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Criteria associated with Health Technologies Assessment funding decision

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Special Thanks

To Marie and Joachim

The use of evidence is most successful when local differences are factored into the decision-making process, whether at clinical, system or policy level.
John M Eisenberg [1]

Evidence does not make decisions, people do
RB Haynes

Contents

Ps: update via the key F9

List of acronyms

ASMR	*Amelioration du Service Medical Rendu*
CADTH	Canadian Agency for Drugs and Technologies in Health
CEDAC	Canadian Expert Drug Advisory Committee
CDR	Common Drug Review
CEPS	*Comité Economique des Produits de Santé*
EMA	European medicines agency
FDA	Food and Drugs administration
FJC	Federal joint committee
HAS	*Haute Autorité de santé*
HTA	Heath technology assessment
IQWiG	*Institut fur Qualitat und Wirtschaftlichkeit im Gesundheitswesen*
JODR	Joint Oncology Drug Review
NME	new molecular entities
NICE	National Institute for Health and Clinical Excellence
NHS	National health service
OECD	Organisation for economic cooperation and development
PBAC	Pharmaceutical benefit advisory committee
QALY	Quality-adjusted lifeyear
R&D	Research and development
SMC	Scottish medicines consortium
SMR	*Service Medical Rendu*
TAR	Technology assessment report
TLV	Pharmaceutical benefit board (Sweden)
UNCAM	*Union Nationale des Caisses d'Assurance Maladie*
WHO	World health organization

Introduction

Pharmaceutical industry is facing unprecedented challenges to its business model. In recent years the productivity of pharmaceutical research and development (R&D) has experience the downturn. From 1998 – 2008, the number of new molecule entities approved per year declined, where as attrition rates, development times and R&D expenditures have all increased [2, 3]. The cost of development of new drugs have increased, as have total R&D expenditures, while the rate of introduction of new molecular entities has at best remained approximately constant and attrition rate have risen sharply, especially in late phase clinical trials [2]. The industry's profitability and growth prospects are also under pressure as healthcare budgets become increasingly strained [4].

In the other hand the sustainability of health care systems worldwide is threatened by a growing demand for services and expensive health innovation technologies. In most developed countries, health care expenditure has increased. In 2010, the average expenditure on health in France, United kingdom (UK), Germany, Canada, United States (US) was about 12.4% of gross domestic product, with the highest leveling US 17.6%. This translates to about US$ 4885 per capita on average. In these countries, more the 70% of health expenditure is share by government (table 1). One major drivers of health care cost has been the discovery and the diffusion of health technologies. Expenditures on pharmaceutical are the fastest growing sector within health care in developed countries [5].

The increase of health care expenditure have stimulate health policy maker to explore more efficient and effective health care delivery option. Organization responsible to managing healthcare budgets increasingly required evidence on value for money. To be good value, drug has to provide health gain at a price that is deemed affordable. Health technology assessment has emerged as one of the ways to addressing the increasing tension face by all heath care systems when they are managing the introduction of new and often costly health technologies with finite health care budgets [6, 7]. HTA was adopted by governmental and quasi-governmental agencies in many other countries as a tool to assist in controlling the use of new medical technologies. Canada, Australia were early pioneers of this approach, and by 2011, many major market have established processes that consider the value or efficiency, of new drugs as part of the reimbursement de decision making. Across Europe there is an emergency and growth of official health technology assessment agencies with responsibilities for determining reimbursement norms and pricing of health innovation technologies [8].

Today, HTA is an accepted part of the decision-making process for use and reimbursement of new and existing health technologies in many industrialized countries and is also gaining traction in many developing nations. HTA has been defined as ‘‘a

multidisciplinary field of policy analysis, studying the medical, economic, social and ethical implications of development, diffusion and use of health technology.'' It examines the impact on society of health technologies and "makes possible the acceptance, modification or rejection of technologies on a rational basis". It does this by asking four questions: does the technology work, for whom, at what cost, and how does it compare with alternatives? [9]. The goal of HTA is to optimize the health outcomes for a population of insured patients by considering all available treatment options while accounting for budgetary constraints [10].

The decision making process of HTA organisation can be conceptualized as and evidence based decision making process. This process included two elements: assessment – the process of collecting, synthesizing, assessing, and interpreting all relevant available evidence on epidemiology, burden of disease, effectiveness, cost, system impact, acceptability in a systematic unbiased and transparent manner; and decision making – the appraisal of information from assessment together with all other relevant information, to arrive decision that reflect the values and priorities of the system to which the decision are accountable [11].

As it is presented in figure 1, in the majority of case, pharmaceutical industries should prepare a submission dossier for reimbursement, which included evidence on clinical efficacy and safety of the new product, relative efficacy of the new products compared the what already exist in the indication, economic modelling, etc. The collection and the structure of evidence provided in this dossier are generally predefined by guidance set up by HTA organisation. For pharmaceutical industry perspective the HTA process is a new hurdle added in the complex and long process for market access.

Several tensions encompasses the decision making process in these agencies: in one respect these agencies are charge to produce evidence based decisions, but in the other regard these agencies are politicised in that the have to afford interested parties access to the decision making process, through the myriad of stakeholders involved in process (health professional, patients advocacy representative, health insurance representative, etc.). These raise questions about the extent to which recommendations should reflect contextual experience rather than just research evidence, the extent to which practical constraint should shape recommendations. Do decision maker take all dimension reported in the dossier into account in their decision process? Which information's are considered necessary and sufficient by decision maker for their recommendation?

To address these issues we have analysis the decision making process of HTA in order to answer the following questions:

- What criteria are used by decision maker in HTA in their actual practice?

- What is the relative weight decision maker attached to each of these criteria?

Answering these questions promotes transparency in decision making process and will enable pharmaceutical industries to improve the quality of dossier submitted to HTA for reimbursement and at the end minimize systematic risk and reduce uncertainty to market access associate to HTA agencies.

Objective

Achieving market access for a new product involves understanding the current evidence requirements for reimbursement, recognizing the challenges these hurdle pose to pharmaceutical industries and define a strategy to address these challenges.

There is a need of more research into the use of evidence in HTA agencies and its linkage to with policy making in country by conducting detailed comparative studies of different countries decision making.

Using retrospective analysis of past decisions, we have analyzed the decision making process of HTA agencies to identify what factors have influence decision and explore how these issues might be associate with reimbursement decision.

The main questions of interest were:

- What criteria are used to make reimbursement decision?
- What is the relative weight of decision maker attach to these criteria

To have a full picture of decision making process and to understand the impact of these criteria, two other questions were explored:

- What is the level of agreement among HTA agencies in their reimbursement decision?
- What methodology is used for decision making in HTA agencies (organization, who are decision makers, etc.)

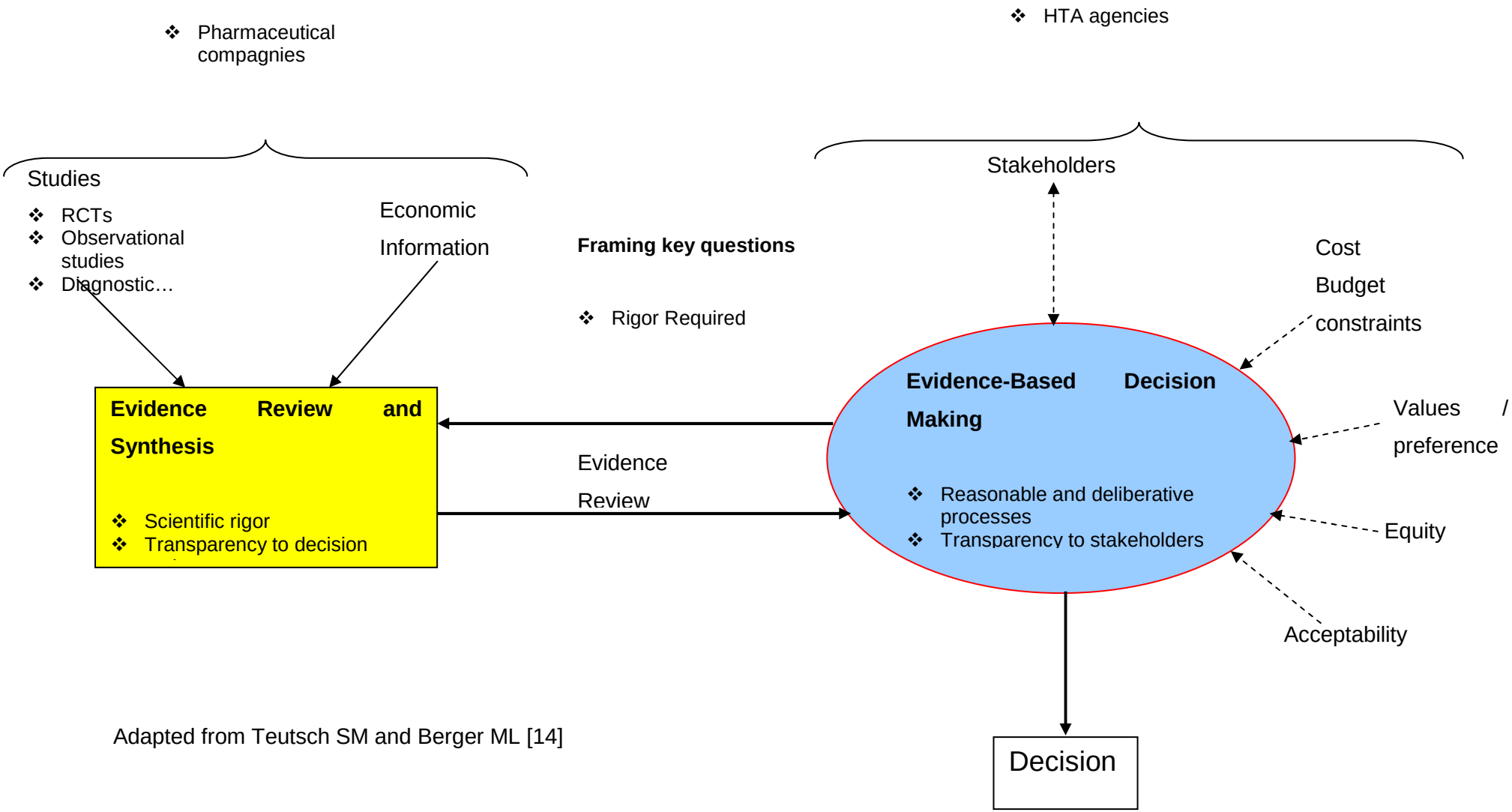
Before the analysis of these questions, the economy of drug development was synthesized.

Table 1. Health care expenditure in five developed countries (sources WHO and OECD [12, 13])

Country	Health expenditure as percent of Gross domestic product (GDP)		Percent of total health expenditure that is government founded		Per capita total health expenditure (average exchange rate US$)	
	2006	2010	2006	2010	2006	2010
France	11%	11.6%	79.7%	77%	3,937	3974
UK	8.2%	9.6%	87.3%	83.2%	3,332	3433
Germany	10.6%	11.6%	76.9%	76.8	3,718	4338
Canada	10.0%	11.4%	70.4%	71%	3,917	4445
US	15.3%	17.6%	45.8%	48.2%	6,719	8233

UK United Kingdom; US = United states

Figure 1. Process evidence synthesis and evidence based decision making in HTA.



Adapted from Teutsch SM and Berger ML [14]

2 Economy of drug development and market access

Transforming pharmaceutical discoveries into new medical products is a lengthy, risky and expensive process and is based on the expectations that future market environments will reward successful drug innovation with premium returns. Risk in pharmaceutical industry is a result of scientific, regulatory and economic uncertainty.

2.1 Scientific risk of the development process of new drug

The development of pharmaceutical is a highly regulate process. Pharmaceutical companies should follow established guidance of regulatory agencies for market authorization on a designate indication. To successfully complete the decision process for market access regulatory agencies require considerable among of evidence at each step along the drug development continuum. The development of new marketable drug product requires the establishment of basic knowledge related to a disease, the discovery of possible treatments, the engineering of methods of drug production, and the performance test to establish safety and efficacy. Each stage may be costly because of the complexity of human health, compound manufacturing, and treatment response.

Because of this regulation, the process for drug development is somewhat standardized. Roughly a new drug development process can be divided into four major phases (figure 2):

- Discovery and Pre-clinical research
- Phase I clinical study
- Phase II clinical study
- Phase III clinical study

Discovery and Pre-clinical research

The most important part of this stage is the discovery of a key molecule. It involves an understanding of the molecular mechanisms provoking the target disease, and the screening of chemical or biological molecules. The chosen molecule is then being investigated in both laboratory experiments and animal models for potential safety and biological activity. These trials normally involve toxicity tests on different animal species, usually rodents (rats, mice) and non-rodents (dogs, monkeys). As the result of this research, a candidate drug is selected with the conclusion that it may be useful in treating sick patients in the target therapeutic area. The length of this stage is very difficult to estimate, as the time of a discovery is almost unpredictable.

Phase I clinical study

Once the pre-clinical study is completed with favorable results, the drug candidate is filed to apply for permission to administer to humans. Namely, a committee must ethically approve these trials, as for any others and the volunteers must be closely monitored throughout the study. When authorities give their ethical approval, the potential drug is then tested in the frame of clinical phase I on 50 to 100 healthy volunteers. The primary goal of this stage is to assess safety, tolerance and drug metabolism in humans. These trials may last one or two years.

Testing is conducted in a small number of healthy volunteers to obtain information on toxicity and safe dosing ranges in humans. Also, drug's absorption, distribution in the body and elimination from the body are investigated

Phase II clinical study

Phase II clinical studies are carried out to investigate the effect of the potential drug on patients. This is the first time when the drug candidate is tested to treat the people with targeted disease. The objective of this phase includes evaluate the dose response efficacy, controlling side effects, and obtaining dosing information. These trials are carried out on 200 to 400 patients with target disease and may last one or two years.

Phase III clinical study

Phase III clinical studies involves thousands of patients, and is, therefore, the most important and costly part of the drug development process. This phase is the major efficacy and safety trial performed in the patient population. It provides further evidence of therapeutic effects and expands knowledge of side effects, toxicity, and general safety of the drug candidate. The experiments are typically double blind using randomization and test of new treatment versus control groups (placebo or active comparator). Consisting of 1000 to 3000 patients with targeted disease, phase III trials are of an order of magnitude larger than that of phase II trials, and therefore may last on average 2 to 4 years.

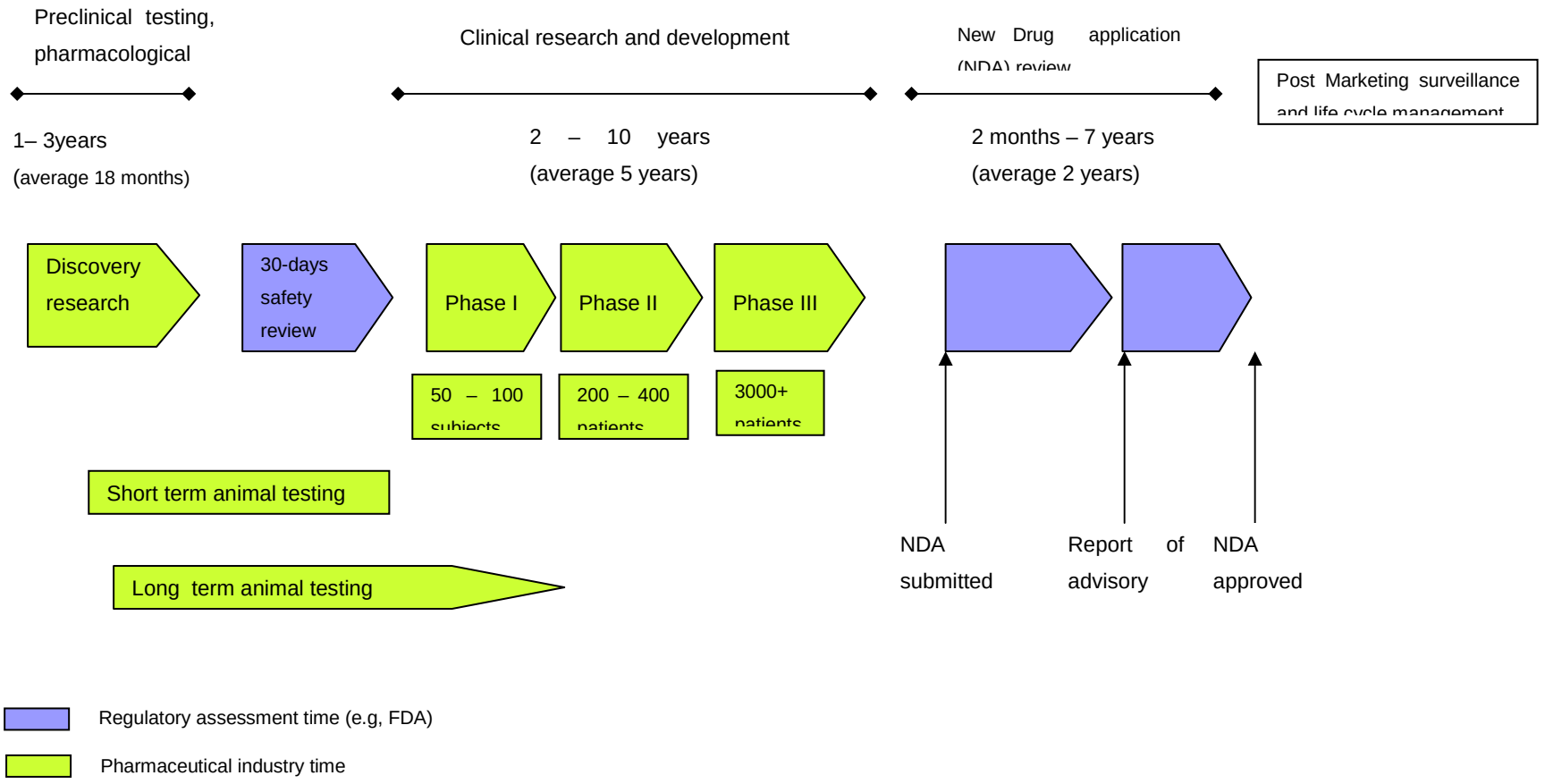


Figure 2. The drug development and approval process.

2.2 Economic uncertainty of drug development

Total cost estimate of drug development

There is evidence from a number of studies that the average R&D cost for a new drug introduction has been growing significantly faster than general inflation [15]. Survey from 1983 to 2000 estimated that pharmaceutical companies costs for launching a new drug were ~USD$802 million. Refined estimates using more recent data from 1997 to 2001, suggest that the figure is closer to USD$1.7 billion. In studies were various estimate of cash spent per successful drug were provided, Morgan S et al [16] found that the cost of development of new compound have increased 8 fold over 30 years; from USD $92 million for drugs developed in the 1960s and 1970s to USD$737.7 million for drugs developed in the 1990s and 2000s (all figures in years 2009 dollars). Over this period, their estimates of capitalized costs have increased nearly 9-fold: from USD$161 million to USD$1446.8 million. While part of the increased in their total estimated cost of drug development results from failure of drugs at later stages in the development process. Much of the increase in their estimates over time stems from higher cost at each stage of the development process [17].

The productivity of pharmaceutical R&D

The productivity of new drug R&D has been attracting attention for decades. The pharmaceutical industry is struggling against ever increasing R&D costs while its output, the number of new drugs successfully marketed, is decreasing. Despite technological advancements and large R&D investments, the number of new drugs (New molecular entities (NMEs) and New biological entities (NBEs) approved per year by FDA was the lowest (20–25 per year) during six years (2005–2010) [18]. In 2003, a report on suggest that R&D productivity was declining rapidly, with only 1 in 13 discovered compounds making it to the market as compared with launch rate in 1 in 8 compounds between 1995 to 2000 [19, 20]. Furthermore, the average time of development has increased from 9.7 years for products launched during the 1990s to 13.9 years for products launched from 2000 onwards [2, 21]

Many experts believe that total number of drug approvals per year may not rise dramatically during the coming two to five years at least for primary indications. This low approval rate is also compounded by rising drug development cost [18]. Incorporating success rates observed at various clinical phases, table 2 shows the 2010 productivity trend and percentage of molecules surviving at each clinical phase. The drug discovery

productivity (6%) during 2009 and 2010 seems to be one of the lowest in pharmaceutical history [18].

Table 2. Productivity trend in 2010, the clinical success is presented as a percentage surviving at each clinical stage

	Preclinical*	Phase I	Phase II	Phase III	FDA approval
Success rate	100%	70%	17.5%	8.5%	6%

*start point.

2.3 Regulatory risk in drug development

Regulatory risk occur because the time required for new drug approval further delays product marketing, and because marketing approval is not assured [21]. In all major market, before a new drug can be marketed, it is rigorously reviewed and follows an approval process set by regulatory agencies. The most recognized agencies responsible for approval of pharmaceutical drugs are Food and Drug Administration (FDA) in Unites states and European Medicines agency (EMA) for European Union [10, 22].

The assessment performed by these regulatory agencies focus on benefit–risk assessment; that is, they address the question of whether the drug will do more good than harm in a defined group of patients. This objective is illustrated by EU regulation governing marketing authorization at the level of the European Medicines Agency (EMA): “Authorisation decisions … should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations”3. The US Food and Drug Administration (FDA) and regulators in other jurisdictions are governed by similar statutes. This legal mandate implies that each new drug is evaluated on its own merit, but does not require a new drug to be assessed against other available treatments [10]. The process of marketing authorization (or licensing) is often referred to as the first three hurdles: quality, safety and efficacy, or benefit risk assessment [10].

Regulatory system for monitoring and approving pharmaceutical drugs has been developing over time. This assessment process for granting of marketing approval is now well-established and use standardized registration procedures. Regular meetings now take place between pharmaceutical firms and regulatory agencies. When the clinical studies have been completed with a successful outcome, documentation detailing their results is assembled and submitted to these agencies for approval. This documentation is

known as a Product License Application in the case of a biopharmaceutical, or New Drug Application in the case of a traditional pharmaceutical company. FDA takes about one year to review the application. It may approve the drug for the indicated therapeutic area, but may ask for additional information or studies, or may not approve the drug.

3 The emergence of health technology assessment agencies

Until the 1990s, the marketing authorization (or licensing) was the sole hurdle to market ass for pharmaceutical industry. However in the past 20 years there was heightened concern regarding reimbursement and market access for newly discovered drugs, which had led to the gradual development of an additional hurdle to market access: Health technology assessment agencies (or payers) [8]. Today, for most approved prescription drugs, pharmaceutical company holder of marketing authorization will the seek reimbursement from a third party payer such as national health service in the European Union or Medicare or private – sector pharmacy benefit manager in united states [10]. The HTA agencies assessment determines the usefulness of the drug to decide on coverage by national (or private) health insurance funds. The usefulness of a drug is usually given by:

- its efficacy (“does the drug work under optimal circumstances?”),
- effectiveness (“does the drug work in routine care?”),
- and efficiency (“is the drug used to maximize value for money?”).

The determination of effectiveness and efficiency is thus part of the post-listing assessment process. They depend on national priorities, taxation rules, and culture [10, 22].

Several industrialized countries have national-level decision making process to select drugs to be covered by public health care system (for example, Australia, UK, France, Canada, Sweden, etc). in these countries, official HTA agencies are actively implemented. The requirement to justify the reimbursement of pharmaceuticals innovation through HTA agencies is become an important hurdle, with significant additional layer of uncertainty, for pharmaceutical industries. It is an additional barrier to market access, after demonstration of product quality, efficacy, and safety to obtain a product license by regulatory agencies. Figure 3 summarized the value chain of market access including HTA agencies and table 4 provide a comparative description of HTA agencies and regulatory agencies

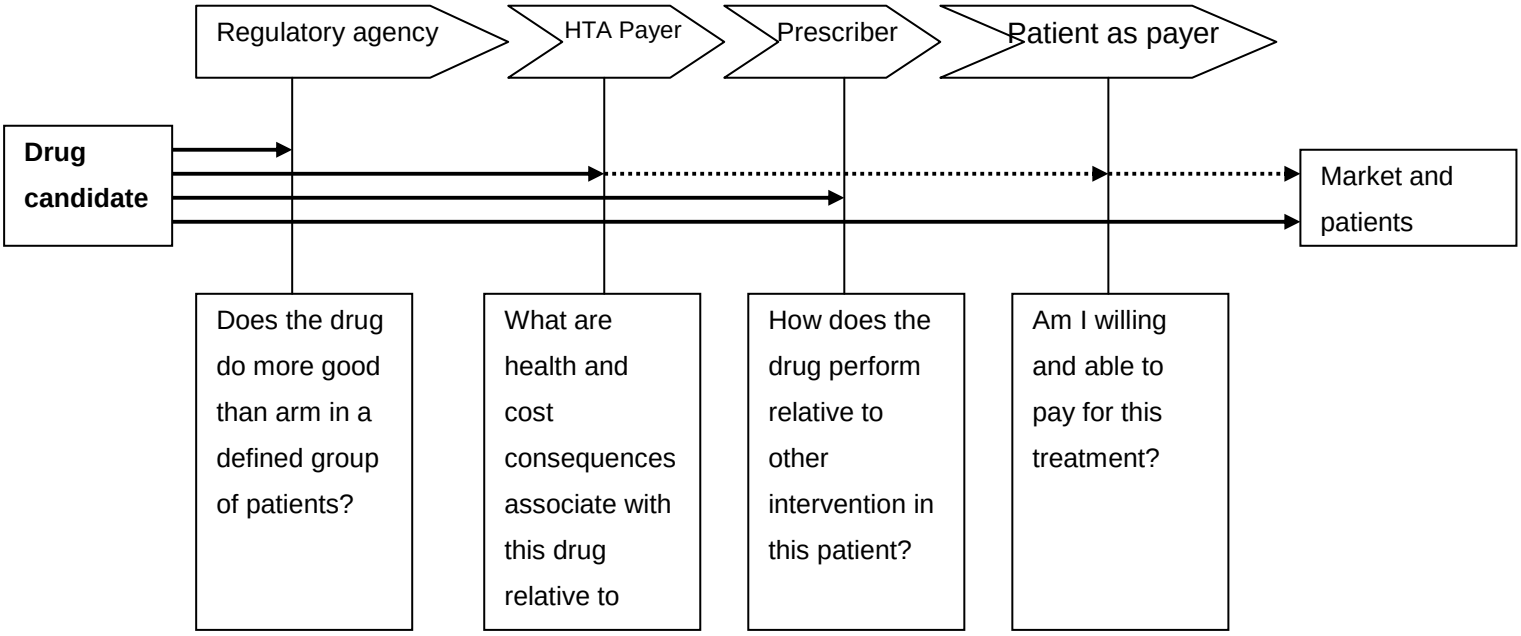


Figure 3. The value chain of market access

3.1 The potential impact of HTA

Increase uncertainty in reimbursement decision

Recently, Kanavos et al. [23] have analyzed technology appraisal performed across six agencies in order to better understand the similarities and the difference in appraisal process and the recommendation that follow. The agencies selected were common drug review (CDR) in Canada, the pharmaceutical benefit advisory committee (PBAC) in Australia, the national institute of clinical excellence (NICE) in England, the Scottish medicines consortium (SMC), the Dental and Pharmaceutical benefits board (TLV) In Sweden, The national Health Authority (HAS) in France.

In this analysis HTA recommendations between agencies differ in more than half of the cases, whereby some agencies accepted these drugs in most cases, whiles others rejected theme in almost 50% of the cases.

The poor agreement between reimbursement recommendations made by the CDR and PBAC and between NICE and PBAC was further confirmed by Clement F et al. [24]. These authors have analysed the 91 submissions in which the same drug was reviewed between the three agencies they found that the level of agreement was moderate between NICE and CDR [24].

Moreover, in Pomedli S study [25], of the 21 pairings of dossier of anti-cancer drugs evaluated by at least two agencies, 14 had convergent recommendations, while 7 were

divergent. These results highlight the unpredictability of HTA decision making by pharmaceutical industries. Two case studies are presented below to illustrate the new challenges (the impact) of HTA bodies for pharmaceutical industries. These studies highlighted the increased of uncertainty in drug coverage. Pharmaceutical industries need to find the way to reduce this uncertainty.

Reduction of probability of reimbursement of pharmaceutical innovation

Furthermore it seems that the final decisions of HTA tend to reduced market access and then they reduce the size of the target population. For example, Ferner and McDowell [26] have analyzed the final decision of the NICE (UK HTA agency) guidance published between 1999 and 2005. In this study, the authors found that the positive outcome (Yes) was given to less than a quarter of drugs submitted to NICE. 19% of drug received "NO" outcome meaning insufficient evidence to used or lack of cost-effectiveness (Table 3). In another study Clement FM et al. [24] have analysed the outcomes of submission dossier to NICE in UK, CDR in Canada and PBAC in Australia. They found that the probability of listing (recommendation) was 87.4% for NICE, 54.3% for PBAC and 49.6% for CDR. Comparatively, CDR seems to be more likely to provide negative recommendation. In another study, Pomedli S [25] found the same trend among these three HTA bodies for the recommendation of the specific class of anti-cancer therapy. In Pomedli study the final recommendation was position for 47% of dossier submitted to CDR, 80% by NICE and 81% by PBAC.

Table 3. Summary of final decision of NICE guidance

Outcomes	Meaning	Frequency
Yes	▪ Should be used routinely ▪ Can be consider as an option	27 (23%)
Yes with major restrictions	▪ Used only as second or subsequent line of treatment ▪ Used only if intolerant of other treatment must show response within a specify time ▪ Restricted to sub-groups within licensed indications	38 (32%)
Yes with minor restriction	▪ Use the least cost option ▪ Monitoring required ▪ Use by specialist only	30 (26%)
No	▪ Insufficient evidence for use ▪ Do not used because of poor cost-effectiveness	22 (19%)

With HTA appraisals having such an important role in decision making for adoption of an intervention and making or breaking market access, pharmaceutical industries need to understand the process of decision making involved in reimbursement-focused decision makers, and elucidate factors determining which type of recommendation is made. The understanding will increase probability of good HTA recommendations.

Table 4. Regulatory approval, HTA, and coverage processes (adapted from Van nooten F et al. [27] and levy AR et al. [28]

	Regulatory approval	**Health technology assessment (HTA)**	**Coverage**
Legal authority	Generally defined in national public health legislation, with regulatory bodies accountable to the government in their jurisdiction.	HTA may be undertaken by a group within and accountable to a coverage body itself, and/or by groups within and accountable to a government department, university, hospital, research institute, or industry	Generally defined within the rules and regulations of the healthcare system in which decisions are being made, with coverage bodies generally being accountable to the healthcare system within which they operate. In some healthcare systems, the role and responsibilities of a coverage decision making body may be defined in legislation and such a body may be accountable to government
Role	To decide on market authorization for a product in the relevant jurisdictions on the basis of assessments of safety, quality, efficacy, and benefit risk profile. Regulatory bodies often also have a role to promote or support the development of new treatments addressing important unmet health needs	To provide the best evidence available to inform decisions about coverage, and decisions about use by patients and clinicians and/or tools to support those decisions, such as clinical practice guidelines	To decide whether a product should be covered, paid for, and/or reimbursed within a particular healthcare system, on the basis of assessments of relative effectiveness, cost, and in some systems affordability and/or value for money, given current practice, funding, priorities, and social values within the system
Decision	Does the product do more good than harm for patients with defined indications in this jurisdiction?	HTA seeks to support decisions on whether an intervention offers useful, appropriate, and affordable benefits for patients in a particular healthcare system	Will the product offer useful, appropriate (and affordable) benefits for some or all eligible patients in this healthcare system?

Evidence considered	Pre-launch, typically evidence on efficacy from randomized controlled trials (RCTs), usually placebo-controlled, although active controls may be required particularly when placebo control would not be ethical. Post-launch, evidence on relative efficacy, effectiveness and/or relative effectiveness may also be considered when reviewing a product's ongoing benefit-risk profile.	Such evidence on relative effectiveness/ efficacy (and costs and opportunity costs across the system) as can be assembled from all relevant trials (of the product and alternatives) with placebo or active controls, and where necessary other study designs and/or analytic techniques such as modelling	Initially, such evidence on relative effectiveness (and costs and opportunity costs) as can be assembled from all relevant trials (of the product and alternatives) with placebo or active controls, and where necessary other study designs and/or analytic techniques. Coverage or ongoing coverage may sometimes be made conditional on the collection and review of further evidence post-launch or initial/provisional coverage. Evidence considered may or may not be in the form of an HTA

4 Methods

Case studies

To illustrate the similarities and difference of recommendations between different HTA bodies, three drugs class were selected:

- Cancer drugs, (there is a important clinical need for innovative therapy in cancer and most new anti-cancer drugs are associated with high costs)
- Diabetes (important public health problem with high prevalence and incidence around the world),
- Central nervous system (Alzheimer and Multiple sclerosis drugs).

Each serves to highlighted different key issues commonly encountered in the decision making outcomes of HTA.

Selection of HTA bodies

The report will focus is on the decision-making process of HTA bodies in France, United kingdom (UK), Germany and Canada. The choice of these countries relies on conceptual basis, not on representative grounds. The selection was based on the following criteria: country system analysed during the EHMBA, the country have to have had an established agency history, operate nationally and be mainly publicly financed.

Data and information collection

Web sites of agencies and literature search were consulted to identify relevant data. A comprehensive literature search was performed in Pubmed with a structure search strategy that combined “decision making”, “HTA”, “payers”, “resource allocation”, “health technology assessment”, “comparative effectiveness” with “prioritisation criteria”, “reimbursement”, “coverage”. A search of grey literature on internet was also conducted.
In order to focus on the analysis of actual decision making processes and to gain the best insight into decision making process as a whole, we included only studies that focused on decision making bodies. The majority of studies found in review were qualitative studies. The estimated relative importance of decision making criteria in the studies in based on interpretation of studies results.

Framework

To analyse the available data of HTA bodies, the framework proposed by Hutton J et al. [9] was followed. These authors have used a modified Delphi process to develop an analytical framework to described HTA. The framework included 2 levels:

- Policy implementation level:
    - the establishment of the fourth hurdle system as a policy decision of government, the policy objectives of the system, its legal status, and its

relationships with the remainder of the health system, with other public sector bodies, and with other stakeholders, such as industry and patient groups.

- Individual technology decision level:
    - the processes by which individual technologies are dealt with by the system, for example, assessment processes, how decisions are made, and how they are implemented.

For the purpose of this report, we will focused only on the individual technology decision level which include 3 dimensions:

- the assessment of evidence,
- the actual decision making,
- and outputs and their implementation.

These sets were grouped in four areas: (i) constitution and governance, (ii) methods and processes, (iii) use of evidence, and (iv) accountability and transparency.

Decision making framework.

	Assessment	**Decision**	**Output and implementation**
Constitution and governance	Consultation and involvement of stakeholders	Who makes the decision	Appeal and dissent
Methods, processes	Methodology	Decision-making process	Implementation and communication
Use of evidence	Evidence-base for assessment	Evidence-base and additional influences on decision	Monitoring and reappraisal
Transparency, accountability	Presentation and communication of assessment results	Content and documentation of the decision of the decision	Evidence of impact

5 Results

5.1 Structure and characteristics of HTA in England, Germany, France and Canada

In the literature, HTA has been call the “bridge between evidence and policy making”, because it seek to provide a range of stakeholders (typically involved in funding, planning, purchasing, commissioning and investing in healthcare) with accessible, usable and evidence based information that will guide decisions about technology and the efficient allocation of resources. It is a multidisciplinary activity that systematically examines the safety, clinical efficacy and effectiveness, cost effectiveness, organisational implication, social consequences, legal and ethical consideration in the application of a health technology – usually a drug, medical device or clinical/surgical procedure [6]. The full descriptive analysis of HTA agencies from England, Germany, France and Canada is presented in appendix 2.

England (NICE)

In **England**, the National Institute for Health and Clinical Excellence (NICE) was established in 1999 to provides a centralized HTA function for those technologies expected to have “major health implications, budgetary impact, or controversy over effectiveness” [23, 29]. NICE issues guidance on health technologies and clinical practice, with the underlying policy target to maximize health gain within NHS budget [30].

NICE follow a post-listing assessment process. Prices are fixed by pharmaceutical companies. The effectiveness of a drug class (multiple health technology assessments) is assessed once results under real-life conditions have become available (negative list). An appraisal committee comprising National Health Service (NHS) clinicians and managers, academic experts, industry, and lay representatives discuss and amend a systematic review of the clinical and economic evidence on the drug—the so-called Technology Assessment Report (TAR) [22]. Standard Multiple Technology Assessments take 52–62 weeks. A Single Technology Assessment (STA) process was implemented to ‘fast-track’ appraisals for urgently needed drugs (examining only manufacturer submitted evidence) reducing assessment time to 39 weeks. A key dimension of the NICE assessment is the cost/utility ratio, that is, the cost per quality-adjusted lifeyear (QALY) gained by an average patient from the use of the drug. QALYs are estimated from the revealed preference of patients. Recommendations made by NICE are required to be implemented by the

Primary Care Trusts (PCTs) within three months of being published (though in practice this may not be the case, and coverage administered at local level may be differential).

Germany (IQWiG)

In **Germany** the establishment of the Institute of Quality and Efficiency in Health Care (IQWiG; *Institut fur Qualitat und Wirtschaftlichkeit im Gesundheitswesen*) in 2004, under the SHI Modernisation Act, represents an effort to introduce health technology assessment (HTA) as a formal element of decision making in health care. IQWiG is financed through a levy on SHI contributions (IQWiG, 2012); its tasks and functions are laid out in the Social Code Book V, especially § 139 a-c and § 35 a-b (Sozialgesetzbuch V – SGB V, 2012) [31]. IQWIG was established to provide the committee with evidence-based evaluations of the benefits and cost benefits of services, and functions in an advisory role. It currently produces 6 types of evaluations and assessments: reports, rapid reports, dossier assessments, addendums, health information and working papers. Reimbursement and pricing decisions are taken some time after listing (delisting, negative list) [22]. Decisions about reimbursement of pharmaceuticals and other medical services (therapeutic and diagnostic procedures) by the sickness funds are made by a Federal Joint Committee (FJC) composed of provider, insurer, and patient representatives [32]. IQWIG sets a ceiling price for drugs in a given therapeutic area. The price set by the pharmaceutical company is reimbursed until the HTA report becomes available. Once the report is available, the German Federal Joint Committee (G-BA, *Gemeinsame Bundesausschuss*), which includes all stakeholders, takes the decision on reimbursement level. In other words, the analyses and the coverage decisions are split between IQWiG and the Federal Joint Committee, respectively. IQWiG and the Federal Joint Committee are funded through a system using revenues from surcharges on SHI payments to providers.

France (HAS)

In France, the Haute Autorité de Santé (HAS) (French National Authority for Health) operates at the central level and provides coverage recommendations on every new drug, procedure and medical device. HAS was created by the National Health Insurance Reform Act of 2004 and was established on January 1, 2005. HAS was established to assist decision-making by public institutions, with the goals of optimizing the basket of reimbursable goods and services and helping health care professionals continuously improve their clinical practice by defining best-care standards and identifying relevant tools and methods. It is an independent, scientific, public authority that has financial autonomy and a unique legal identity [22, 33]..

Unlike in England and in Germany, the effectiveness of each and every drug is assessed immediately after listing (positive list) to help set price and ensure early reimbursement. The assessment of effectiveness is performed by the Transparency Committee of the HAS with the help of a large body of experts.

The twenty appointed voting members of the Committee rate the clinical value of the drug (SMR for *Service Medical Rendu*—Actual Benefit) reflecting the medical and public health benefits and therapeutic value it provides [22]. SMR can be:

- important,
- moderate,
- minor,
- or insufficient)

Drugs are then evaluated against their comparators to assess its added value compared with existing treatments (ASMR for *Amelioration du Service Medical Rendu*, Improvement in Actual Benefit) from 1 (major improvement) to 5 (no improvement).

Based on these rating the French Ministry of Health decides whether or not to place the drug on the positive list for reimbursement. Specifically UNCAM (Union Nationale des Caisses d'Assurance Maladie) uses SMR to determine the reimbursement rate and the Comité Economique des Produits de Santé (CEPS) uses ASMR to support the price. This process thus clearly separates the assessment of effectiveness (HAS) and of efficiency (Ministry of Health). HAS does not conduct economic analysis but is primarily concerned with the drug's efficiency based on clinical (safety and efficacy) endpoints [22, 23].

Canada (CDR)

In **Canada**, HTA is conducted at both provincial and federal levels. The two most populous provinces, Quebec and Ontario, have their own HTA units, which publish advisory reports. At the federal level, HTA is conducted separately for drugs and other medical technologies. For medical technologies, the Canadian Agency for Drugs and Technologies in Health (CADTH) carries out HTA and produces reports that are widely disseminated and available at no charge on their website. These reports are typically commissioned and assessed by experts with some form of peer review [23, 28].

HTA for drugs is performed centrally by two independent bodies: the Common Drug Review (CDR), which is within CADTH, and the Joint Oncology Drug Review (JODR), which is based on the Government of Ontario's existing processes to assess cancer drugs. The CDR, undertaken by the Canadian Agency for Drugs and Technologies in Health (CADTH), operates a decentralized evaluation process. Only new chemical entities (NCEs) and new combination products (excluding anti-cancer drugs) are reviewed, on a first-come, first-served basis. Individual drug plans are not compelled to follow CDR recommendations; however, 90% of the time there is concordance. Roughly 25 appraisals

are conducted annually. Manufacturer-initiated submissions are assigned to clinical and pharmacoeconomic reviewers, who evaluate the product with respect to cost, clinical outcomes, QOL and therapeutic advantages over other available products. The manufacturer is given a chance to respond to the review, after which it is presented to the Canadian Expert Drug Advisory Committee (CEDAC), the advisory group for the CDR. In turn, the CDR provides a national recommendation. The entire review process takes about 26 weeks [28].

Canada has universal, publicly funded health care, although the availability of publicly funded drug insurance varies across provinces and territories [24, 28]**.** Drug reimbursement decisions are made at the provincial/territorial level, with each province and territory maintaining an independent insurance system and formulary. Provinces and territories are free to make independent formulary decisions, but decisions are generally consistent with CEDAC recommendations, although some regional variability is present. The transparency of the decision-making process in Canada is limited, with only brief summary reports made available to the public. There is a formal appeal process in place for manufacturers to challenge negative decisions.

5.2 Reimbursement decision process in HTA agencies

The full process of reimbursement decision in these agencies is described in appendix 1. The description included the following dimension: advisory/decision committee composition, step of review, use of cost effectiveness, timeline for review/decision and appeal mechanism.

The criteria summarized in table 5 are main criteria available in published guidances of these HTA agencies. Overall criteria common to all HTA agencies included:

- clinical need (informed by severity of the condition, burden of illness and availability of already funded, alternative interventions/therapies);
- clinical benefit value (i.e. benefits risk balance derived from evidence of safety, efficacy and effectiveness compared with current care);
- affordability (budget impact, taking into account the number of patients expected to receive the technology and per-patient costs over duration of its use, as well as other resource implications);
- and innovativeness (potential to encourage innovation).

Less common criteria included

- alignment with government health-related priorities;
- feasibility (ease of implementation).

Table 5. Comparison of keys factors considered during committee deliberation

Country	HTA body	Unmeet clinical need			Clinical benefit/value				Cost benefit ratio (value for money)	Impact on health resources affordability (budget impact)	Innovativeness	Others
		Disease burden (severity and number of patients)	Availability of alternatives	Place of drug in care pathway/ strategy	Safety (risk-benefit ratio)	Efficacy/ effectiveness	Side effects	Acceptability (tolerance, convenience)				
France	**HAS (National authority for health)**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not specify	Yes	Yes	Public health impact Cost relative to current treatment
England	**NICE (National institute of clinical excellence)**	Yes	Yes	Yes	Yes	Yes (across patients subgroup)	Not specify	Not specify	Yes	Not specify	Yes	Level of uncertainty surrounding evidence Whether technology represents life-extending end of life treatment Wide societal cost and benefit Quality of evidence Public health impact Alignment with broad government priorities ICERs of already funded drugs
Germany	**IQWIG**	Yes	Yes	Not specify	Yes	Yes	Not specify	Not specify	Yes	Yes	Yes	
Canada	**CEDA (Canada expert drug advisory committee)**	Yes	Yes			Yes		Yes	Yes	Yes	Yes	Solidarity Accessibility to the service Strategic issues consistency with previous decision and precedents Quality of evidence

Adapted from Stafinski et al, 2011.[34]

5.3 What is the impact of HTA on the value chain of pharmaceutical drugs market access?

5.3.1 Case studies

Insulin Glargine

Insulin glargine (a long-acting insulin analogue indicated for adults with Type 1 and 2 diabetes) was recommended for listing in October 2002 by NICE in patients with type 1 diabetes and in a subset of type 2 patients on the basis of 13 randomized trials. In 2006, the CDR reviewed the results of 20 unblinded randomized trials (many of which were unpublished), noting variable results for overall and nocturnal hypoglycemia. Although the CDR felt that the use of insulin glargine may reduce the frequency of nocturnal hypoglycemia, it did not feel that these benefits justified the 3-fold cost and did not recommend listing. The PBAC rejected listing for insulin glargine on 5 separate occasions on the basis of clinical uncertainty resulting from reporting bias in the presented meta-analysis as well as unacceptable cost-effectiveness. On the fifth resubmission, and after extraordinary discussions with the manufacturer, the PBAC agreed to list insulin glargine as an unrestricted benefit based on acceptable cost-effectiveness at a new proposed confidential price. Thus, although each of the committees agreed that insulin glargine offered small incremental benefits over insulin NPH, all felt that unrestricted use at the price submitted was not cost-effective. In response to this, NICE listed insulin glargine for patients with type I diabetes and identified a small niche of type II patients who might be more likely to benefit, while the PBAC was able to negotiate a price that offered reasonable cost-effectiveness, an approach outside of the scope of the CDR's mandate [24].

Anticancer drugs

Another way to assess the impact of the introduction of HTA process is to compare the outcomes between countries were there is an HTA bodies to country where there is no formal HTA bodies. In contrast to European country, the formulary decision is made by private health plans in USA, the process varies widely across private health plan and it is the exception rather than the rule to use HTA process.

In order to understand the degree to which HTA played a role in the decisions, Mason A et al. [35] have compared the restrictions on access to new anticancer drugs imposed in the United States and United Kingdom. The HTA bodies were National Institute for Health and Clinical Excellence (NICE) in the United Kingdom and the Scottish Medicine Consortium (SMC) in Scotland. They have analysed 59 anticancer drugs licensed by US food and

drug administration from 2004 through 2008. Their analysis shows that coverage decisions differed between the United Kingdom and US bodies. In the US, all 59 anticancer drugs were covered by all the decision-making bodies, with some drugs subject to partial restrictions. In the United Kingdom, only 46 anticancer drugs were licensed for use. NICE made positive recommendations for 39% of the 46 drugs, of which 22% were subject to restrictions. For the (final) Scottish Medicine Consortium (SMC) decision the corresponding percentages were43%and 28% [35].

Central nervous system drugs (e.g. Alzheimer's disease and Multiple sclerosis)

Nicod Elena [29] has compared the final recommendations of reimbursement of central nervous system drugs among HTA bodies in Europe, Canada and Australia. Data of HTA report published from 2007 to 2009 were analysed. The HTA recommendation between agencies was classified as follow:

- Positive recommendations
- Positive recommendation with criteria
- Negative recommendation

In France, drug are classified into 5 level according to the relative medical value benefit (ASMR)

- ASMR level I = Major innovation
- ASMR level II = Important improvement
- ASMR level III = Significant improvement
- ASMR Level IV = Minor improvement

ASMR level V = no improvement (equivalent to negative recommendation)

The results of the analysis for Alzheimer and multiple sclerosis drugs are summarized in table 6 for HTA bodies in France, Canada, Australia and England. For these two indications, five drugs were evaluated. The full recommendation was found only for Natalizumab in one HTA Bodies (NICE). For the majority of case the drugs were recommended with criteria, meaning reduction of target population.

Table 6. Comparison of HTA agencies recommendations for Alzheimer's disease and Multiple sclerosis drugs in 4 countries [29]

Generic name	Indication	HTA recommendations			
		Canada (CDR)	England (NICE)	Australia (PBAC)	France (HAS)
Galantamine	Alzheimer's disease		Recommended with criteria	Not recommended	ASMR V
Memantine hydrochloride	Alzheimer's disease	Not recommended	Recommended with criteria	Recommended with criteria	ASMR IV
Rivastigmine, patch	Alzheimer's disease	Not recommended		Recommended with criteria	ASMR IV
Rivastigmine, Capsules	Alzheimer's disease		Recommended with criteria		ASMR IV
Interferon beta 1b	Multiple sclerosis		Not recommended	Not recommended	ASMR I - II
Natalizumab	Multiple sclerosis	Recommended with criteria	Recommended	Recommended with criteria	ASMR III

ASMR : Amélioration du service médical rendu.

5.4 What are important criteria for the decision making process?

Qualitative analysis of important criteria

The emphasis only on core sets of rationales factors limits the analysis of decision making and exclude some important factors such broader personal and political factors which can influence the final recommendation. The decision making process in HTA is partly subjective and value base in nature because of multidisciplinary set of experts and stakeholder others that experts are involved in the process. Few studies have analyses these factors in the setting of health technology assessment. We were able to identify the study of Wirtz et al. [36]. These authors performed in-depth interviews with a range of policy makers and stakeholders in UK. They have identified two important dimension of decision making which are not captured in the rational normally cited criteria:

- One dimension associated with "subjectivity" – personal factors which influence the kinds of evidence and interpretation of the evidence used such as experiences related to the disease, excitement about the novelty or benefit of the technology.
- The other dimension id related to the social and political functions of the decision – such as importance of maintaining relationships, the achieving politically and defensible decisions and the reduction of organizational burden.

In another study, Fitzgerald et al. [37] have analysed, through a qualitative study, what make clinical professional decide to adopt and implement the health innovation in their clinical practices. They found that health innovations were more readily adopted if a number of following key factors were favourable:

- availability of robust evidence to support the innovation;
- the innovation is applicable to many patients or without the intervention, patients will suffer severely adverse outcomes;
- there are neutral cost implication or cost saving;
- the new treatment is not complicate to use by patients;
- the new treatment raise patient satisfaction level.

Quantification of criteria weight

Vuorenkoski et al. [38] have reviewed studies that have empirically analysed a macro and meso-level decision-making process for including drugs in and/or excluding drugs from reimbursement lists and drug formularies in industrial countries. Six studies performed in France, Canada and Finland meet their inclusion criteria. These studies explore questions such as what technical methods are used, what criteria are behind the decisions, what are the procedural frameworks. Analyses of these studies have shown that the criteria used varied between decision making process, however they were able to identify most important criteria in the context of HTA decision, which are summarise bellow.

Table 7. Most important criteria in HTA decision Vuorenkoski et al.[38].

Criteria	Number of studies who reported the criteria
Clinical benefit	6
Cost/ budget impact	5
Past decision (including decision for other HTA)	4
Quality of evidence	3
Safety	2
Size of target population (number of patient with the disease)	2
Availability of alternatives treatment	2
Pressure from physician (excitement from physician)	2

Patients group	2
Disease severity	1
Company activities	1

In Canada, Husereau et al. [39] have evaluated the weight of eleven categories of criteria used by HTA advisory committees. Two committees were used in the studies. Committee members consist of representatives from the health authorities that are responsible for the provision of health services in their jurisdictions across Canada. One committee consists of fourteen representatives from federal, provincial, and territorial publicly funded drug plans (the CADTH Advisory Committee for Pharmaceuticals), while the other consisted of twelve representatives serving various roles in the federal, provincial, and territorial ministries of health. Through face-to-face discussion with both committees, six common core criteria were selected by a majority vote:

- potential clinical impact,
- disease burden,
- potential economic impact,
- potential budget impact,
- available evidence
- available alternatives,

These criteria were considered the most influential in creating priorities for HTA research, representing 73 percent of the weight behind committee members' decisions. The weight associate to each of these criteria in the decision process was 2.58% for clinical impact, 2.16% for disease burden, 16.7% for economic impact, 14.3% for budget impact 13.5% for the quality of available evidence and 8.1% for availability of alternatives.

In the analysis of criteria that drive the NICE recommendations in UK, Dakin HA et al. [40] found that the number of randomized controlled trials (RCTs) and systematic review has significant impact on NICE decision. These variables were particularly influential in the decision between recommending an intervention for routine use. For example, the presence of one additional RCT reduced the probability of an intervention being restricted or not recommended rather than being recommended for routine use by 7 – 10%. Other potential variables included budget impact: the analysis shown that intervention recommended for restriction hade higher budget impact than those recommended for routine use). The cost effectiveness ratio had also a significant impact on decision between restricted and not recommended. However, it is important to note the model developed in this analysis suggest that technical variable explained only 23% of variability of NICE recommendations.

Discussion

The decision making process for market access of a new drug is a complex process taking place along the continuum that start with evidence generation, followed by deliberation on a particular drug and then communication of the resulting decision to key stakeholders. The analysis has shown that the adoption of new health innovation through the HTA process is influence by a range of factors including: clinical benefit, unmet medical needs (disease burden), cost/budget impact, quantity and quality of evidence, size of the target population, availability of alternative.

Table 8. Summary of main criteria with impact on HTA decision

Criteria	Definition	Weight
Clinical benefit	Effect on important outcome, quality of life	High
Unmet need	Severity of disease, availability of alternatives	High
Available evidence	Quantity and quality of evidence	High
Efficiency	Cost effectiveness, budget impact	High
Safety	Effect on safety outcomes	High
Past decision	Previous decision of HTA agencies in the same indication	Moderate
Pressure for physicians	Role of early adopter in the decision making process	Low
Pressure for patients	Action of patient advocacy or representatives	Low

Should the same evidence lead to the same decision in different decision making contexts? In this analysis, low level of agreement between recommendations among HTA agencies was also found. Some HTA agencies were able to fully recommend a product for their population and other will recommended it with restriction or no recommended the new pharmaceutical innovation. There was also a large discrepancy among different countries regarding what should and should not be reimbursed.

Moreover our analysis highlighted that HTA agencies varied in the configuration of institutions responsible for decision and in the sophistication and transparency of the processes undertaken. In some systems, the assessment phase was merged with decision making; whereas in others, separate steps were undertaken by different groups.

The low level of agreement among HTA agencies suggests the critical role of context in the adoption or recommendation. Although the same level of evidence is provide to

different HTA, there was important variability in their final recommendations. This can be explained by the structural difference between the HTA bodies. In fact, the similarity of the structure, the procedural elements and the characteristics of HTA organizations is low. The mandate and process these HTA organisation differed. Overall Schwarzer et Siebert [41] found that the magnitude of similarities, expressed as percentage of identical characteristics in pairwise comparison across agencies ranged between 17% to 40%. Scientific evidence is important but not sufficient to ensure adoption of new pharmaceutical innovation by HTA agencies.

The variability in recommendation can also be analysis through the mechanism of interpretation of evidence, which included recognition of evidence, appreciation and determination of the relevance, applicability, acceptability and utility of different sources o evidences for supporting a decision[42]. As highlighted by Fitzgerald et al.[37], credibility of evidence is only partially dependent on the quality of research and it is influence by other factors such as source of evidence, professional network and trust. All these factors are involved in the mechanism of interpretation of evidence which can lead to different recommendation in difference context.

This analysis should be interpreted while taking into account some potential limitation. First the report included only retrospective published data. It would be of interest to complete the analysis with deep interview with decision maker in real life. Despite increase activity of HTA agencies worldwide, there is currently lack of understanding of the difference in HTA recommendation and the main reason that drive their recommendations. Second the available criteria in the literature focus much more of technical criteria. However one author have found that this criteria explained only 23% of variability in HTA decision making. Although, whatever the decision making process (explicit or implicit) social value judgement affect the decisions [43]. These social value judgment may included both the value of the population found in their civic culture, as well as ethical consideration as weighted by policymaker in their decision. Such decision making involved a range of value including justice, autonomy, beneficence, respect for person, etc. Few studies have analysed the impact of the social value judgment in the decision making process [43]. More research is need in this topic since it can explain important part of variability.

This analysis should also be put into context of other works performed to improve the quality of dossier submitted by pharmaceutical industries to HTA agencies [44] and thus improved the probability of positive recommendation for reimbursement.

Implication for pharmaceutical industry.

Three main recommendations have emerged from this analysis. These recommendations are summarized in table below with their rational.

Recommendations	Rational
Localised the development of evidence for reimbursement dossier in affiliate	Decision in HTA agencies seems to be country specific. There was low agreement between HTA recommendations, due to difference in structure, objective, political perspective and overall strategy of HTA in each country. The "one side fit all" development of evidence process does not hold in the context of HTA. Country affiliate will be more able to understand the need of HTA of their country, since the better we understand the context, the better our position to utilise high quality evidence of all type Evidence to support economic evaluation, budget impact are generally country dependent evidence.
Improved to knowledge and skill of pharmaceutical team who prepared the reimbursement dossier on "evidence based medicine"	The importance of number of RCTs and systematic reviews reflect the adoption evidence base medicine methodology in the HTA agencies
Improved early dialogue with Agencies for scientific advice	To fulfill the need of HTA an early dialogue should be implemented in the drug development with HTA agencies, as it is the case with regulatory agencies. In analysis factor associate with positive outcome by regulatory agencies, Regnstrom et al. [45] found that early scientific advices and compliance to advice was associated to positive recommendations.

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Appendices

Appendices 1. Comparative analysis of HTA decision making process in 4 countries

	France (HAS)	England (NICE)	Germany (IQWIG)	Canada (CDR)
Committee composition	Transparency committee (TC) within French national authority for health : 20 voting member (includes chair): 4 from public institutions 3 from main health insurance fund 1 from pharmaceutical industry 12 with medical and pharmacological expertise	Academics (eg, health economists) Health care providers in National Health Service Representatives from patient and Carer organizations Manufacturers	13 members including representatives from Associations of physicians, dentists, and physiotherapists Hospital associations Sickness funds Patient organizations (nonvoting)	13 members including: 9 physicians 2 general public 2 pharmacists
Steps in review	1. Manufacturer submits application for reimbursement to French National Authority for Health secretariat 2. Internal staff prepares evaluation report based on evidence submitted by manufacturer (focuses on clinical effectiveness, target population, conditions of use, and already reimbursed technologies) 3. External clinical	Single technology appraisal 1. Topics selection panel selects technology for review 2. National Institute for Health and Clinical Excellence invites stakeholders (ie, consultees and commentators (cannot make a submission or appeal recommendation)) to participate 3. Non-manufacturer consultees invited to nominate clinical and/or patient	1. Federal Joint Committee makes decision to assess technology and notifies Institute for Quality and Efficiency in Health Care 2. Institute for Quality and Efficiency in Health Care appoints internal staff to manage and/or conduct assessment 3. Institute for Quality and Efficiency in Health Care carries out consultations with external clinical experts and patient/carer organizations to define assessment scope and protocol 4. Institute for Quality and Efficiency in Health Care posts draft scope and protocol on website for public comment	

	and methodological experts review evaluation report 4. TC reviews evaluation report and expert opinions to appraise the "medical benefit" of the pharmaceutical (on a 5 point scale; I – major to V – insufficient to justify reimbursement) 5. Minister makes final decision on the medical benefit level/score 6. TC then performs comparative assessment of pharmaceutical with already reimbursed alternatives to appraise the "improvement in medical benefit" (on a 6 point scale; 1 – major innovation to VI – negative opinion regarding inclusion on benefit list) 7. Once positive reimbursement recommendation is received, the Comite Economique des produits de Sante	experts to take part in Technology Appraisals Committee meetings 4. Manufacturer completes evidence submission (assessment) 5. Independent academic group commissioned to review submission, along with information received from consultees and nominated experts, and prepare evaluation report 6. Technology Appraisals Committee meets to review evaluation report and hear from nominated clinical and patient experts 7. Technology Appraisals Committee formulates draft recommendations, which are presented in appraisal consultation document 8. Appraisal consultation document made available to stakeholders for comment 9. Technology	5. Internal staff, supported by external experts, prepares assessment, first considering clinical benefit or innovativeness (ie, is the first active ingredient or offers therapeutic improvement); If deemed non-innovative, technology is assigned to 1 of 3 groups: - identical active ingredient; - therapeutically comparable and one active ingredient; - therapeutically comparable and two active ingredients); Technologies with similar efficacy/effectiveness must demonstrate comparable efficiency through findings from efficiency frontier analysis; If deemed innovative (ie, offers added therapeutic value over already reimbursed alternatives), "cost-benefit" analysis is performed to set maximum reimbursable amount; if technology treats life-threatening condition for which there are no alternatives, cost must not be considered. IQWIG steering committee reviews draft report and recommendations for quality assurance 7. IQWIG posts draft report and recommendations on website for public comment 8. Staff prepare final report, incorporating comments received and recommendations, and	

	= negotiates price with manufacturer and the Union Nationale des Caisses d'Assurance Maladie fixes the reimbursement rate 8. Minister for Health and Social Security makes final decision on reimbursement level and price	Appraisals Committee meets to consider comments and formulate final recommendations (final appraisal determination) 10. Technology Appraisals Committee submits final recommendations to Guidance Executive 11. Guidance Executive makes final reimbursement decision	submit it to the IQWIG steering committee for final quality assurance review and then to the Board for final approval 9. Board sends recommendations to Federal Joint Committee, who makes final decision	
Use of cost effectiveness threshold	NO	No fixed threshold, but range of £20,000 - £30,000 / QALY used as guide	No	NO
Timeline for review/decision	90 days for inpatients pharmaceuticals (includes pricing and reimbursement decision) 180 days for outpatients pharmaceuticals (includes pricing and reimbursement decision)	Single technology appraisal approximately 30 weeks	No information found	
Appeals mechanism	May appeal recommendation to French national authority for health, requesting a hearing or providing written comments Once decision has been made, may appeal to administrative court	Final recommendations may be appealed on procedural grounds only Appeals may only be initiated by consultees identified at the beginning of the assessment and who are not representing National Health Service trusts or local boards	May not appeal recommendations Decision may be appealed to administrative court	Formal process available to challenge negative decision

Appendice 2. comparison of health technology assessment across 4 countries

	France	England and wales	Germany	Canada
HTA body (year of current process established)	National health authority (HAS) transparency commission advisory	National institute of clinical excellence (NICE) 1999	Institute for quality and efficiency in heath care (IQWIG) advisory	CEDAC (2003)
Function	coverage	coverage	Coverage and pricing	coverage
Decision scope -Reimbursement -Linkage to pricing	-Yes -Yes	-Yes -NO	-Yes -Yes	-Yes -NO
Stated objectives	Improve the quality of health care services through hospital accreditation, best care standards, and continuous professional development; evaluation of medical effectiveness, public health impact, and health technology assessment.	Reduced variation in practice, accelerate uptake of new technology, set quality standard and improved efficiency		CDR was set up to reduce duplication, and provide equal access to high-level evidence and expert advice, thereby conducting to the quality and sustainability of Canadian public drug plan
Subject and scope of assessment	Medical technologies including drugs, devices, procedures, and diagnostic test; clinical guideline for disease management; public health guidance on disease prevention	Pharmaceutical technologies, drugs, devices, procedures	Pharmaceutical technologies, drugs, devices, procedures	Pharmaceutical technologies
Topic selection and prioritization	Every new drug	Department of health refer drugs to be prioritized based on criteria, such as health impact, disease burden, and clinical/policy relevance	Drug that cannot classify under reference pricing system	All new non oncology drugs (Oncology drugs are reviewed by a committee cal joint Oncology Drug review)
Is cost effectiveness	Varies by assessment	Yes Direct cost	Yes Direct costs	Yes Direct cost

used as criterion		Indirection cost Budget impact analysis	Indirect costs Budget impact analysis	Budget impact analysis
Synthesis and analysis of evidence: in-house, contracted or submitted by manufacturer	Manufacturer through submission requirements	Manufacturer through submission requirements	Manufacturer through submission requirements	Manufacturer through submission requirements
Type of Evidence	RCT data preferred, health economic information recommended but not required	RCT data preferred, health economic data required	RCT data preferred; health economic data required	RCT data preferred; health economic data required
Evidence requirement	Target population and indication (therapeutic claim) Current management Place of technology in care pathway Safety Efficacy Effectiveness (across population subgroup)	Target population and indication (therapeutic claim) Severity, burden of illness Current management Place of technology in care pathway Comparative Safety Efficacy Effectiveness (across population subgroup) Indirect comparison	Target population and indication (therapeutic claim) Severity, burden of illness Safety Efficacy Effectiveness (across population subgroup)	
Structured and relationship with health care system	Independent of central government, health ministry, or insurance fund. Accountable to French parliament	Part of NHS; independent of central government, issues guidance directly to health service and broader public sector (local authorities, transport, and education boards)	Established by joint committee (FJC), independent from government, private foundation, receive commissions from FJC and Ministry of health and advices FJC who issues their directives to statutory heath insurance funds.	
Groups with membership on the committee	Heath professionals, patients representatives,	Health professionals, patient representatives and industry	Health professionals	Heath professionals, patients representatives
Budget and source of founding	In 2006, 70 million funded by : 34% through earmarked taxed levied on drug	£35 million per year: funded by department of health	15 million; 50% from a levy on every hospital case to be invoiced and	

	companies spending on advertising, 15% from hospital accreditation fees, 7% from fees from manufacturers, 32% by NHI, 10% by government, 2% by investment income		50% from increased in reimbursement rate of medical and dental outpatient services pay by the health insurance funds. Details determines by federal joint committee	

<Name>	< First name >	<Defense date>

EHMBA

Class of: 2011-2012

Criteria associated with health technologies assessment funding decision

University partnership : ESCP Europe, LSE, Mailman School of Public Health

Abstract

Background: The increase of health care expenditure have stimulated health policy maker to explore more efficient and effective health care delivery option, through the development of health technology assessment (HTA) agencies. Criteria which drive HTA actual decision making process are not well known.

Objective: to review criteria use in actual decision making process by HTA agencies. To evaluate the level of inconsistence among HTA agencies.

Methods. A comprehensive literature search was performed in Pubmed with a structure search strategy. To illustrate the impact of HTA, 3 cases studies was performed. HTA analysis focused on England, France, Canada and Germany.

Results. The analysis has shown that the adoption of new health innovation through the HTA process is influence by a range of factors including: clinical benefit, unmet medical needs (disease burden), cost/budget impact, quantity and quality of evidence, size of the target population, availability of alternative. Overall the level of agreement among health technology assessment agencies was low.

Conclusion. The current analysis show that to improved the probability of positive reimbursement recommendation, pharmaceutical industries should localised more the development of evidence for HTA submission, implemented early dialogue with HTA agencies and improved the expertise in evidence base medicine and economic evaluation.

Key words **:**

Health technology assessment, criteria, reimbursement, decision making process