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15. Role of Health Technology Assessment in Pharmaceutical Market Access in Developed Countries

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15.1 Introduction

Introduction and use of a health technology in a health care setting has clinical, economic, as well as organizational, social-cultural, legal and ethical impacts. Health Technology Assessment (HTA) is a multidisciplinary field that addresses these impacts, considering the healthcare context as well as available alternatives. HTA mainly aims to inform policy and clinical decision making. While systematically evaluating the effects of the health technology, HTA addresses direct and intended effects as well as the indirect and unintended effects. It is a multidisciplinary field with well-developed systematic processes and methods [1,2].

A health technology is defined as an intervention that may be used to promote health, to prevent, diagnose or treat acute or chronic disease, or for rehabilitation. Health technologies include pharmaceuticals, devices, diagnostics, procedures and other clinical, public health and organizational interventions [1,2].

Before a health technology is provided to the right patient, who could benefit from it at an affordable price, traditionally several hurdles are faced: the efficacy and safety of a health technology need to be proven; and must be produced with a high quality. These

three are necessary for marketing authorization. The fourth hurdle, being assessed for cost-effectiveness, is often a payer's requirement for reimbursement. HTA is mostly done or requested by relevant authorities to assess how the new product compares with the current alternatives and whether it adds value. Perhaps a decade ago, the distinction was more straightforward and the fourth hurdle was separated from the first three. But today the processes are more integrated and redesigned to provide earlier access to valuable technologies.

Health authorities across countries, including western countries, are finding it increasingly difficult to fund all new premium priced medicines [3]. The situation is exacerbated by changing demographics, increasing prevalence of chronic diseases especially non-communicable diseases, the continued launch of new premium priced medicines to address existing unmet need adding to therapeutic complexities, alongside population fragmentation with increasing knowledge of pharmacogenomics, as well as rising patient expectations [4-6].

In this chapter, we aim to explore HTA's role in market access with specific examples from different countries. In line with the scope of the book, we will focus on the pharmaceuticals and developed markets only. We will outline how HTA might lead to different outcomes in different settings and cover new possibilities and challenges to be addressed.

15.2 History of HTA

A healthy society plays a key role in the development of a country and this makes health services one of the most important indicators of a countries' development level [7,8]. The fundamental purpose of healthcare services is to provide the public with equal access to high quality and timely services at a sustainable cost [4,8]. The organization of healthcare and funding systems differ according to the socioeconomic conditions and political context of the relevant country [5,9].

As countries develop economically, health technologies advance rapidly. Rapid developments increase the demand for health care services, and consequently health expenditure dynamics increase [9].

The rapid diffusion of health technologies challenges governments to provide high quality, equal and accessible care for the citizens while managing the health care budgets effectively. Questions about the effectiveness of experimental technologies, as well as increased health care expenditures and restricted health care budgets, led to the development of HTA [10].

Health Technology Assessment became a concept in 1976; it initially spread from the United States (U.S.) to Western Europe and in recent years HTA is rapidly developing worldwide. In 1967, HTA was first used as a term in United States Congress [11]. In 1972, the U.S. Congressional Office of Technology Assessment (OTA) was established and OTA initiated a health program in 1974. During this program OTA pub-

lished eighty different HTA reports [12], especially focusing on efficacy, safety, and cost-effectiveness [13]. The early products of OTA and evidence based reviews derived by the Cochrane Collaboration displayed the most important roles on shaping the field of HTA.

Inspired by the reports of OTA, The Swedish Council on Technology Assessment in Health Care (SBU) started HTA development in Europe [13]. This first period of synthesizing the available evidence with efficacy and cost-effectiveness supported policy-makers in national health programmes with regard to evidence-informed decision-making [11]. After 1985, HTA has gradually spread to nearly all western and southern European countries, then to Central Europe, Latin America, and Asia. International organizations such as the World Bank, World Health Organization (WHO), International Society of Technology Assessment in Health Care (ISTAHC), its successor Health Technology Assessment International (HTAi), and the International Network of Agencies for Health Technology Assessment (INAHTA) all benefit the development and use of HTA [13].

15.3 HTA and Market Access

Market access is defined as "openness of a country's markets to foreign goods and services" [14]. Although this is the basic definition, pharmaceutical market access can be considered as a longer and comprehensive process. This is a challenging process where many stakeholders are involved. Processes such as HTA, pricing and reimbursement; industry processes such as R&D, registration, marketing authorization and launch might impact the access process [15]. Furthermore, although there are common frameworks to demonstrate the quality, safety and efficacy of a product, there remains fragmentation regarding marketing authorization applications across the countries in Europe [5].

Due to financial crisis or economic concerns, governments face difficult times and priorities need increasingly to be set given the extent of unmet need that still exists [4,16]. Especially, the last decade has witnessed cost-cuts and increased price negotiations and in this context, HTA has been increasingly recognized to meet policymakers' needs by providing them information on the costs and benefits of drugs. Although the focus lies on providing value for money, it has been quite hard to measure value, interpret it and have data on the appropriate impact on the outcome [17].

HTA serves the purpose of providing policymakers with reliable assessments of the pharmaceuticals that would reflect the real world, but also will aid the manufacturers to prove the value of the drugs they have produced. HTA might highlight the drugs that are expensive compared to their benefits, or might outline the indications and patient groups that would have additional value. Unsafe and ineffective drugs will also be discovered during these processes, leading to active dissemination [18-20].

15.4 HTA, Regulation, Pricing and Reimbursement of Pharmaceuticals

It is relatively easier to harmonize regulatory processes across countries, while pricing and reimbursement decisions on pharmaceuticals depend more on the local context [4,5,21]. For example, it is very difficult to translate cost-effectiveness from one setting to another. Furthermore, the political and health care context, national/regional priorities and social values differ across countries, making it more complex to transfer the outcomes of HTA evaluations. This is quite challenging for the manufacturers as they need to understand expectations of HTA organizations which may vary from country to country. To address this, for instance European countries are seeking to collaborate on HTA assessments (EUnetHTA – discussed later) as well as trying to find ways to collaborate on methodology development and approaches regarding earlier access to medicines including adaptive pathways, and several stakeholders are involved in this collaboration. The approaches will further be explored later in this chapter.

In many countries, pricing and reimbursement decisions are taken at the national level. The manufacturer needs to submit a dossier for this purpose after obtaining marketing authorization; i.e. a license issued by a medicines agency approving a medicine for market use based on a determination by authorities that the medicine meets agreed requirements of quality, safety and efficacy for human use in therapeutic treatment [5]. Many countries use HTA to subsequently guide or inform the pricing and reimbursement processes by assessing the drug's benefits compared to its alternatives alongside cost considerations [21]. In addition to clinical and economic aspects, increasingly other aspects related to the use of a particular medicine are considered. In certain cases, such as life-threatening conditions or orphan diseases, the assessment might find limited evidence or low cost-effectiveness, but the (unmet) need might be high as there are limited therapeutic alternatives. In this case, HTA can be used as a tool to support prioritization ensuring a more rational investment of funds, based on social needs and policy priorities [22]. HTA seems to be the preferred strategy as it addresses both price and appropriate indications for the use of the medicine and the relation between additional value and additional costs [4,22,23].

HTA might inform policymakers about different options and scenarios where there is more flexibility on pricing and reimbursement policies. Rather than an absolute yes or no to reimbursement, companies might need to bring in more evidence to showing benefit on certain conditions. The increasing number of high-priced drugs has started to challenge even wealthier countries to develop policies on how to improve access to medicines in an affordable way. Europe, for example, has set this issue high on their agenda [4,24]. This led to innovative ways of pricing and reimbursing pharmaceuticals, such as value based pricing or managed entry agreements [4,5,25]. These approaches, especially managed entry agreements, were created to enable access to (coverage/reimbursement of) a product subject to specified conditions, such as price negotiations. While this is a way

to provide access to the drug, it risks transparency and transferability at the global level [4,25]. We will discuss this further in this chapter.

The European Commission has financially supported several HTA projects to promote the collaboration between Member States (MS) in the European Union (EU) since 1993 [4]. The European Commission and Council of Ministers designated HTA as "a political priority" in 2004, recognizing «[...] an urgent need for establishing a sustainable European network on HTA» [26]. EUnetHTA has coordinated these activities since 2006. EUnetHTA is defined as a «network of government appointed organizations [from EU MS, EU-accession countries, plus European Economic Area (EEA) and European Free Trade Association (EFTA) countries] and a large number of relevant regional agencies and non-for-profit organizations that produce or contribute to HTA in Europe». The collaboration has already resulted in methodological guidelines and tools such as the HTA Core Model – a methodological framework for shared production and use of HTA information in the era of diagnostic technologies, medical and surgical interventions, drugs and screening technologies. The purpose is «to enable production of high quality HTA information in a structured format to support the production of local (national or regional) HTAs and reuse of existing information». HTA organizations use this model as the value framework when assessing technologies within the EU [27].

Since 2009, EUnetHTA collaborated with the European Union and the European Commission partners to administer joint assessments and implement the results. EUnetHTA has finished 20 joint assessments until 2015. This cooperation on HTA projects has the potential to increase the quality of HTA. An assessment can be done in two different ways; a rapid Relative Effectiveness Assessment (REA) and a full HTA. We can evaluate the incremental therapeutic value of technologies with a rapid REA; however, a full HTA has a broader perspective. A rapid REA covers the following domains: health problem and current use of technology, description and technical characteristics, safety and clinical effectiveness; furthermore, a full HTA also includes the following domains: costs and economic evaluation, ethical analysis, organizational aspects, patient and social aspects, and legal aspects [27].

Relative effectiveness is defined as «the extent to which an intervention does more good than harm compared with one or more alternative interventions under the usual circumstances of healthcare practice». Especially payers are more interested in evaluating the relative effectiveness of new healthcare technologies compared to standard care or other technologies, and have documented their preferred comparators [21]. This interest in relative effectiveness information in Europe is due to the early information need for guiding reimbursement and funding decisions about new health technologies [3-5,28].

EUnetHTA published a review about REA in 2011. According to this report, most countries surveyed use REA to support national reimbursement decisions of drugs, but the subject and methodology vary across countries due to the health system, reimbursement processes, the socio-cultural structure and the level of GDP per capita of the country [27].

15.5 How HTA Differs from One Setting to Another

The scope and methods of HTA may be adapted to the needs of a particular health system, but it is known that each country has its own priorities, sources and unique decision-making processes. Below we will give four country examples on how HTA structures change from setting to setting and discuss how they compare with regard to the decisions made with certain pharmaceuticals.

HTA in France

In France, HTA is governed and organized officially based on the legislations of the government and the SHI (Statutory Health Insurance or *Assurance Maladie* in French) [29]. The French government established the main French HTA organization, called HAS (French National Health Authority or *Haute Autorité de Santé* in French) in August 2004 [29,30]. The main goal of the HAS was determined as being the single organization which covers many activities aiming to improve the quality of health care and ensure equity within the health system [30]. In order to achieve this goal, this organization assesses drugs, reagents, tests, medical devices, practices and procedures as well as health programmes; develops guidelines; provides training and information about quality; accreditates health care providers and certifies physicians [29,30]. As an independent (non-governmental) public institution, HAS has financial autonomy and collaborates with several partners such as governmental health agencies, national health insurance funds, research centres, societies of healthcare professionals and patients [30].

HAS has extensive in-house scientific expertise, nevertheless it is also authorized to undertake commissions external experts (e.g. academicians, professionals, other experts) [29,30]. HTA is done by the HAS before inclusion of new medicines on the positive list for reimbursement can occur [29]. After a health technology receives the regulatory approval from EMA (European Medicines Agency) or AFSSAPS (French Health Products Safety Agency or *Agence Française de Sécurité Sanitaire des Produits de Santé* in French), an HTA report is an obligation in order to be considered for pricing and reimbursement by French decision makers [29,30]. Necessary HTA is conducted by two specific commissions within the HAS [29]. The Transparency Commission (*Commission de la Transparence* in French) evaluates drugs, while CNEDIMTS (National Commission for the Evaluation of Medical Devices or *Commission nationale d'évaluation des dispositifs médicaux et des technologies de santé* in French) evaluates medical devices and procedures [29]. Obligatory HTAs, which are done for all new health technologies by the aforementioned commissions based on the documents presented by the manufacturers before the market launch, have a direct influence on the reimbursement rate of SHI and a less direct influence on the price (statutory tariff) [29,30]. Two reviewers evaluate and criticize each HTA study, before it is discussed by the relevant commission. The HTA procedure in France may be classified into two steps [29,30]:

- First step is the assessment of the product's medical benefit or therapeutic value which is called SMR *(Service Medical Rendu* in French*)* [21,29,30]. This assessment is done in absolute terms for all different types of use of the product, based on its clinical efficacy and safety, its importance within the therapeutic strategy, existence or absence of its alternatives, severity of disease which is indicated to treat, type of the treatment (preventive, curative or symptomatic) and its impact on public health which reflects epidemiological issues and quality of life [29,30]. The SMR level of the health technologies (e.g. major or considerable, important, moderate, low or weak but justifying reimbursement, insufficient) play an important role with reimbursement decisions and the reimbursement rate (from 0 to 100%) decisions [29,30].
- The second step is the assessment of the product's relative medical benefit compared to similar alternatives which is called ASMR (Improvement in the Relative Medical Benefit or *Amélioration du Service Medical Rendu* in French) for drugs or ASA (Improvement in Expected Benefit or *Amelioration du Service Attendu* in French) for medical devices and procedures [21,29,30]. This assessment is done and a grade, based on the improvement in medical effectiveness over similar alternatives, is given by the Transparency Commission for drugs and CNEDIMTS for medical devices and procedures [29]. ASMR or ASA grades of the health technologies (e.g. 1 for "major improvement" or "life-saving health technology", 2 for "important improvement", 3 for "significant or moderate improvement", 4 for "minor improvement", 5 for "no improvement") affect the decisions on pricing explicitly [21,29,30]. Therefore, this step of the assessment incentivizes the manufacturers to provide sufficient data about their products [29].

The HAS commissions examine the documents of the manufacturers, reviews the existing literature systematically and eventually updates all previous decisions about existing health technologies once every five years [29].

Since 2013, another HAS commission called CEESP (Commission for Economic Evaluation and Public Health or *Commission d'Évaluation Économique et de Santé Publique* in French) conducts an economic assessment under specific conditions such as; having a health technology which is considered as ASMR/ASA grade 1, 2 or 3 and may influence SHI expenditure significantly by its price and/or its effect on health care services' organization, medical practices or coverage conditions of patients or having a health technology which have or is expected to have a 20 million Euros or higher turnover after two years on the market [29].

The Ministry of Health is the responsible body to commission the assessment of other technologies such as the necessary equipment for a procedure [29]. Waiting until any additional information becomes available, or asking for surveys or observational research, are possible advices which follow the HTA reports [29]. It is usual that the manufacturers finance the research [29]. However, the researchers should be independent from the financiers [29].

There are multiple criteria used in the appraisal process that is done by the Transparency Commission. The most important criteria for the opinion are actual benefit, improvement in actual benefit, and target population. There is a formal appeal process of 90 days

in which companies get the chance to appeal and contest the decision. The HAS makes a recommendation to UNCAM (National Union of Health Insurance Funds or *Union Nationale des Caisses d'Assurance Maladie* in French), which provides the Ministry of Health with a final recommendation about inclusion in the SHI [31].

HTA in the Netherlands

The health system of the Netherlands includes a social health insurance system in which public insurance is compulsory. Citizens older than 18 years pay a flat premium per year for the basic insurance, while people with low incomes are financially compensated. In addition, complementary (voluntary) insurance exists. Through the Health Insurance Act, citizens are entitled to a basic benefit package, although for some entitlements co-payments exist. Health insurers play an important role in implementing the Health Insurance Act, and they are obliged to accept each citizen that wants to pursue a health insurance with them [32].

In 2016, around 10% of GDP was spent on health care, while this was around 9% in 2007. The Health Insurance Act governs curative care, including primary care and hospital care. Around 60% of the health care budget (700 million Euros in 2016) is allocated to this part of health care [32,33].

The Ministry of Health, Welfare and Sports (VWS) is responsible for the content of the benefit package, which comprises essential medical care, medical aids as well as pharmaceuticals. The National Health Care Institute (ZIN) also plays an important role – it has a legal advisory task with regard to the benefit package; its Appraisal Committee (ACP) has an advisory role in coverage-decision-making, while the Ministry of Health makes the final decision.

HTA has been introduced in the Netherlands in the early 1980s. At that time, the Health Insurance Council (now ZIN*)* and the Ministry of Health became concerned about the rapid developments in health technology (e.g. transplantations, and IVF) and their impact on health care and society, especially in terms of cost. During the 1980s and the 1990s, a series of policy-oriented reports were published that either focused on HTA or included HTA as part of future policy in the Netherlands. All these reports recommended a strong program of HTA as part of Dutch health care. An important impetus for HTA in the Netherlands was the launch of a national HTA research program in 1988 [34]. The Ministry of Health funds the program, which is currently running for the years 2016-2018 and 2019-2021 [35]. The program has evolved over the years, from being a more academic program, towards a program that is addressing the needs of health care professionals, patients and decision-makers [36]. In 1991, the Committee on Choices in Health Care (*Commissie Dunning*) suggested to use HTA for coverage decision-making using four criteria: necessity, effectiveness, efficiency and whether or not the interventions can financial borne by the individual (affordability) [34]. Since 2006, the main role of ZIN is managing the benefit package of health care, and one of its tasks is to advice the Minister of Health about coverage decision-making. ZIN currently makes use of four criteria, clearly inspired by those set out by the Dunning Committee: necessity, effectiveness,

cost-effectiveness and feasibility. Franken et al [37] questions whether economic evaluation play an important role in the Dutch system as actual cases (e.g. orphan drugs for Pompe and Fabry disease) [6] showed that it seems rather difficult to put restrictions even though the economic evidence is clear. This situation might prove different in the near future as ZIN is in the process of further optimizing the current (appraisal) system, by further operationalizing the criteria necessity and cost-effectiveness, as well as using deliberative processes based on Daniels and Sabin's Accountability for Reasonableness framework [38].

HTA in Germany

Germany was relatively late compared to other European countries to engaging in HTA activities [39]. In the early years, HTA was mainly conducted by individual researchers. HTA has now become an official necessity in decision-making with regard to which health technology should be covered through *SHIs (Statutory Health Insurance)*, as a result of the SHI Modernization Act, which was announced in 2014 [39,40].

Currently, the main organizations involved in HTA are IQWiG (Institute for Quality and Efficiency in Health Care or *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* in German) for assessment and G-BA (Federal Joint Committee or *Gemeinsamer Bundesausschuss* in German) for the appraisal [39,40]. The G-BA has a department which can provide scientific advice for assessment, but they almost never produce HTA reports.

The G-BA is a multisectoral committee, which consists of dentists, physicians and representatives of hospitals, (non-voting) patients and SHIs [40]. It has a responsibility to control coverage and limitations on prescribing in order to ensure efficiency in the system [40]. Therefore, it evaluates new examination and treatment methods, assesses new medicines, categorizes them into reference price groups and publishes clinical guidelines, which need to be presented to the Federal Ministry of Health for approval [40]. The G-BA decisions based on the level of additional benefit may be appealed based on evidence and legislation [40]. Additional benefit is determined by assessing mortality, morbidity and health related quality of life of the new medicine versus current standards, similar to France [41]. The G-BA makes the final decision publicly available. Most HTAs are conducted by IQWiG.

IQWiG is an independent institute, which was founded in 2004, to assess medical efficiency, quality and effectiveness [40]. Since the new Competition Enhancement Act was announced in 2008, formal cost-effectiveness analyses have become an indispensable part of the German system and IQWiG is authorized to assess cost-benefit ratios of medicines in Germany [40]. It prepares HTA reports either at G-BA requests or self-initialized (for non-pharmaceutical products) [40]. It does not have any decision-making powers and its advice to the G-BA (e.g. including or excluding health technologies into the SHI coverage) are not binding [39,40]. The most important criteria used in the assessment phase are patient relevant outcomes, including mortality, morbidity and health related quality of life as opposed to surrogate measures. Context and implementation issues are partly taken into account (e.g. prescribing restrictions for certain pharmaceutical prod-

ucts are investigated). IQWiG is forced by law to make the evidence report of the assessment publicly available [31]. IQWiG has an informal collaboration with HAS (French National Health Authority) and NICE (National Institute for Health and Care Excellence), which provides bilateral sharing of basic information and scientific evidence with France and the England (in the United Kingdom) [40].

HTA in England/Wales, UK (United Kingdom)

HTA processes are usually aimed to evaluate value for money and eventually inform health policy-making at the national level in the UK [42]. NICE (National Institute for Health and Care Excellence), which is an independent public body founded as a Special Health Authority in 1999, is the main organization which is responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health [42]. Therefore, it supplies national guidance on specific health technologies (e.g. drugs and medical devices) through its HTA processes and on clinical practice through its clinical guideline development processes based on existing evidence [42,43]. However, in course of time after its foundation, it has taken up further duties in the field of public health as well [42].

Purchasers in the UK have local freedom to choose which health technologies they will buy and they are not obliged to purchase only cost-effective health technologies [43]. In other words health technologies, which are not found cost-effective, may also be covered locally [43]. The NHS (National Health Service) organizations in England and Wales are obliged to finance drugs and therapies approved by NICE based on HTA reports since 2002 [42]. It is also an obligation for NHS organizations to revise their clinical management procedures when NICE clinical guidelines are published [42].

NICE is responsible with both the assessment and the appraisal. Once a technology is referred to NICE for evaluation, NICE writes a draft assessment report together with the Department of Health, including health outcomes and costs. After stakeholder consultations, the scope of the HTA is finalized and all consultees and others are invited to make a submission. The evidence provided by the manufacturer is then reviewed by an independent academic group [31]. The Appraisal Committee of NICE comprises of 20-25 members from diverse backgrounds and includes lay members. It is the Committee's role to appraise the evidence gathered in the assessment phase, including clinical effectiveness and health-related factors, cost-effectiveness, social value judgements and costs (savings) outside NHS or non-health gains. Additional criteria are taken into account for end of life medicines. The Committee summarizes the key evidence and their own view on the evidence, and provides a preliminary recommendation, which is open for consultation. Comments are considered in a second Appraisal Committee meeting, after which the final recommendation to the NHS follows.

There is evidence showing that NICE guidance may affect the market share of drugs, patient access to medicines, prescription attitudes and clinical practices [42]. Most of the drugs, which exist on the market of the UK, are assessed and relevant guidance is published by NICE [43]. Additionally, Northern Ireland, Scotland and Wales have their own

advisory organizations to provide recommendations about clinical effectiveness, cost-effectiveness and prescription of medicines with health care devolved in the United Kingdom [43]. SMC (Scottish Medicines Consortium) takes this responsibility in Scotland, while AWMSG (All Wales Medicines Strategy Group) does it in Wales. NHS boards in Scotland should act in line with SMC recommendations [43]; however, this may not always be possible in view of budgetary issues.

Comparison on HTA and Decision Outcomes in Different Settings

As described above, the way in which HTA bodies/programmes are organized and provide input to decision making differs between health systems. In some countries, the HTA body (e.g. NICE in the UK) or an advisory council (e.g. National Health Care Institute in the Netherlands) develops guidance and/or recommendations concerning reimbursement of health technology. In other countries, there is a strong separation between the assessment and appraisal procedure (e.g. in Germany, IQWiG provides the assessment and the national authority – G-BA, decides on the added benefit of pharmaceutical products). Other models also exist – e.g. in France, where HAS (*Haute Autorité de Santé*) is mainly responsible for providing recommendations regarding the reimbursement of pharmaceuticals. The CEPS *(Comité Économique des Produits de Santé)*, also a separate body, is responsible for price negotiations with pharmaceutical companies.

Abbreviated indication	Brand name (generic)	HTA recommendation					
		Germany	The Netherlands	France	England/ Wales	Scotland	Poland
Breast cancer	Eribulin	Equal benefit	Added benefit	Added benefit	Negative	Negative	Negative
Colorectal cancer	Aflibercept	Added benefit	Not assessed	Equal benefit	Negative	Negative	Positive
Gastric cancer	Tegafur/ Gimeracil/ Oteracil	Not assessed	Lesser benefit	Lesser benefit	Not assessed	Positive	Negative
Melanoma	Ipilimumab	Added benefit	Added benefit	Added benefit	Positive	Negative	Positive
Non-small cell lung cancer	Crizotinib	Equal benefit	Not assessed	Added benefit	Negative	Negative	Negative
Prostate cancer	Abiraterone	Added benefit	Equal benefit	Added benefit	Positive	Negative	Positive
Renal cell carcinoma	Axitinib	Added benefit	Not assessed	Added benefit	Positive	Negative	Positive

Table 1. Recommendation regarding (selected) oncology drugs having received marketing authorization (2011-2013) in selected EU countries [27,47]

With regard to the use of HTA in decision making, it can be observed that in addition to the level of clinical benefit and cost-effectiveness, increasingly other aspects are taken into account in the appraisal [44]. For orphan drugs different criteria might apply in either the assessment phase (e.g. France), the appraisal phase (e.g. The Netherlands) or both (e.g. Germany) [45]. The approach taken seems to be correlated with the institutional context and the organization making the recommendation or decision, the financing and governance of the health system, as well as the culture and values of a country [46]. Obviously, this might lead to different decisions. This can also be seen in the Table 1, in which selected countries used the same assessment results based on relative effectiveness (using EUnetHTA Core Model). The diverging results could also be due to the fact that the scope (comparators and cost considerations) and the methodology used vary across countries [47]. Allen et al [48] found similar results in a study on national reimbursement decisions in nine countries for more than 100 new active substances approved by the European Medicines Agency.

15.6 Ongoing Developments Impacting on the Role of HTA to Improve the Managed Entry of New Medicines

There have been particular issues with the funding of new medicines for Hepatitis C given the potential number of patients, the possibility of a cure for this chronic infectious disease, the high launch price in a number of countries with associated potential budget impact, as well as concerns with the high level of profitability in some countries at over 99.9% gross profit at the initial requested prices [49-51]. This has resulted in extensive negotiations for discounts as well as restricted use, including managed entry agreements, which is not in the best interests of patients or health authorities [50-54]. There have also been concerns and issues with increasing prices of new cancer medicines and those for orphan disease despite little evidence that new cancer medicines extend or improve life [4,5,55,57]. The cost of new medicines to treat patients with cancer have risen more than tenfold in the past decade despite the low cost of goods of some new cancer medicines, lower than publicized R&D costs as well as current levels of profitability [58-61]. High reimbursed prices for new cancer medicines has been helped by the emotive nature of the disease area, which has typically translated into greater leeway among payers for granting premium prices even for very modest improvements in patient outcomes [4-6,55,57,61-63]. These concerns have already resulted in requests for price moderation for new cancer medicines for future sustainability [61,64,65]. Health authorities, particularly those providing universal access, are increasingly concerned if prices continue to rise given the appreciable number of new cancer medicines in development [4,5,65-67]. A similar situation is also seen for new medicines for orphan diseases given ever increasing prices [4,5,68], with public pressure resulting in, for instance, new medicines for orphan diseases in the Netherlands funded up to 15 million Euros/QALY [69].

Having said this, independent drug information journals, particularly in Europe, believe very few new medicines are truly innovative; with the vast majority seen as similar in their impact on health, or only marginally better, than existing medicines [5,6,70,71]. Consequently, these new medicines should command lower or similar prices to existing standards; or at best only limited increases versus existing standards based on HTA as well as key pricing and reimbursement considerations [4,5,21,41,72]. However, currently concerns with the definition of innovation and value, as well as issues of priority, unmet need and emotion, cloud such discussions and deliberations [63,73-76]. This is a challenge for the future especially in Europe to maintain the ideals of equitable and comprehensive healthcare.

There have also been concerns with some of the marketing activities of pharmaceutical, especially if this leads to inappropriate prescribing which add to costs and/ or potential patient safety [3,77-83]. This includes issues of 'evergreening' of medicines further adding to costs without necessarily improving patient care [84]. However, there are ongoing moves to address key stakeholder concerns particularly regarding the promotion of new medicines [85-87]. This includes improving the core competencies and standards of pharmaceutical physicians [88,89]. In addition, educating physicians that patients enrolled into clinical trials may be different to those seen in routine clinical care, which can mean additional vigilance [3,90].

There are also concerns among some health authorities regarding risk sharing arrangements, or Managed Entry Agreements (MEAs), to improve the affordability of new medicines and reduce uncertainty [25]. These have to be balanced though against no reimbursement if no agreements are reached. These concerns include potential savings in reality, whether health systems have the ability to monitor patient outcomes in routine clinical practice, and the administrative burden and costs associated with such schemes [3,25,75,91-93]. However not surprisingly given rising prices for new medicines, the number of such arrangements has grown in recent years especially for new anti-cancer medicines, although this is not universal [4,25,94-96]. It is likely these schemes will continue, certainly in the short to medium term, given increasing financial pressures and limited alternatives [96,97]. However, this has to be balanced with the need for health authorities and pharmaceutical companies to publish the outcomes of such schemes against their objectives to guide future decision making. Currently, there is a paucity of such information [4,25].

Alongside this, there are also increasing concerns among payers across Europe regarding issues relating to the potential introduction of adaptive pathways for new medicines to accelerate access to new innovative medicines [98,99]. Key concerns include i) issues of payment, i.e. who will pay for the new medicine during its testing phase among patients and at what price, ii) where does the product liability lie prior to full marketing authorization, pricing and reimbursement, iii) how is innovation and unmet need defined, iv) how long are new medicines in the adaptive pathways process prior to full evaluation, v) whether such schemes are needed in reality with fast-track schemes for new medicines already in existence, vi) whether health authorities currently have the necessary ability to monitor the effectiveness and safety of new medicines in routine clinical care, vii) wheth-

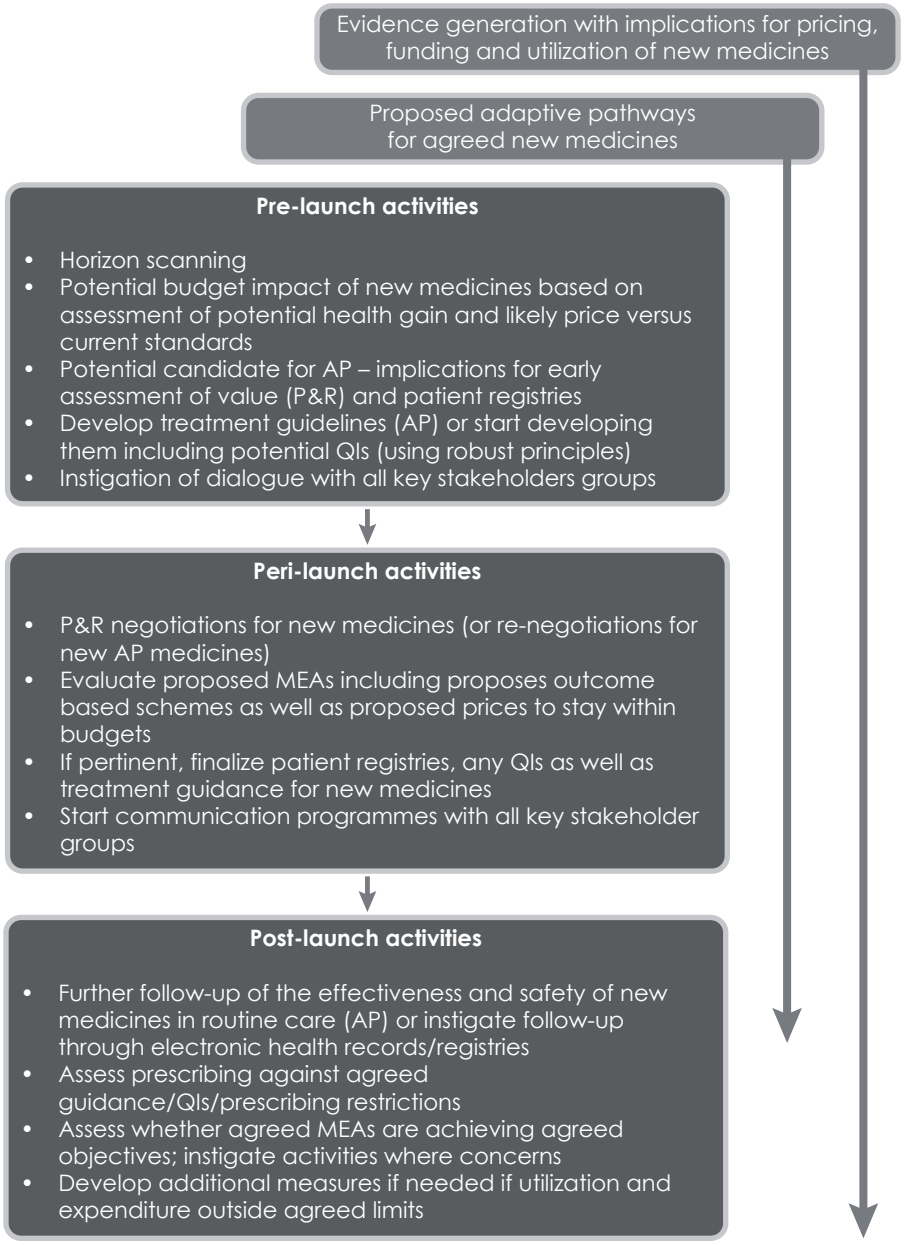

Figure 1. Schematic representation of ongoing models across Europe to improve the managed entry of new medicines. Modified from [3-6,98,108-112]

AP = Adaptive Pathways; MEAs = Managed Entry Agreements; P&R = Pricing and Reimbursement; QIs = Quality Indicators

er payers have the necessary powers to disinvest in new medicines if found not to be cost-effective in reality and manufacturers are reluctant to lower prices. Additionaly, if health authorities do not have the necessary IT systems, who would pay for their subsequent development [99]? However, the use of patient registries post launch have helped address issues of appropriateness and concerns with new medicines such as potentially increasing rates of infection and cancer with the use of biological medicines to treat immunological diseases such as rheumatoid arthritis and psoriasis. Such concerns have not proved to be the case in long term follow-up of these patients [100-106]. Long term follow-up of patients in public healthcare databases have also demonstrated significantly improved long-term graft survival in kidney transplant patients prescribed cyclosporine versus tacrolimus despite current beliefs [107].

These issues and concerns have resulted in the development of new models, especially among European countries, to better manage the entry of new medicines, which also includes potential new models for valuing new medicines for orphan diseases given current concerns [3-6,66,108]. The proposed models include the role of HTA. In addition, HTA activities are increasingly used to guide disinvestment activities, with monies transferred to fund more effective and/or more efficient medicines [18-20]. Discussion of disinvestment activities is outside the scope of this chapter. However as mentioned, there have been published case histories regarding the disinvestment of medicines from a number of countries [18]. More recently, the authorities in Brazil have published a new approach that also includes assessing the effectiveness and safety of potential medicines for disinvestment in the real world, adding robustness to any decisions [19].

New Models to Improve the Managed Entry of New Medicines

A three-stage model has been proposed, and is now being implemented, to improve the managed entry of new medicines especially from a health authority perspective [3-6,66,108,109] (Figure 1). The model begins with pre-launch activities including horizon scanning and forecasting, the potential development of quality indicators for new medicines, as well as including new medicines that could go through the proposed adaptive pathways program especially in Europe [98,109-111]. This will increasingly include in Europe potential new medicines going through the adaptive pathways scheme [98,99].

Peri-launch activities including a fuller assessment of the potential value, requested prices and likely reimbursement, with or without a managed entry agreement, of new medicines versus any preliminary evaluation pre-launch [5,21,66,94]. Post-launch activities include the evaluation of ongoing managed entry agreements including continuing assessment of the effectiveness and safety of new medicines in routine clinical practice as well as the monitoring of prescribing against agreed quality indicators and guidelines.

Pre-launch activities

Pre-launch activities include horizon scanning and budgeting activities [109]. Horizon scanning is seen and defined as «identifying new medicines or new uses of existing medicines that are expected to receive marketing authorization from the Regulatory Author-

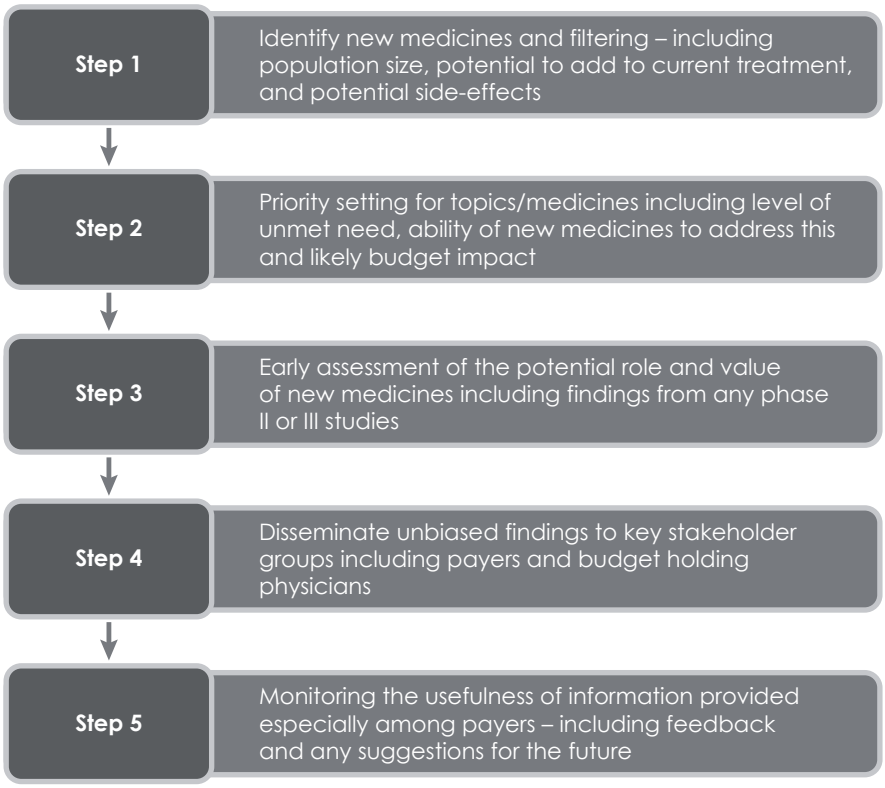

Figure 2. Horizon scanning sequencing activities. Modified from [109,118,121]

ity in the near future and estimating their potential impact on patient care» [113-116]. Since 1999, 18 countries across continents including Europe have been collaborating under the EuroScan project [111,116-118]. Each member agency is unique in its approach; however, they all have a common goal of informing particularly health authorities and hospital managers about new and emerging technologies that could have a significant impact on their health system [104,117,119,120]. Typical activities regarding horizon scanning among leading Western countries, including leading Western European countries, are discussed in Figure 2.

Key filtration and information components of reports in European countries including Austria, Italy, Sweden and the UK are contained in Table 2.

Horizon scanning units can issue different reports as new medicines approach potential marketing authorization to further help heath authorities in their planning [109,111]. This includes Italy (Table 3), with medicines selected based on an agreed filtration process (Table 2).

Criteria	Key considerations
Filtration Criteria	• Current status, e.g. how close to marketing authorization • Likely population size • Severity of the disease area in question/whether a current priority area • Ability to meaningfully improve patient outcomes/address a situation currently associated with appreciable morbidity and mortality – consequently potentially influence treatment guidelines • Potentially innovative way of treating current diseases/level of innovation • Possibility of safety concerns, e.g. dabigatran • Potential budget impact including the potential for savings; part of a new growing class of medicines • Potential for off-label use • Could potentially require reorganization of healthcare services • Likely media/public interest • Likely non-optimal introduction rate following marketing authorization • Potentially legal, ethical or politically interesting considerations
Key components of early assessment reports	• Description of the medicine including disease area and mode of action • Likely clinical need and size of the likely patient population(s) • Current treatment approaches and alternatives; and possible pipeline products • Summary of efficacy in Phase II and III studies (depending on availability and timing of the reports) • Current completed and ongoing studies • Likely budget impact as well as any early pharmacoeconomic assessment • Potential to monitor utilization post-launch against agreed guidance • Possible marketing approaches among companies

Table 2. Key filtration criteria and components of horizon scanning reports in Europe. Modified from [3,109,111,116-118]

Enhancing the robustness forecasts concerning the likely utilization and expenditure of new medicines is increasingly essential to improve subsequent planning and resource allocation given ever increasing pressure on resources [3,4]. One example combining a number of factors to improve budget forecasting, which involves multiple expert groups, is from Stockholm County Council in Sweden [110]. Their forecast with expert groups, including physicians, pharmacists and health authority personnel, involves assessing the likely role of new medicines as well as the future utilization of existing medicines. Regression analyses are conducted on aggregate sales data and predicted trends are adjusted for possible changes in the market including possible patent expiries, with implications for appreciably lowering the price of medicines, as well as potential chang-

Reports available 36 months before potential MA for selected medicines	Reports 18 months before potential MA for selected medicines	Report 12 months before potential MA for selected medicines
The report provides data from Phase II trials as well as of ongoing Phase III trials of targeted medicines. These reports help identify areas of research of interest to the Italian NHS which are currently not being met by pharmaceutical companies.	These reports are essentially for internal purposes among regional health authorities in Italy. The reports critically assess available results of completed Phase III trials and their implications. They help identify and prioritize emerging medicines likely to have a clinical and economic impact on the Italian NHS.	These reports critically evaluate available efficacy and safety data on new agreed medicines. The Italian Unit assesses their possible level of innovation, possible place in therapy (target population) as well as the potential economic (budget) and social impact. The reports are seen as particularly useful for national and regional health authorities.

Table 3. Different reports and their timescales from the Italian Horizon Scanning Project (IHSP) prior to potential EMA marketing authorization (MA). Modified from [109,111]

es in the reimbursement status of medicines [109,110,122]. All of these factors are combined into a yearly forecast, which is subsequently monitored to improve future forecasting [109,110,118].

These activities in Europe will grow with the potential introduction of new medicines under the adaptive pathways scheme [98]. Similarly, for any early access schemes where budgetary responsibility is borne by the payers rather than pharmaceutical companies. These potentially include conditional approval schemes to accelerate access to new medicines for serious debilitating or life-threatening conditions; however, there are concerns [123,124]. This is different to fast track schemes, which are already in existence [98].

Whilst proposed adaptive pathways are welcomed by European payers and their advisers to accelerate early access of new medicines, especially those for debilitating diseases and where currently limited or no therapies are available for treatment, there are still considerable concerns. These concerns have been summarized in a number of published papers [98,99,123,125,126], and include the fact that there will still be inequity in the availability of new medicines across Europe depending on potential prices. Payer HTA considerations for assessing potential prices for new medicines going through the adaptive pathways route will also need to evolve to consider how to effectively deal with increased uncertainty, and build this into their negotiations with pharmaceutical companies [99,127].

Peri-launch activities

As already mentioned in previous paragraphs, European countries typically adopt different approaches to the pricing and reimbursement of new medicines, which can poten-

tially be classified into those countries that assess the level of innovation of new medicines against existing standards using HTA principles as part of price negotiations such as Austria, France and Germany [4,5,21,128]. Alternatively, basing reimbursement and funding decisions on economic criteria such as cost/QALY with or without threshold levels [4,5,21,129,130]. Currently, only a minority of countries using economic principles set threshold levels [21]; with suggestions by some that threshold levels should be lowered for long term sustainability [131].

European health authorities are increasingly requesting Budget Impact Analyses (BIA) as part of health economic assessments for reimbursement/funding and formulary approval decisions [4,109]. This will help with future forecasting, building on current initiatives [109,110] as BIAs help estimate the possible financial consequences with the envisaged diffusion of new technologies into healthcare systems [132]. Key components of any budget impact analyses include [109,133]:

- The perspective of the budget holder/payer.
- The defined time horizon (which is typically up to 3 years).
- Clearly defining the setting.
- Expressing the results as undiscounted cost differences between the use of the new medicines and the current situation.
- Taking into account potential trade-offs in terms of healthcare resources taking account of the potential variable effectiveness of the new medicine in different populations, especially if there are likely to be differences in the patient populations in routine clinical care compared with the Phase III trials.

There are concerns though with the majority of published BIAs including issues of bias, which negatively impacts on their current usefulness to health authorities [134].

Peri-launch activities also increasingly include assessing possible managed entry agreements (MEAs), sometimes referred to as risk sharing arrangements or other definitions [25,91,94,95], especially in Europe. However as mentioned, there are increasing concerns with such schemes, whether financial based or outcome based, among health authority personnel [25,91,109]. A key consideration, especially for outcome based schemes, is the availability of IT systems to routinely collect data on the use, effectiveness and safety of new medicines as part of these schemes. The use of individual patient records or registries for each new medicine, as well as any paper based scheme, quickly becomes challenging for clinicians and other healthcare professionals [91]. However, these concerns have to be weighed against the potential benefits of MEAs including [91,94,109]:

- Improving the opportunity for reimbursement, especially if decision making includes economic considerations such as cost/QALY and/or strict pricing criteria for new medicines, and for 'payers' to work within defined budgets.
- Such schemes help limit the 'off label' use of new medicines and/ or indication creep in clinical practice.
- Potential for payers to only fund new medicines that produce the desired health gain and/or help target physician prescribing to those patients where health gain is greatest through for instance biomarkers and other strategies.

- Enhance the ability of health authorities to monitor the safety and effectiveness of new treatments in routine clinical practice, especially where patients may be more elderly and/or more co-morbid than those enrolled into Phase III clinical trials.

In addition, with respect to ultra-orphan medicines, given the complexities of R&D, conditional approval and reimbursement including managed entry schemes may be one way forward to enhance their reimbursement and funding [135]. However, a prerequisite should be the demonstration of a minimum significant clinical benefit within a reasonable time frame, with limited reliance on any surrogate measures [135].

Consequently, there is an urgent need for publications assessing the impact and usefulness of MEAs against agreed criteria to provide future direction.

There are also concerns with current approaches to the pricing of cancer medicines and those for orphan diseases leading to proposed changes. These are summarized in Sections "New Cancer Medicines" and "New Medicines for Orphan Diseases" below. New proposals are also being considered for gene therapies given their likely costs, which include annuity payments [136,137]. Debates regarding the funding of new gene therapies will continue as more are launched.

New cancer medicines

Concerns with increasing prices of new cancer medicines, the limited health gain of an appreciable number of them including potential 'targeted treatments', and the number in development [4,5,55,57,61,62,138], have resulted in suggestions for establishing minimum targets for stating whether new cancer medicines are an advance, or not, for pricing and funding justifications [139,140]. As a result, potentially address concerns that funding of new cancer medicines at high prices, with often limited health gain, has been enhanced by the emotive nature of the disease [63,141]. As a result, negatively impacting on available resources for other patient populations within finite budgets. Similar considerations exist where specific budgets have been assigned to new cancer medicines to the detriment of other disease areas [142]. However, such concerns with the potential impact on raising the bar for licensing and funding considerations are not universal [143,144].

Suggestions for advanced cancers center on minimum increases in additional survival, especially given concerns with surrogate markers such as progression free survival, and overall response, on their impact on overall survival [4,55,139,145-148]. These debates will continue, with HTA analyses playing an increasing role.

Other suggestions to help improve future pricing and reimbursement considerations in challenging areas include multi-stakeholder debates to better align the needs for robust evidence requirements, given concerns with surrogate markers, and a collectively shared definition and acceptance on what are clinically relevant benefits for patients and society across disease areas [149]. As a result, help better shape the concepts of value to improve pricing and reimbursement deliberations in the future and reduce current controversies. This is particularly important in the cancer area given the appreciable number of new cancer medicines in development, and their likely prices, coupled with considerable unmet need [5,16,67].

New medicines for orphan diseases

There is also increasing concern regarding the funding for new orphan medicines given ever increasing prices [4,5], despite potential offsets with risk sharing arrangements [135]. Such concerns are exacerbated by situations where new medicines for orphan diseases have been funded up to 15 million Euros/QALY the non-classic form of Pompe disease [69]. However, this is not always the case with ten (over 50%) of 19 orphan drugs available on the EMA website in November 2013, for which health economic data were available, met a threshold level of 30,000 GB£/QALY [150].

Such deliberations have resulted in the development of multicriteria decision analyses tools involving all key stakeholder groups [4-6,151,152]. Examples include the Transparent Value Framework developed via an EU initiative [6]. It is expected such developments will grow given the number of orphan medicines in development, including very targeted cancer therapies [67,153].

Post-launch activities

Post launch activities are increasing as payers and others wish to assess the effectiveness and value of new medicines in routine clinical care, building on examples in for instance France. This includes any assessment as part of adaptive pathways programmes or MEAs.

As mentioned, this has included assessing rates of infection and cancer with the use of biological medicines to treat immunological diseases such as rheumatoid arthritis and psoriasis [100-106], as well as assessing long-term graft survival in kidney transplant patients prescribed either cyclosporine or tacrolimus [107]. Other examples including assessing the appropriateness of prescribing, as well as the effectiveness and safety of new oral anti-coagulants such as dabigatran given early concerns [3,154-156] as well as the use and potential risks associated with medicines for weight loss [157]. Post launch activities also include risk management plans, which incorporate risk evaluation and mitigation strategies normally required by the EMA and FDA as part of any medicine approval process to help ensure that the benefits of any new medicine outweighs its risks [158,159].

Conclusion and Next Steps

It is likely that the managed entry of new medicines will become more formalized with increasing horizon scanning and budget activities before launch, especially with developments such as adaptive pathways. This will require an increasing role for HTA and the development of additional skills dealing with increasing uncertainty.

It is also likely that we will see developments in reimbursement decision making especially for new cancer medicines and those for orphan diseases, as well as new gene therapies. This is essential given their potential budget impact and continuing concern with available resources coupled with continuing unmet need. All key stakeholder groups should be part of such developments in the future.

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