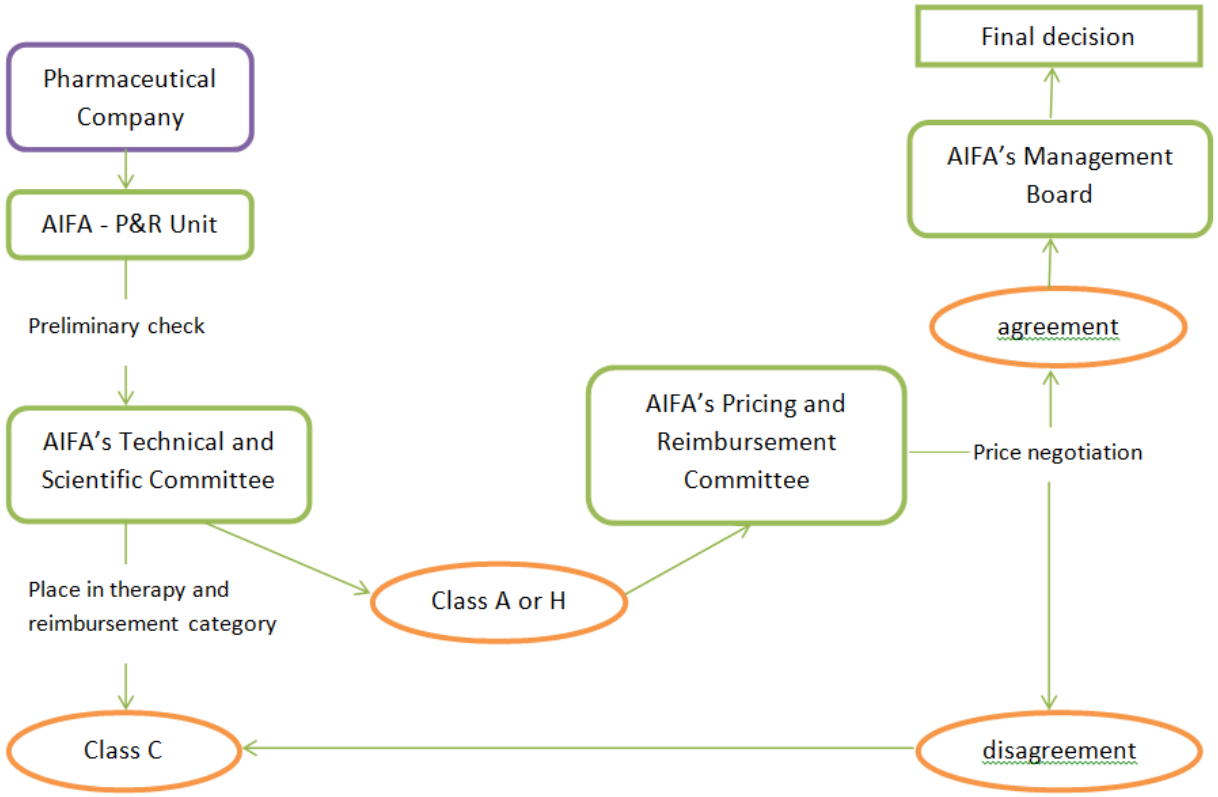
[214] Deliberation of CIPE No. 3/2001 of 1 February 2001.

[215] Lo Scalzo A. et al, 2009 Health Systems in Transition, Italy, Health system review, WHO European Observatory on Health Systems and Policies, Vol. 11, No. 6. Available at: http://www.euro.who.int/__data/assets/pdf_file/0006/87225/E93666.pdf AIFA will monitor the pricing of class C medicines for which a prescription is needed, making sure that prices are increased not earlier than every two years and that they do not exceed the scheduled inflation rate.

[216] The reference countries can vary.

[217] *Meridiano Sanitá, rapporto finale 2008*, p. 138 available on http://www.ambrosetticlub.eu/ricerche/altre-ricerche-ambrosetti/item/7033-meridiano-sanita-le-coordinate-della-salute-rapporto-finale-2008.

Figure 4: Pricing and reimbursement process



Source: adapted from the website of Agenzia Italiana del Farmaco.

Regional authorities also play a role in the process. The State-Regions Conference[218] nominates four of the members of the Technical Scientific Committee, and the Pricing and Reimbursement Committee. Regional authorities may also decide upon patient co-payments per prescription, with possible adjustments for population categories (e.g. based on age, income or clinical condition)[219].

Assessment of added therapeutic value

AIFA's working methods are continuously evolving, with both the assessment of added therapeutic value, and the cost-benefit analysis of medicines, the object of ongoing reform and reorganisation. However, this chapter will seek to provide a snapshot of the current legal framework and working methods.

[218] The State-Regions Conference is advisory body composed by the Presidents of all Italian regions and autonomous provinces.

[219] Minister of Health's Decree, 29 March 2012, n. 53.

While there is no requirement for manufacturers to provide data on the added therapeutic value of their products in order to obtain a marketing authorisation, such information becomes fundamental when the company wishes their product to be recognised as "innovative" or included in the list of reimbursable medicines by AIFA[220].

While deciding whether or not a new medicine should be reimbursed by the SSN, the Technical and Scientific Committee considers whether a product with positive cost-effectiveness:

- has proven to be useful for the prevention or treatment of conditions or relevant symptoms for which no effective treatment exists;
- has proven to be useful for the prevention or treatment of conditions or relevant symptoms for which current treatments are inadequate;
- has a better cost/benefit ratio compared to existing treatment for the same condition[221].

The first two items are intended to evaluate the added therapeutic value in terms of Relative Efficacy, whereas the third introduces an economic dimension. The failure to fulfil any of the above criteria may mean that the medicine will not be reimbursed, although it could still be considered reimbursable in cases where there are other mitigating factors, and its efficacy is not inferior to that of the best standard care[222]. This can be the case for off-patent products, where producers are required to propose a lower price compared to that of the corresponding branded product in order to obtain a positive decision on reimbursement. The impact of cost-effectiveness and therapeutic value on the reimbursement decision was further reinforced by the annual stability law, which provided for their use in a revision of the list of reimbursed medical products[223].

In order to conduct its assessments, AIFA uses data reported by the manufacturer, expert advice and clinical guidelines[224]. Clinical end-points (such as the reduction of mortality or morbidity) are preferred, but validated surrogate end-points can also be used[225].

In addition, in 2007 AIFA adopted a method to evaluate the "innovativeness" of medicines, which includes an assessment of added therapeutic value[226]. While this assessment is the object of an on-going reform, it still provides an interesting example of the way in which ATV might be incorporated into the pricing and reimbursement process.

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[220] AIFA, *Gruppo di Lavoro dull'innovativitá dei farmaci, Criteri per l'attribuzione del grado di innovazione terapeutica dei nuovo farmaci, ed elementi per l'integrazione del dossier per l'ammissione alla rimborsabilitá*, 10 July 2007.

[221] Deliberation of CIPE No. 3/2001 of 1 February 2001.

[222] Ibid. Best Standard care is defined as the treatment used for the same indication in practice.

[223] Italian Stability Law 2015, Law 190, 23 December 2014, art. 585.

[224] Kleijnen, S. et al, July 2011, *Relative Effectiveness Assessment (REA) of Pharmaceuticals, background review*, p. LXIX.

[225] Ibid, p. LXXVIII.

[226] AIFA, 2007, *Gruppo di Lavoro dull'innovativitá dei farmaci, Criteri per l'attribuzione del grado di innovazione terapeutica dei nuovo farmaci, ed elementi per l'integrazione del dossier per l'ammissione alla rimborsabilitá*.

The prevalence and severity of the disease are considered as the starting point. Next, the availability of alternative treatments, the Added Therapeutic Value and the efficacy of the medicine are estimated. According to its composite score, the medicine can then be classified as:

- important innovation;
- moderate innovation;
- modest innovation;
- potential innovation.

Innovative medicines are included in the list of reimbursable medicinal products. Their Innovative medicines are included in the list of reimbursable medicinal products. The innovative medicines are immediately included in regional formularies and financed through a specific fund[227]. The Stability Law 2015 provided that the marketing authorisation holder of an innovative medicine with an annual sales revenues below EUR 300 million is not required to pay back any excess revenue not covered by the above-mentioned fund. Should its annual sales revenue be over EUR 300 million, the company will only need to reimburse 20 % of the excess revenue. The financial benefits last 36 months. Moreover, the Stability Law 2015 has introduced a 1 billion EUR fund for the acquisition by Regions of innovative medicines for years 2015 and 2016[228].

In addition, AIFA is also responsible for promoting non-profit clinical trials that aim to assess the added therapeutic value of new drugs compared to those already on the market[229]. These studies can be funded through part of the special fund mentioned above, which is subsidised by a 5 % tax on promotional expenses collected from pharmaceutical companies[230].

Health Technology Assessments

In Italy, the analysis of the medical, social, ethical and economic effects of medical products (Health Technology Assessment or HTA) is a relatively recent discipline and its uptake has not been uniform. Single hospitals, national authorities, and some regions, have been developing significant expertise, even though this is not always coupled with an explicit recognition of HTA's role.

Some regional authorities and hospitals have recently been using HTA as a tool to inform decisions in healthcare[231]. Nevertheless, AIFA remains in charge of the coordination of HTA activities[232] and is the main institution conducting regular assessments of medicines' Added Therapeutic Value as part of the authorisation, pricing and reimbursement of medicinal products.

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[227] See Law of 29 November 2007, n. 222, Law of 7 August 2012, n.135 as amended and Accordo Stato Regioni 18 November 2010.

[228] Italian Stability Law 2015, Law 190, 23 December 2014, art. 593-598.

[229] Lo Scalzo A. et al, 2009, Health Systems in Transition, Italy, Health system review, WHO European Observatory on Health Systems and Policies, Vol. 11, No. 6. Available at: http://www.euro.who.int/__data/assets/pdf_file/0006/87225/E93666.pdf.

[230] Legge 326/2003, Comma 18-19.

[231] Chiave, P., March 2012, *Health Technology Assessment a livello regionale: fra mito e realtá*, Quaderni di farmacoeconomia.

[232] Italian Stability Law 2015, Law no. 190, 23 December 2014, art. 588.

National guidance documents

The CIPE Deliberation n.3/2001 provided the criteria to be considered for pricing and reimbursement decisions and other requirements for the pricing and reimbursement submission. Updated guidelines on the type of information to be included in the pricing and reimbursement dossier are currently under development.

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Annex 3: In-depth country study: Austria

The Austrian health system is organised as a social insurance system. Residents in Austria with a regular income are subject to compulsory insurance, via health insurance funds or institutions. There are separate rules for the unemployed, children and pensioners[233].

Industrially produced medicines, so-called 'medical products'[234] can only be placed on the market after an authorisation by the Austrian Federal Office for Safety in Health Care *(Bundesamt für Sicherheit im Gesundheitswesen - BASG)*[235]*.* Exempted are:

- medical products that have already been authorised under the *centralized authorisation procedure* based on Regulation EC No. 726/2004 or Regulation EC No. 13994/2007;
- medical products that have been imported in compliance with the Drug Import Law (*Arzneimitteleinfuhrgesetz)*; and
- medical products that have been authorised under the Animal Diseases Act *(Tierseuchengesetz)*[236]*.*

During the national authorisation process, the Austrian Medicines and Medical Devices Agency (*BASG/AGES Medizinmarktaufsicht)* controls the efficacy, safety and quality of the medical product[237].

Market authorisation

The Austrian Federal Office for Safety in Health Care *(Bundesamt für Sicherheit im Gesundheitswesen - BASG)* and the Austrian Medicines and Medical Devices Agency (together referred to as: *BASG/AGES Medizinmarktaufsicht)* which are part of the Austrian Agency for Health and Nutrition Safety *(Österreichische Agentur für Gesundheit und Ernährungssicherheit – AGES),* are responsible for the market authorisation, and for the control of medicines that are already on the market. *BASG/AGES Medizinmarktaufsicht* oversees the effectiveness, potential side effects, the production, the transport and the storage of the medicines.

As mentioned above, during the national authorisation process *BASG/AGES Medizinmarktaufsicht* controls for the same criteria as those required for the EU centralised procedure: efficacy, safety and quality of the medicine[238].

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[233] Centre fédéral d'expertise des soins de santé (2010) 'The systems of reimbursement of medicines : international comparison and recommendations for decision-makers' *(Les systèmes de remboursement des médicaments : comparaison internationale et recommendations aux décideurs)*, KCE reports 147B, p.68.

[234] 'Medical products' *(Arzneispezialität)* are medicines that 'are always prepared in advance in the same composition and placed on the market under always the same name in a form specific for the delivery to the consumer or user, as well as medicines for sale to consumers or users who are otherwise manufactured industrially or that are produced commercially.' (§ 1 (5) Pharmaceutical Drug Law *(Arzneimittelgesetz)*).

[235] § 7 (1) Pharmaceutical Drug Law *(Arzneimittelgesetz).*

[236] ibid.

[237] Portal of the Austrian Federal Office for Safety in Health Care/ Austrian Medicines and Medical Devices Agency 'Medicines', http://www.basg.gv.at/en/medicines/ , date of access: 16/04.

[238] Portal of the Austrian Federal Office for Safety in Health Care/ Austrian Medicines and Medical Devices Agency 'Medicines', http://www.basg.gv.at/en/medicines/ , date of access: 16/04.

A medical product has to have an adequate benefit-risk profile in order to be authorised. This must be proved by the applicant, who has to submit 'clinical studies or other robust data which show the effects, side effects and other characteristics of the substance and of the medicine as a whole in the body'[239]. A medical product will only be authorised if the benefits exceed the risks[240].

An authorisation is initially granted for five years.

The question whether a medical product is innovative, i.e. has an added therapeutic value, only plays a role in the reimbursement procedure (see next section).

Pricing and reimbursement

Pricing

Pricing occurs through the Price Control Commission (Preiskommission) within the Ministry of Health. The ex-factory price can be set by the selling company itself. However, for patented medicines that are supposed to be added to the Reimbursement Code (see below), the price is calculated based on the EU average price. The Preiskommission calculates an average price based on prices in other EU Member States. The Preiskommission calculates the price on the basis of indications by the selling enterprise, taking into account estimations by Gesundheit Österreich GmbH – GÖG, a national research and planning institute for health care.

For medicines in the red box (see below), the price must not be higher than the EU average price. If the EU average price cannot be determined, the price indicated by the enterprise shall be used preliminarily, but the price has to be re-evaluated every six months by the *Preiskommission*[241]. For medicines where a generic is available, the price of the original product has to be reduced after six months as soon as a chemically identical product is added to the Reimbursement Code, the price of which must be at least 48 % below the price of the original[242].

Austria applies prescription fees for outpatient drugs, meaning that patients have to pay a deductible per-drug package[243].

Reimbursement

The costs for a medicine will only be reimbursed if an enterprise applies for a medical product to be added to the Reimbursement Code of the Social Insurance *(Erstattungskodex*

[239] Public Health Portal Austria, 'Safe medicines: authorize, test and control' *(Sichere Arzneimittel: zulassen, pruefen, kontrollieren),* https://www.gesundheit.gv.at/Portal.Node/ghp/public/content/Sicherer_Arzneimittel_in_Oesterreich_HK.html , date of access: 16/04.

[240] Portal of the Austrian Federal Office for Safety in Health Care/ Austrian Medicines and Medical Devices Agency 'Medicines', http://www.basg.gv.at/en/medicines/ , date of access: 16/04.

[241] ASVG, Abschnitt V Erstattungskodex § 351c. (7).

[242] Public Health Portal 'Pricing of medicines' *(So kommt ein Arzneimittel zu seinem Preis),* https://www.gesundheit.gv.at/Portal.Node/ghp/public/content/SokommtArzneimittelzuPreis_HK.html , accessed on: 20/04.

[243] Centre fédéral d'expertise des soins de santé (2010) 'The systems of reimbursement of medicines : international comparison and recommendations for decision-makers' (Les systèmes de remboursement des médicaments : comparaison internationale et recommendations aux décideurs), KCE reports 147B.

– *EK)*.Medical products that have a therapeutic effect and a value for patients in treating diseases can be added to this Code[244].

Within the Reimbursement Code, a medical product is assigned one of three categories: a red box, a yellow box or a green box (see Table 4)

The assignment of a medical product to one of these boxes mainly depends on its medical and the economic effect (added therapeutic value and price), which is verified by the Pharmaceutical Evaluation Board *(Heilmittel-Evaluierungs-Kommission - HEK).*

Table 4: Description of classification of medical products within the Reimbursement Code[245]

REIMBURSEMENT CODE		
	Conditions	Reimbursement
RED BOX (preliminary permission, up to 180 days)	Medical products that are new to the Austrian market and for which an application into the Reimbursement Code has been filed	Reimbursable only if approved by the chief-and control medical service of the Social Insurance Association; These medicines may be reimbursed at the EU average price
YELLOW BOX	Medical products that have a significant added therapeutic value, and which are not included in the green area due to medical or health-economic reasons	**Dark yellow box:** Reimbursable only if approved by the chief-and control medical service of the Social Insurance Association **Light yellow box:** can also be reimbursed if the prescribing physician documents that the prescription is in accordance with the medicine's use These medicines may be reimbursed up to the EU average price.
GREEN BOX	Medical products with the same or a similar therapeutic effect compared to medicines that are already in the green area, AND a sufficient price difference to those If the new medical product has a higher price than the comparable product, it has to have an added therapeutic value	These medical products do not have to be approved by the chief-and control medical service of the Social Insurance Association

[244] ASVG, § 31 (12).

[245] ASVG, § 31 (12), and Association of the Pharmaceutical Industry *(Verband der pharmazeutischen Industrie)* http://www.pharmig.at/DE/Infothek/Rund%20um%20das%20Gesundheitssystem/Erstattungssystem/Erstattungssystem+in+%C3%96sterreich.aspx.

NO BOX	1) Negative list: not accepted to Reimbursement Code; reimbursement extremely limited 2) Not listed in the Reimbursement Code, but reimbursable in certain cases	Prior authorisation possible

Bodies included in the Reimbursement Procedure and their duties (see also Figure 5).

Figure 5Federation of Austrian Social Insurance Institutions (*Hauptverband der Sozialversicherungsträger - HVB*):

- has to decide within 90 days (if there is already a price) or 180 days (if there is no price) whether a medical product can be forwarded to either the yellow or green box;
- has to regularly check the Reimbursement Code to ensure that the listed medicines still correspond to the relevant criteria. It can move or delete medicines from the Code if the conditions are not or no longer met, especially because due to new pharmacological or medical-therapeutic or health economic circumstances.

Pharmaceutical Evaluation Board (*Heilmittel-Evaluierungs-Kommission - HEK*)[246]*:*

- has to screen all requests for inclusion in the Reimbursement Code to determine whether or not they have a significant added therapeutic value, and how this can be assessed economically;
- provides suggestions to the Federation of Austrian Social Insurance Institutions (see below);
- advises the Federation as to which medical needs and epidemiological necessities a medical agreement of the Chief and Medical control service should be applied.

Chief-and Control Medical Service of the Social Insurance Institutions *(chef-und kontrollärztlicher Dienst der Sozialversicherungsträger):*

- Have to approve reimbursement of medical products ex-ante, or control the use ex-post in the no, red, and yellow boxes.

Medical and economical assessment for inclusion/categorisation in the Reimbursement Code:

The enterprise submitting the request to have its medical product listed in the Reimbursement Code has to submit pharmacological, medical-therapeutic, and health-economical documents which will be taken into account during the assessment[247]. On the basis of these, the Pharmaceutical Evaluation Board has to assess:

1. 'if, and for which indications and groups of patients, a significant added therapeutic value of a medicine could be found, and how this can be assessed economically, so that the medicine can be moved to, or stay in, the yellow area;
2. if a therapeutic added value (added value for patients) of a medicine could be found, and how this can be assessed economically, so that a medicine can be moved to or stay in the green area.'

Furthermore, the Commission has to advise the Federation of Social Insurances:

[246] The Pharmaceutical Evaluation Board is an independent advisory body to the Federation of Social Insurances. See: Mandlz, Gregor 'Arbeitsbehelf Erstattungskodex' https://www.sozialversicherung.at/portal27/portal/esvportal/content/contentWindow?&contentid=10008.555012&action=b&cacheability=PAGE.

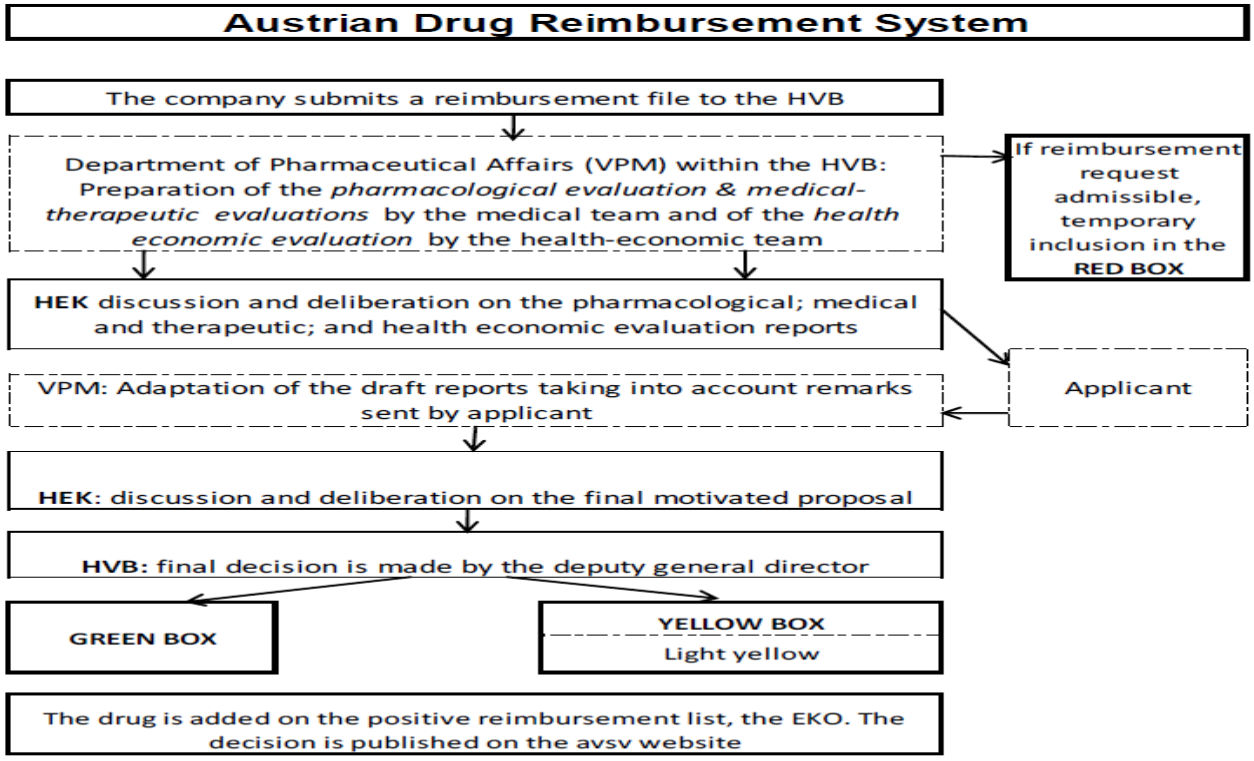
[247] ASVG, § 351c. (3).

3. 'if a tendering procedure for substances or groups of substances shall be introduced, in order to reach cheaper conditions for the reimbursement of the medicine'[248].

Figure 5 illustrates the reimbursement procedure:

[248] ASVG, § 351 g. (2).

Figure 5: Actors involved in the Austrian Drug Reimbursement and their functions



Abbreviations: VPM: Department of Pharmaceutical Affairs/ *Abteilung Vertragspartner Medikamente*; HVB: Main association of Austrian Social Security/ *Hauptverband der Östereichischen*; HEK: Pharmaceutical Evaluation Board/*Heilmittel-Evaluierungskommission*; EKO: Reimbursement Code/ *Erstattungskodex*; AVSV: Official Journal of Austrian Social Security/ *Amtliche Verlautbarung der österreichischen Sozialversicherung*

Source: Centre fédéral d'expertise des soins de santé (2010) 'The systems of reimbursement of medicines : international comparison and recommendations for decision-makers' (Les systèmes de remboursement des médicaments : comparaison internationale et recommendations aux décideurs), KCE reports 147B

Assessment of added therapeutic value

The procedure for medical products to be included in the Reimbursement Code is regulated by the Regulation of the Reimbursement Code *(Verordnung Erstattungskodex)*, published by the Federation of Social Insurances. Accordingly, the assessment whether a medical product should be included in the yellow or green boxes of the Reimbursement Code is based on three successive evaluations: the pharmacological, the medical and therapeutic, and the health-economic evaluation.

Types of assessment:

Pharmacological assessment

- Defines possible comparators (i.e., the medical product which is already listed in the EKO and has the same dosage with which the new medical product will be compared); usually comparators are chosen with the same ATC level that are already in the same box (green or yellow).

- Measures the *degree of innovation* of the new medical product on an *eight-point scale*. The lowest degree of innovation (degree 1) means that the new medical product has "the same substance, the same strength of substance, and the same or similar pharmaceutical form" as the comparable medical product. The highest degree of innovation (degree 8) is assigned when the new medical product "allows treating an illness for the first time"[249].

Medical-therapeutic evaluation

- Defines patient groups that can potentially be treated with the new medical product.
- Defines the therapeutic benefit in comparison with other alternatives.
- Defines the level of effectiveness and the level of evidence the data must contain if pharma-economic studies are submitted by the applicant to examine the cost-benefit ratio (see section below on "health-economic evaluation").

The medical product is to be assigned to one of *six groups*, depending on *whether it has an added therapeutic value at all*; whether it has a *significant added therapeutic value*; whether it has an added or significant added therapeutic value for the majority or only a sub-group of patients[250].

Validity of evidence for the medical-therapeutic evaluation is assessed according to six types of evidence. The first group (prospective, double-blind, randomised-control studies representing a large population, or meta-studies of such studies) are assigned the highest level of validity. They are followed (in descending order) by 2. systematic reviews; 3. randomised-control studies with less data; 4. Non-randomised and uncontrolled studies; 5. consensus judgements of an expert committee; 6. statements of experts.

Health-economic evaluation

This type of evaluation assesses the cost-effectiveness of the new medical product, based on the medical-therapeutic evaluation. It takes into account the direct costs of the healthcare system (expenditures for medical treatment, such as physician aid, medicines, medical aids) and of the institutional care, as well as measures of rehabilitation. Potential costs carried by patients are not taken into account.

Cost-effectiveness is essentially judged as a ratio between the added therapeutic value and the price of a medical product or the costs of treatment with this medical product. For medical products to be added to the green box, the ratio has to be "better" than comparable medical products in the green box. This means that it either has to be cheaper than a comparable medical product, or it has to have an added therapeutic value. Furthermore, the price for medical products of all groups has to be below the EU average if the medical product is to be added to the green group[251]. The HEK publishes some objective and verifiable economic criteria that have to be met so that medical products may be added to

[249] VO-EKO § 23. (2); for a definition of all scale points, see the respective paragraph in the legislation.

[250] VO-EKO § 24. (2); for a full description of the six groups, see also: Centre fédéral d'expertise des soins de santé (2010), p. 77.

[251] VO-EKO § 25. (2).

the green or yellow boxes. A document published by the HVB lists these criteria, along with the main legislation on the distribution of reimbursable medical products[252].

The same principle applies for medical products to be added to the yellow group. However, if there is no comparable medical product already in existence, a positive cost-benefit-ratio for a group of patients needs to be proven. The applicant needs to provide a pharma-economic study to prove the economic benefit[253].

For medical products with an important added therapeutic benefit, there is no threshold for the incremental costs.

Comparison with other products: Regarding all three types of evaluations, the applicant has to provide a comparison with available therapeutic alternatives, taking into account the most frequent indication, the most appropriate medical dose, and the most affected groups of patients.

Sources/data: The documents provided by the applicant have to correspond to the most up-to-date research. Only data published in peer-reviewed journals or in evaluations of independent institutes and authorities shall be taken into account, unless otherwise specified[254].

Bodies involved: The *applicant* has to submit, together with its application to the HVB**,** a number of documents for the pharmacological, the medical therapeutic, and the health economic evaluations. The documents to be provided are listed in an Annex to the Regulation on the Reimbursement Code. The HEK has to check all applications for uptake and applications for changes.

Assessment of the economic aspects of medicinal products

Health-economic evaluations are conducted when new medical products are proposed to be added to the Reimbursement Code.

National guidance documents

The procedure of acceptance of a medical product into the Reimbursement Code is subject to a general rule – the *'Verfahrensordnung Erstattungskodex – VO EKO'* - established by the HVB, and has to be approved by the Ministry of Health and Women. The Austrian Chamber of Commerce has to be heard before it is published.

'This rule of procedure regulates the amount, quality, form and point in time of the documents that have to be provided by the applicant and has to include rules in which cases further studies are necessary.' (ASVG, § 351g. (1))

This *rule of procedure* is published on the website of the HVB.

Furthermore, the HVB publishes the Reimbursement Code itself, which is updated once a month. There is also an online *information tool for the Reimbursement Code* (published on

[252] Mandlz, Gregor (2015) 'Working Guide Reimbursement Code' *(Arbeitsbehelf Erstattungskodex),* HVB, available at: https://www.sozialversicherung.at/portal27/portal/esvportal/content/contentWindow?&contentid=10008.555012&action=b&cacheability=PAGE.

[253] VO-EKO § 25. (3).

[254] VO-EKO § 22. (2)**.**

the website of the HVB), where visitors can search for information on medicines that are in the yellow or green box, and therapeutic alternatives. This information tool is also available for Smartphones and Tablets (Application EKO2go).

In 2012, a *Handbook on Methods for HTA* was published on behalf of the Ministry of Health. It explains, in general terms, how to conduct an HTA, what the products are, how to gather and analyse data, how to assess and synthesise medical studies and how to carry out an economic assessment[255].

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- Mandlz, G., 2015, Working Guide Reimbursement Code *(Arbeitsbehelf Erstattungskodex),* HVB, available at: https://www.sozialversicherung.at/portal27/portal/esvportal/content/contentWindow?&contentid=10008.555012&action=b&cacheability=PAGE.

Webpages

- Portal of the Austrian Federal Office for Safety in Healthcare/ Austrian Medicines and Medical Devices Agency, http://www.basg.gv.at.
- Public Health Portal Austria, https://www.gesundheit.gv.at.
- Website of the Association of the Pharmaceutical Industry, www.pharmig.at.

[255] Gesundheit Österreich (2012) 'Method Handbook for Health Technology Assessment – preliminary version 1.2012' *(Methodenhandbuch für Health Technology Assessment Vorab-Version 1.2012)* , on behalf of the Ministry of Health, available at: http://www.goeg.at/de/Bereich/HTA-Methoden-und-Prozesse.html.

Annex 4: In-depth country study: Poland

The Polish health insurance system is a public system managed by the National Health Fund (Narodowy Fundusz Zdrowia). Public health insurance is compulsory for employers and workers and can be complemented with private health insurance. The system of private health insurance is not formally regulated, the prices are high and consequently, this system covers only a small percentage of the population (about 2 % - but the market for private health insurance in Poland is growing[256]).

Placing a new medicine on the market requires, in the first instance, market authorisation - at this point the medicine is available at full cost. Secondly, the decision on pricing and possible (partial) reimbursement must be taken. Market authorisation for medicines other than those approved by the European Medicines Agency (EMA) is carried out by the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych).

The decision on pricing and reimbursement is taken by the Ministry of Health. When the active substance of the product has not been covered by the reimbursement yet, a full set of HTA analysis is compulsory for an assessment and recommendation of the Agency for Health Technology Assessment and Tariff System (Agencja Oceny Technologii Medycznych I Taryfikacji, AOTMiT). Following this, price negotiations between the Ministry of Health and the applicant are undertaken. For products for which the active substance is already reimbursed, only a Budget Impact Analysis is compulsory and the decision is made without the involvement of AOTMiT.

Market authorisation

Market authorisation is granted on the basis of the centralised procedure carried out by the EMA, or on the basis of the procedures implemented by the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. This Office implements the mutual recognition procedure, the decentralised procedure and the national procedure. Both the mutual recognition and the decentralised procedures are based on the recognition by national competent authorities of a first assessment performed by the authorities of another Member State. The National procedure is carried out within the timeframe set out in the Act on Pharmaceuticals at 210 days, and involves the following steps:

- submission of the application form and documentation,
- validation (no longer than 30 days),
- assessment of the documentation
    - Pharmaceutical
    - Preclinical
    - Clinical
- review of the summary of project characteristics, labelling, leaflet,
- granting the authorisation.

[256] http://wyborcza.biz/biznes/1,101562,14238681,Z_prywatnych_ubezpieczen_zdrowotnych_korzysta_w_Polsce.html.

The applicant must attach the results of clinical and non-clinical trials to the application. The Office for Registration can request additional studies to be performed by an independent institution, as indicated in the ordinance of the Ministry of Health[257] prior to the market authorisation. In order to be granted market authorisation, the medicine should be characterised with a certain ratio of clinical efficacy to safety. This ratio does not have to be better than the same indicator for other products in the market – it is sufficient if it is not worse (as proved in the non-inferiority study). Standard market authorisation is issued for five years, after which time the applicant can apply for an (unlimited) extension. Only after the procedure of market authorisation is completed, can the applicant apply for price reimbursement.

Pricing and reimbursement

Two main legislative acts govern the area of pricing and reimbursement procedures, the Act on Healthcare Benefits[258] and the Act on Reimbursement[259]. These provide for several possible paths of evaluation.

The Act on Healthcare Benefits allows for the qualifying, or the removal, of a medicine from the list of reimbursed products, as follows:

- qualification to the basket of guaranteed services (Art. 31c); and
- removal or change of the method of financing of the guaranteed service (Art. 31e).
  The Act on Reimbursement indicates the following instances to qualify/remove a medicine from the list of reimbursed products:
- application path (art. 35, including provision of the HTA by the applicant and the verification analysis by the AOTMiT260. See Figure 1, below);
- issuing statements regarding the legitimacy of refunding of medicines not registered in Poland, financed on the basis of the consent for an individual patient (Art. 39; HTA is, in this case, not obligatory. However, the Minister of Health uses it when there are many requests regarding a specific, expensive medicine).

All of the instances listed above result in the issuing of a recommendation by the President of the Agency following the statement of the Transparency Council on the basis of HTA.

The Act on Reimbursement also incorporates the following tasks for the Transparency Council:

- issuing opinions on financing medicines in the indications which are not registered for market use (in "off-label indications", Art. 40);
- issuing opinions on the establishment of limit groups (Art. 15); and
- issuing opinions on the removal of a refunded medicine from the list. (Art. 33).

[257] Art. 8 paragraph 1a item 3 and Art. 22 of the Act on Pharmaceuticals, O.J. 26 position 1381 of 2001.

[258] Act of 27 August 2004 on healthcare benefits financed from public funds, O.J. 164 item 1027 of 2008.

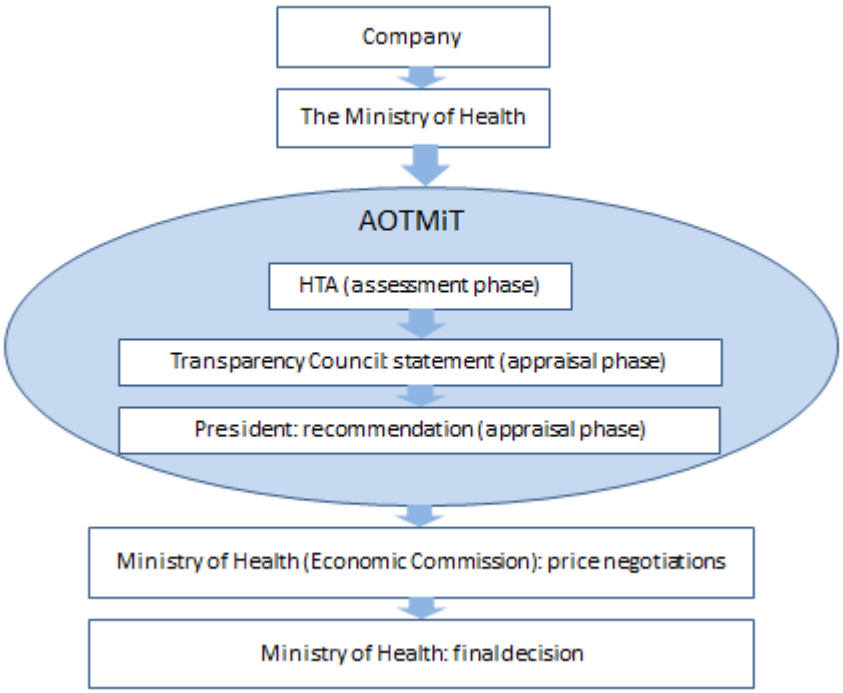
[259] Act of 12 May 2011 on reimbursement of medicines, consumption goods for special use and medicinal products, O.J 122 item 696 of 2011 with later amendments.

[260] Further in this document AOTMiT is referred to as 'the Agency'.

The Council can issue such opinions without carrying out the HTA. The Minister of Health or the President of the AOTMiT may, at the same time, order the preparation of such an analysis (under Art. 31n paragraph. 5). In these instances the opinion of the President is not required. It should be noted that the status of an opinion is weaker than the status of a statement.

Figure 6 presents the decision-making process regarding pricing and reimbursement of medicinal products in Poland, following the application path (Art. 35 of the Act on Reimbursement).

Figure 6: Decision making process regarding pricing and reimbursement of medicines in Poland based on the application path



Source: own elaboration based on information received from Anna Zawada, AOTMiT.

As visible in the Figure above, the decision on pricing and reimbursement is ultimately taken by the Minister of Health, after receiving a recommendation from the President of AOTMiT. The recommendation is based on *appraisal* which builds on the stage of *assessment*[261]. The appraisal, in addition to the clinical effectiveness analysis, cost-effectiveness analysis and budget impact analysis carried out during the assessment stage, includes the organisational, ethical and social aspects of using a given medical technology. The appraisal stage adds normative statements on the top of the objective analysis conducted at the assessment phase. The appraisal is carried out in Poland by the Transparency Council and

[261] The term 'Added Therapeutic Value' is not used in Poland, the analysis of clinical effectiveness included in the HTA is probably the nearest in scope to the ATV.

the President of the Agency. The applicant submits the application to the Ministry of Health, which subsequently transfers it to the Agency and requests the appropriate assessment.

The content of the statement of the Transparency Council (for the application path) is set out in Art. 31s of the Act on Healthcare Benefits, while the content of the recommendation of the President of the AOTMiT is set out in Art. 35 of the Act on Reimbursement. These documents must contain a recommendation on whether or not the medical product should be reimbursed, the suggested level of reimbursement comments related to the drug programme design and risk-sharing instrument, if applicable. The recommendation should be justified by the conclusions from the analysis of the clinical and economic aspects, it should indicate alternative technologies used in a given clinical state, and discuss reimbursement recommendations from other countries. It must also refer to the threshold price and to the comparison with the medicinal products which are currently refunded.

The final decision on pricing and reimbursement is taken after negotiations between the applicant and the Economic Commission of the Ministry of Health. The Agency is not routinely informed by the Ministry about the decisions taken regarding the medicinal products which have been assessed by the Agency. Analysis of data regarding the application path reveals that between January 2014 and March 2015, the Agency received 137 applications for reimbursement of medicinal products. 118 of these applications have been assessed, with the following recommendations of the President: 69 positive, 32 negative, and 17 conditional[262].

The decision on pricing and reimbursement taken for the first time for a given medicine is valid for two years (second and third positive decisions may be issued for three and five years, respectively; Art. 11 p. 3 of the Act on Reimbursement). With respect to medicinal products which were already on the list of the products covered with (partial) reimbursement, the duration of the validity of the decision depends on the previous period of coverage.

The following sections provide more detail about the methodology of the assessment carried out by the Agency.

Health technology assessment

The Agency carries out an independent health technology assessment which feeds into the statements of the Transparency Council and the recommendations of the President of the Agency. These statements and recommendations are ultimately used by the Minister of Health when taking a decision on reimbursement. The scope of analysis depends on the regulatory path. The conditions for placing products on the reimbursement list are the same for drugs, nutritional products of special use, and medical devices, also for so-called orphan drugs[263].

In the application path, the analysis carried out by the Agency includes the following elements:

- clinical effectiveness assessment, and
- economic assessment, including cost-effectiveness assessment and impact on the budget of the payer and of the health system.

[262] Information based on AOTMiT website: http://www.aotm.gov.pl/bip/.

[263] Drugs which have been developed specifically to treat a rare medical condition.

This assessment is carried out within the statutory deadline of 60 days following an order of the Minister of Health. The application is submitted to the Ministry of Health, which subsequently transfers it to the Agency in order to receive its recommendation.

After issuing the statement of the Transparency Council and the recommendation of the President of the Agency, the analyses are published on the Agency's website[264]. The analysis of the Agency, together with the analyses provided by the applicant, are published at least 7 days before issuing the statement/recommendation in order to give the public an opportunity to comment on them.

***Assessment methodology*[265]**

In general, the assessment follows the methodology described in the Guidelines for conducting health technology assessment (HTA)[266]. However, from January 1st 2012 it should also be in line with the Act on Reimbursement, which sets out some further details and additional requirements.

The assessment in case of the verification process begins with checking whether the documentation submitted by the applicant meets the minimum requirements enshrined in the relevant Regulation of the Minister of Health[267]. This Regulation lays down the rules corresponding to the internationally-recognised methodology for assessing medical technologies, adapted to the requirements of Polish legislation (the Act on Healthcare Benefits and the Act on Reimbursement). The Regulation, to some extent, transposes the HTA Guidelines into Polish law. While the strong legal basis can be seen as an advantage, the accompanying lack of flexibility within the rules can be perceived as a disadvantage. Fulfilment of the methodological requirement depends on, among other things, the availability of relevant data.

In case of any deviations from the minimum requirements, the Minister of Health (based on the statement prepared by the Agency) asks for additional information to supplement the analysis, for which the applicant has usually 14 days. This waiting time is added to the statutory 60-day evaluation period.

The elements verified in the evaluation process include analytical search strategies, selection of comparators, evidence from clinical studies, correctness of the synthesis of the results including calculations and qualitative summaries, timeliness of costs and other assumptions adopted in the calculations, and adequacy of the model used in the economic analysis. Correctness of the estimated results is checked using the calculators attached to the analyses, as well as in-house tools. In addition, a summary is made of the following elements:

- the clinical guidelines (preferably on the basis of a systematic review principle),
- the reimbursement recommendations issued by foreign HTA agencies and the conditions for refunds in other countries.

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[264] http://www.aotm.gov.pl/bip.

[265] This section draws extensively on: Zawada, A. & Andrzejczyk, L., Rola oceny technologii medycznych w refundacji leków w Polsce (article in Polish), Zdrowie Publiczne i Zarządzanie 2013; 11(1): 28-34.

[266] http://www.aotm.gov.pl/www/index.php?id=765.

[267] The Regulation of the Minister of health of 2 April 2012 regarding minimum requirements which have to be fulfilled by the analyses included in the applications for coverage of medicines, medicinal products and nutritional products of special use with reimbursement and for setting their official prices or increasing their official prices, O.J. 12 position 388 of 2012.

In addition, medical experts' opinions are included in the assessment process as well as, where possible, the opinions of the representatives of the patients' organisations who are invited to present their views.

It should be noted that the assessment is carried out in order to provide the information necessary for taking the reimbursement decisions at the Ministry of Health. According to the Act on Reimbursement, the selection of comparators must reflect the technologies that are currently reimbursed. This is a significant methodological limitation in cases where the randomised clinical trials compare a given medical product to products which are not refundable in Poland. In such situations, indirect comparisons should be made with the refundable technologies. If the clinical analysis does not include randomised trials which would prove higher effectiveness of the medical technology under assessment, as compared to other medical technologies (which have so far been reimbursed), the applicant must meet the requirements described in Art. 13 paragraph 3 of the Act on Reimbursement: "the official sales price of the medicine must be calculated in such a way that the cost of using it [...] is not higher than the cost of medical technology [...] financed from public funds so far with the best ratio of therapeutic outcomes to their costs (CER - Cost Effectiveness Ratio)."

The link between the reimbursement recommendation and the REA outcome has been analysed for Poland[268]; a positive recommendation was strongly affected by the clinical effectiveness and a negative recommendation had the strongest correlation with safety issues. Both factors contributed most to the final recommendations.

Assessment of the economic aspects of medicinal products

Assessment of the economic aspects is carried out in two stages: 1) cost-effectiveness analysis and 2) impact on the payer's budget.

Cost-effectiveness is calculated according to the HTA guidelines using the Incremental Cost-Utility Ratio (ICUR), which is calculated as the ratio of the additional costs to the quality adjusted life years (QALY) gained, with the current (reimbursed) clinical practice set as the baseline. When data to calculate ICUR are missing, an alternative indicator can be used, the Incremental Cost-Effectiveness Ratio (ICER), which is the ratio of the incremental cost to the incremental clinical effects of the new medical technology. Clinical effects needed to calculate ICER should be estimated in terms of life years gained (LYG). According to Polish law, if the cost-effectiveness indicator for the clinical effects expressed as QALY or LYG (i.e. ICUR or ICER, respectively) does not exceed 3 x Gross Domestic Product (GDP) per capita, the technology is cost-effective and eligible for refund (subject to the approval of total costs).

In the case of medicinal products which do not pass this cost-effectiveness test, a so-called "threshold price" is estimated (the price setting ICUR/ICER at the level of 3xGDP per capita threshold), which sets the base for negotiations with the Economic Commission.

The total increase in expenditure in case of adoption of the new technology for refund is calculated in order to assess the budgetary impact.

[268] Niewada, M., ISPOR annual European Congress 2011, Madrid.

The final adoption of the refund depends on the acceptability of these estimates. The applicant can improve the ICER by offering a confidential "risk-sharing" agreement and proposing a lower implicit price. The final price and risk-sharing instruments are negotiated with the Economic Commission at the Ministry of Health.

Quick procedure

Because of the limited resources of the Agency, often the procedure of Rapid Assessment is used. Within this procedure, the assessment is limited to the aspects listed below:

- description of the medical problem and the method of use of the technology being assessed;
- characteristics of the evaluated technology;
- characteristics of comparators;
- assessment of its clinical effectiveness;
- assessment of its safety;
- clinical guidelines and reimbursement recommendations from other countries regarding the evaluated technology;
- estimation of the impact on the budget of public payer and reimbursement status in other countries, with special focus on the countries with GDP per capita level similar to the Polish one (where such data are available).

National guidance documents and transparency issues

The assessments of new medicinal products are made publicly available, as the Agency publishes both the recommendations of the President and the statements of the Transparency Council, as well as the protocols of the Council gatherings. All these documents should be published with respect to the regulations related to confidentiality of both personal and corporate information[269],[270]. The Agency also published the HTA guidelines in 2009[271]. However, as already noted above, from April 2012 these guidelines must take into account the scope set out by the Ordinance of the Minister of Health[272]. Every other month the Ministry of Health publishes the lists of the medicinal products which are approved for reimbursement[273] .

Additional information: Patient co-payment limits

Prices and mark-ups for the medicinal products in Poland are fixed (with the mark-up rates decreasing as the price increases). Prices of medicines are negotiated between the Ministry of Health and the manufacturers. Medicines eligible for reimbursement have designated limits of reimbursement, set by "limit-groups". In each group there is a medicine whose cost

[269] The Act of 29 August 1997 on the protection of personal data, O.J. No. 133 iten 883 of 1997.

[270] Act of 16 April 1993 on combating unfair competition, O.J. No. 47 item 211 of 1993.

[271] Guidelines for conducting Health Technology Assessment (HTA), Warsaw, April 2009, http://www.aotm.gov pl/www/index.php?id=765.

[272] Ordinance of the Minister of Health of 2 April 2012 on the minimum requirements to be satisfied by the analyses accounted for in the applications for reimbursement and setting the official sales price and for increasing the official sales price of a medicine, a special purpose dietary supplement, a medical device, which do not have a reimbursed counterpart in a given indication, O.J. No. 388 of 2012.

[273] http://www.mz.gov.pl/leki/refundacja/lista-lekow-refundowanych-obwieszczenia-ministra-zdrowia..

determines the limit, as set out in the Act on Reimbursement[274]. Thus patients' co-payment falls into one of the following categories:

- Free-of-charge. This group includes medicines and medical devices whose effectiveness is proven in the treatment of malignant disease, psychotic disorders, mental retardation, developmental disorders, or infectious disease with high epidemic specific risk for the population. These medicines are primarily used in hospital treatments.
- Flat fee. This group includes:

a) the medicines and medical devices requiring, according to current medical knowledge, usage lasting more than 30 days and with the cost for the beneficiaries in case of 30 % of patient co-payment exceeding 5 % of the minimum wage as published in a notice of the Prime Minister, or

b) the medicines and medical devices requiring, according to current medical knowledge, usage lasting not more than 30 days and with the cost for the beneficiaries in case of 50 % of patient co-payment exceeding 30 % of the minimum wage as published in a notice of the Prime Minister.

If the price of the medicine is equal to, or lower than, the reimbursement limit (flat fee), the patient pays the flat fee (currently 3.20 PLN) per pack containing not more than 30 DDD, or the amount proportionately greater for packages containing more than 30 DDD. Conversely, if the retail price of the medicine is higher than the flat fee, the patient will pay the flat fee plus the difference between the retail price of the medicine and the reimbursement limit.
If the retail price of the medicine is lower than the value of the flat fee (3.20 PLN), the patient pays the retail price of the medicine.

- 50 % patient co-payment. This group includes medicines, foodstuffs intended for particular nutritional use, and medical devices, which - according to current medical knowledge - require treatment lasting not more than 30 days. If the price of the medicine is equal to, or lower than, the reimbursement limit, the patient will pay half of the retail price of the medicine. Where the price is higher than the reimbursement limit, the patient will have to pay, in addition to the above, the difference between the retail price of the medicine and the reimbursement limit.
- 30 % patient co-payment. This group includes medicines, foodstuffs intended for particular nutritional use, and medical devices that are not eligible for the above categories. If the price of the medicine is equal to, or lower than, the reimbursement limit, the patient will pay 30 % of the retail price of the medicine. Where the price is higher than the reimbursement limit, the patient will have to pay, in addition to the above, the difference between the retail price of the medicine and the reimbursement limit.

[274] Art. 6 of the Act on reimbursement of medicines, consumption goods for special use and medicinal products, O.J 122 position 696 of 2011 with later amendments.

Annex 5: In-depth country study: Slovakia

The Slovak **healthcare system** is based on universal coverage, compulsory health insurance, a basic benefit package and a competitive insurance model with selective contracting and flexible pricing. Healthcare, with some exceptions, is provided to those insured, free at the point of service as benefit-in-kind (paid for by a third party). Health insurance companies operate under private law and are obliged to ensure accessible healthcare to those they insure through healthcare providers. The Health Care Surveillance Authority (HCSA) is responsible for monitoring health insurance, healthcare provision and the healthcare purchasing markets[275].

Before new medicinal products can enter the market in Slovakia, they must first receive **market authorisation** by either the European Medicines Agency (EMA) or the State Institute for Drug Control (SIDC). The SIDC is the national competent body responsible for monitoring the safety of medicines in Slovakia, including reporting on adverse effects that apply to patients, pharmacists and nurses, and on the pharmaceutical quality[276]. Once market authorisation has been granted, **reimbursement** by the health insurance is decided by the 'Categorisation Committee' of the Ministry of Health. This decision is based on an assessment referred to as the 'categorisation process of pharmaceuticals'. This process involves an assessment of the medicine's effectiveness and safety, as well as a pharmaco-economic analysis.

Health Technology Assessments (*Hodnotenie Zdravotníckych Technológií*) are still a relatively recent concept in Slovakia and the country is in its early stages regarding the implementation of such assessments. In 2012, the Working group for Pharmaco-economics, Clinical Outcomes and Health Technology Assessment of the Slovak Ministry of Health, was established[277]. Members of the Working Group are responsible for the evaluation of pharmaco-economic dossiers submitted as part of the reimbursement application process and all aspects concerning health technology assessment.

The Working Group is representing the Slovak Republic in the EUnetHTA Joint Action, and a representative of the Working Group is also participating within the European HTA Network (Directive 2011/EU/24). The participation of Slovakia in the EUnetHTA Joint Action and the European HTA Network are likely to facilitate the dissemination of HTA activities and the use of HTA is starting to appear in decision-making processes in Slovakia[278].

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[275] European Observatory on Health Systems and Policies, Szalay, T. et al, Slovakia – Health system review, Health Systems in Transition Vol 13 No.2, 2011. Available at: http://www.euro.who.int/__data/assets/pdf_file/0004/140593/e94972.pdf (Accessed April 2015).

[276] Idem.

[277] MINISTERSTVO ZDRAVOTNÍCTVA SLOVENSKEJ REPUBLIKY, Štatút Odbornej pracovnej skupiny pre farmakoekonomiku, klinické výstupy a hodnotenie zdravotníckych technológií, VESTNÍK, Čiastka 35-38, Dňa 27. novembra 2012, Ročník 60.

[278] Webpage Mediweb: Aj lieky sú zdravotnícka technológia. V ich hodnotení sme aktívni, 17 January 2014, Available at: http://mediweb.hnonline.sk/spravy/aktualne/aj-lieky-su-zdravotnicka-technologia-v-ich-hodnoteni-sme-aktivni (Accessed April 2015).

Market authorisation

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Pricing and reimbursement

In Slovakia, a single application is filed for both the pricing and the reimbursement of medicinal products. In the following section the two processes are, however, described separately. The comparative data and information required for the assessments are provided by the pharmaceutical company who has produced the new medicine. This includes basic drug information (name, manufacturer, authorisation holder, pharmaceutical form, pack size and strength), evidence on its effectiveness, the standard therapeutic dose and the number of the standard therapeutic doses per pack. Applications also present the desired reimbursement rate, the proposed indication and any prescribing restrictions[280].

The explicit criteria that are being examined during the assessments of medicinal products are: efficacy, effectiveness, safety, quality of life, cost-effectiveness and budget impact. Implicit criteria include: ethical, equity and social issues, impact on vulnerable groups, and burden of illness. The final decision on whether or not the new medicinal product can enter the healthcare market is made by the Ministry of Health, and should be taken within 180 days.

Pricing of medicinal products

Slovakia has implemented a reference pricing system for medicinal products. This means that a maximum price is set for a standard daily dose in each specific reference group of medicinal products. All medicines included in such a reference group (5-digit Anatomical Therapeutic Chemical classification system (ATC)[281]) contain the same active substance per dose and are administered in the same form. For some therapeutic groups, internal reference pricing is extended to medicines that have the same molecular structure (4-digit ATC). This means that the actual reimbursement of products with different active ingredients is linked to the cheapest alternative in that specific 4-digit ATC category[282]. Changes in price for a specific medicinal product may thus influence the reimbursement of other medicines in the same reference group.

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[279] European Observatory on Health Systems and Policies, Szalay T. et al, 2011, Slovakia – Health system review, Health Systems in Transition Vol 13 No.2. Available at: http://www.euro.who.int/__data/assets/pdf_file/0004/140593/e94972.pdf (Accessed April 2015).

[280] Assoc. Prof. Tesar, T., 2012, Health Technology Assessment in reimbursement policy of the Slovak Republic, Journal of Health Policy & Outcomes Research, ISSN 2299-1247, DOI:10.7365/JHPOR.2012.1.5.

[281] WHO Collaborating Centre for Drug Statistics and Methodology, Structure and Principles of the Anatomical Therapeutic Chemical (ATC) classification system, available at: http://www.whocc.no/atc/structure_and_principles/ (accessed April 2015).

[282] Assoc. Prof. Tesar, T., 2012, Health Technology Assessment in reimbursement policy of the Slovak Republic, Journal of Health Policy & Outcomes Research, ISSN 2299-1247, DOI:10.7365/JHPOR.2012.1.5.

The prices of medicinal products that are covered by the social health insurance (SHI) are regulated both in the outpatient and inpatient sectors. After a medicine has obtained market authorisation, the 'maximum retail price' (ex-factory price) is determined by the Ministry of Health through external reference pricing. This price may not exceed the average of the three lowest prices of the same pharmaceutical sold across the EU. Prices of over-the-counter medicines and prescription medicines that are not covered by the health insurances have been deregulated[283].

This pricing system has raised the concern that the price levels of new medicines are thus adjusted to wealthier countries that might have a greater willingness to pay for the quality-adjusted life years gained[284].

Reimbursement of medicinal products

As described in the previous section, the **reimbursement** assessment, advice and decision of a new medicinal product is made by the Categorisation Committee of the Ministry of Health. This Committee consists of 11 members: three representatives from the Ministry of Health, five representatives of the health insurance companies, two representing the professional public, and one temporary expert, rotating according to the topic of discussion. The Committee is assisted by the medical board (assessing the effectiveness, safety and importance of the medicine) and the Working group for Pharmaco-economics, Clinical outcomes and Health technology Assessment of the Ministry of Health[285].

The decision by the Committee is based on an assessment referred to as the 'categorisation process of pharmaceuticals' and involves an assessment of the medicine's effectiveness and safety as well as a pharmaco-economic analysis[286].

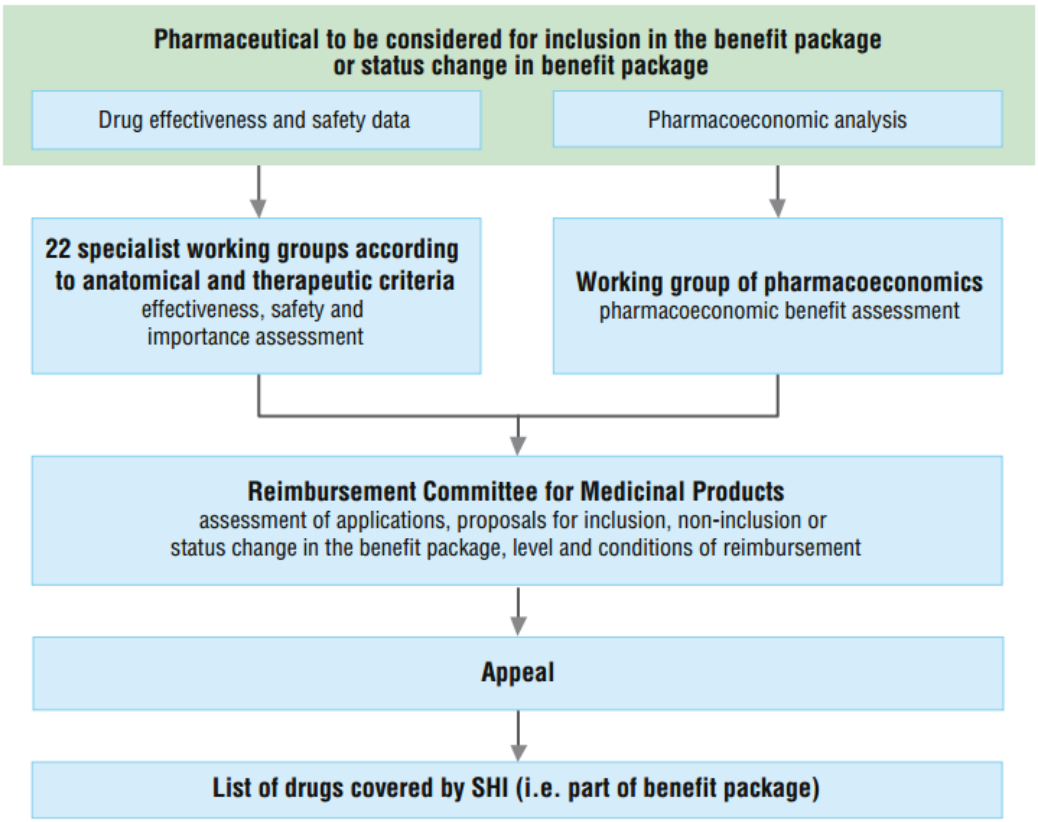
[283] European Observatory on Health Systems and Policies, Szalay T. et al, Slovakia – Health system review, Health Systems in Transition Vol 13 No.2, 2011. Available at: http://www.euro.who.int/__data/assets/pdf_file/0004/140593/e94972.pdf (Accessed April 2015).

[284] Assoc. Prof. Tomas Tesar, Health Technology Assessment in reimbursement policy of the Slovak Republic, Journal of Health Policy & Outcomes Research, ISSN 2299-1247, DOI:10.7365/JHPOR.2012.1.5 (2012).

[285] MINISTERSTVO ZDRAVOTNÍCTVA SLOVENSKEJ REPUBLIKY, Štatút Odbornej pracovnej skupiny pre farmakoekonomiku, klinické výstupy a hodnotenie zdravotníckych technológií, VESTNÍK, Čiastka 35-38, Dňa 27. novembra 2012, Ročník 60.

[286] European Observatory on Health Systems and Policies, Szalay T. et al, 2011, Slovakia – Health system review, Health Systems in Transition Vol 13 No.2. Available at: http://www.euro.who.int/__data/assets/pdf_file/0004/140593/e94972.pdf (Accessed April 2015).

Figure 7: Categorisation process of pharmaceuticals



Source: European Observatory on Health Systems and Policies, Slovakia: Health System Review (2011).

Assessment of added therapeutic value (effectiveness, safety and importance)

Firstly, the new medicinal product is assessed according to its therapeutic and anatomic classification. Specialist working groups have been set up (22 in total) for this assessment step, which investigate the effectiveness, safety and importance of the pharmaceutical. The outcomes of the assessment are provided to the Categorisation Committee for Medicinal Products of the Ministry of Health[287].

Based on the evaluation of the medicine's effectiveness, safety and importance, as well as its economic benefits (see next section), the Categorisation Committee determines the therapeutic and social value of the medicinal product. The criteria determining the therapeutic value of a medicine are[288]:

- effectiveness,
- safety,
- cost-effectiveness,
- Whether it is a first or second option or adjunctive treatment, and
- whether it is a causal treatment, prophylaxis or symptomatic treatment.

[287] ibid.

[288] ibid.

The criteria determining the social value of a medicine are[289]:

- severity of the disease,
- impact on society if not treated (e.g. spread of infection),
- social value (e.g. orphan drugs),
- risk of abuse, and
- impact on total costs.

Finally, the Categorisation Committee develops a proposal for inclusion, non-inclusion, exclusion, or change of status in the benefit package. The Committee also prepares proposals for reimbursement levels, co-payment and conditions for reimbursement. For those medicinal products designated as eligible for partial reimbursement, the decision on the specific reimbursement level is based on the following criteria: the therapeutic benefit of the drug, its retail end price, and the reimbursed prices of other products within the same reference category. The recommendations by the Committee can be overruled by the Minister of Health[290,291].

The list of medicinal products that are eligible for reimbursement can include drugs that are reimbursed with restrictions, such as their being limited for prescription by by certain specialists or by certain hospitals.

Assessment of the economic aspects of medicinal products (pharmaco-economic analysis)

The Slovak 363/2011 law states that the pharmaco-economics reports are mandatory in the decision process on reimbursement of medicinal products. As stated by Decree no. 422/2011, the decision of drug reimbursement process requires a pharmaco-economics analysis (cost minimisation, cost-utility analysis or cost-effectiveness analysis), budget impact analysis and sensitivity analysis. The pharmaco-economic analysis is conducted by a specialist working group separate to the one assessing its anatomic and therapeutic value. The discount rate for benefits and costs has been set at 5 %. The threshold that defines whether the product can be considered cost-effective has been defined in Slovak legislation (Act No. 363/2011[292]) as follows:

- Lambda 1: 24 x average monthly salary EUR / QALY
- Lambda 2: 35 x average monthly salary EUR / QALY

[289] ibid

[290] ibid.

[291] Assoc. Prof. Tesar T., Health Technology Assessment in reimbursement policy of the Slovak Republic, Journal of Health Policy & Outcomes Research, ISSN 2299-1247, DOI:10.7365/JHPOR.2012.1.5 (2012).

[292] Available at: http://jaspi.justice.gov.sk/jaspiw1/htm_zak/jaspiw_mini_zak_zobraz_clanok1.asp?kotva=k1&skupina=1 (accessed April 2015).

For 2015, Lambda 1 has been set at EUR 19,776/QALY, while Lambda 2 has been set at EUR 28,840/QALY. Medicinal products that have a cost per QALY lower than Lambda 1 can be included in the reimbursement list. Medicinal products that have a cost per QALY between Lambda 1 and Lambda 2 can be included conditionally. Medicinal products that have a cost per QALY higher than Lambda 2 cannot be included in the reimbursement list. These thresholds do not apply to medicinal products for orphan diseases that have a prevalence of less than 1:100,000.

Some highly innovative medicines - where costs exceed the Lambda thresholds but (effective) alternative medicines do not exist on the market - can be covered through Health Insurance Funds. These funds have a legal remit to make exceptions for certain innovative medicines based on specific patient access schemes. Manufacturers of innovative drugs that are not reimbursed through the national list can negotiate such schemes with the health insurance funds by offering price discounts or value limits for reimbursement. It can therefore be stated that the Lambda thresholds are a tool to assess cost-effectiveness, rather than a rule to exclude medicines from eligibility for reimbursement.

National guidance documents

The HTA policy brief of the WHO European Observatory on Health Systems and Policies forms the basis of the HTA assessment in the Slovak Republic. The document has been translated into Slovak[293].

In 2008, the first Slovak guideline for pharmaco-economic analysis was published by the Ministry of Health of the Slovak Republic[294]. These methodological guidelines provide guidance to manufacturers, sponsors and healthcare providers preparing health economic evaluations that support the reimbursement process. They aim to provide standardised, reliable and high-quality information for the Categorisation Committee and, ultimately, to facilitate the cost-effective use of healthcare resources[295].

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[294] Available at: http://www.health.gov.sk/?Dokumenty-Farmako-ekonomicky-a-medicinsko-ekonomicky-rozbor (accessed April 2015).

[295] Assoc. Prof. Tomas Tesar, Health Technology Assessment in reimbursement policy of the Slovak Republic, Journal of Health Policy & Outcomes Research, ISSN 2299-1247, DOI:10.7365/JHPOR.2012.1.5 (2012).

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Annex 6: In-depth country study: Sweden

Sweden has a largely decentralised healthcare system where responsibilities are shared by central government, the county councils and the municipalities. The 21 county councils organise healthcare for their residents and manage their own health budgets. Municipalities are responsible for health and social care for elderly people. Counties are free to adopt measures to limit healthcare expenditures and protect against prescription medicine misuse and abuse. Outpatient medicinal products are publicly subsidised by the county council through an annual state subsidy based on past medicine consumption in each county. Inpatient care is financed only by county councils, for which they have the right to levy taxes. Both are co-financed by patients.

Putting a new medicine on the market requires a **market authorisation**, delivered by the European Medicines Agency (EMA) if the product goes through the centralised or mutual recognition procedure, or by the Swedish Medical Products Agency (MPA) if the product goes through the national procedure. The decision on **pricing and reimbursement**, is taken by the Dental and Pharmaceutical Benefits Agency (TLV), a central government agency, after having evaluated the application from the pharmaceutical company. This decision is, however, not compulsory in order to put a pharmaceutical product on the market.

Market authorisation

The Medical Products Agency (MPA) is the competent authority for delivering market authorisation through the national procedure, and approving medicines going through the mutual recognition or decentralised procedures. The MPA is a government body under the authority of the Ministry of Health and Social Affairs. The Applicant must demonstrate the efficacy, safety and quality of the product, and that the product does not have harmful effects disproportionate to its intended effect. A market authorisation for medicinal products is valid for five years.

Pricing and reimbursement

The Dental and Pharmaceutical Benefits Agency (TLV) is the government agency responsible for decision on reimbursement and price regulation of medicines. The Agency is therefore responsible for both the health economic assessment and the final decision on reimbursement. TLV evaluates new medicines when receiving an application for

reimbursement from a pharmaceutical company and is also responsible for reviewing reimbursable medicines. Another agency, the Swedish Council on Technology Assessment in Health Care (SBU) is however responsible for Health Technology Assessment. TLV is also responsible for setting purchase and sale prices in outpatient pharmacies.

Pricing and Reimbursement decisions

Decisions on pricing and reimbursement are not separated in Sweden. In deciding whether or not a medicine should be included in the so-called pharmaceutical benefits scheme, TLV sets its price. There are no price negotiations. Prices of medicines are proposed by the pharmaceutical company to TLV as part of its application, and TLV takes the proposed price into account as part of the assessment. If the assessment concludes that the proposed price is too high, TLV will reject the application and it is then the company's decision to reapply with a lower price. Consequently, Sweden has stopped external price referencing since 2002, in favour of a pricing system based only on the value of the medicine. A pharmaceutical company may also apply for a price change, or a request for a price change can also come from a county council. TLV can, on its own initiative, decide on price changes or determine that a medicine is no longer subject to reimbursement after a review.

Decision-making process

Inside TLV, the Pharmaceutical Benefits Board is the main body responsible for decisions on pricing and reimbursement. The Director-General of the Agency makes decisions concerning subsidies and pricing in a certain number of cases - new generic medicines, new parallel-imported medicines and new parallel distribution, new strengths of already subsidised medicines, new packages of medicines which have already been granted reimbursement status, price changes of medicines, and withdrawal from the benefits scheme[296].

When a pharmaceutical company makes a request for reimbursement, TLV appoints a team of three experts, composed of a medical reviewer, a health economist, and a legal adviser, to examine the application. Among them, one is the responsible investigator who has the overall responsibility for the processing of the application. If necessary, the investigator can obtain information and input from other authorities[297]. After the review, the team drafts a review memorandum, which contains a proposal for a decision, and is the basis for discussions and decision from the board. The memorandum is systematically sent to the company and, when the decision is to reject the application or grant a subsidy subject to conditions or restrictions, the company is invited to attend for deliberations. Before the final decision is communicated, the company and the county council have the possibility to discuss the application and its decision with the agency. After the final decision has been taken, it is made public on the TLV website. If the applicant is not satisfied with the decision, the company can appeal to a general administrative court[298]. The decision must be communicated within 180 days of receipt of the complete application from the pharmaceutical company.

To accelerate the marketing of new medicines, applications can be submitted to TLV before a medicine is granted market authorisation. There is then only a short period of time between the market authorisation and the decision on reimbursement.

[296] TLV (2012) Guide for companies when applying for subsidies and pricing for pharmaceutical products.
[297] TLV (2012) Guide for companies when applying for subsidies and pricing for pharmaceutical products.
[298] TLV (2012) Guide for companies when applying for subsidies and pricing for pharmaceutical products.

County councils take part in the decision through their representatives in the Pharmaceutical Benefits Board within the TLV. The Board is composed of representatives of counties, patients, medical experts and health economists. TLV also works with patients' groups but they take no part in the decision.

County councils are, however, not bound to implement the decisions of TLV. They can impose additional restrictions on the use of a medicine for financial reasons.

Reimbursable medicines

Reimbursable medicines are included in a database of reimbursable outpatient medicine[299]. As costs of inpatient medicines are covered by county councils, there is no such list for inpatient medicines.

The pharmaceutical benefits scheme is product-oriented, which means that a new medicine is granted a subsidy for all its approved fields of use, or no subsidy at all. However, in certain cases, a medicine can be included in the pharmaceutical benefits scheme for a particular use or a specific patient group, and be granted a restricted subsidy. The same rules are applicable for orphan medicines.

Patients pay a percentage of the price for both outpatient and inpatient care. State subsidies are based on the total cost of products a person buys in a year; the subsidy is granted at each purchase, based on the total cost of products prior to that date and on that occasion[300]. In practice, patient co-payment rates decrease if the patient's healthcare expenditure is rising. No subsidy is granted under a total cost of SEK 1100 (EUR 117), and the subsidy rises progressively until 90 % for a total cost of SEK 5400 (EUR 575)[301]. The county pays the full cost of inpatient medicines. Patients pay the full price for prescription drugs that are not subject to reimbursement, and over-the-counter drugs.

Review of reimbursement status

There is no requirement in Sweden to carry out reviews after a certain time or in a specific order. However TLV can, on its own initiative, decide to review an individual medicine or group of medicines within the pharmaceutical benefits system, if the Agency considers that the medicine is no longer cost-effective and therefore should be excluded from the pharmaceutical benefits. TLV's right to start a review does not require any changed conditions other than a medicine no longer fulfilling the criteria to be included in the pharmaceutical benefits system.

[299] Available in Swedish: http://www.tlv.se/beslut/sok/lakemedel/.

[300] Act (2002:160) on Pharmaceutical Benefits, of 11 April 2002, Section 5.

[301] TLV, How reimbursement works: http://www.tlv.se/In-English/medicines-new/the-swedish-high-cost-threshold/how-it-works/.

TLV maps annually those medicines which have the highest sales volumes, reimbursement costs and costs per daily dose. Consultation with county councils also enables TLV to determine which medicines or group of medicines should be reviewed. Priority for reviews is given to classes of medicines where most resources can be saved and used for more urgent areas in the healthcare system, such as severe diseases. The decision to start a new review is formally taken by the Unit Head of the Unit for reviews of pharmaceutical reimbursements[302]. The same principles and criteria are used in reassessments as were required for the initial assessment.

Health economic assessments of new medicines

The current reimbursement system was introduced in 2002 by the Pharmaceutical Benefits Act[303]. The Pharmaceutical Benefits Act sets forth two main criteria on which TLV makes decision on reimbursement and pricing: cost-effectiveness and marginal benefits. According to section 15 of the Act, 'prescription drugs shall be included on the Pharmaceutical Benefits Scheme and the price for the drug shall be set provided that:

- the costs of using the drug […] appear reasonable from the medical, humanitarian and economic aspects, and
- there are no other available drugs or treatment methods which after overall consideration of the intended effects and harmful effects as referred to in Section 4 of the Medicinal Products Act can be judged as significantly more suitable for the purpose.

The marginal benefit (the fact that there are no other available medicines that are significantly more suitable) is closely related to cost-effectiveness. If the marginal benefits is high, the price of the medicine may be higher, as long as it is considered reasonable. However, if the marginal benefit is considered small or null, the medicine might not be reimbursed if the proposed price is too high. The cost-effectiveness and the marginal benefit of a medicine are assessed by comparing it to other comparable treatment options available on the market[304].

In addition, in order to be reimbursed, a medicine should comply with three principles:

- The *human value principle*, which underlines the equality of care for all individuals. Access to treatment should not be influences by ability, social status, income, or age, of patients.
- The *need and solidarity principle*: the people with greatest medical needs should be given priority, which means that the severity of the illness is an important indicator in the reimbursement decision. More resources are given to medicines improving the health of people with severe diseases or poorer quality of life, than to medicines improving well-being.
- The *cost-effectiveness principle*: the cost of a medicine should be reasonable from a medical, humanitarian, and socio-economic perspective. In particular, the cost should be reasonable in comparison to achieved health benefits and improved quality of life.

[302] TLV (2012) Handbook – reviewing the reimbursement status of pharmaceuticals.

[303] Act (2002:160) on Pharmaceutical Benefits, of 11 April 2002.

[304] TLV (2012) Guide for companies when applying for subsidies and pricing for pharmaceutical products.

The need and solidarity principle and the cost-effectiveness principle need to be weighed against each other.

The assessment is based on the documentation provided by the pharmaceutical company. The Agency essentially uses internal expertise to avoid any conflict of interest with industry. The manufacturer's report is frequently supplemented by with existing health technology assessments (made by SBU – see section 1.1.4), existing literature, European and national public assessment reports and, where relevant, by reports from other HTA authorities, unpublished clinical data, or confidential data[305].

Cost effectiveness assessment

Cost effectiveness is evaluated from a social perspective, which means all the relevant costs and benefits for the treatment and disease must be considered, irrespective of who bears the costs – the State, the county council, the local authority or the patient. All of the costs associated with using the drug are combined - such as costs for the drug, costs related to visits to the doctor, costs for possible further healthcare measures, and costs due to the side-effects of the drug – and balanced with the benefits of using the drug – effects on health and cost savings. Health benefits are understood to mean longer life expectancy or a higher health-related quality of life[306], for instance that a patient does not need to go to the doctor as often, can avoid surgery, can work instead of being on sick leave, or that an older patient can cope better and not need as much help from geriatric care services or relatives[307]. The result is documented in QALYs (Quality-Adjusted Life Years), which captures both length of life and quality of life in one measurement. The new medicine is considered cost-effective if the cost per QALY gained is under a certain level.

In the cost-effectiveness assessment, a comparison must be made between the evaluated medicine and the most relevant alternative in Sweden. The comparator can be another pharmaceutical, or a non-pharmaceutical product. The most relevant alternative is that which is most widely used, and it is generally suggested by the pharmaceutical company in its application. If there is no comparator relevant in the Swedish context, the analysis must be supplemented with model calculations.

The assessment must include the whole patient population target by the medicine. When cost-effectiveness is expected to vary across target population, separate calculations must be made for different target groups (for instance, based on gender, age, degrees of severity of the illness, different risk levels). If clinical tests are not sufficient to cover all target populations, modelling can be used to demonstrate cost-effectiveness in other patients groups[308]. If the patient group is small (orphan or rare diseases) and little data is available, a greater uncertainty is accepted in the cost-effectiveness assessment.

The timeframe of the cost-effectiveness analysis must cover the period when the main health effects and costs happen; for example, if a treatment affects survival, the assessment should take a lifelong perspective to properly evaluate life years gained. This is done via modelling as data from clinical trials are not sufficient. For chronic illnesses, cost-effectiveness often varies with age. Consequently, treatment period of one to five years

[305] Kleijnen, S. et al, 2011, Relative Effectiveness Assessment (REA) of Pharmaceuticals, background review.

[306] TLV (2007) The Swedish pharmaceutical reimbursement system.

[307] TLV (2012) Guide for companies when applying for subsidies and pricing for pharmaceutical products.

[308] TLV (2003) General guidelines for economic evaluations from the Pharmaceutical Benefits Board (LFNAR 2003:2).

should be considered at different ages[309].

In the assessment, hard clinical endpoints are preferred; these include the effects on mortality, morbidity, disease-specific quality of life. Safety data, contra-indications and ease of use are also taken into account. Surrogate endpoints can be used, but complemented with modelling from these endpoints to illustrate the effects on mortality and morbidity. If the treatment affects mostly survival, life years gained should be presented in addition to QALYs. If QALYs cannot be used, cost-benefit analysis with the willingness to pay may be used as a measure of effect. If the drug has the same health effects as the best comparable treatment, a cost comparison can be sufficient.

There is no QALY threshold value under or over which the medicine is not considered to be cost-efficient. Decisions are made by TLV on a case-by-case basis. The severity of the disease is a critical criterion in the decision: cost-benefit ratios accepted for medicines treating severe diseases are higher those accepted for treatments for less severe diseases with no impact on life expectancy[310].

Budget impact is not considered a relevant criterion in the assessment, but county councils can, once the reimbursement decision is made, impose additional restrictions on the use of a medicine for budgetary reasons.

Health assessments

In Sweden, the Swedish Council on Technology Assessment in Health Care (SBU), established in 1987, is responsible for Health Technology Assessments. SBU has no regulatory functions, it has been established to inform health policy and the general public by making 'scientific assessments of new and established health technologies from a medical, economic, societal, and ethical perspective'[311].

The Board of SBU sets the priorities in terms of health Technology Assessment. SBU can receive proposal for assessments from diverse governmental agencies, organisations, or other decision-making bodies. The SBU Scientific Advisory Committee also recommends topics for assessment. In certain cases, the Ministry of health can require SBU to conduct an assessment of a specific class of products. Topics are prioritised according to 1) available data – there must be sufficient scientific basis for the assessment, 2) the importance of the topic to people's health and quality of life, 3) the size of the target population or the recurrence of the health problem, or the substantial economic, ethical, organisational, or human resource implications of the topic, and 4) evidence of variations in practice[312]. In general, HTA are conducted for all technologies for a specific indication and/or all pharmaceuticals within a therapeutic class. SBU disseminates the results of the assessments – full reports and summaries – on its website.

[309] TLV (2003) General guidelines for economic evaluations from the Pharmaceutical Benefits Board (LFNAR 2003:2).

[310] Paris, V. and Belloni, A., 2013, Value in Pharmaceutical Pricing, OECD Health Working Papers No. 63.

[311] Regulation (2007:1233) with instructions for the Swedish Council on Technology Assessment.

[312] Jonson, E., 2009, History of health technology assessment in Sweden, International Journal of Technology Assessment in Health Care, 25: Supplement 1 (2009), 42–52.

The assessments of SBU include a systematic review of all relevant studies in the international literature - clinical studies, economic evaluations, and studies addressing other issues such as nursing, ethical, social aspects – and a summary of the findings, including recommendations for health policy and practice[313]. The assessment is performed by a group of reviewers appointed by the Scientific Advisory Committee of SBU, which comprises both SBU staff and external experts. SBU submits an annual report to the Ministry of health including finished projects and their impact on health policy and practice, and future plans. SBU reviews the benefits, risks and costs of health technology, identifies important knowledge gaps, and highlights areas that are ineffective, or not cost effective. SBU has strict criteria for inclusion and exclusion of literature in the review, and grades evidence presented in the studies on a strength of evidence scale from 1 to 4.

National guidance documents

TLV has produced guidelines to support companies in their reimbursement application in 2012[314]. The Agency has also published general guidelines on health economic assessment[315] and reassessment of medicines[316].

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[313] Jonson, E. (2009) History of health technology assessment in Sweden, International Journal of Technology Assessment in Health Care, 25: Supplement 1 (2009), 42–52.

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Websites:

- Swedish Dental and Pharmaceutical Benefits Agency: http://www.tlv.se/In-English/in-english/.
- Swedish Council on Technology Assessment in Health Care: http://www.sbu.se/en/.
- Swedish Medical Products Agency: https://www.lakemedelsverket.se/english/.

NOTES

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ISBN 978-92-823-7168-8 (paper)
ISBN 978-92-823-7167-1 (pdf)

doi: 10.2861/135713 (paper)
doi: 10.2861/214395 (pdf)

Publications Office

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