



Short- and Long-Term Effects of Value-Based Pricing vs. External Price Referencing

**Panos Kanavos¹, Elena Nicod¹, Jaime Espin² and Stacey van den
Aardweg¹**

¹ LSE Health - London School of Economics

² Andalusian School of Public Health

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LIST OF ABBREVIATIONS

AE	: Adverse event
AIFA	: Italian Medicines Agency (AIFA)
ASMR	: Amélioration du Service Medical Rendu (France)
APC	: Area Prescribing Committees (UK)
AWMSG	: All Wales Medicines Strategy Group
CaHTA	: Catalan Agency for Health Technology Assessment
CDR	: Common Drug Review (Canada)
CEA	: Cost-Effectiveness Analysis
CED	: Committee for Evaluating Drugs (Canada)
CEPS	: Economic Committee for the Health Products (France)
CIP Farmaci	: Committee on Pharmaceuticals (<i>CIP Farmaci</i>) (Italy)
CT	: Transparency Commission (France)
CvZ	: College Voor Zorgverzekeringen (Dutch Health Insurance Board)
DACEHTA	: Danish Centre for Evaluation and Health Technology Assessment
DAHTA	: German Agency for Health Technology Assessment
DH	: Department of Health (UK)
EFPIA	: European Federation of Pharmaceutical Industries and Associations
EPB	: External Price Benchmarking
EPR	: External Price Referencing
EU	: European Union
FinOHTA	: Finnish Office of Health technology Assessment
FJC	: Federal Joint Committee (Germany)
GDP	: Gross Domestic Product
HAS	: Haute Autorité de Santé (France)
HTA	: Health Technology Assessment
ICD	: International Classification of Diseases
ICER	: Incremental Cost-Effectiveness Ratio
IRP	: International Reference Pricing
IQWiG	: Institute for Quality and Efficiency in Health Care
LNDG	: London New Drugs Group
LNCDG	: London New Cancer Drug Groups
MA	: Marketing Authorisation
MH	: Ministry of Health (Czech Republic)
MoH	: Ministry of Health (Sweden)
NPC	: National Prescribing Centre (UK)
NHS	: National Health Service (UK)
NICE	: National Institute for Health and Clinical Excellence (UK)

NCCHTA	: National Coordinating Centre for Health Technology Assessment (UK)
OECD	: Organisation for Economic Co-operation and Development
OFT	: Office of Fair Trading (UK)
OLS	: Office of Life Sciences (UK)
PBAC	: Pharmaceutical and Benefits Advisory Committee (Australia)
PCT	: Primary Care Trust (UK)
PPB	: Pharmaceutical Pricing Board (Finland)
PPRS	: Pharmaceutical Price Regulation Scheme (UK)
QALY	: Quality Adjusted Life Year
QoL	: Quality of Life
R&D	: Research & Development
RP	: Reference Price
SBU	: Swedish Council on Technology Assessment in Health Care
SMC	: Scottish Medicines Consortium (UK)
SPC	: Supplementary Protection Certificate
SUKL	: State Institute for Drug Control (Czech Republic)
TLV	: Dental and Pharmaceutical Benefits Board (Sweden)
UKMi	: United Kingdom Medicines Information Group
VBP	: Value Based Pricing
WTP	: Willingness-to-pay

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EXECUTIVE SUMMARY

Background

Among other models of price setting or regulating the supply-side in pharmaceutical markets, both value based pricing (VBP) and external price referencing (EPR) are currently used to inform decisions on pricing and reimbursement of pharmaceutical products. VBP is frequently used in different contexts to inform pricing and reimbursement decisions of new products typically seeking a price premium over existing therapies, whereas EPR is used more generically either as a tool to explicitly set prices or as a criterion (among other criteria) to inform the pricing process across a range of pharmaceutical products. Both methods have advantages and disadvantages to different stakeholders and have different short- and long-term implications especially on the market dynamics.

This study debates the relative merits of VBP and ERP over the short- and the longer-term by taking into account the views and perspectives of key stakeholders including governmental bodies, key purchasers and pharmaceutical manufacturers, as well as analyse market and pricing dynamics. It, therefore, relies on both primary and secondary material and evidence. Although a significant body of evidence exists surrounding the use of EPR and VBP to inform pharmaceutical pricing and reimbursement, there is lack of comparative analysis and their impact on individual stakeholders both in the short- and the longer-term.

Conceptual framework of VBP and EPR

VBP is associated with a robust conceptual/theoretical framework relating to efficiency in resource allocation. To the extent that the principle of cost effectiveness is underpinned by the concept of technical, rather than allocative, efficiency, VBP can be associated with benefits for most, but losses for some. This is an element that requires adaptation of the (technical) efficiency framework so that equity, disease severity and the principle of humanity can underscore efficiency arguments.

EPR is often criticized not to adhere to a particular conceptual, analytical or theoretical framework. Rather, it relies on a set of seemingly “arbitrary” criteria, relating to the basket of countries, the price taken from that basket, and the intensity of revisions, among others. Yet, the rationale appears to be clear in terms of policy objectives: first, to ensure that countries applying EPR do not overpay for new medicines in relation to (some of) their neighbours and, second, by aiming to achieve reasonable prices, in relation to their ability to pay, to contribute towards the principle of *macroeconomic* efficiency (overall budget constraint) by means of exerting pressure on price.

Capacity of VBP and EPR to inform decision-making

VBP clearly has a significant potential to inform rational decision-making in the sense that it evaluates (health) benefits and – in the majority of cases – costs by employing often complex methodologies and drawing on scientific evidence generated by robust designs. Where the assessment of (relative) costs and benefits is subject to uncertainty complex modelling is used to assess relative benefits.

Yet, at a fundamental level the techniques embodied in VBP, as it is currently applied in the HTAs in Member States, do not always provide robust answers to a number of concerns. There remain a range of methodological and allied limitations relating to the practical application of VBP for medicines, as well as other – higher level – conceptual limitations. They include (a) the determination of affordability thresholds and overall affordability, (b) the relative lack of evaluation of additional health benefits, (c) problems associated with the use of aggregated data in circumstances where there is substantial variance within populations, (d) inherent challenges of measuring and comparing utilities of different types, (e) lags between best practice developments and the publication of supportive evidence and (f) a lack of evaluating the long-term external benefits and the impact these are having on future innovation (dynamic efficiency).

EPR by design serves the objectives of decision-making based on pricing information received. However, most EPR schemes are often supplemented with other important information, which forms part of the submission dossier and, consequently, assist in the decision-making process. EPR has often been criticized as overly simplistic, nevertheless, it is defensible in smaller countries with limited resources to pursue their own regulation and value assessment.

Despite the above, there is an element of “path dependency” characterizing EPR systems in the sense that the information that informs the decision-making process and the way it is arrived at, influence, to a certain degree the final outcome. This is probably more inherent in EPR than it is in VBP. For instance, the type of data required from a particular scheme influence price levels, e.g. country selection, available prices from across the country basket, revision dates. To that end, EPR seems to be relying a lot on external factors influencing pricing (and reimbursement) decisions, without necessarily paying due attention to factors intrinsic to the health care system in which it operates. In addition, the intensity of information required often makes EPR schemes administratively complex.

Processes and operational/analytical framework of VBP and EPR

VBP relies on a clear analytical framework enabling decisions to be made on health benefits and costs via well-established processes. Indeed, there are elaborate processes in place outlining the role of the agency that assesses value and whether it is regulatory or advisory, its remit, the type of technologies it appraises and its position within the health care system. Specific issues relating to processes include: (a) assessment procedures and methods (topic selection, data and evidence requirements, analytical design, assessment methods, incl. comparators and dealing with uncertainty); (b) application of evidence to decision-making esp. criteria and

timing of assessments; (c) stakeholder involvement: clear provisions for stakeholder engagement in the process; (d) appeals process: a framework to enable stakeholders to appeal against decisions and the independence of that process; (e) a framework exists on Evidence dissemination and implementation.

While elaborate processes have been set up to ensure transparency, clarity, visibility and stability, these are not without limitations, which include: (a) poor timing, as it can take too long to fully appraise the evidence; (b) methods are very diverse and this can lead to different decisions for the same treatment (cross-border post-code lottery) across countries and agencies; (c) a decision-making process that allows “value judgements” in decision-making rather than enabling a clear-cut decision of whether or not to cover a particular technology; (d) path dependence, in the sense that decisions depend on inputs and assumptions around them; (e) willingness to pay (WTP), whereby WTP thresholds are not transparently set, while the way they are interpreted can vary across settings and can refuse reimbursement based on unclear threshold or unclear interpretation of value; (f) there is no clear framework around affordability and this is usually outside the remit of the Agency appraising the evidence, unless an explicit threshold is used; (g) monitoring of recommendations made usually lies outside the remit of agency conducting value assessment, but could be internalised in order to have better compliance of stakeholders; and (h) the stakeholder involvement is often criticised as unfair among certain stakeholder communities in the sense that it places a great deal of burden and exceeds their capacity to respond adequately.

Countries using EPR as the main method of pricing pharmaceuticals have developed detailed, elaborate and robust structures and processes enabling them to undertake the task of pricing based on international prices, informing reimbursement through the same process and examining, among other things, which products require flexibility in the above assessments and on what basis. Important aspects of this include: (a) the legal framework, which is essential to underwrite transparency; (b) the pricing process, which needs to be in place in order to select a basket of prices; (c) the reimbursement process; (d) the frequency of price revisions at the request of various stakeholders – both for pricing and for reimbursement; (e) an appeals process; (f) a framework for deviating from existing procedures and regulations on pricing and/or reimbursement should the need arise; (g) procedures dealing with new products with no apparent comparators or in a new therapy class, in which case, provisions are made to review additional clinical or other information that can be instrumental in determining a fair price; (h) dealing with external shocks, e.g. exchange rate depreciations/appreciations and overall volatility; and (i) the frequency of price revisions at the request of various stakeholders – both for pricing and for reimbursement.

It is widely perceived that EPR systems are fairly straightforward, are not administratively complex and do not require a lot of information, since much of what is required is either available at arms’ length, or can be supplied by the manufacturer. Nevertheless, the evidence suggests the opposite: it looks as though EPR systems can be quite complicated and resource intensive in the interests of

transparency and stability. EPR systems can be criticized for path dependence (i.e. what inputs feed the system in terms of countries and prices, pretty much determine the outcome) as well as exposure to external shocks, such as excess volatility in exchange rates used.

Prices and price levels, launch prices, launch sequencing and delays under VBP and EPR

Value Based Pricing

Across agencies, assessments of value tend to rely on similar studies and evidence in order to inform pricing decisions, but are usually limited by evidence that does not sufficiently address questions of impact on clinical effectiveness, quality-of-life, adverse events or costs, relative to pertinent comparators. Because of this similar core body of evidence, there tends to be reasonable convergence of reimbursement decisions among agencies, although divergence has also been observed (and is increasingly the case) in a number of instances relating to expensive treatments. Divergent outcomes are often the result of varying interpretations of evidence, and seemingly different degrees of willingness to undertake sub-group analysis, make indirect comparisons, negotiate pricing or innovative reimbursement schemes, or rely on expert opinion, as opposed to outright rejection if adequate data was not available.

This differing willingness to use less-than-ideal types of evidence demonstrates varied responses to the challenging trade-off between using the best available—though incomplete—evidence or simply turning away reimbursement for potentially beneficial (and cost-effective) drugs due to lack of strong evidence. There is no straightforward solution, nor a broad consensus among these agencies: some are likely to reject an application if inadequate evidence was submitted, but also engaged in pricing negotiations to reach positive outcomes; others tend to navigate uncertainty and poor evidence by using indirect comparisons and expert opinion as necessary, along with the development of risk-sharing agreements; others still tend to encourage price negotiations and the development of risk-sharing agreements to overcome informational uncertainty.

Special considerations relating to the life-extending role of specific treatments such as orphan and anti-cancer drugs, as well as the lack of alternative therapies for many conditions (esp. certain types of cancer), tend to favourably impact reimbursement decisions across agencies, and in certain cases, overruled otherwise unacceptable incremental cost effectiveness ratios. Additional factors, such as patient perspectives, market conditions, or the pragmatics of drug use relating to wastage also seem to affect appraisal decisions in a variety of ways.

While some level of uncertainty will always be present, the concern regarding the quality of evidence may be mitigated in part by more transparent guidelines for manufacturers as to the types of data needed by HTA agencies to make rapid, clear decisions on value (subject to constraints present at the time of the value

assessment), or by stipulating that certain data requirements must be available at the time of marketing authorisation that fulfil these value assessment needs. This pressure to develop more relevant evidence would potentially improve the overall process of value assessment and expedite the approval of truly clinically- and cost-effective therapies. Unfortunately, the lag between evidence generation and its subsequent use in VBP may still result in data gaps if the methods, data requirements, or market presence or clinical use of relevant comparators change substantially during this lag period.

Clearly clinical- and/or cost-effectiveness drives pricing decisions based on value assessments. In settings where cost-effectiveness is used additional elements or processes can inform pricing decisions. It is, therefore, important to consider the impact of factors such as disease severity, unmet medical need in the indication as well as human dignity. Put together, these factors can alter and, often, enhance strict cost-effectiveness paradigms by introducing elements of flexibility in its interpretation. This can apply to a variety of treatments including orphans and end-of-life therapies.

Similar situations arise in value assessments from a societal perspective, where stakeholders are in a position to submit information on the new treatment's usefulness not only for the health sector but also for a number of other areas, which were hitherto excluded from impact assessment, such as indirect cost and impact of the treatment on sickness absenteeism, among others.

Generation of further evidence (than is available for MA) by manufacturers may be encouraged by increasing adoption of risk-sharing schemes through partnership of healthcare payers and manufacturers, in order to provide early access to innovative therapies, develop robust data, and partially insulate the payer from undue health outcome or financial risk. However, such schemes are not without complications, and must be balanced against the risks of expediting marketing approval. Ultimately, the pragmatics of such schemes will have to be further developed before they can be widely applied to the many new compounds entering the market.

More broadly, despite their different locales and contexts, the different HTA agencies generally seek the same types of information regarding clinical and economic consequences of new therapeutics, and encounter the same obstacles during the assessment and appraisal processes. Thus, the formal development of standardised methodologies, international harmonisation of data requirements for new therapeutics, and sharing of HTA expertise and results across countries would further develop the field, reduce duplicative effort in collecting and analysing HTA-relevant data, and help address the data gaps that currently persist. While it would be difficult—and likely undesirable and impractical—to create a central HTA agency that would render binding reimbursement decisions, given the differing national agendas and values which impact upon final appraisal decisions (even within an international country bloc such as the European Union), striving for harmonised methods, data collection, and evidence repositories could streamline the HTA process and allow for more complete evidence-based assessments across the health technology spectrum. This would reduce the cross-border post-code lottery that

seems to arise particularly in cases where the evidence appears controversial and is viewed differently by different agencies.

Based on a limited number of cases analysed in the context of this report, it appears that the level of innovation, as defined by the payer, seems to be rewarded accordingly. New treatments perceived to be significant innovations receive a substantial price premium in relation to comparators, moderate innovations receive a lower price premium, and those perceived as not adding to existing treatment paradigms achieve –at best– price parity in relation to existing treatments/comparators. Prices of new treatments show little effect of being affected downwards by the outcome of the appraisal process, even if that process results in a negative recommendation in one or more jurisdiction(s), although, as was pointed out during interviews, it could well be the case that pricing decisions had already been shaped prior to the appraisal process, when decisions would need to have been made in connection with comparators that would need to be used in each jurisdiction (and which differ depending on the jurisdiction).

Given the evident disparity in time lapse between MA and HTA recommendation, the diverse criteria (and narrow sub-groups) dictating reimbursement eligibility and inconsistencies in appraisal outcomes across countries, there is a strong indication that an international “postcode” lottery exists in terms of access to medicines. Not only does this have broad repercussions for cost, media attention and public opinion, it also highlights an area of ongoing debate regarding whether citizens with conditions for which treatment is not reimbursed (or not yet assessed) in their home country should be refunded (by their national health system) for seeking care in other EU Member States, or in fact, seek treatment elsewhere, where it may be available.

External Price Referencing

There are a number of consequences of using EPR. First, some evidence points to market launch delays in low-price countries. Second, EPR might produce convergence in international prices because manufacturers could try to impose a single price worldwide and be unwilling to offer lower prices to any country, especially those that are or might be used as a reference by other countries. Consequently, countries that in the past were able to obtain relatively lower prices might not be able to do so in the future. Although some evidence exists on convergence of international prices of new drugs and marketing delays in low-price countries, it is difficult to assess how far this phenomenon may be due to the expected spillover effects of EPR, to the possibility of parallel trade, or to the fact that these markets are less attractive to suppliers - a set of factors that are often simultaneously present in some countries.

The effects of EPR depend on the specific local details of the practice: number and characteristics of the reference countries, how the national target price is calculated or derived from the prices of the reference countries (minimum price, average, median), and on whether the computed reference price is strictly enforced or simply used as a relatively flexible benchmark. Evidence compiled from meetings with

stakeholders and previous experience, suggest that the theoretical reference price often does not become the actual market price, especially in the case of drugs that enjoy a monopolistic position.

An important issue to consider in relation to EPR is whether it has any unintended effects beyond its immediate impact on drug prices, particularly negative effects on the various stakeholders in the country applying it or on other countries. In analysing the effects of EPR as well as other forms of price regulation, two perspectives must be considered: the individual country perspective and the global perspective. Drug regulatory policies are usually a national responsibility, although there are clear trends towards globalisation of some of its aspects, particularly on efficacy and safety standards for market authorisation and intellectual property rights. The pharmaceutical market's globalisation, however, spreads the effects of national P&R regulations well beyond the regulating a country's own national boundaries.

A further unintended consequence of the way EPR operates at times relates to the issue of price revisions and the use of exchange rates for that purpose. In environments where multiple currencies are used and in the presence of exchange rate volatility, the latter can have a significant adverse effect on prices denominated in local currencies, far and beyond what is reflected in actual price movements. If price revisions need to take place and exchange rates be used, then stability and predictability could be maintained if longer period averages or moving averages are used.

Some of the potential effects of EPR might be the result of strategies adopted by the affected stakeholders, mainly manufacturers, in response to new conditions created by the widespread use of EPR. When a large number of countries began using EPR, companies became aware of spillover effects that stemmed from prices that were being set in a given country. They reacted by designing and implementing appropriate international pricing and marketing strategies to counteract the effects of EPR and maximise global profits under the new conditions. These strategies might affect not only the countries that apply EPR, but others as well, especially those used as reference countries by the former.

The main strategies adopted by manufacturers are, first, trying to set a single international price for their products; second, delaying the launch or even giving up the marketing of new products in countries that try to attain the lowest prices, especially if they are small markets, where the opportunity cost of the strategy is smaller, and if the countries are referenced by other countries with larger markets; and, third, "gaming" the system in order to minimise the likelihood of spillover effects caused by international price differences.

EPR is not only distorted by the above strategies, but also by national or regional policies and regulations that affect final prices, for instance, (a) the use of payback as a mechanism through which manufacturers previously agree to return money to public institutions in the form of annual lump-sums; (b) the general discount system used in some countries where manufacturers have to return part of their sales

revenue to the Ministry of Health; (c) the profit control system in the UK, whereby manufacturers can reduce prices or return excess “profit” to the Department of Health; (d) Different risk-sharing agreements, where the health service does not have to pay for medicines that do not provide a quantifiable benefit, but the price listed is the one that applies when the medicine works for 100% of the patients.

Coverage of and access to new therapies under VBP and EPR

Value-Based Pricing

The implementation of VBP can, on a number of occasions lead to access problems, although, in principle, a number of safeguards exist for these to be avoided. If the Agency performing value assessments has a mandate to implement its decisions/recommendations, then in the case of “approval” of individual technologies access should be unrestricted. There have been problems of interpretation of this particular policy statement as well as problems of access that have materialised as a result and required clarity. In case the competent Agency does not have a mandate to implement its decisions/recommendations, access problems can indeed arise, particularly in circumstances where the payer is at arms’ length from the Agency, as is the case in some decentralised health care systems. This gap can be bridged either through the competent Agency receiving a mandate or by allowing strong participation of the payer community on the competent Agency’s Board with a view to arriving at decisions combining clinical and/or cost effectiveness and affordability.

For new – and often expensive - technologies approval with criteria and approval with a risk sharing scheme in place can indeed give rise to access issues for the part of the indication population(s) that are not covered, but, on the other hand, both risk sharing and coverage criteria provide the rationale for coverage of such technologies for certain sub-groups. Enforcing and monitoring these agreements – particularly risk sharing – can be resource-intensive and complex and is usually outside the remit of the agency performing value assessments.

It is increasingly the case that the value of the same technology is perceived differently across settings; there have been some, but, alarmingly, increasing phenomena of the same technology being approved in one setting, approved with restrictions in another and rejected in a third. This highlights that the levers decision-makers use to assess value differ significantly across settings, despite the fact that the body of evidence is usually the same. This may cause distress and confusion to patients particularly in therapeutic areas such as cancer, which are politically sensitive and requires some attention and, possibly, collaboration, by decision-makers.

Finally, value assessments, depending on how they are conducted and what evidence feeds into them, can be time consuming and can lead to significant delays in access, often in excess of one year. Arms’ length value assessments usually require significant input, which is often produced and provided independently and

is subsequently compared and contrasted with that produced by manufacturers. Clearly, there are significant tradeoffs at this juncture, notably, robustness in evidence base production leading to informed decisions versus timely coverage and access. Rapid reviews can take some of this pressure off combined with ex-post value assessments.

External Price Referencing

EPR does not necessarily restrict access once agreement has been reached but can lead to delays in launch, which, in itself can cause access problems. It can also be the case that manufacturers will not launch in a particular EPR market if they feel that the price they receive from that market is prohibitively low and can threaten their global pricing strategy.

Expensive products may be subject to the usual arrangements via prices collected across a range of countries, but, depending on the value they bring, such products can be treated in a slightly different way, notably, be given the opportunity to prove their value in the local context by enabling local clinical studies, whilst in the meantime, a temporary reimbursement status is granted.

Finally, it is possible that EPR can be combined with additional policy measures for reimbursement purposes in order to deliver a lower price for a particular volume level. It can be further combined with paybacks, should this volume be exceeded. This is one form of risk-sharing that gives the payer the security of capped expenditure in a particular therapeutic class or across the board.

Assessment of value of new therapies under VBP and EPR

Value-Based Pricing

Ex-ante evaluation provides manufacturers with the incentive to invest in gathering the evidence that health services require to approve and encourage innovation in areas/therapies where a substantial clinical benefit can be demonstrated. One drawback, however, of the use of ex-ante as opposed to ex-post evidence is that there will be uncertainty surrounding the clinical-cost-effectiveness of the drug outside the RCT setting at the time of launch. Although further ex-post reviews can also be suggested, these may be difficult to ensure as once a pharmaceutical product is approved, the incentive to carry out further trials is diminished and may even be deemed unethical. Nonetheless, a balance between the value of the economic information surrounding the drug and the value of availability of the drug to patients needs to be achieved (as is often emphasised in HTA).

On the other hand, both payers and manufacturers seem to believe that ex-post evidence is as crucial as ex-ante evidence in proving the value of new treatments. There needs to be acceptance of data obtained in naturalistic settings and methodologies on how best to extract value from such data need to be strengthened but some agencies admit they do not provide any (substantive) guidance to manufacturers on methods, process and likely outcomes. Indeed, further reflection and consultation are needed to determine criteria and processes for such appraisals

to take place. Overall, evidence prior to the launch of a new product is not always available and there may be significant data limitations and concomitant uncertainty. Ex-post assessments may prove instrumental in many cases in determining product value for health services, patients and society, but criteria, methods and processes need to be set up as to which products should undergo these, together with arrangements allowing access to patients in the meantime. An ex-ante price premium in the case of ex-post assessments would provide a signal to the innovator of the willingness by the payer to reward high risk-taking. Equally, flexibility in pricing arrangements based on the quality of the available evidence should be a highly desirable feature of VBP in that prices could be adjusted downwards as well as upwards depending on the emerging evidence.

Criteria and metrics from a societal perspective should be considered when assessing drug value and setting pricing/reimbursement levels and ought to include all elements of value. When they do assess value though, pricing/reimbursement systems have frequently chosen to focus on value almost exclusively from the healthcare system (payer) point of view rather than the broader societal or patient/physician perspective with few notable exceptions. New standards and tools for more accurately and consistently assessing the more challenging metrics may need to be developed. Patient groups, for instance, strongly believe that some of the quality of life elicitation tools that national agencies use currently do not capture preferences appropriately, e.g. capturing fatigue in the EQ5D, or initiating patient reporting outcomes.

Within the above context, payers (whether health systems or health insurers), providers, patients and manufacturers must work together, not antagonistically, to establish pilots to investigate new pragmatic ways of eliciting value taking into consideration inputs from across the spectrum of the stakeholder community. Some agencies have already established procedures whereby clinical and patient views are heard and form part of the value assessment process. It is not uncommon to have a well-established programme that provides guidance on patients and patient groups on the type of evidence required in this context and assisting them in fulfilling this requirement. Against this background, patients widely applaud this opportunity, but, are nevertheless faced with the daunting task of presenting “evidence” on their perception of the disease and the new treatment, before a highly specialized audience. In order to face the challenges, an inclusive process for defining pragmatic, effective changes to drug approval and pricing approaches must be developed, ensuring these are transparent to all as well as ensure that stakeholder participation is meaningful. Where appropriate, capacity building may be required to enable interested parties to participate.

A final issue that deserves greater attention is that payers continue to be of the view that manufacturers can maximise their effectiveness and increase the probability of a new drug receiving a positive recommendation by designing trials to provide more comparative data, powering trials to indicate superiority rather than only non-inferiority and structuring economic models from both a health and societal perspective, applying the agency preferred methods for discounting and quality-

adjusting utility values. Manufacturers highlight that in the process of eliciting value at an early stage when a product is launched, there is a significant knowledge gap, assuming a rising knowledge curve over time and contend that in the assessment of value payers need to be flexible as the knowledge curve is continuously rising and that there is a clear trade-off between optimal knowledge base and timely introduction. If the regulatory environment is to evolve and if more complex evidence is required ex-ante, then it might be necessary to re-think intellectual property rights protection or market exclusivity periods. Patients, on the other hand, are obviously in favour of faster access, particularly for those treatments that can have a significant therapeutic effect, however short-lived this may be, but, at the same time highlight that there is a significant discontinuity between MA requirements and HTA/VBP requirements, which needs to be debated and addressed.

External Price Referencing

From an EPR perspective it is clear that the potential for enabling value assessments, and, therefore, taking into consideration the value of innovation, exists. This can take place in two cases: first, with regard to *new products that do not belong to an existing therapeutic class*, then for the process of reimbursement alternative arrangements can be made other than including these into (internal) reference clusters. These arrangements include the establishment of a new therapeutic category, provided that evidence justifies this.

The second case is similar to the conundrum faced by HTA agencies in VBP relating to uncertainty. Where medical benefit is not always clearly defined from the available data, then from an EPR perspective, very expensive products can be granted temporary reimbursement only with the proviso that additional evidence is generated to prove the benefit claimed by the manufacturer. Governments and payers, including those who operate with an EPR system, are increasingly keen to have local information about health benefit, which often goes through the establishment of a local registry to elicit clinical value in a real setting.

There are also instances the operation of an EPR scheme does not take into account the value of innovation. For instance, an issue arises when EPR is combined with molecular or therapeutic price referencing, the latter being a frequently-used option setting a reference price across a range of molecules, of which at least one is patent-expired. It is likely that these two effects can be combined and can spill-over across borders. The propagation mechanism for this to take place is differences in patent term dates across countries. Despite EU-wide provisions concerning intellectual property rights protection, patent term dates are not always identical among Member States. Under these circumstances, it is probable that the patent for a product in one country may expire earlier than in others. This would, of course, allow generics to enter in the country where the patent expires and could force the originator price to decline particularly if an internal price reference system is in place. This decline may trigger price adjustment in other countries if the product in question is subject to EPR provisions elsewhere. To that end, such patent term

differences across member States can have unintended consequences and lead to cross border price reductions if combined with internal price referencing elsewhere.

Overall, EPR systems are not equipped to provide explicit assessments of value of new treatments, but the above evidence suggests that such assessments can take place in particular circumstances. More broadly, if EPR fixes prices at launch only, then there may be no further impact on the value of the product along its life cycle, but, frequent adjustments do have an impact because they are usually conducted to take into account price reductions in individual components of the basket or broader adjustments therein.

Encouraging and rewarding pharmaceutical and biomedical innovation under VBP and EPR

The varying nature and emerging complexity of health technologies, in combination with limited national budgets, has resulted in tensions between delivering cost-effective health care and improving or sustaining a country's manufacturing and research base. As a result, it has become increasingly important to achieve a balance between affordable health care and the use of innovative pharmaceuticals. To that end, considering the value of a new pharmaceutical in clinical and economic terms, is as important as defining who benefits, how the technology diffuses optimally and how it is placed most appropriately in the spectrum of care.

Value-Based Pricing

VBP can address the above challenges by determining which technologies are ineffective versus those with value, and by defining the most appropriate indications for use of the technology. VBP can also serve to validate a new technology and define its role in a health care system. To that end, it provides important benefits by enabling governments to make decisions driven by value, which concurrently supports innovation, and garners patients and physicians with the information needed to make the best treatment choices.

However, the effectiveness of VBP in achieving the above benefits, particularly in terms of encouraging innovation, seems to depend on properly performed assessments and the appropriate implementation and use of subsequent recommendations. VBP can encourage innovation if the assessments are properly conducted, consider a wide range of costs and benefits associated with a new technology (ie adopt a societal perspective), rather than focus solely on acquisition costs. The utility of VBP in encouraging innovation and value-added health care also depends on the assessment process, including when and how a review is performed, the chosen comparators and the resulting decision-making procedures, including implementation.

Whereas from a dynamic efficiency perspective, it is not clear how the currently implemented VBP frameworks incentivise future R&D, from a static efficiency perspective, the requirements placed on data available at launch are substantial. Yet,

processes and pathways are available to improve the flow of information, and the quantity and quality of the data and information.

Whereas approaches to VBP reviewed in the context of this report encompass some of the above elements, in practice, it is the case that a number of these elements remain aspirational in most cases, including the perspective of value assessment, and the comparators used from an *ex-ante* and an *ex-post* perspective. More fundamentally, the process of value assessment in relation to encouragement of innovation raises the question of whether changes may need to take place to enable better data to become available at launch. This is clearly an issue that may deserve further exploration and discussion in the very near future, between payers and HTA bodies, regulators (eg EMA) and other stakeholders (manufacturers and patients) and has been raised on several occasions in discussions with key stakeholders in the context of writing this report.

External Price Referencing

EPR in itself is not a methodology that explicitly encourages and rewards (future) innovation, or that by design serves this particular objective and the process often leads to a price low from the selected basket of countries. Current innovation may be rewarded in the context of the selected country prices within the basket and if the regulator allows flexibility for the manufacturer to prove its case in particular situations, where high uncertainty does not allow optimal decisions to be taken. Within the context of EPR future innovation can only be encouraged by the approach undertaken by the regulator and the extent to which additional policies exist to foster and encourage R&D investment.

Policies encouraging pharmaceutical and biomedical innovation

Stimulating, steering and facilitating innovation and innovative research is a proactive policy role and the aim is to create a sustainable R&D environment to maximise the likelihood of valuable pharmaceutical innovation reaching the market place. Several countries that implement VBP and/or EPR do have their own innovation policies providing a mix of financial and non-financial incentives directly or indirectly to manufacturers to locate and conduct R&D activities among others. Implicit in this is the fact that encouraging innovation passes through pricing and reimbursement as well as a wider set of issues underpinning the quality of the science base, research priorities that can create synergies between public and private R&D, and research funding from both the public and the private sector.

Do VBP and EPR present opportunities for gaming?

Despite the relative advantages and limitations of VBP and EPR, they both have a common similarity, namely they present opportunities for “gaming” to manufacturers. These are the result of “regulating” the market, either explicitly (e.g. through the introduction of a set of rules, as is the case is EPR), or implicitly (e.g. by requiring that certain processes are adhered to, as is the case in some elements of VBP).

Under VBP, such opportunities manifest themselves in (a) explicit thresholds, (b) comparator choice and product positioning, and (c) risk sharing. In the case of explicit thresholds, manufacturers have an obvious incentive to price up to the threshold provided the product in question can potentially justify it. The choice of comparator is very tricky indeed and is influenced, in part, by increasing calls for payers to consider a generic (if this exists) as the most appropriate comparator. In this context, manufacturers will do their best to avoid a genericised molecule as a comparator, even if this means positioning their product as a second or third line therapy. In this case, the comparator is usually an in-patent medicine, the market is smaller and, as a result, the likely payoffs are higher. Finally, in the case of risk sharing, although manufacturers have reservations and fear that such schemes will become the standard for all new drugs, their pursuit is usually associated with maintaining the originally applied price.

EPR offers significant opportunities for “gaming” to manufacturers. It can become an incentive for manufacturers to adopt international pricing strategies that, in the end, may have a negative impact on individual country prices and unexpected consequences in countries applying such policies. The main alleged negative effects can be: 1) higher prices in lower income countries that in the absence of EPR policies might benefit from lower prices; and 2) delays in launching new products, or, indeed, no launch of certain products in low price countries fearing spread of their prices more widely. Manufacturers may prefer to launch products in free price countries in the first instance. In contrast, countries with smaller markets, or with lower disposable income, are definite followers in this process. The above have implications for the amplitude and extent of parallel trade. In an environment where opportunities for arbitrage are propagated by (significant) cross-border price differences, any reduction in these works to the manufacturer’s benefit, but it is unclear whether overall welfare increases as a result.

1. BACKGROUND AND OBJECTIVES

1.1. Background

New pharmaceutical products are protected by patents, as standard up to 20 years, subject to upward revisions by Supplementary Protection Certificates (SPC), granting the manufacturer monopoly rights and thereby protecting their invention, rewarding their creativity and preserving incentives for future research and development (European Commission 2009). Patents allow manufacturers to negotiate or price a medicine far higher than its marginal cost of production, particularly so for medicines that are considered breakthroughs or offer potentially significant improvements on current treatment choices. The high research and development (R&D) costs, and high failure rate especially for oncology and orphan drugs, mean that prices higher than production costs are warranted to protect future innovations in medicines.

This raises the question of how to provide the correct balance between rewarding and encouraging manufacturers for producing innovative new treatments, be it incremental or breakthrough, and protecting payers from paying too much for medicines under monopoly conditions.

Among other models of price setting or regulating the supply-side in pharmaceutical markets, both value based pricing (VBP) and external price referencing (EPR) are currently used extensively to inform decisions on pricing and reimbursement of pharmaceutical products. VBP is frequently used in different contexts to inform pricing and reimbursement decisions of products seeking a price premium over existing therapies, whereas EPR is used more generically either as a tool to explicitly set prices or as a criterion (among other criteria) to inform the pricing process across a range of pharmaceutical products. Both methods have advantages and disadvantages to different stakeholders and have different short- and long-term implications especially on the market dynamics.

In situations of perfect information, the price setting exercise may be simple, however, both EPR and VBP, pricing mechanisms used in Europe, suffer from significant information asymmetry, making such negotiations difficult. Thus, pharmaceutical prices vary between countries, reflecting information available, negotiation skills, industry presence, degree of innovation, perceptions of value as well as other factors.

1.2. Objectives

This study is primarily concerned with how EPR and VBP exist in Europe and how they may exist in the future. In particular, the study debates the relative merits of VBP and ERP over the short- and the longer-term by taking into account the views

and perspectives of key stakeholders (including governmental bodies, key purchasers and pharmaceutical manufacturers), as well as analyse market and pricing dynamics. Although some evidence exists surrounding the use of EPR and VBP – particularly the latter - to inform pharmaceutical pricing and reimbursement, there is lack of comparative analysis and an understanding of their impact on individual stakeholders both in the short- and the longer-term. This is more prominent in the case of EPR, where the available information is scarce and evidence on its impact non-existent. This study attempts to fill this void in a more systematic way by bridging the gap between concepts, practice and impact.

2. DATA AND METHODS

Both primary and secondary sources have been used to inform the discussion and analysis in the sections that follow. Secondary data sources comprised a systematic review of the peer review literature since 1995 alongside other available literature (reports, books, etc) that was available, on how VBP and ERP are used from an international perspective and experience. Databases, including Medline and the Social Science Citation Index, were searched in this context. Additional reports in the English language were found on the internet. Search keywords included “value based pricing”, “cost-effectiveness pricing”, “external reference pricing”, “international reference pricing” and were used either on their own or in combination with one or more of the following keywords: “pharmaceuticals”, “pharmaceutical policy”, “pharmaceutical pricing and reimbursement”, “value assessment in pharmaceuticals” and “pricing models for branded pharmaceuticals”. The identified studies were subsequently filtered to identify their suitability for inclusion in this analysis. This was determined based on whether studies discussed the salient features of VBP and EPR and analysed the impact either VBP or EPR was having on a number of key endpoints, notably, the prices of medicines (and surrogate issues such as parallel trade), drug use, access to treatments, assessment of value, the impact on (pharmaceutical and biomedical) innovation

Primary data were collected via telephone and face to face semi-structured interviews with key stakeholders. Beyond understanding the salient features of VBP and EPR as they applied in individual policy settings, important endpoints for the questionnaire survey/semi-structured interviews comprised both short- and longer-term effects of implementing either strategy (Value-Based Pricing or External Price Referencing) in pharmaceutical pricing, for instance:

- (a) impact on prices, both domestically and internationally;
- (b) impact on drug use and access to medicines;
- (c) operational and administrative requirements for VBP and ERP systems;
- (d) access to (modern) treatments;
- (e) quality of the available evidence to reach informed decisions;
- (f) impact on (pharmaceutical and biomedical) innovation; and
- (g) implications for or the effect of parallel trade.

The stakeholders included (a) governmental agencies, (b) key purchasers at national or/and local level, (c) representatives of pharmaceutical industry, (d) patient groups, (e) representatives from the European Medicines Agency (EMA) and

(f) others, e.g. academics, related experts and representatives of the distribution chain.

Governmental agencies have included ministries of health, insurance associations, reimbursement committees and Health Technology Assessment (HTA) agencies in a number of countries, where either VBP or EPR (or both) are implemented. A total of 8 EU Member States were selected for this purpose, as follows: UK (DH, NICE and SMC), Sweden (MoH, TLV), The Netherlands (CvZ), the Czech Republic (MH, SUKL), France (HAS), Germany (IQWiG), Spain and Denmark. These Member States were selected because of the tradition in implementing either one or the other of the two measures, whereas in the case of the Netherlands, experimentation with both. In the UK, the completion of an advanced draft of the report in mid-December 2010 coincided with the publication of the UK government's proposals, by means of a consultation document, to implement a value-based pricing approach for pharmaceuticals as of 2014 after the expiry of the current PPRS agreement in December 2013.¹ Where relevant and appropriate and in order to inform the process, evidence from agencies outside the European Union was brought in, e.g. from Australia (PBAC - Pharmaceutical Benefits Advisory Committee) and Canada (CDR – Common Drug Review).

Key purchasers have included hospitals, purchasers operating at regional level or/and regional governments (e.g. county councils) making decisions about product reimbursement. The views of Industry representatives have also been sought via meetings with EFPIA and LIF members, as well as individually with a number of senior company representatives. Meetings with patient organisations have also taken place to inform specific aspects of this research in relation to practice, notably, patient involvement in the decision-making process and patients' perception of regulation.

Additional meetings have taken place with key informants from a health system, purchaser, patient, provider, and industry perspective in order to obtain views and perspectives as well as validate individual pieces of information. This has been an iterative process, where views obtained from stakeholders were checked and validated with others. The number of interviewees in the context of this report reached N=69.

Finally, in the absence of recent empirical evidence about several aspects of the research exercise, additional material was collected, processed and is presented to

¹ Department of Health (2010). A new value-based approach to the pricing of branded medicines – a consultation. 16 December; available on: http://www.dh.gov.uk/en/Consultations/Liveconsultations/DH_122760; accessed 17 December 2010.

inform certain aspects of VBP and EPR, particularly those pertaining to pricing and access to treatments.

The remainder of the report is structured as follows: chapter 3 presents the salient features of VBP and EPR in brief, by drawing on international literature. Chapter 4 discusses the processes and information required to inform pricing decisions under VBP and EPR; chapter 5 discusses the impact of VBP and EPR on pharmaceutical prices; chapter 6, elaborates on the impact of VBP and EPR on coverage, diffusion and access, while chapter 7 presents the evidence on assessing the value of innovation. Chapter 8 attempts to provide insights into the future by examining the extent to which VBP and EPR encourage and reward innovation. Chapter 9 puts the advantages and limitations of both schemes side by side in order to enable a better comparison. Finally, chapter 10 produces a brief summary of the conclusions reached.

3. OPERATING FRAMEWORK FOR VBP AND EPR

3.1. Salient Features

3.1.1. Value Based Pricing and definition of “value”

The varying nature and emerging complexity of health technologies, in combination with limited national budgets, has resulted in tensions between delivering cost-effective health care and improving or sustaining a country’s manufacturing and research base. As a result, it has become increasingly important to achieve a balance between affordable health care and the use of innovative health technologies, including pharmaceuticals. To meet this end, it is necessary to not only consider the value (in both medical and economic terms) of a product, but also who benefits from innovations, the optimal usage², and the appropriate placement in the spectrum of care (Drummond 2006).

VBP is often abstractly defined as integrating value into the price of medicines reflecting the health benefits it delivers. To that end, the purpose of VBP is two-fold; first, to reward medicines that have better than current outcomes and second (but also linked to the first objective), to encourage future innovation in the development of new therapeutic agents.

VBP can assist in meeting these challenges by determining which technologies are ineffective versus those with value, and by defining the most appropriate indications for use of a technology. Moreover, it can serve to validate a new technology and define its role in health care system. VBP thus provides important benefits by enabling governments to make decisions driven by value, which concurrently supports innovation, and garners patients and physicians with the information needed to make the best treatment choices (Sorenson et al. 2008).

The mechanisms for determining value and consequent price setting are not simple. Important elements such as the definition of value need to be The primary method for determining value is using clinical (and in most cases) cost effectiveness analysis (CEA) and determination of the incremental cost effectiveness ratio (ICER). The evidence used to determine the clinical cost effectiveness, and thereby set the price, can be ex ante (pre-launch data; currently used in Australia, Canada, Sweden and perhaps UK), ex post (post-launch data) or a combination thereof.

² Variation in uptake and diffusion can signify the sub-optimal use of technology. Excess use is signified when the costs outweigh the benefits for any additional level of technology diffusion or use. Under-use can occur when the foregone benefits outweigh the costs of additional diffusion or use. Both scenarios are sub-optimal, potentially resulting in economic costs and/or reduced health outcomes.

3.1.1.1 Defining value of innovation

The main difficulty in defining price via VBP is how to define the value of innovation. Technically, value may be defined as an incremental or radical change in thinking, products, processes or organisations (Mckeown 2008). In terms of medical advances, innovation may be incremental or radical (breakthrough) and is treated differently in price and reimbursement negotiations. Further issues arise with measurement of outcomes (i.e. terminal illnesses, orphan disease), how to deal with uncertainty, how to manage insufficient sample sizes or heterogenous diseases (i.e. rare diseases, paediatric illnesses) and quality of life versus quantity of life (i.e. side effects, activities of daily living, location of treatment, invasiveness of treatment, dignity, patient time), in addition to transition and implementation issues of adopting a new system. How this information may be integrated within VBP is still the subject of intense debate (Kennedy 2009; Walsh et al. 2009; Office of Fair Trade 2007).

3.1.2. External Price Referencing

External Price Referencing (EPR), known otherwise as External Price Benchmarking (EPB) or International Reference Pricing (IRP), involves the selection of a basket of countries, which can change over time, to compare pharmaceutical prices and create a reference price (RP) for the country in question. The purpose of EPR may be to (a) negotiate or set prices within a country, (b) negotiate coverage and reimbursement, or (c) authorise product marketing. Negotiations or setting of pharmaceutical reference prices based on prices of other countries may be wholly dependant on EPR, or only part of the process with the remainder including cost-plus, internal or therapeutic pricing.

It is important to note in this context that EPR is often only one of the several pricing and reimbursement tools available to countries and very frequently provides a benchmark or a starting point for negotiations between industry and health insurance organisations (e.g. Austria or the Netherlands, where it applies). In other countries (e.g. Czech Republic or Greece) EPR has a significant impact on the ex-factory price, as it is the key price-setting methodology.

The method for setting or calculating the External Reference Prices can vary in several aspects and depends on a number of variables. Key factors to be considered include:

First, the criteria used to choose the 'basket' of reference countries, including the adequacy of the selected countries and their medicines regulatory system; the criteria used in country selection include, chiefly, geographical proximity,

comparable GDP levels, country of origin of the intervention considered, and price levels of comparators.

Second, the number and specific set of countries in the basket used as reference; this usually ranges from a few select to a wider range of countries selected from a geographical area.

Third, the date of the price in the reference countries (e.g. current price vs. price at launch) and the selection or calculation of the RP (lowest price in the basket, simple average of all prices, weighted average, or a combination of these);

Fourth, the frequency of price adjustments, which can be biennial, annual, less or more frequent, depending on need, relevance of price adjustments in comparator countries, or other criteria;

Fifth, the elements in the drug's formulation that will be referenced (content referencing); and

Sixth, the resulting figure might be adjusted by a certain parameter, for instance, to take into account the lower economic capacity of the country relative to the reference countries.

Ideally, this process is transparent with comparator countries named, pricing data properly stated and sourced and any additional adjustment procedures realistic. Its use is not uncommon globally, with 24 out of 30 OECD and 23 out of 27 EU Member States include ERP in some form in their pharmaceutical pricing methodologies.

3.2. Practical application of VBP and EPR

3.2.1. Value Based Pricing

The effectiveness of VBP in determining the value of new treatments as well as in encouraging innovation, hinges on, *first*, properly performed assessments and, *second*, the appropriate implementation and subsequent use of any recommendations made in this context. VBP can encourage innovation if the assessments are properly conducted and consider a wide range of costs and benefits associated with a new technology, rather than focus solely on acquisition costs. In particular, the costs of adoption need to be viewed in terms of the broader benefits that would ensue if a technology were integrated into the health system, as budget-driven constraints on the general diffusion of technologies do not necessarily result in the selection of the most effective or cost-effective products. This may require governments to allow additional funding and flexibility between budgets, so that expenditure levels are driven by value.

The utility of VBP in encouraging innovation and value-added health care also depends on the assessment process, including when and how the review was performed, and resulting decision-making procedures. The literature suggests that the following issues can potentially affect the effective use of VBP in meeting these objectives:

- delays in the value assessment process can result in deferred reimbursement decisions, restricting patient access to needed treatments;
- evidence requirements can pose a significant hurdle for manufacturers, particularly small, innovative companies, which may serve to discourage sponsors from pursuing breakthrough technologies;
- as VBP becomes increasingly widespread, assessments are occurring earlier in the technology diffusion process, which may introduce greater uncertainty in the process and the potential for innovations to appear more or less beneficial when assessed at an early stage.
- current assessment methodologies may limit the comparability and transferability across countries and studies;
- lack of transparency, accountability, and stakeholder involvement in the value assessment process can decrease the acceptance and implementation of assessment results;
- limited skilled personnel and international collaboration between review agencies can stymie the efficiency and effectiveness of assessments;
- separate processes for and organizations dedicated to economic assessments, reimbursement/pricing decisions, and practice guideline development may hinder the effectiveness and efficacy of the overall decision-making process, and lead to unnecessary duplication of efforts and resource use.

In addition, value assessments are more likely to be utilised by decision makers if policy instruments (e.g. reports, practice guidelines) are available to act on the assessment and if prior commitments to effectively use the assessments are established. Moreover, as the cost-effectiveness of a technology can change over time, in addition to patient demand, it is important to review the recommendations of HTA agencies on a consistent basis. To achieve these objectives, greater participation and collaboration among stakeholders, particularly HTA personnel, government officials, industry, health providers and patients, is required. Without adequate input and understanding of the HTA process, stakeholders may mistrust the evidence and subsequent recommendations of the assessment.

The role of HTA in encouraging innovation and value in health care could be improved by better understanding and addressing the inherent challenges in the HTA process, as outlined below.

The introduction and growth in VBP and HTA in Europe parallels an era in health policy that places greater emphasis on measurement, accountability, value for money and evidence-based policies and practices. Moreover, the advent of randomised control trials and subsequent availability of data, growth in medical research and information technology, and increased decentralisation of health system decision-making, all contributed to an increased need for HTA activities (OECD 2008).

In Europe, the first institutions or organisational bodies dedicated to the evaluation of health care technologies were established in the 1980s, initially at the regional and local level in France and Spain and, later, on the regional level in Sweden in 1987 (Velasco-Garrido and Busse 2005; Garcia-Altes et al. 2004). Over the following decade, in almost all countries, HTA programmes have been established either through the provision of new agencies or institutes, or in established academic units or governmental and non-governmental entities (Table 3.2.1). Broadly speaking, such bodies fall into two general strands: 1) independent (“arms-length”) review bodies that produce and disseminate assessment reports on a breadth of topics, including health technologies and interventions, and 2) entities under governmental mandate (e.g., from health ministries) with responsibilities for decision-making and priority-setting, typically pertaining to the reimbursement and pricing of health technologies. The latter type of HTA body serves either an advisory or regulatory function.

In parallel with establishing HTA entities, many EU countries are investing resources in HTA and associated evaluation activities. For example, Sweden dedicates €5 million per year on the Swedish Council on Technology Assessment in Health Care (SBU) and the Dutch Fund for Investigative Medicine spends €8.6 million per year on health evaluations (Sorenson et al. 2008).

Table 3.2.1 : Institutions and advisory bodies responsible for HTA activities in selected EU countries, 2009

1. Denmark	<ul style="list-style-type: none"> • Reimbursement Committee/Danish Centre for Evaluation and Health Technology Assessment/ <i>Center for Evaluering og Medicinsk Teknologivurdering</i> (DACEHTA/CEMTV)
2. Finland	<ul style="list-style-type: none"> • Pharmaceuticals Pricing Board – PPB • Finnish Office of Health technology Assessment (FinOHTA)
3. France	<ul style="list-style-type: none"> • Economic Committee for the Health Products (CEPS) • Transparency Commission (CT) • Haute Autorité de Santé (HAS)
4. Germany	<ul style="list-style-type: none"> • Federal Joint Committee (FJC) • Institute for Quality and Efficiency in Health Care (IQWiG) • German Agency for Health Technology Assessment (DAHTA)
5. Italy	<ul style="list-style-type: none"> • Committee on Pharmaceuticals (<i>CIP Farmaci</i>) • Italian Medicines Agency (AIFA)
6. Netherlands	<ul style="list-style-type: none"> • National Health Insurance Board/Committee for Pharmaceutical Aid
7. Spain¹	<ul style="list-style-type: none"> • Spanish Agency for Health Technology Assessment • Catalan Agency for Health Technology Assessment (CaHTA) • Agency of Health Technology Assessment of Andalusia (AETSA)
8. Sweden	<ul style="list-style-type: none"> • Dental & Pharmaceutical Benefits Board (TLV) • Swedish Council on Technology Assessment in Health Care (SBU)
9. UK ¹	<ul style="list-style-type: none"> • National Institute of Health and Clinical Excellence (NICE) • Scottish Medicines Consortium (SMC) • All Wales Medicines Strategy Group (AWMSG) • National Coordinating Centre for Health Technology Assessment (NCCHTA)

Source: The authors from various sources; adapted and enhanced from Velasco-Garrido and Busse 2005; Zetner et al. 2005.

Note: ¹ These are not an exhaustive list of the agencies available in the country.

3.2.2. External Price Referencing

It appears there are two policies for using ERP in price negotiations, either a non-conditional external reference policy or a conditional external reference policy. The former uses the other countries' prices as a reference to set maximum price, regardless of the other countries' success in their own price negotiations, while the latter use depends on the presence of the product in its list of subsidised medicines.

Analysis of these mechanisms suggests ERP is primarily useful in the latter conditional external reference policy (Garcia-Marinoso et al. 2008).

In practice, a survey of 8 countries found ERP are used differently between countries, some using it for only reimbursable drugs, some for all drugs and others only for patented or generic drugs (Espin and Rovira, 2010). Although usually regional comparisons are used due to similarities in income and culture, farther comparisons may be used where transparency, lower prices and accessible price information exist, or where similar levels of pharmaceutical industry involvement exist. Common elements include the ex-factory price, the lower priced countries are selected into the basket and data sources include manufacturer's certificates and country websites but not international databases.

ERP can be used as the only criterion to inform the target price estimation, or can be one among several criteria, such as, cost-plus or internal reference pricing. These different values can be brought together as part of the deliberations of the decision-making body. The reference price can be enforced rigidly as a condition to either authorise the marketing of the product in the country, or (more commonly) as a condition for health system's coverage and reimbursement. Alternatively, it can be used as an explicit or undisclosed benchmark in a negotiation process.

In the case of EPR, predictability and the need for transparency require the specification of the list of reference countries, the sources of data for the prices in the reference countries, the procedure to follow if the relevant price data are not available, the adjustments, if applicable, to account for confidential discounts or rebates in list prices or for differences in income levels and so on. The description of the procedure for arriving at the RP should include, if applicable, the way other criteria besides ERP contribute to the calculation of the target or reference price.

European countries tend to select as reference countries those that share economic similarities or geographic proximity (OECD 2008; Espin and Rovira 2007; Espin and Rovira 2010). However, differences abound across countries. For instance, the number of countries or sources utilized varies considerably (Table 3.2.2). It is worth noting that a majority of countries use either the average or the minimum price taken from the set of reference countries.

In Slovakia the pharmaceutical companies, before introducing the medicine on the market, must inform about the price of the medicine in nine European countries: Country of origin, Austria, France, Germany, Italy, Spain, Czech Republic, Hungary and Poland. This method could cause high prices in Slovakia because, normally, the country of origin has high prices. Therefore, there could be some delay in the decision until having information about the prices the neighbour countries (Czech Republic, Hungary and Poland), but delay rules are not explicit.

In Estonia, EPR is used for reimbursed innovative and generic medicines, using the manufacturer price level. EPR may include all EU Member States, but examines explicitly the prices of three countries: Latvia, Lithuania and Hungary. Latvia and Lithuania were chosen because these are the closest neighbouring countries to Estonia with similar economic situation, population structure and epidemiological status. Hungary was chosen because has a similar pricing procedure (negotiations with manufacturers) to Estonia.

Table 3.2.2: External Price Referencing in EEA and pre-accession countries, 2010 *

	AT	BE	BG	HR	CY	CZ ¹	DK	EE	FI	FR	DE	GR	HU	IE	IT	LV	LT	NL	NO	PL	PT	RO	SK	SI	ES	SE	CH	UK	
AT		✓			✓	✓		✓	✓			✓	✓	✓		✓			✓			✓	✓	✓				✓	
BE	✓		✓		✓	✓		✓	✓			✓	✓	✓		✓		✓	✓				✓	✓		✓			
BG						✓		✓								✓						✓	✓						
CY	✓					✓		✓				✓				✓							✓						
CZ	✓		✓	✓				✓				✓	✓			✓	✓			✓		✓	✓						
DK	✓	✓			✓	✓		✓	✓			✓		✓		✓			✓			✓	✓				✓		
EE	✓		✓			✓						✓				✓	✓			✓			✓						
FI	✓	✓				✓		✓				✓		✓		✓			✓				✓						
FR	✓	✓	✓	✓	✓	✓		✓	✓			✓	✓	✓	✓	✓		✓			✓		✓	✓	✓		✓		
DE	✓	✓			✓	✓		✓	✓	✓		✓	✓	✓	✓	✓		✓	✓				✓	✓	✓	✓		✓	
GR	✓	✓	✓		✓	✓		✓	✓				✓			✓				✓	✓		✓		✓				
HU	✓		✓			✓		✓	✓			✓				✓	✓			✓		✓	✓						
IE	✓	✓				✓		✓	✓			✓	✓			✓			✓				✓		✓				
IT	✓	✓		✓	✓	✓		✓	✓	✓		✓	✓			✓					✓	✓	✓		✓		✓		
LV	✓		✓			✓		✓	✓			✓					✓			✓			✓						
LT	✓		✓			✓		✓	✓			✓				✓				✓		✓	✓						
LU	✓					✓		✓				✓				✓							✓						
MT	✓					✓		✓				✓				✓							✓						
NL	✓	✓				✓		✓	✓			✓		✓		✓			✓				✓		✓		✓		
NO								✓	✓							✓													
PL	✓					✓		✓				✓	✓			✓	✓					✓	✓						
PT	✓		✓		✓	✓		✓	✓			✓	✓			✓							✓		✓	✓			
RO			✓			✓		✓								✓							✓						

SK	✓		✓			✓		✓				✓	✓			✓	✓			✓		✓						
SI	✓			✓		✓		✓				✓	✓			✓							✓					
ES	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓					✓	✓		✓					
SE	✓	✓			✓	✓		✓	✓			✓				✓				✓			✓					
CH								✓				✓				✓						✓	✓					
UK	✓	✓				✓		✓	✓	✓		✓		✓		✓	✓			✓	✓			✓		✓		✓
Formula	A	A	L	A	L 4	L ³		L	M	L		A 3+1	L	A	L	L	A - 5%	A	L3	L	A	L3	L6	L	L			A
Freq (per y)	1*	AL	2	1	0.5	1		1	1	1**		1	AL	AL	AL	1	1	2	1	1	1	1	-	2	2	1		***

Source: Adapted from Kanavos and Vandroos 2010.

Notes: * Country abbreviations: AT – Austria; BE – Belgium; BG – Bulgaria; HR – Croatia; CY – Cyprus; CZ – Czech Republic; DK – Denmark; EE – Estonia; FI – Finland; FR – France; DE – Germany; GR – Greece; HU – Hungary; IE – Ireland; IT – Italy; LV – Latvia; LT – Lithuania; NL – The Netherlands; NO – Norway; PL – Poland; RO – Romania; SK – Slovakia; SI – Slovenia; ES – Spain; SE – Sweden; CH – Switzerland; UK – United Kingdom.

¹ Countries in top row referenced by countries in first column.

² The Czech Republic has a basket of 8 countries (highlighted with Bold) to inform pricing decisions; an average price rule is applied, notably the price is calculated based on the average of the 3 lowest in the basket. This basket is extended to all new EU Member States (Latvia, Poland, Slovenia, Slovakia, Bulgaria and Romania), if at least 3 prices cannot be found from the original basket of 8 countries. Finally, for the process of reimbursement, the Czech Republic uses prices drawn from all EU Member States.

³ Reflecting reimbursement decisions. The average price rule applies in pricing decisions.

A: Average; A3+1: Average of 3 lowest EU-15 and 1 lowest from EU-10; A-5%: average minus 5%; L: Lowest; M: Median; L3: Lowest 3 prices; L6: Lowest 6 prices; AL: At launch.

* Most oncology drugs exempted.

** Only for the first 5 years, not automatically implemented.

*** 2 and 7 years after rmb patent expiry or 15 years after rmb and 2 years later.

*** 3 months after each change in ref. min prices.

4. PROCESS AND INFORMATION REQUIRED TO INFORM PRICING/REIMBURSEMENT DECISIONS UNDER VBP AND EPR

4.1. Overview

In this section we examine how VBP and EPR fit into national decision-making processes and what are the respective processes and information required to inform pricing and reimbursement decisions in different jurisdictions.

The relevant issues from a VBP perspective are whether agencies assessing value of new pharmaceutical products are regulatory or advisory, what assessment procedures and methods are in place, what are the criteria and timing of assessments, and what the evidence is on implementation, dissemination and monitoring of recommendations made.

From an EPR perspective, issues under consideration are the legal framework, the framework that describes processes on pricing and reimbursement, the definition of the basket of countries and the types of prices taken, the frequencies of price revisions and the exchange rates used, the extent to which there are departures from the overall framework and under what circumstances, the perceived and actual transparency of the mechanisms used to determine pricing and reimbursement and whether the EPR scheme as it works promotes stability.

We discuss each of these parameters for VBP and EPR respectively in the sections that follow.

4.2. Process and information required under VBP

4.2.1. Current practices

4.2.1.1 Responsibility and membership of HTA entities

Most national bodies conducting VBP can be categorised as serving either an advisory or regulatory role in the decision-making process, depending on the intent and type of assessment required. Those entities that act as advisors, as seems to be the case in the Netherlands and Denmark, make reimbursement or pricing recommendations to a national or regional government, a ministerial department, or to a self-governance body. Alternatively, regulatory-focused review bodies are completely independent from health care decision-making and with regard to the evidence they produce for the benefit of health care decision makers, such as ministries of health and/or social health insurance funds. The HTA agencies in France (HAS), Sweden (TLV), Finland and the UK (NICE, SMC, AWMMSG) subscribe to

this type of structure. Other entities primarily coordinate HTA assessments and produce and disseminate evidence (e.g., Health Council in the Netherlands, SBU in Sweden). The mandates or responsibilities of the assessment bodies vary by their general mission and overall policy objectives. As one component in the broader health care decision-making process, the role of HTA programmes typically reflects the current national policy landscape, such as the need to contain costs or improve access to a given area of intervention or service. Consequently, economic evaluations often coincide with policies regarding the reimbursement, pricing, and utilisation of health technologies. However, assessments also frequently assume a role in providing information to providers via practice guidelines and supporting decisions regarding the investment and acquisition of health technology.

4.2.1.2 Assessment procedures and methods

HTA processes within the EU differ on a variety of issues regarding the actual assessment process, including topic selection, evidence/data requirements, analytical design, and the methodological approach(s) employed.

Topic Selection

Most HTA agencies struggle to keep pace with newly approved or introduced technologies. As a result, priority-setting has become an important aspect of the HTA process in determining which products are assessed. Countries set HTA priorities using a number of different mechanisms and criteria, both in terms of emphasis given to different approaches (i.e., proactive, reactive, or mixed) and in the process of needs identification itself. The topic agenda of some review bodies are set by national authorities (typically, the Minister of Health) or Departments of Health. However, in Germany and the UK, processes have been established to receive suggestions for HTA topics from a wide range of stakeholders, including the public. For instance, in Germany, a board of trustees comprised of public administrators, patients, and industry, determines HTA topics using a Delphi process.³

³ The Delphi method is a structured communication technique, originally developed as a systematic, interactive [forecasting](#) method which relies on a panel of experts. In the standard version, the experts answer questionnaires in two or more rounds. After each round, a facilitator provides an anonymous summary of the experts' forecasts from the previous round as well as the reasons they provided for their judgments. Thus, experts are encouraged to revise their earlier answers in light of the replies of other members of their panel. It is believed that during this process the range of the answers will decrease and the group will converge towards the "correct" answer. Finally, the process is stopped after a pre-defined stop criterion (e.g. number of rounds, achievement of consensus, stability of results) and the [mean](#) or [median](#) scores of the final rounds determine the results

In the UK one review body, the Scottish Medicines Consortium (SMC), however, aims to evaluate every new drug, formulation, and indication within 12 weeks of market launch. The review bodies that primarily make reimbursement decisions determine products to be assessed by the medicines' licensing authorities and manufacturer submissions. Furthermore, HTA agencies differ in terms of the breath of assessment topics. Specifically, some focus on health technologies (specifically drugs or devices, or both), while others attend more to particular disease areas or health conditions.

The criteria used to select topics varies across agencies, but generally includes health benefit, impact on other health-related government policies (e.g., reduction in health inequality, improving access), uncertainty about effectiveness/cost-effectiveness, disease burden, potential benefits and impact of the assessment, and innovation capacity.

Evidence/Data Requirements

HTA systems vary regarding the type and quality of evidence required for economic evaluations. Typically, manufacturers are required to submit a comprehensive summary of data on a product's effectiveness and cost-effectiveness. Review entities differ, however, on the role of industry data in the assessment process. In Austria, Norway, and the Netherlands, for instance, competent authorities review and validate relevant data provided by industry. In Austria, social insurance reviews this information for in-patent products applying for reimbursement for the first time. Other organizations, typically at arms' length (e.g., NICE, SBU), perform systematic reviews of the literature in-house or commission independent evaluation groups for the purpose; evidence used in the assessment may or may not include manufacturer data and generally involves broader review of various information sources. Some countries, such as France, Switzerland, and Finland, do not require systematic reviews (although preferred), basing assessments primarily on a definite number of studies (e.g. pivotal clinical trials) provided by industry. Assessment of unpublished evidence (e.g., commercial in confidence data) is explicitly considered in Austria, the Netherlands, Sweden, and the UK. The majority of HTA institutions have published guidelines to outline the methodological requirements for manufacturers and reviewers.

Analytical Design

Most evaluations assess a variety of criteria including safety and clinical effectiveness, patient need and benefit, cost-effectiveness, and cost of therapy (typically in relation to benefit). Some HTA bodies also frame the evaluation around

other factors, including psychological, social, and ethical considerations, organisational impacts, disease burden and severity, equity, patient perspective (i.e., quality of life), industry R&D, budget impact, compliance with government-defined priorities, lack of alternative treatment(s) (Table 4.2.1).

Table 4.2.1: Criteria for assessment of therapeutic value of new products in selected EEA countries, 2010*

Criteria	AT ⁴	BE	CH	DE	FI	FR	NL	NO	SE	UK
Therapeutic benefit	X	X	X	X	X	X	X	X	X	X
Patient benefit	X	X	X	X	X	X	X	X	X	X
Cost-effectiveness	X	X			X		X	X	X	X
Budget impact		X			X	X	X	X		X
Pharmaceutical/innovative characteristics	X	X				X	X			X
Availability of therapeutic alternatives	X						X		X	X
Equity considerations								X	X	X
Public health impact						X				
R&D					X					

Note: * Country abbreviations: AT – Austria; BE – Belgium; CH – Switzerland; DE – Germany; FI – Finland; FR – France; NL – The Netherlands; NO – Norway; SE – Sweden; UK – United Kingdom.

Source: Adapted from Zentner et al. (2005) and case studies.

Assessment Methods⁵

HTA embraces a diverse group of methods, with most HTA programs employing an integrative approach. While the majority of agencies share similar methodological approaches and emphasise the most rigorous types of studies (e.g., use of

⁴ AT=Austria, BE=Belgium, CH=Switzerland, DE=Denmark, FI=Finland, FR=France, NL=Netherlands, NO=Norway, SE=Sweden, and UK=United Kingdom.

⁵ This section primarily refers to those decision-making bodies reviewing clinical and economic evidence for product reimbursement and pricing.

randomised controlled trials, use of cost-utility analyses), there is no standard approach for conducting assessments. Given their varying orientations, resource constraints and other factors, assessment programs tend to rely on different combinations of methods. In particular, assessments often differ on the following issues: (a) Type of economic assessment required; (b) Classification of product benefit (benefit vs. harm) – hierarchy of evidence; (c) Choice of comparator; (d) Specification of the outcome variable; (e) Costs included in the analysis; (f) Discounting; (g) Use of cost-effectiveness threshold; (h) Allowing for uncertainty; and (i) Missing and incomplete data.

Type of economic assessment

In general, requirements for economic assessments are similar across countries. Among existing guidance, cost-effectiveness or cost-utility analyses are most often considered appropriate analytic designs, particularly when the proposed product has significant clinical advantages to the comparator and the relative benefits need to be considered against costs.

Evidence to classify product benefit

All countries deem randomised controlled head-to-head trials (RCT), with a high degree of internal and external validity, the most reliable and objective evidence to demonstrate product's relative therapeutic benefit. This also applies to systematic reviews and meta-analysis of such RCTs. To supplement available clinical data, findings from different types of studies should be combined or synthesised in order to formulate effective and comprehensive policies. To that end, other types of studies (e.g., case series, registries) may be preferred to RCTs for different policy questions. For instance, modelling is useful when making decisions under uncertainty.

Choice of comparator

Given that an existing treatment is to be employed for comparison in an assessment, the choice of comparator is of significant importance in determining the outcomes of clinical and pharmacoeconomic analyses. Consequently, selecting an appropriate comparative treatment is crucial. Some institutions (Finland, Sweden – for new pharmaceuticals only) require that a product be compared with up to three well-defined comparators or, in the case of the UK, all relevant comparators. Typically, the most cost-effective existing therapy is deemed the most appropriate comparator. However, for practical considerations, HTA bodies often accept that a product be evaluated against routine treatment or the least expensive therapy. Other institutions (e.g. Sweden) require that products be compared to all therapies of the same therapeutic group, based on the WHO ATC (Anatomical-Therapeutic-

Chemical) classification system⁶. As such, only currently reimbursed or marketed products can be employed as comparators. France, however, combines both approaches, whereby all drugs in the same therapeutic group are considered, and the most frequently prescribed, the least expensive, and the most recently listed (positive list for reimbursement) are selected for comparison.

Selection of the outcome variable

Assessments typically employ a variety of health and economic outcome measures. As with the selection of an appropriate treatment comparator, specification of the outcome measure(s) can influence the conclusions of the assessment. While final outcome parameters reflecting the delineated long-term treatment objective (e.g., changes in mortality, morbidity, and quality of life) are generally preferred, countries differ in how outcome measures are selected and what is required in the specification process. In the Netherlands, the outcome variable is outlined by the assessment body, while in most countries, product sponsors serve as key decision-makers in the specification of the outcome variable.

Costs included in the analysis

HTA bodies and governments differ on the type of costs allowed for inclusion in assessments. The specification of costs is typically related to the purpose of the analysis and the overall objectives of the assessment entity. The difference between varying approaches lies in the inclusion of direct and indirect costs. Some countries, such as Sweden, allow all costs to be included in the assessment, whereas others (e.g., the Netherlands, UK) use only direct costs⁷. In addition, some systems, such as Sweden, assume a societal cost perspective, despite such costs extending beyond budget constraints.

Discounting

The use and effects of many products extend for years, especially in the case of chronic conditions. In those instances where a product impacts health and utilisation for longer than one year, it is considered good practice to employ discounting to appropriately assess the changes in costs and benefits over time.

Use of a threshold

⁶ The ATC classification system is used for the classification of drugs. It is controlled by the WHO and was first published in 1976. Drugs are divided into different groups according to the organ or system upon which they act and/or their therapeutic and chemical characteristics.

⁷ The UK includes only those direct costs to the NHS and Personal Social Services.

In economic evaluation, the results of a cost-effectiveness analysis is summarised by the cost-effectiveness (CE) ratio⁸. The CE ratio compares the incremental cost of an intervention with the incremental health improvement attributable to the intervention. The health improvements resulting from the intervention are typically measured in QALYs gained.⁹ Therefore, the CE ratio is usually expressed as a cost per QALY gained. A treatment with a relatively lower CE ratio is considered most cost-effective. The majority of countries do not employ a formal or fixed threshold, or at least do not make such a decision rule totally explicit. In the UK, for example, NICE is believed to apply a threshold £20,000-£30,000/QALY, although the Chairman of NICE and others have stressed that “this is a tool not a rule.”¹⁰

Allowing for uncertainty

Given the uncertainty inherent in conducting health technology assessments, namely the value of particular estimates and their relative effect on costs and benefits, most review bodies either conduct or require sensitivity analyses on all variables that could potentially influence the overall results or on a subset of inputs (e.g., imprecise estimates only). The stipulation for sensitivity analyses is grounded in the need to test or verify the robustness of the assessment findings. As countries have different requirements for sensitivity analysis (e.g., application of univariate or multivariate methods), it is important that the choice of parameters and methods employed be substantiated and well documented (which, is typically recommended or required in most countries). This is especially important in the case of assessments for new technologies, where the necessary data for performing evaluations is seldom evident. Most countries also require some form of modelling to allow for uncertainty in the variables and estimates used in assessments.

Missing and incomplete data

For many HTA agencies receiving data from product sponsors, there are analytical challenges associated with the data used in the assessments. For example, data may be incomplete, poorly presented, or lack transparency. These data issues may be due to a failure to follow specific assessment guidelines or incomplete clinical trial data. Moreover, sponsors may be asked to report on the same information in

⁸ Suppose 1 and 0 denote the intervention under study and the alternative to which it is compared, respectively. If C_1 and C_0 are the net present values of costs that result when the intervention and alternatives are used, and E_1 and E_0 their respective health outcomes, the incremental CE ratio is simply: $CE\ ratio = (C_1 - C_0) / (E_1 - E_0)$. This ratio, which is a cost per unit incremental health effects, is often used as a measure of value.

⁹ Where QALYs indicate quality adjusted life years. The QALY incorporates quality of life assessments alongside improvements in hard clinical endpoints, e.g. overall survival. Thus, a treatment delivering an additional year of life at quality of life found to be 70% of a healthy person’s quality of life, delivers 0.7 QALYs.

¹⁰ Presentation and discussion at LSE, 13 September 2010.

various formats for different countries, which presumably increases the cost of complying and reduces efficiencies.

4.2.1.3 Application of VBP evidence to decision-making: Criteria and timing of assessments

Countries employ a variety of HTA evidence to support priority-setting and other modes of decision-making. Countries typically consider a drug's therapeutic benefit¹¹ in comparison to available treatment alternatives.¹² In fact, this tends to be the leading criterion to assess a product's added value in the majority of evaluations. Health-related quality of life is deemed a key criterion for a technology's added value from a patient perspective and several HTA bodies consider this on a routine basis. Other factors are often or routinely considered along with efficacy and cost-effectiveness evidence, including: (a) Necessity (i.e., disease burden and severity); (b) Public health impact; (c) Availability of alternative treatments; (d) Equity; (e) Financial/budget impact; (f) Projected product utilisation; (g) Innovation of product (e.g., pharmacological characteristics, ease of use); and (h) Affordability.

The transparency of the criteria used in decision-making, however, is often lacking in many countries and some review entities rarely, if ever, explicitly outline the relative weight and importance of the criteria used in making recommendations.

The timing required to complete an assessment can impact the application of HTA evidence to decision-making. Specifically, the duration of HTAs can introduce pressure between achieving dual goals of ensuring comprehensive evaluations and providing timely information to decision-makers and, in turn, products to patients. More specifically, assessments typically require a couple of weeks to a few years to complete, with the average duration around 3 months to one year. Countries, such as France, tend to take less time (e.g., a couple of weeks), as compared to other review entities, such as the UK (NICE) and Sweden, where a one-year assessment is typical, although, increasingly "rapid assessments" and "fast track" procedures have been introduced to address the length of time required to complete assessments.

¹¹ A product is considered as having a therapeutic benefit if it demonstrates an improved benefit/risk profile compared to existing treatment alternatives. In the case of therapeutic equivalence, a drug is typically not accepted for public reimbursement or is subject to a reference pricing system. A therapy with an inferior benefit/risk profile than other viable therapies are not typically reimbursed, even in the case of lower costs.

¹² The study included the following countries: Austria, Australia, Canada, Switzerland, France, Netherlands, Norway, New Zealand, Sweden, and the UK.

4.2.1.4 Evidence dissemination and implementation

As previously mentioned, the results or evidence associated with HTA are used on a wide range of decisions to:

- Plan resource capacities
- Shape the benefit catalogue
- Guide treatment provision
- Inform corporate investment decisions
- Identify R&D proprieties and spending levels
- Change regulatory and payment policy
- Acquire or adopt a new technology(s)

Almost all countries require assessments to ascertain reimbursement status, although differences exist regarding the importance of economic evidence in the decision process. France, for example, rarely considers such information when determining reimbursement status. Moreover, some reimbursement committees may only require assessments for patented drugs and new indications, or apply varying requirements to different types of products, such as generic drugs (Anell, 2004). Overall, health economic evidence appears to have the most significant impact on coverage decisions regarding those drugs with broad use (thus, significant potential budget impact) and when cost-effectiveness varies by indication or patient subpopulation.

To that end, economic evidence is also used to restrict the use of products, especially innovative and expensive technologies where there may be uncertainty around important decision parameters. Specifically, reimbursement of such technologies can be conditioned to certain indications, patient populations, treatment settings, and therapeutic positioning (i.e., first- or second-line therapy).

From an evaluative perspective, the ability of HTA to maximise health for a given health care budget is difficult to assess in practice. Few countries have formal processes to measure the impact of HTA evidence and dissemination mechanisms. Hurdles to effective impact assessment include, as aforementioned, that HTA is only one factor of many that influence policy and practice decisions, and the long-term nature of some of the effects of HTA (e.g., changes in expectations and behaviour patterns of users).

4.2.2. Discussion and stakeholder views

Although there is some crossover in terms of the clinical, safety and economic information considered by different HTA agencies, there are considerable disparities in the information required, the interpretation of evidence, rigour of the appraisal process and stated motivations for listing or not listing drugs. The following paragraphs explore these by drawing on discussions with HTA bodies and a review of the appraisals produced over the 2007-2009 period.¹³

4.2.2.1 Selection criteria and national priorities

The number of appraisals completed by each agency varies, and the drugs assessed are not necessarily the same across agencies. In terms of the types of drugs classified per ICD code, we have seen that certain classes are appraised more often than others. Moreover, when looking at the three classes with the highest proportion of appraisals per agency, these also differ from one agency to another.

These differences, in part, are a result of the selection criteria for HTA appraisals established by each agency, as well as each country's national priorities. Table 4.2.2 summarizes these selection criteria for each agency. For example, when considering that HAS appraises all drugs, the fact that they have appraised the highest number of drugs is more easily understandable. Similarly, NICE, having appraised the lowest number of drugs, focuses only on those which are deemed to fulfil the highest need.

Table 4.2.2 : Selection criteria for HTA appraisals by four agencies: NICE, TLV, HAS and SMC, 2010

	England NICE	Sweden TLV	France HAS	Scotland SMC
All pharmaceuticals			x	
Highest need for guidance	X			
All out-patient pharmaceuticals		X		
All newly licensed drugs and formulations				x
New indications				x

Source: The Authors from the literature.

National priorities may be reflected to some extent in the ICD codes of the appraised drugs. For example, in England the majority of cancer treatments (C00-D48) have been appraised as this is a priority because of the need, the severity of illnesses they

¹³ See also Euro-Observer, December 2010.

treat and the cost implications for the National Health Service. In contrast, TLV, which selects all out-patient drugs for HTA appraisals, has a more balanced amount of appraisals across indications, which may suggest that all drugs are considered equally important, regardless of the price, need, or severity of disease.

4.2.2.2 Clinical and economic evidence

A preference for robust Phase III trial data (particularly head-to-head trials where available) is visible across all agencies, where (possibly due to a scarcity of evidence) the same trials were examined by all (Table 4.2.3). NICE examined numerous additional Phase II, extension and open-label trials, while HAS focused, among others, on pharmacovigilance information, case studies and retrospective surveys. Where Phase III trials had been conducted, SMC rarely considered any additional clinical information. Only NICE explicitly considered clinical and patient expert opinions. TLV did not explicitly list any clinical studies examined. Considering clinical endpoints – TLV focused on general endpoints¹⁴, while NICE, HAS and SMC examined the full spectrum of primary, secondary and general endpoints. Primary trial endpoints were usually identified by all the agencies in some manner. All give some consideration to quality of life indicators such as SF-36 and 15D measures.

¹⁴ That is, endpoints that were considered, but not focused on or given additional weight to the extent that primary and secondary endpoints were considered key indicators of clinical efficacy by some agencies.

Table 4.2.3 : Clinical and economic indicators used across 6 agencies to reach decisions on value of new treatments, 2010

	<i>Clinical evidence</i>	<i>Economic evaluation</i>			<i>Safety information</i>
HTA	Preferred trial data	Preferred economic model	Preferred ICER units	Budget impact considered	Emphasis on adverse effects
NICE	All available evidence including: Phase III RCT (head to head where available); Phase II, Clinical and patient expert opinion	CUA	QALY	Yes	Some
HAS	Phase III RCT, pharmacovigilance information, observational studies	n/a	n/a	No	Strong
TLV	Trial data used rarely specified in public documentation	CMA (CEA, CUA, CA)	QALY	No	Weak
SMC	Phase III RCT	CUA (CEA, CMA, DES)	QALY, LYG	Yes	Some

Source: The authors from the literature.

The economic dimensions of treatment are commonly assessed by looking at cost-effectiveness or budget implications. It appears that NICE accepts only cost-effectiveness models with QALY outcomes. SMC received predominantly cost-utility analyses specifying QALY outcomes. HAS focused on the assessment of clinical efficacy and conducted no economic evaluations. Commonly in the case of orphan drugs, high and uncertain ICERs are driven primarily by the high cost of treatment. However, in some cases this is exacerbated by limited evidence of additional efficacy, particularly over best supportive care.

HAS placed the strongest emphasis on drug safety and detailed every adverse event (AE) listed in the trial data, consistently identifying not only the most common, but also the most serious AEs. SMC listed the majority of common AEs, while NICE provided a comprehensive list of AEs arising in common medical practice and those depicted by patient experience. TLV rarely listed specific AEs.

4.2.2.3 HTA timing and interpretation of data

The type of evidence required and the factors that play a significant role in arriving at a decision are summarized on Table 4.2.4 below. In some instances, where the

same Phase III data was considered key by different agencies, there was a marked difference in the resulting recommendations, suggesting that the interpretation of clinical data is not uniform across agencies. For example, in the case of the orphan drug idursulfase, all appraising agencies focused on the same Phase III placebo-controlled RCT. HAS concluded that, in the absence of alternative treatment, it demonstrated “significant superiority” compared to placebo on 6MWD¹⁵ and all other secondary endpoints. In contrast, SMC concluded that the drug was “significantly more effective” than placebo, but rejected it based on insufficiently robust economic evidence.

Table 4.2.4 : Criteria used in shaping decisions on value, 2010 (data pooled across 4 agencies and for 293 appraisals)

		NICE	HAS	TLV	SMC
Clinical efficacy	Non-inferiority/ Superiority		Superiority vs therapeutic comparators	Non-inferiority to comparator	Superiority/non-inferiority vs comparators
	Clinical benefit	✓	✓	✓	✓
	Strength of trial design	✓			
Economic evaluation	Cost-effectiveness (low, certain)	✓		✓	✓
	Cost vs comparators			✓	
	Economic model validity (inputs, methods)	✓		✓	✓
	Value for money				
	Budget impact	✓			
Need	Rx alternatives available/not		✓	✓	
	Population medical need	✓		✓	
Safety	Toxicity/safety profile				✓
	Efficacy/safety ratio (high)		✓	✓	✓

Source: The authors.

There is little uniformity in the time taken by each agency to assess a drug subsequent to receiving marketing authorization (MA). Recommendations are commonly narrowed to a population sub-group within the broader MA indication, suggesting a discrepancy between the two processes, with MA requiring proof of

¹⁵ 6-minute walking distance.

quality, safety and efficacy only, while reimbursement decisions include broader, and often more subjective criteria.

4.2.2.4 Recommendations and thresholds

The key driver for NICE was cost-effectiveness, with cost implications frequently outweighing evident clinical benefit in instances where the ICER estimate lay outside the 'threshold' of £20,000-30,000 discussed in the literature.^{6,7} Yet, closer examination of individual ICER estimates submitted to NICE suggests that this threshold may not be a rigidly adhered to for orphan treatments. In some cases, drugs with base case ICERs up to £59,000 per QALY were recommended even if they considered the drug to not be cost-effective, although this just suggests that, for orphans, greater weight is placed on other factors (patient need, ethics and lack of alternative treatments).

For TLV a weak pattern indicates that clinical benefit, population need and the efficacy/safety ratio may hold greatest importance. An examination of cases in which ICER information was published suggests that TLV did not reject any of the orphans it considered on the basis of a high cost-effectiveness ratio; rather, the criteria for usage were restricted to reduce the budget impact. TLV seems to be more driven by need than cost and it has accepted up to €110,000 per QALY when there is a high clinical need in certain sub-populations.

As mentioned before, HAS does not consider economic criteria; the full weight of its decisions are based on the drug's clinical benefit and efficacy/safety ratio, with a higher ASMR classification resulting from evidence of superior efficacy over comparators. SMC emphasizes the need for a demonstrated economic case for a drug. As such, model and clinical trial design are heavily scrutinized. The efficacy/safety ratio is frequently cited as an additional motivation for recommendation. The threshold value of SMC seems to be under £30,000, with rejections of higher values.

Given the scarcity of adequate clinical trial and cost data for some orphan drugs, agencies frequently restricted criteria for reimbursement to isolate patient sub-groups in order to increase drug efficacy in these populations, reducing the cost-effectiveness outcomes to within acceptable levels (particularly NICE and PBAC).

4.2.2.5 Rigour of process and appeal

Across indications NICE and HAS require the greatest amount of clinical evidence and most rigorously assess it. HAS and TLV strongly emphasize treatment safety and

AEs. NICE conducts the most thorough cost-effectiveness examinations, assessing the manufacturer's model submission, frequently re-running the model with modifications and in every case building their own economic model. There does not appear to be a correlation between requirement stringency and the resulting recommendations, although the timeframe is undoubtedly positively related to the rigour of assessment.

An important aspect of the entire process of value assessment is the possibility for applicants and stakeholders to appeal against decisions made by the competent authority and for these appeals to be heard comprehensively and with due diligence. Agencies typically have appeals processes in place where stakeholders (particularly manufacturers and patients) can express views and provide their justification against the decision(s) made.

4.2.2.6 Comparators

The choice of the appropriate comparator has shown to have an important effect on the HTA outcome. Most often the choice of comparator reflects agencies' requirements or preferences, which varies depending on the agency and may also help to understand differences in the outcomes achieved. The requirements for the number and type of comparators vary. Most include the current best alternative or relevant comparator, whereas CDR and HAS also make requests for the cheapest available comparator, and TLV for a placebo comparison. All agencies request evidence on clinical efficacy and cost-effectiveness, except for HAS, that requires evidence on clinical efficacy and safety.

4.2.2.7 Efficacy and safety

With regard to the type of evidence considered, it appears that the agencies put different emphasis on different endpoints. In terms of efficacy, TLV most often consider the primary endpoints, whereas SMC and HAS look at all primary and secondary endpoints. NICE have been shown to appraise the main endpoints while including an assessment of Quality of Life (QoL). Thus, we may conclude that the value judgment of a drug's efficacy may vary according to whether it is based on one endpoint or several endpoints (i.e. if the effect on QoL is included in one assessment and not in the other, the judgment may be different).

Generally, safety is considered by all agencies but at different levels. HAS and SMC seem to put more weight on the drug's toxicity profile, and request the full list of most common adverse effects, whereas NICE makes a general safety assessment while highlighting the most relevant cases. TLV, on the other hand, most often

makes a general assessment, and in some cases no mention of the drug's safety profile has been found. Although the drug's safety profile has only been included by both HAS and SMC in the recommendation justifications, it does not seem to have an important impact on the end result.

4.3.Process and information required under EPR

4.3.1. The Evidence

Countries using EPR as the main method of pricing pharmaceuticals have developed detailed, elaborate and robust structures and processes enabling them to undertake the task of pricing based on international prices, informing reimbursement through the same process and examining, among other things, which products require flexibility in the above assessments and on what basis. Two examples of countries using EPR as the main method of pricing and reimbursing pharmaceuticals are the Czech Republic (SUKL) and Spain (Ministry of Health). Within the context of these two bodies, it is important to reflect on the following parameters that characterise their system and which are described in detail and are enshrined in legislation:

- Legal framework: In the interests of transparency, the process of pricing and reimbursement regulation is described in detail in the law;
- The pricing process, which needs to be in place in order to select a basket of prices to inform prices in the country in question;
- The reimbursement process, whereby a process needs to be in place to establish product reimbursement;
- The frequency of price revisions at the request of various stakeholders – both for pricing and for reimbursement;
- Appeals process, which are important in the overall structure of the system and enable interested parties to have a safeguard against decisions made by the competent authority;
- Procedures for deviating from existing and regulations on pricing and/or reimbursement; these may exist in order to account for cases of medicines which depart from “clear cut” paradigms;
- Procedures dealing with new products with no apparent comparators or in a new therapy class, in which case, provisions are made to review additional clinical or other information that can be instrumental in determining a fair price;¹⁶

¹⁶ This may take into consideration not only clinical but also economic criteria.

- Related to the above, is the process of dealing with expensive products, uncertainty and poor evidence at launch;
- Dealing with external shocks, e.g. exchange rate depreciations/appreciations and overall volatility; and
- The frequency of price revisions at the request of various stakeholders – both for pricing and for reimbursement;
- The acceptance or not of rebated (net) prices, or simply rely on prices that are widely available, but do not include rebates, clawbacks or discounts.

4.3.2. Discussion and stakeholder effects

From a member state’s perspective, EPR is not an overtly complex system and, in the majority of cases, it relies on available information that can be obtained at arms’ length. In terms of administration, it is thought that EPR systems are fairly straightforward, are not administratively complex and do not require a lot of information, since much of what is required is either available at arms’ length, or can be supplied by the manufacturer.

Nevertheless, the view that seems to emerge from meetings and interviews with stakeholders that the administrative process is quite complicated and resource intensive, not least because “there is a requirement to produce evidence on and validate every claim made along the way, particularly as the process is open and transparent”.¹⁷ Within the Czech context, 41 - 45 people in total are directly employed to deal with the agenda. This is becoming even more onerous as the process is divided between a pricing process and a reimbursement process, with different baskets of countries each.

It is important that the system is appropriately equipped with mechanisms to ensure transparency and safeguard the interests of all stakeholders. For instance, at interview, it was pointed out that the Czech Republic has a two-stage appeals process in its statutes; the first stage is outside the courts system and rests on an interaction between SUKL and the MoH, where the latter can provide an opinion on the resolution arrived at by the former. If manufacturers do not agree with this resolution they can turn to the court system. As a first step within that process, the county court is responsible for hearing a case and, should the decision be upheld, the manufacturer can appeal to the supreme administrative court. Appeals can be launched 15 days after an original decision has been made and the MoH can review these within 1 to 2 months, the latter for more complicated cases. The view is that

¹⁷ Interview with SUKL.

manufacturers have significant rights and they can use these rights to slow down the procedure should they wish to.

From a country's perspective it is important to ensure that the system of EPR is transparent; this is important in order to ensure its perceived credibility among the stakeholder community. In this spirit, systems of EPR do not take into consideration rebated or discounted prices, even if there is an opportunity for these to be identified. These prices are not always fully transparent and, therefore, not defensible before the stakeholder community.¹⁸

A further issue that seems to be having significant unintended consequences was raised in the context of EPR was the exchange rates that are used to translate prices from one currency to another, when prices in different currencies are taken into consideration. The Czech view in this context is that exchange rates over the period 3 months prior to the revision are taken into consideration, whereas the Spanish view is that mostly Euro-denominated prices are taken into account, to ensure stability in the process and eliminate the effect of exchange rate volatility. While the latter approach altogether avoids exchange rate volatility, the former approach does not necessarily do so (unless a moving average in the exchange rates is taken into account over a long time period), as the past 2 years already seem to suggest. This can be can become even harsher if frequent price revisions are envisaged by the system and these coincide with protracted periods of exchange rate volatility.

¹⁸ Interview with SUKL.

5. IMPACT OF VBP AND EPR ON PHARMACEUTICAL PRICES

5.1.Overview

In this section we examine what impact, if any, VBP and EPR are having on the prices of new pharmaceutical products. In particular, we are considering four broad areas related to pricing and prices of pharmaceuticals, as follows:

- First, considering that EPR is a price-regulation scheme and that VBP rests on value appraisal to inform pricing, how does the implementation of either VBP or EPR affect launch pricing of new pharmaceutical products?
- Second, does the application of either scheme lead to launch delays? If so, under what circumstances, for which products and what evidence is there to support that?
- Third, considering that price revisions may take place through either EPR (e.g. through a statutory process requiring that prices be revised annually or more or less frequently) or VBP (depending on whether new evidence is produced about product efficacy/effectiveness), how does the implementation of either VBP or EPR impact subsequent price revisions?
- What information is used to inform decisions about price premia for new pharmaceutical products in circumstances where VBP and EPR are used?

The evidence informing this section is based on the available literature, research conducted for the purposes of this report only and information acquired from decision-makers, manufacturers and other stakeholders via interviews.

5.2.Impact of VBP on Pharmaceutical Prices

5.2.1. Launch prices

In order to inform the impact that VBP is having on the (launch) prices of new medicines, an analysis was conducted of 4 therapies and the clinical evidence that accompanied them across different settings. The objective was to determine the impact of HTA recommendations on price levels in terms of their fluctuations as different HTA recommendations are made over time, and the level of price premiums over their comparators at launch and across the study duration. The products considered were imatinib, sunitinib, erlotinib and bortezomib and the agencies considered were TLV, HAS, NICE and SMC. All clinical evidence was acquired from publicly available sources from the countries where the assessment

took place. Pricing data was identified for France, Sweden, the UK and Germany (the latter being included as a control country) from publicly available sources. The results for imatinib and sunitinib are shown in Box 5.2.1 and 5.2.2 respectively, whereas erlotinib and bortezomib are shown in the Appendix.

The four case studies were selected and considered according to their level of innovation: Imatinib is considered to be a highly innovative drug with an ASMR I-II rating from HAS, sunitinib has a significant level of improvement with an ASMR rating II-III, while erlotinib is considered to have no improvement compared to existing therapies with an ASMR rating V. The fourth case, bortezomib, is quite specific since it has received different ASMR ratings for its different indications (1st, 2nd, or 3rd line treatment).

Imatinib and erlotinib have both received homogeneous positive recommendation across the study HTA agencies (apart from the ASMR rating V for erlotinib in France). Sunitinib and Bortezomib can be considered to have received mixed HTA recommendations. Sunitinib was given an ASMR II-III by HAS, is restricted to a subpopulation by NICE, and rejected by the SMC. Bortezomib, when looking only at the appraisals for 2nd line therapy, received a positive recommendation across all agencies (ASMR IV in France, Listed in Sweden, and covered by NICE and the SMC with a risk sharing agreement, covering only the positive responders to the treatment). It must be noted that at this stage, the treatment most probably would not have been reimbursed in the UK setting without this risk sharing agreement.

The indexed prices of the four drugs analyzed show that, generally, once prices are set they remain stable across time. The main exception to this occurs in Germany, whose prices in all four cases have risen after the launch of the product, but this may be due to the pricing system in the country enabling free pricing. Additionally, in the case of imatinib, a price increase was also seen in the UK and (slightly) in Sweden. This is most likely because the information on the therapeutic advantage of the drug was limited at its launch, and as it proves to be superior to its competitors, prices rise. Moreover, the price in France for bortezomib decreases twice, the first time following an ASMR level IV rating as 2nd line treatment, and the second time after an ASMR level III rating for its use as 1st line therapy.

The price premium of a drug is set exponentially according to its level of innovation (or ASMR rating in France). For highly innovative products, the relative price can range up to 100 times or higher than its comparators, for moderately innovative products, the relative price can range between 15 and 25 times higher, whereas for products demonstrating no improvement, the price is set at the same level as its therapeutic alternatives. This is demonstrated in the four case studies:

- Imatinib received an ASMR I-II rating (major innovation-significant improvement). Its price was set approximately 100 times higher than hydrocarbamide's (in France, Germany, and UK), with the exception of its relative price in the Sweden, found to be 25 times higher than its comparator. Similarly, the price of imatinib is also between 30 to 60 times higher than bufulsan in Germany, France, and the UK and significantly higher (>360 times) in Sweden. In the UK, risk sharing agreements have been implemented for bortezomib, whereby only the patients that respond to the treatment are covered. The value of the treatment in this subpopulation (successfully treated) can be considered as high, which as a result may justify its price level set 109 times higher than its comparator. In Germany its price is set 90 times higher than dexamethasone. In France, bortezomib first received an ASMR level II rating for its use as 3rd line treatment, and its price was set at launch 555 times higher than dexamethasone. As its indication was extended to 1st and 2nd line treatments, lower ASMR ratings (V, IV, and III) were given and its price decreased as a result of (price-volume) negotiation.
- Sunitinib received an ASMR rating II-III (important-significant improvement). The relative prices of imatinib with IFN-alpha are similar in France and in the UK, 12 to 15 times higher, and is slightly higher in Sweden (24 times). In contrast, the relative prices of imatinib compared to interleukin-2 and sorafenib are set at a similar level. Most probably because IFN-alpha is the current best practice so more closely compared to sunitinib, and sorafenib is a second-line treatment (once treatment with IFN-alpha has failed). In Sweden, bortezomib was considered for 2nd and 3rd line therapy, and priced 28 times higher than dexamethasone. For these indications, the respective ASMR ratings given in France varied between level II to IV. If we assume that this ASMR rating is representative of its level of innovation in Sweden, the price level of bortezomib, set 28 times higher than its comparator, becomes easily justifiable and understandable (and is also similar to the relative price and ASMR rating for sunitinib mentioned at the beginning of the paragraph).
- Finally, in the case of erlotinib its price ranges close to its two comparators: docetaxel and pemetrexed.

Based on the limited number of cases examined in this section, it appears that the level of innovation, as defined by the payer, is rewarded accordingly. Significant innovations receive a substantial price premium in relation to comparators, moderate innovations a lower price premium, and me-toos achieve –at best- price parity in relation to existing treatments/comparators.

Box 5.2.1 : Case study 1 Uniformly positive recommendations with criteria.

Imatinib mesylate (GLIVEC®) Chronic myeloid leukaemia (CML) (C92.1)

(100mg, 400mg tablets - NICE and SMC do not specify dose form, HAS only considered 100mg)

Imatinib is authorized in Europe for the treatment of chronic myeloid leukemia (CML), when patients are « Philadelphia chromosome positive » (Ph+). It is used in adults and patients that are newly diagnosed with Ph+ CML and are not eligible for bone marrow transplant. It is also used in the chronic phase of the disease if it is not responding to interferon alpha, and in more advanced phases of the disease (“accelerated phase” and “blast crisis”). Furthermore, it should also be noted that the marketing authorization of imatinib was granted under “exceptional circumstances” because of the rarity of the disease and despite the limited amount of evidence available.

Glivec first received a positive HTA appraisal in Scotland, restricted to its administration under the supervision of a haematologist or oncologist. The treatment was recognized as a significant advance in the available treatment for this indication. In 2007, a negative appraisal was granted because of the absence of a submission to SMC for the treatment of relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) as monotherapy and in combination with chemotherapy. In Sweden, imatinib has been approved for the treatment of CML, although the appraisal is not available on their website and as a result we may not have all the details on the recommendation. In France, an ASMR rating level I has been issued based on the positive results in terms of cytogenetic responses and because of its oral administration in the treatment of the chronic phase of CML after failure of treatment with interferon alpha, and for patients with newly diagnosed CML Ph+ who are not eligible for a bone marrow transplant; an ASMR level II was issued for the treatment of the more advanced phases of the disease (accelerated phase and blast crisis). In the UK, NICE restricted the use of imatinib to patients with CML in the chronic phase of the disease, to patients with Ph+ CML who initially present in the accelerated phase or with blast crisis, or progress to these phases from the chronic phase. In cases where imatinib is given in the chronic phase but fails to stop the disease progression, it is recommended only in the context of further clinical study.

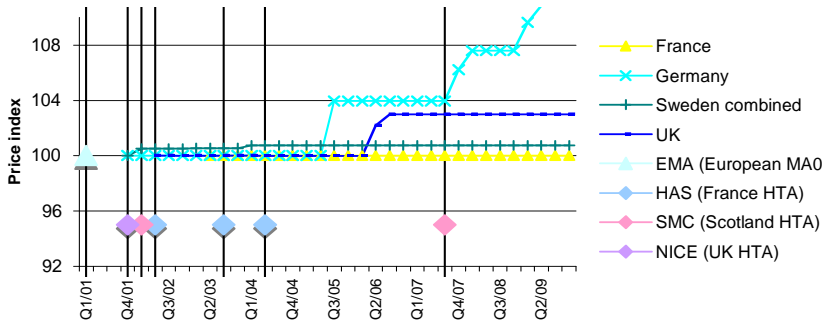
Given that this drug has been authorized in the UK although limited and long term evidence was available, that SMC recognized it as a significant advantage in treatment options, and that it received an ASMR rating I-II in France, this drug can be considered as highly innovative. Treatment alternatives for these indications include allogeneic stem cell transplant, interferon alpha, and conventional chemotherapy (buparfenone or hydrocarbamide).

Figure 5.1 represents the dates when the market authorisation (MA) by EMA, and the HTA appraisals were issued in the respective countries (given that the data was available). Since the launch of the product, prices are stable in France and in Sweden, while in the UK and in Germany, there is an increase in prices that is more pronounced in Germany. Surprisingly, the second increase occurs at the same time as the negative recommendation from the SMC.

Figure 5.2 illustrates the relative prices of imatinib and its two comparators buparfenone and hydrocarbamide¹⁹. The price of imatinib is set at a generally substantially higher price level than buparfenone and hydrocarbamide in all four countries: the price is set between 25, 94, 96 and 108 times higher than hydrocarbamide respectively in Sweden, France, Germany and the UK; and between 32, 46, 63, and 360 times higher than buparfenone for respectively Germany, France, UK, and Sweden. This shows that imatinib is generally considered as providing a clinical advantage over the existing alternatives, however, the level of price premium over its comparators does vary across countries.

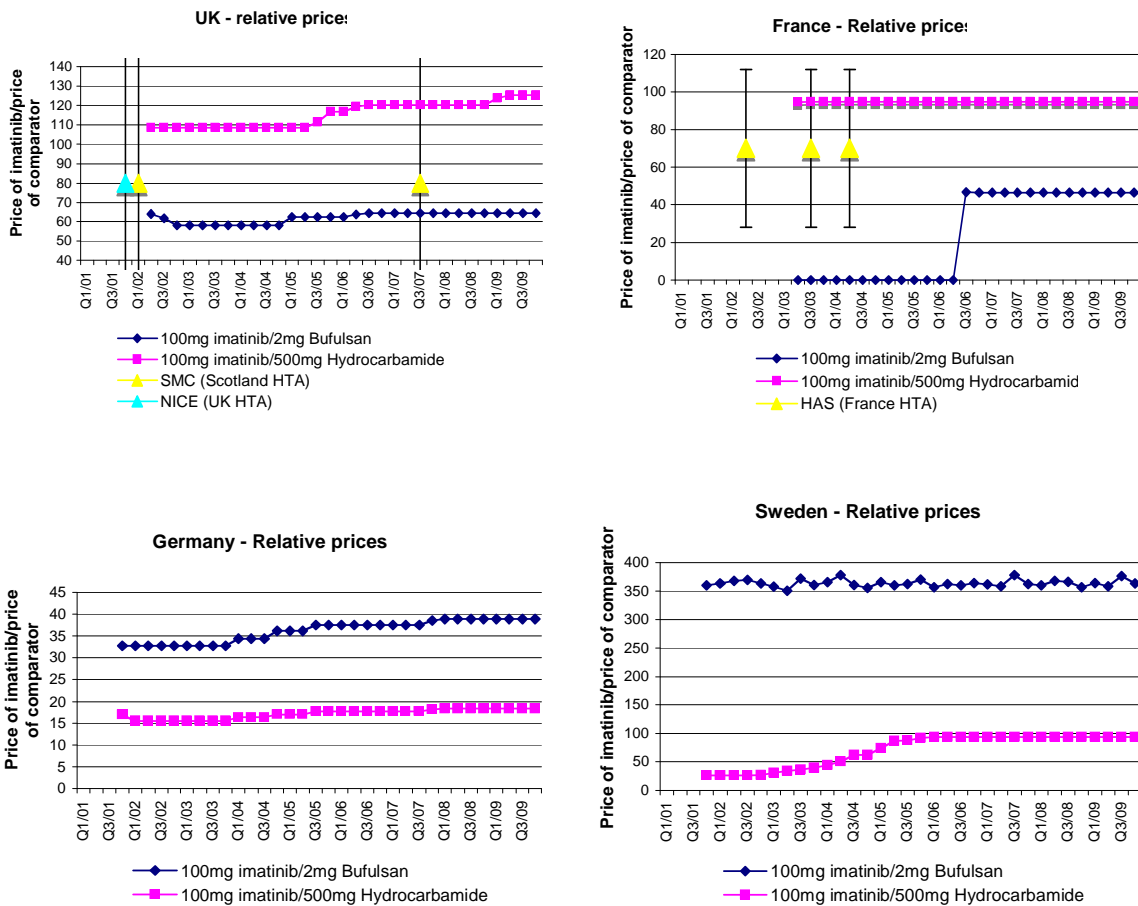
¹⁹ The comparative dosages were provided by the different available doses indicated in the HAS appraisals.

Figure 5.2.1 Imatinib 100mg - indexed prices (in euros), marketing authorization and HTA dates



Source: LSE analysis, based on IMS data.

Figure 5.2.2 : Relative prices of imatinib and its comparators (in euros)



Source: LSE analysis, based on IMS data.

Box 5.2.2 : Case study 2 Varying outcome appraisals

Sunitinib (SUTENT®), 12.5mg, 25mg, 50mg; metastatic renal cancer (MRCC)

Sunitinib has received market authorization for the treatment of metastatic renal cancer (MRCC) by the EMA. We examined HTA appraisals conducted in England, Scotland, and France. In England, its use is restricted to patients who are suitable for immunotherapy and have an Eastern Cooperative Oncology performance status of 0 or 1. In France, it has received a positive recommendation both for the treatment of advanced and metastatic RCC, and for MRCC in patients who have failed treatment with interferon-alpha and interleukin-2. It has been granted an AMSR level II-III²⁰. In contrast, a negative recommendation was issued by the SMC (Scotland) on the basis that results were based on an interim analysis, that there was insufficient information available on overall survival due to the treatment, and that the economic case was not demonstrated.

Interferon alpha-2a (REOFERON®) and interleukin-2 are the two available treatments for advanced or metastatic RCC. Sorafenib is the only alternative in cases where prior treatment with interferon alpha has failed. These comparators have been considered by all three agencies.

Figure 5.3 illustrates the indexed prices of sunitinib since its launch in 4 European countries (France, Germany, UK, and Sweden). All prices are stable from the initial price (France, Sweden, and UK), except for the German price, that increases as of Q2 2008. One negative appraisal from the SMC was issued in Q1 and Q2 2007, and NICE has restricted the use of this treatment in Q1 2009. Around this same period of time (before and after Q1 2009), the price of sunitinib has increased in Germany, which raises the question whether these restrictions/negative appraisals are the cause of this price raise.

Comparative treatment doses between sunitinib and sorafenib, interleukin-2 and interferon alpha-2a were used to establish the relative price of sunitinib at launch until end of 2009²¹. Figure 5.4 illustrates these relative prices and demonstrates substantial differences in the price levels set across the countries. The price of interleukin-2 was available in only the UK and Germany. The price of sunitinib in the UK has been set 2.544 times higher than interleukin-2 and then continuously decreases over time, and 1.4 times higher in Germany. The price of sunitinib varies between 11.57, 15.489, and 23.886²² times lower than the one of interferon alpha-2a in the UK, France and Sweden respectively. The data is not available for Germany. The price of sunitinib is set between 1.342 and 1.459 times higher than the price of sorafenib in Sweden, Germany and France.

The price of sunitinib was set between 11 and 23 times higher than the price of interferon-alpha, and 1.4 and 75 times higher than interleukin-2, which may represent the price premium for a new treatment option that is considered offering a significant improvement (ASMR III rating from France).

The price of sunitinib is set only slightly higher than sorafenib (1.3-1.4 times higher), although it was granted an ASMR level II rating, considered as an important improvement. This lower price premium may be explained by the fact that this is considered as a second-line treatment (after failure of treatment with interferon alpha-2a).

²⁰ AMSR II was given for the treatment of advanced or metastatic RCC, and AMSR III for the treatment of MRCC after failure of treatment with interferon-alpha and interleukin-2.

²¹ The comparative doses were based on the SMC appraisals (08.06.2007 and 12.01.2007) and are the following :

Sunitinib daily for 4 weeks (28 days) = sorafenib 400mg twice daily for 28days = interleukin-2 18 x 10⁶ subcutaneously for 5 days on week1, then on days 3 and 5 for weeks 2-4 = interferon alpha-2a 3MIU 3 times a week 1st + 6Miu 3 times a week 2nd week + 9MIU 3 times a week 3rd week.

²² In Sweden, only the price of the 3M dose was available. This dose has been taken 9 times to compare with sunitinib (instead of 3*3M+3*6M+3*9M).

Figure 5.2.3 : Indexed prices of sunitinib 50mg across European countries (in euros)

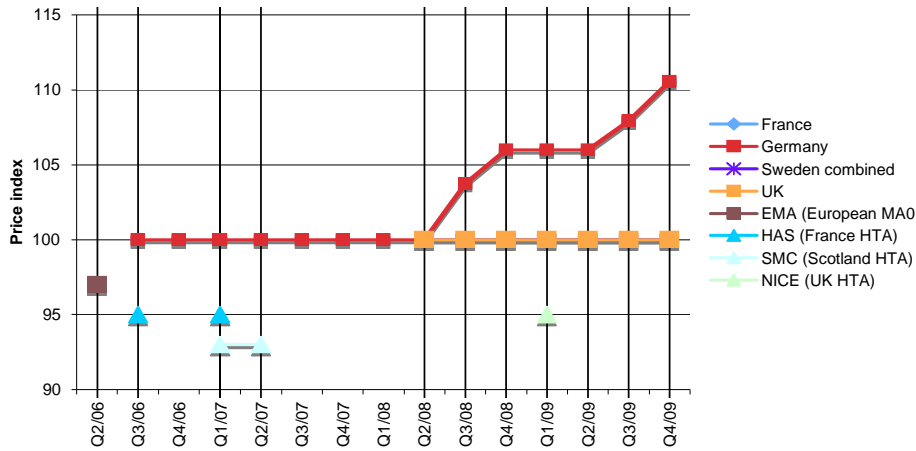
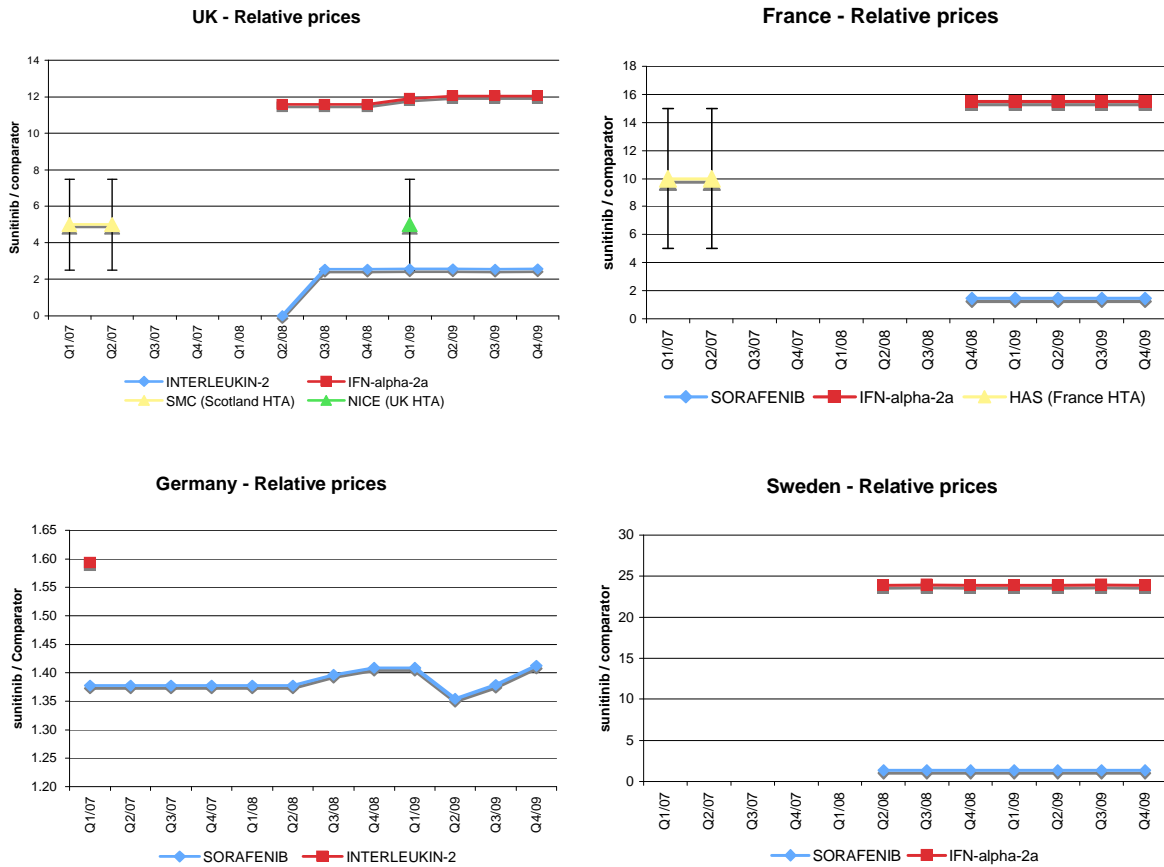


Figure 5.2.4: Relative prices of sunitinib and comparators (in euros)



Source: LSE analysis.

5.2.2. Price revisions, risk-sharing and spill-over effects

HTA agencies, through the formal assessment and appraisal process, can exert pressure on manufacturers to decrease the price point of the compound in question in order to improve ICERs and increase the likelihood of reimbursement approval. This pressure may be direct (e.g. reimbursement decisions directly contingent upon pricing requests or recommendations) or indirect (e.g. manufacturer-initiated price decreases upon appraisal resubmissions), but both types require willingness on the manufacturer to make pricing concessions. Table 5.1 lists multiple examples of pricing changes and risk-sharing that occurred as part or outcome of the value assessment process in oncology indications and across agencies such as NICE in the UK, PBAC in Australia and CDR in Canada. This evidence mirrors further work that has been produced on the subject by the EMINet team in 2010.²³

Pressure on the manufacturer to improve cost-effectiveness ratios can also be reflected in the development of various forms of risk-sharing agreements, which HTA agencies can use to overcome manufacturer-proposed price points that are considered to be excessive. Further, unlike simple price alterations, such risk-sharing agreements respond to the lack of adequate evidence from which robust cost-effectiveness ratios can be determined—especially when the specifics of therapy may be unknown, such as the optimal number of cycles required per patient, or the duration of therapy—and require the manufacturer to bear a portion of the inherent risk when these future costs are uncertain.

In this sample, there were a few instances of risk-sharing agreements, all with different stipulations: for bevacizumab (mCRC, PBAC), the manufacturer is required to pay the costs of monitoring tests, as well as costs of treating adverse events; for erlotinib (NSCLC, NICE), the manufacturer guarantees a set overall treatment cost that covers costs for acquisition, administration, treatment of adverse events and monitoring costs; and for sunitinib (GIST and RCC, NICE) the manufacturer pays for the first cycle of therapy.²⁴

From a sample of 21 compound-indication oncology-related HTAs, 13 involved discussion of price or risk-sharing agreements by at least one HTA agency. Though the sample size here is small, for pricing negotiations the trend suggests that the Canadian process may lean towards putting pressure on the manufacturer to adopt

²³ Espin J. et al (2010). Experiences and impact of European Risk Sharing schemes focusing on oncology medicines. Eminent.

²⁴ There were several other requests for the development of risk-sharing agreements through PBAC's HTAs for letrozole, docetaxel, and exemestane.

pricing decreases in order to be approved for reimbursement, the English process favouring development of risk-sharing agreements, and the Australian model variously applying both strategies (though, it should be noted that there was little overlap in the strategies used for the same compounds among these agencies).²⁵

Despite their advantages and potential to lower expenditure, in some instances, though, such risk-sharing agreements and pricing pressure may indeed allow manufacturers to “game the system” in certain respects. There seems to be a trend by which manufacturers provide submission documents, evidence and economic analyses in which the suggested costs and cost-effectiveness estimates exceed explicit or commonly-known implicit funding thresholds: subsequent resubmission of evidence or pricing negotiations allow the manufacturer to eventually meet criteria for cost-effectiveness. One concerning interpretation is that the formal HTA process, as it currently exists, may allow manufacturers to essentially “feel out” these thresholds, and gradually reduce prices or provide altered reimbursement terms until their submissions just meet the approval threshold. While clearly this is a useful strategy to maximise revenue from the perspective of the pharmaceutical manufacturer, this system of appraisal submissions and resubmissions, or allowing the manufacturer to respond to the recommendations or demands of the respective agencies may be somewhat counterproductive to the overall financial goals of the health system to which the HTA agency is accountable if it in fact incentivises manufacturers to charge some maximum allowable price, rather than offering increased value-for-money at decreasing prices. This is an important area for further critical examination and potential institutional/process changes.

²⁵ These trends are not solely determined by the mandates of the various agencies but also by the willingness of manufacturers in the various countries to engage in different types of negotiations. For example, pharmaceutical manufacturers in the UK are less interested in negotiations that alter the list price of their products as these listings are often used by other countries in international reference pricing schemes. Therefore, in the UK, manufacturers would be expected to be more amenable to engage in risk-sharing agreements that, while reducing the cost and risk faced by the payer, do not alter the list price.

Table 5.2.1 : Price and Risk Sharing agreements in cancer HTAs in 3 countries (England, Australia and Canada), 2007 – 2009.

	NICE		PBAC		CDR/CED	
	P↓	Risk sharing	P↓	Risk sharing	P↓	Risk sharing
Capecitabine			✓ 7			
Cetuximab (mCRC, 2 nd line)			✓ 7			
Docetaxel			✓	✓ 1		
Letrozole BCA (extended adj)			✓ 1			
Oxaliplatin mCRC					✓ 5	
Pemetrexed (2 nd line NSCLC)					✓ 5	
Trastuzumab mBCA			✓ 7			
Bevacizumab (1 st line) mCRC			✓ 1	✓	✓ 5	
Erlotinib		✓ 2	✓ 1			
Exemestane				✓		
Letrozole BCA (adjuvant)				✓		
Pemetrexed MPM	✓ 3		✓ 3,4			
Sunitinib GIST		✓ 6				
Sunitinib RCC		✓ 6	✓ 1		✓ 5	

- Notes:**
- ¹ Offered by the manufacturer.
 - ² List, based on manufacturer agreeing to supply at overall treatment cost equal to best comparator.
 - ³ Smaller vial size made available to reduce wastage.
 - ⁴ Reduced wholesaler margin.
 - ⁵ Price agreement led to reimbursement.
 - ⁶ Manufacturer to meet the costs of first treatment cycle.
 - ⁷ Price decrease recommended by HTA agency but not met by manufacturer.

Source: Pomedli and Kanavos, 2010.

5.2.3 Discussion and stakeholder perspectives

Across agencies, assessments of value tend to rely on similar studies and evidence in order to inform pricing decisions, but are usually limited by evidence that does not sufficiently address questions of impact on clinical effectiveness, quality-of-life, adverse events or costs, relative to pertinent comparators. Because of this similar core body of evidence, there tends to be reasonable convergence of reimbursement decisions among agencies, although divergence has also been observed (and is increasingly the case) in a number of cases relating to expensive treatments.²⁶ Divergent outcomes are often the result of varying interpretations in evidence, and seemingly different degrees of willingness to undertake sub-group analysis, make indirect comparisons, negotiate pricing or innovative reimbursement schemes, or rely on expert opinion, as opposed to outright rejection if adequate data was not available.

This differing willingness to use less-than-ideal types of evidence demonstrates varied responses to the challenging trade-off between using the best available—

²⁶ See also discussion in section 6 of the report around coverage and access.

though incomplete—evidence or simply turning away reimbursement for potentially beneficial (and cost-effective) drugs due to lack of strong evidence. There is no straightforward solution, nor a broad consensus among these agencies: some are likely to reject an application if inadequate evidence was submitted, but also engaged in pricing negotiations to reach positive outcomes; others tend to navigate uncertainty and poor evidence by using indirect comparisons and expert opinion as necessary, along with the development of risk-sharing agreements; others still tend to encourage price negotiations and the development of risk-sharing agreements to overcome informational uncertainty.

Special considerations relating to the life-extending role of specific treatments such as orphan and anti-cancer drugs, as well as the lack of alternative therapies for many conditions (esp. certain types of cancer), tend to favourably impact reimbursement decisions across agencies, and in certain cases, overruled otherwise unacceptable ICERs. Additional factors, such as patient perspectives, market conditions, or the pragmatics of drug use relating to wastage also seem to affect appraisal decisions in a variety of ways.

While some level of uncertainty will always be present, the concern regarding the quality of evidence may be mitigated in part by more transparent guidelines for manufacturers as to the types of data needed by HTA agencies to make rapid, clear decisions on value (subject to constraints present at the time of the value assessment), or by stipulating that certain data requirements must be available at the time of marketing authorisation that fulfil these value assessment needs. This pressure to develop more relevant evidence would potentially improve the overall process of value assessment and expedite the approval of truly clinically- and cost-effective therapies. Unfortunately, the lag between evidence generation and its subsequent use in VBP may still result in data gaps if the methods, data requirements, or market presence or clinical use of relevant comparators change substantially during this lag period.

Clearly clinical- and/or cost-effectiveness drives pricing decisions based on value assessments. In settings where cost-effectiveness is used additional elements or processes can inform pricing decisions. It is, therefore, important to consider the impact of factors such as disease severity, unmet medical need in the indication as well as human dignity. Put together, these factors can alter and, often, enhance strict cost-effectiveness paradigms by introducing elements of flexibility in its interpretation. This can apply to a variety of treatments including orphans and end-of-life therapies. As the Chairman of NICE put it in a recent discussion, “the QALY

threshold is a *tool* not a *rule*.”²⁷ However, there is no evidence that this is a routinely followed pattern; rather, it is one followed on a case-by-case basis.

Similar situations arise in value assessments from a societal perspective, where “it is important to consider all aspects of benefit and cost; the philosophy of this approach is to place a new treatment in the disease pathway and evaluate its relative merits.”²⁸ To that end, stakeholders are in a position to submit information on the new treatment’s usefulness not only for the health sector but also for a number of other areas, which were hitherto excluded from impact assessment, such as indirect cost and impact of the treatment on sickness absenteeism, among others.

Because extensive trials have not usually been required for marketing authorisation, historically there has been little incentive for manufacturers to continue trials beyond the point at which safety and minimal efficacy have been demonstrated. Thus the rising prevalence and impact of VBP in the reimbursement process may, through profit-maximising behaviour, encourage pharmaceutical manufacturers to design trials with more appropriate comparators based on current clinical practice, and adopt earlier and more rigorous internal analyses of the predicted economic consequences of the drugs in development to aid “go-no-go” decisions, and to incorporate these economic considerations into net-present-value calculations during the research and development process.

Such considerations would also help pharmaceutical manufacturers set prices at a level more likely to result in fast approvals for reimbursement – and would be more palatable to payers. In short, it is in the manufacturer’s advantage in most cases to have the most thorough evidence with appropriate comparators and, because formal VBP processes are still rather new, it may just take some time for the industry to begin developing evidence of this nature.

This generation of evidence by the supply side may be encouraged by increasing adoption of risk-sharing schemes through partnership of healthcare payers and manufacturers, in order to provide early access to innovative therapies, develop robust data, and partially insulate the payer from undue health outcome or financial risk. However, such schemes are not without complications, and must be balanced against the risks of expediting marketing approval. Ultimately, the pragmatics of such schemes will have to be further developed before they can be widely applied to the many new compounds entering the market.

More broadly, and drawing on the sample of assessments examined here suggests that, despite their different locales and contexts, the different HTA agencies

²⁷ Discussion with Sir Michael Rawlins, 13 September 2010; italics added by authors.

²⁸ Discussion with TLV members, October 2010.

generally seek the same types of information regarding clinical and economic consequences of new therapeutics, and encounter the same obstacles during the assessment and appraisal processes. Thus, the formal development of standardised methodologies for HTA, international harmonisation of data requirements for new therapeutics, and sharing of HTA expertise and results across countries would further develop the field, reduce duplicative effort in collecting and analysing HTA-relevant data, and help address the data gaps that currently persist. While it would be difficult—and likely undesirable and impractical—to create a central HTA agency that would render binding reimbursement decisions, given the differing national agendas and values which impact upon final appraisal decisions (even within an international country bloc such as the European Union), striving for harmonised methods, data collection, and evidence repositories could streamline the HTA process and allow for more complete evidence-based assessments across the health technology spectrum. This would reduce the cross-border post-code lottery that seems to arise particularly in cases where the evidence appears controversial and is viewed differently by different agencies.

5.3. Impact of EPR on Pharmaceutical Prices

5.3.1. Price levels, launch prices and delays

In recent years EPR has been criticised for introducing disproportionate price levels in relation to national abilities to pay and for limiting timely access to pharmaceutical products. EPR systems driven by national desires to limit pharmaceutical expenditure may trigger a trade-off across competing policy objectives (Aaserud et al. 2009). Pricing and reimbursement policies have been found to affect manufacturer launch strategy and factors pertaining to launch sequence and timing, which, among others have a strong impact on the availability of a product (Stargardt and Shreyogg 2006).

In separable markets, manufacturers maximise their revenue in all markets that are willing to pay a higher price than the marginal costs of supply. However, the inseparability of markets in the EU, promoted inter alia by EPR, forces manufacturers to consider potential spill-over effects, when launching a product at a certain price in a country. Manufacturers may react to strict pricing policies by changing their launch timing and sequence, which may lead to delayed access to products in certain markets. If national pharmaceutical pricing policies limit the price levels below the manufacturer's reservation price, the manufacturer may decide not to launch the specific product in a given market. Price revisions also play a significant role in this context as their frequency, coupled with factors such as exchange rate volatility and the tendency of country baskets to revert towards the

lowest, might negatively affect the mid- to long-term pricing prospects of individual products in a particular country and lead to cross-border knock-on effects.

The available evidence from the literature on launches, launch prices, launch delays as well as sequence pricing (price revisions) is very limited. In a recent launch date analysis of 85 “globally important” medicines in 25 major markets it was found that countries having lower than expected prices tend to have fewer products launched and longer delays for those products that are launched, after controlling for per capita income (Danzon 2005). In addition, it has been argued that companies avoid price-controlled markets and are less likely to introduce products in additional markets after entering a price-controlled country (Kyle 2007). The above evidence draws across the spectrum of price regulation rather than only referring to EPR.

Another key issue in this context is the definition of how “launch” is defined, in order to subsequently measure delay. Available indicators, such as EFPIA’s Patients WAIT (Patients Waiting to Access Innovative Therapies) indicator collect information on drugs that have obtained an EU marketing authorisation and provide information on (i) the “accessibility” date, i.e. the first date when doctors can prescribe the medicine to patients, who will be able to benefit from reimbursement conditions applicable in the country; (ii) access to the medicine reserved to patients staying in / visiting a hospital; (iii) any additional comment (such as special reimbursement conditions, application for reimbursement rejected, pending negotiations, etc.). Based on this information an access indicator is calculated. The most recent results are publicly available.²⁹ The database leading to the WAIT indicator is held by EFPIA and not readily available. From discussions with representatives from some Member States, it appears the latter do not always agree with the WAIT reporting methodology.

In order to validate or disprove the above findings from the literature and in order to study (a) price levels at launch and (b) potential delays and (c) whether a product has been launched or not as well as the strategic responses, a confidential analysis of 11 products launched by 3 manufacturers in 8 EU countries over the past 6 years (January 2003 – December 2008) was conducted. The 11 products were drawn from publicly available sources (EMA, 2010) and in order to study potential launch delays the products selected were drawn from January 2006 to August 2008. The selected products belonged to the therapeutic areas of diabetes, cancer, hypertension, multiple sclerosis, hepatitis B, and optical care.

The selected countries for this exercise applied EPR as one of the mechanisms of price determination, although other criteria, such as cost effectiveness also applied

²⁹ They can be obtained from the EFPIA website on:
<http://www.efpia.eu/Content/Default.asp?PageID=559&DocID=10200>

in that context. Table 5.2 highlights a number of benchmarks in national EPR schemes, which, ultimately, may have a bearing on the outcome in terms of new products launched: the relevant country basket in each country and the algorithm used in each case, the price variation in each country, the number of products on the market, the number of products on each country's reimbursement list and the launch delay in days; if a product was declined by national authorities, it was excluded from launch delay calculations.

There is a discernible impact on prices in 4 of the 7 countries, where the method of calculating prices rests on the lowest of the basket, or is the result of selecting the lowest available EU prices. Manufacturers did not launch several products (a total of 11) in the 7 countries in order to avoid expected low prices. This also manifested itself in the reimbursement system. Launch delays were due to a combination of supply- and demand-side reasons: first, HTA requirements in some instances, which took some time to complete, second, budget constraints and, third, weak expected price levels prompting manufacturers to either not launch or to launch with a substantial delay.

Table 5.3.1: Effect of EPR on prices, products launched and launch delays (N=11)

Country code	EPR formula used	Price variation from average (%) ¹	No. of products on the market	No. of products on the national reimbursement list	Launch delay in days
Country 1	Average price of EU-26 at launch with irregular revisions	-1.8%	11	9	96
Country 2	Average of 3 lowest of a basket containing 8 EU MS with yearly review	+15.4%	8	7	689
Country 3	Lowest price from 8 low-price EU, conducted twice annually	+3.9%	10	10	337
Country 4	Lowest of a basket containing 14 countries at market entry	-12.9%	8	7	468
Country 5	Lowest of a basket containing 12 EU countries with yearly review	+3.3%	7	6	702
Country 6	Average of 6 EU countries with the lowest EU prices, twice annually	-5.3%	11	10	356
Country 7	Average of a basket of 3 EU countries, twice annually	-3.1%	11	10	224

Source: The authors.

Note: ¹ Price variation in this exercise is the mean variation from the average price per product in all seven countries.

5.3.2. Price revisions and the effect of exchange rate volatility

As in any market in which products are imported from third countries or where arbitrage can take place, exchange rate volatility may have an effect on pharmaceutical prices. In light of the recent currency fluctuations, the effect of external price referencing on drug prices becomes even more significant.

Earlier research has shown that exchange rates have a statistically significant effect on pharmaceutical prices, particularly in an environment where prices of pharmaceutical products are regulated (Danzon and Chao 2000; Kanavos, Costa-Font and Seeley, 2008). However, the goal of these studies was not to demonstrate how exchange rates affect prices, but, rather, to use them as control variables in empirical models in order to control for any changes in prices due to likely exchange rate fluctuations. Also, these studies took into account the absolute value of exchange rates rather than exchange rate volatility.

A recent simulation exercise taking into account a theoretical product (priced at €10) launched in early 2008 tested the likely effect exchange rate volatility might have on its prices 18 months hence in countries that implement EPR, e.g the Czech Republic, the Netherlands and Greece (Kanavos & Vandoros, 2010). The selected period coincides with significant exchange rate volatility as can be seen from Figure 5.3.1 with regard to the exchange rate between the euro and all other EU currencies. Taking into consideration pricing decisions and price revisions in the context of EPR systems as they apply in some countries, exchange rate volatility during the above period was likely to have a -26% impact on Czech prices (Figure 5.3.2) and -6% in the Netherlands and Greece (Figure 5.3.3 and 5.3.4 respectively). In the case of the Netherlands, variation is caused by the GBP/Euro exchange rate fluctuation.

Figure 5.3.1 : External price referencing: The effect of exchange rate volatility on a newly-launched product, 2008 – 2009 (simulated effect)

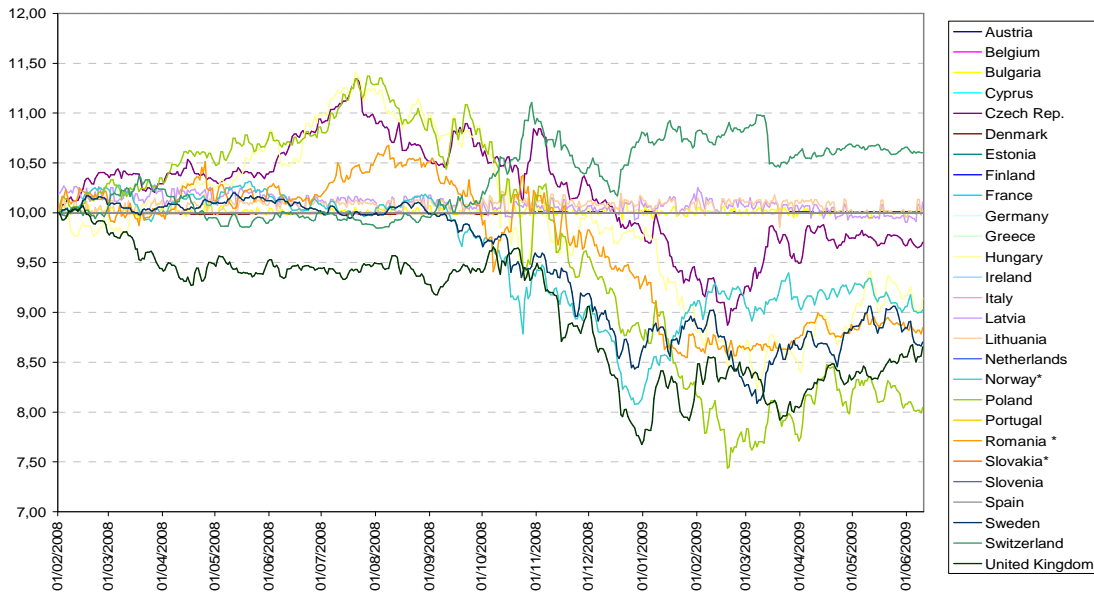


Figure 5.3.2: External price referencing: The simulated impact of exchange volatility on price revisions – Czech Republic (February 2008 – June 2009).

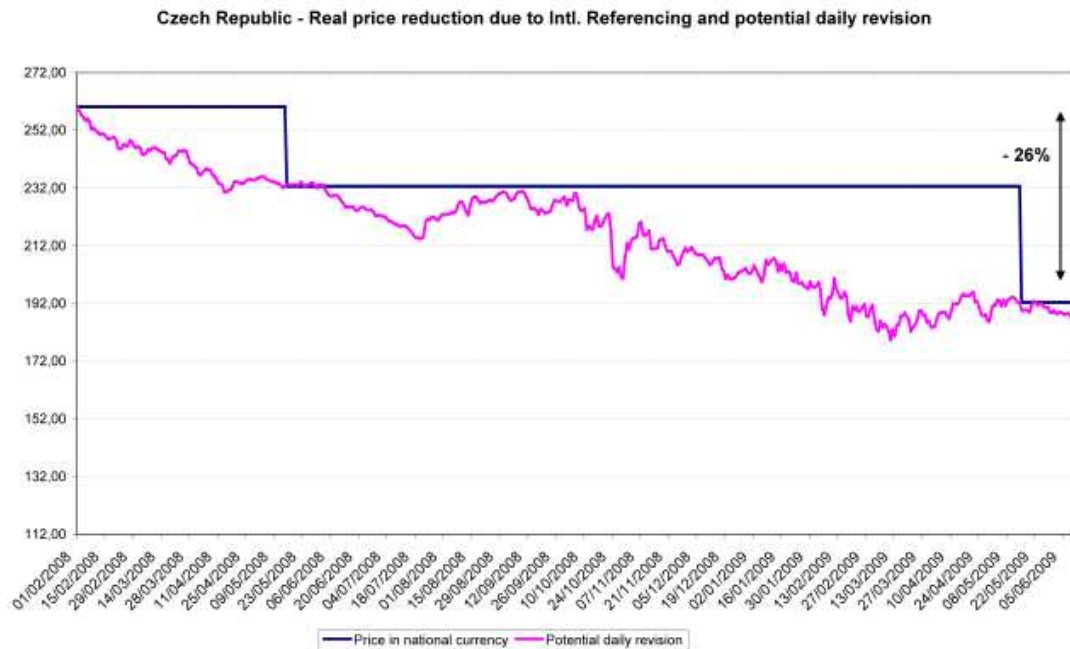


Figure 5.3.3: External price referencing: The simulated impact of exchange rate volatility on price revisions: the Netherlands (February 2008 – June 2009).

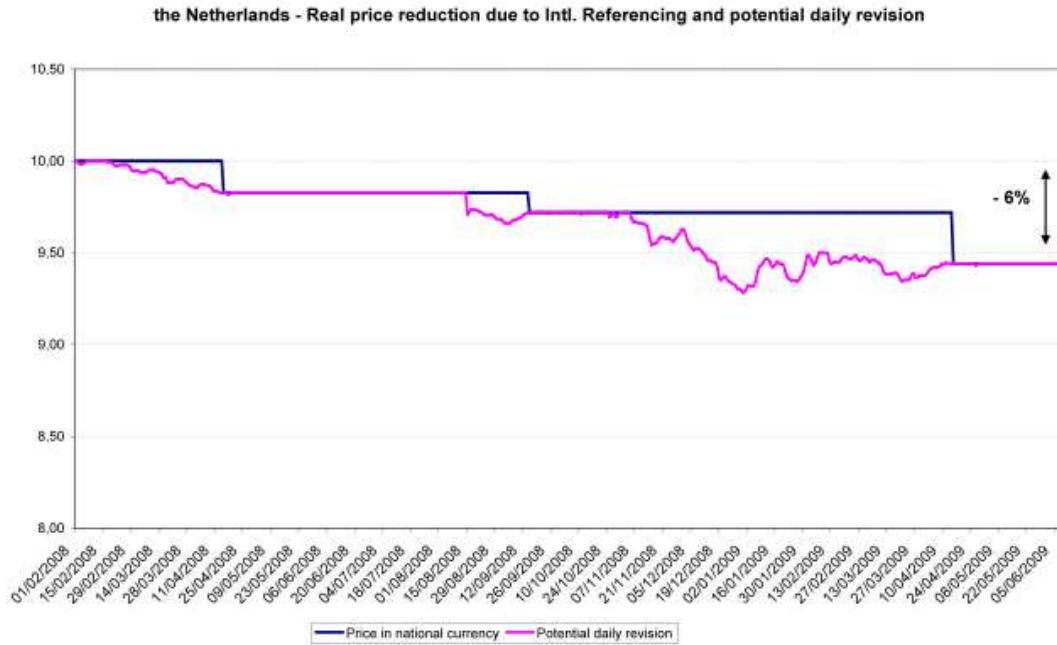
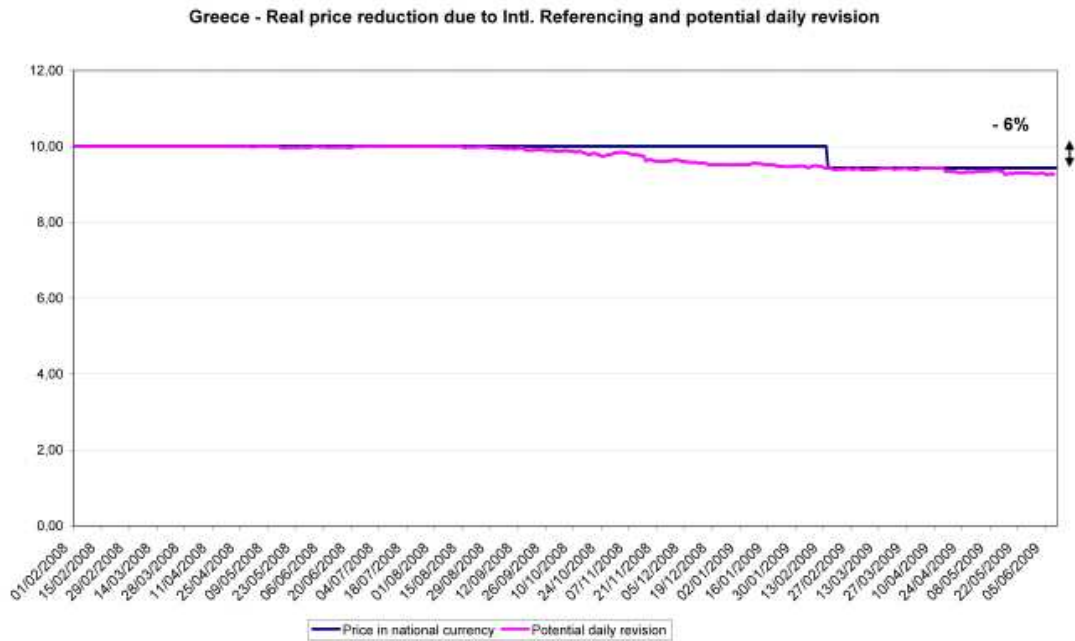


Figure 5.3.4: External price referencing: The simulated effect of exchange rate volatility on price revisions – Greece (February 2008 – June 2009).



Source: Authors' simulations based on real exchange rate movements and Member States' price revision processes.

5.3.3. Discussion and stakeholder perspectives

Pharmaceutical policies face a difficult trade-off between maximising consumer welfare today and creating sufficient R&D incentives to provide for future treatments. The long-term costs of obstructing innovative pharmaceuticals due to strict price regulations should be weighed against short-term savings from lower prices. Low prices may not only affect national markets in isolation, but also global launch strategies or even R&D incentives for future products. In that context, the benefits from innovation, including incremental innovation, also need to be considered, therefore pointing at a difficult balancing act.

Assuming that policy objectives aim at early provision of medicines with “fair” prices that reflect national abilities to pay, an approximation of price levels adjusted to national economic parameters could reduce launch delays in the EU, as well as create a stable, more predictable price environment. It is, nevertheless, questionable whether this can be achieved over the short- to medium-term unless interested stakeholders make significant concessions.

Understandably, decision makers often operate under conditions of severe budgetary restriction(s), whereby upfront and subsequent savings on unit prices contribute to the overall objective of macroeconomic efficiency. This appears to be the key policy objective under EPR, where it exists as the dominant method of pricing and/or reimbursement of pharmaceutical products, as is the case, for example, in the Czech Republic and Spain.

The Czech Republic uses EPR in both the pricing and the reimbursement function, using an originally defined basket of 8 countries (Portugal, Spain, France, Greece, Italy, Hungary, Estonia, Lithuania) in that context, which nevertheless can be extended to include all new EU Member States (Table 3.2.2). Internal price referencing can also be used if a satisfactory number of prices cannot be found in other countries.³⁰ Spain is also looking at foreign prices to arrive at a “fair” price when considering a new product and in this context, the lowest is considered.³¹

In terms of the process of regulating the prices of pharmaceuticals a degree of complexity is usually involved. In the Czech context, three options exist to arrive at the maximum price. First, a basket of 8 countries is used to inform the decision-making process and the price on the Czech market will be based on the average of these 8 countries. Second, if at least 3 prices cannot be found from the original

³⁰ Interview with SUKL.

³¹ Interview with Spanish authorities at MoH.

basket of countries, then the authorities take prices from all new EU Member States and take the average three new Member States' prices. Third, in case where it is not possible to find at least three new prices of the product in the wider basket, then the price of a comparable product in the Czech Republic will be used. So when speaking about the regulation of prices there is a combination of EPR and internal reference pricing, although EPR is the first option. In terms of selecting the countries to be used in the basket, the selection is based on countries which also regulate prices and are countries with similar or comparable purchasing power to the country applying the scheme.

For **reimbursement** purposes, the Czech Republic uses prices drawn from all EU Member States, therefore, the basket comprises all EU-26; the price taken for reimbursement purposes is the lowest available price. Prices for all strengths and pack sizes are considered, although for the EU-wide process of EPR to be launched, the product in question (dose and pack size) must have 3% market share in the active substance total sales in terms of DDDs in the Czech Republic.³² Revisions are conducted once annually, a process that places significant burden on staff and resources and the idea is to be able to do this less frequently in the Czech Republic, say once every 3 years. Within the context of reimbursement, SUKL also has the task of defining the stage at which individual treatments will be placed (e.g. first or second or third line), based on advice received by the relevant medical societies. Within the context of reimbursement, all expensive treatments are classified through the conditions of reimbursement as a class S, which means that they can be administered by physicians only in specialised centres, and have a special contract with health insurance. Within this contract health insurance is limiting or controlling the volume or number of patients and the budget. The criteria for reimbursement include clinical efficacy, reference prices, budget impact, but also a notion of cost-effectiveness to inform budget impact, therefore, EPR is one of the criteria that help decide on reimbursement prices.

In the Czech context, there is a discontinuity with the process of pricing and reimbursement, in that different baskets are used for pricing and for reimbursement and this is the subject of discussion as to how the legal framework can be adapted or changed to unify the range of countries used to inform pricing and reimbursement.

In terms of **rebated prices**, the position is that prices are taken into consideration, which must be published on official websites or another list. It is important to adhere to this paradigm for legal reasons and for reasons of transparency, so that the specified administrative procedures are followed, as failure to do so would harm the right of stakeholders to examine the source of the information used in the

³² Interview with SUKL.

evaluation.³³ Consequently, unofficially quoted prices based on rebates that may be taking place in other EU Member States cannot appear.

Price revisions, particularly if there are observations that some countries have changed their prices for whatever reason, can occur within the context of reimbursement only. Based on the legislation, the **exchange rate** that is used to arrive at a revised price is the average exchange rate for the period up to 3 months prior to the start of the administrative procedure.

Discussions with 4 manufacturers and one industry association member on the issue of pricing via EPR have raised a number of points related to the design of EPR systems.³⁴ The underlying assumption in these discussions has been that “reference” prices are visible across countries and that list and net prices coincide. As discussed previously, this is an unrealistic assumption to a certain extent. Despite that, it is felt that the following are of importance:

First, the reference country basket may need to include a weighed selection of countries with comparable economies, pricing and reimbursement policies as well as other pharmaceutical policies. The use of therapeutic referencing to inform pricing decisions that are also informed by EPR may lead to distortions due to differences in intellectual property rights among countries.

Second, the timing of revisions should be selected carefully to create a stable price environment that stimulates manufacturers to invest in the launch of their products. If EPR takes place biennially and the lowest in the basket is selected, this almost certainly leads to a race towards the bottom.

Third, just as EPR is used to revise prices downwards, it could also be used to revise prices upwards. Unique price cuts or other temporary cost containment measures should be taken into consideration when comparing prices.

Fourth, appropriate exchange rates are essential in ensuring realistic prices rather than prices arising from (excessive) exchange rate volatility. Arguably, both manufacturers and insurers wish to operate in a predictable environment that also provides stability. In order to limit the effect of exchange rate volatility, either a fixed exchange rate could be negotiated at the point of pricing decisions based on historical trends, or multiple currencies – themselves subject to excess volatility - could be avoided.

³³ Interview with SUKL.

³⁴ Individual discussions with manufacturers and associations conducted between April and July 2010.

Fifth, caution should be exercised when referencing in-patent products with generic medicines, in the context of combining EPR with internal price referencing at therapeutic class level.

Sixth, the algorithm used to arrive at a national price from the reference countries should reflect national abilities to pay, relative to the economic strength assessed by a selection of economic parameters.

Finally, manufacturers and their associations recognise that the use of EPR is defensible in small countries with limited resources on the understanding that countries that use value assessment are also included in this process so that a more accurate reflection of value is incorporated in EPR considerations.

6. IMPACT ON COVERAGE, DIFFUSION AND ACCESS

6.1.Overview

6.1.1. Value Based Pricing

Under VBP coverage decisions are made based on a number of criteria that help elicit value. Coverage is not automatic and depends on a multiplicity of factors such as the type and quality of the evidence submitted, the comparators used in assessing value, the perspective used, whether willingness to pay is in line with explicit or implicit threshold levels, and the interpretation of the evidence. These multiple factors can lead to variable interpretations across countries, such that the phenomenon of *cross-border post-code lottery* may exist. Thus, in one jurisdiction a new treatment can be covered, while in another it may be covered subject to criteria, whereas in others it may be rejected. The binding nature of the recommendation by bodies assessing value of new treatments is key in shaping a more or less homogeneous environment in the uptake of new technologies. In countries where this mandate does not exist, inequities in access may exist, depending on how payers perceive the value of a new treatment and its affordability. Increasingly, health insurers accept risk-sharing as a means of providing some access to patients subject to performance criteria. Additionally, on certain occasions the value of new treatments may not be appraised for a variety of reasons, in which case coverage and access can be subject to individual insurers' criteria. Finally, the issue of affordability emerges particularly when the body that appraises the evidence does not have the mandate to implement the recommendation made, which can lead to access problems.

6.1.2. External Price Referencing

In the context of EPR, coverage and access are a direct corollary of the process of application for inclusion of a new product and the provision of prices from selected countries. Occasionally, EPR is supplemented with other measures, such as price-volume agreements, while the process of EPR in itself can lead to launch delays and, consequently, can lead to access problems.

6.2.Coverage decisions and access under VBP

Within the context of coverage decisions and access under VBP, we need to distinguish between medicines whose value has been appraised and medicines whose value has not been appraised. The dynamics for each of the two categories

are different and have important implications for coverage and access. Both are outlined in turn.

6.2.1. Coverage of and access to medicines whose value has been appraised

In the context of enabling coverage of and access to medicines whose value has been appraised a number of phases or options exist, which are inherently interlinked. The first phase relates to the outcome of the value assessment process; in these circumstances, the outcome can be a decision (a) to “list”, (b) to “list with criteria”, (c) to “list with a risk sharing agreement”, or (d) “do not list”. The second phase is quite critical and is linked to the period following the announcement of the value assessment outcome and relates to the implementation of the recommendation. The extent to which an HTA agency performing value assessments has a strict mandate to implement and enforce a recommendation is essential for the uptake and use of new products and their accessibility. Finally, an additional dimension emerges, whereby, within the context of value assessments, different agencies interpret the same evidence differently, and phenomena of differential coverage and access emerge across jurisdictions.

Decisions to List new products as applied

Decisions to list products based on the therapeutic indication(s) applied for mean that their value has been proven to the regulator, based on the processes and allied rules discussed in the previous section to this report. This would involve assessment of clinical cost effectiveness, subject to a threshold, or elicitation of clinical value and the product’s subsequent ranking in relation with the chosen comparators. If the agency that assesses product value has a mandate from the health service to implement and enforce that decision, then in principle, there should be no access issues for patients. In interviews with patient associations this has been strongly contested in the UK and Swedish contexts.³⁵ Patients have on several occasions complained that new treatments are not available even if they have been “approved” by NICE or TLV and that in both instances significant access barriers remained. These barriers relate to significant delays in adopting the decisions, non-availability of the new treatment well after the decisions became public (English NHS) and rejection of these decisions by regional authorities (Swedish county councils).

Within the context of the UK NHS, NICE has a mandate and therefore treatments approved by it need to be adopted by PCTs with a short time lag following the publication of the recommendation. In the Swedish context, the county councils

³⁵ Interviews with patient groups and associations from the neurological, orphan, and oncology disease areas, June and September 2010.

have autonomy in decision-making and can overturn decisions by TLV, despite the fact that they are represented on its Board.

The view of NICE, expressed very strongly by its Chairman³⁶ is that “treatments recommended by the Institute are required to be covered by the PCTs within the English NHS at the latest within 3 months from the publication of the recommendation; PCTs are required by law to adhere to these decisions and if patients detect problems in the implementation of such decisions, they can threaten the relevant PCT with a judicial review³⁷ and it is certain that if the matter reaches the courts, PCTs will have to adopt the recommendation.” In this particular case complaining patients will receive access to the treatment within the relevant PCT’s jurisdiction.³⁸

Within the Swedish context, TLV recognises the problem of regional uptake and has in the past 12 months reviewed its processes enabling a stronger representation of the county councils on its Board with a view to having decisions on value scrutinised by the different sides of the stakeholder spectrum as well as made the process of decision-making more widely known.³⁹ It is unclear what impact this change is having on the county council decision-making since the autonomy of the county councils to make their own coverage decisions has not been impacted in any way. What is important, however is that the government (MoH) and the county councils are holding discussions/negotiations on an annual basis to determine the size of the grant from the former towards the latter. Decisions by the latter to cover a particular new treatment can result in requests to increase the size of the grant from the former.⁴⁰ Other than that, the position of the government is that county councils should implement the decision of TLV.

Decisions to List products but with criteria

Listing with criteria essentially implies that a sub-set of the original population-indication will be covered, usually on grounds of cost-effectiveness for those groups covered and poor cost-effectiveness for all other patient groups. Other than restricting access to the indication-population, the issue of fairness arises in these

³⁶ Discussion with Sir Michael Rawlins, 13 September 2010.

³⁷ Essentially threaten legal action against the PCT does not implement the decision.

³⁸ This is valid currently, although the UK will be reforming the NHS as per the new government’s publication of the White Paper in July 2010. This will also include provisions covering prescription pharmaceuticals, including the PPRS, the role of HTA bodies, such as NICE and SMC and clearer guidance from the government on how VBP will be implemented. In interviews with ministers, the determination is for the UK to move towards VBP from a societal perspective, which is a shift from the current position of VBP from an NHS/PSS perspective, but it is unclear how this will be done and what implications, if any, will there be for the mandate that institutes such as NICE currently have. The above also reflect additional discussions with 2 NICE members.

³⁹ Interview with TLV member, September 2010.

⁴⁰ Interview with TLV member, December 2010.

circumstances, particularly since the evidence generated to arrive at these estimates relates to efficacy rather than effectiveness. Complaints about access are mitigated by robust appeals processes where stakeholders can submit views, perspectives and additional data and information. Similarly, complaints about access can be mitigated by processes which are all-inclusive and encourage active stakeholder participation, however “intimidating this may be for lay people trying to put their case before expert panels and under severe time constraints.”⁴¹

Decisions to list products subject to a risk-sharing agreement

Increasingly payers require greater certainty in treatment efficacy/effectiveness, particularly in situations where the cost of treatment is very high; the proliferation of risk sharing agreements⁴² highlights precisely two issues: first, payer unease about new treatments’ price levels and overall cost in relation to their perceived (comparative) value and, second, the willingness to interrogate the data in order to identify elements that can lead to an agreement that is beneficial for patients, payers and manufacturers. In many cases risk sharing is associated with maintaining the manufacturer’s original price; among other things, this also “protects” the manufacturer from price erosion due to External Price Referencing and can arise in a number of European situations. Equally, it is often the case that payers can signal to manufacturers that they are prepared to “cover” the technology should the latter be prepared to reduce their price; apparently, this has occurred in a number of occasions in the Australian PBAC setting.⁴³

Decisions not to list products

In decisions not to list products there is a significant barrier to access, but it can be justified if there are no improvements in efficacy. Such decisions can lead to significant emotions, particularly since the interpretation of the evidence relies on value judgements which are often subject to criticism due to methodological reasons. Again, as was the case before, it is important that appeal processes are adhered to and stakeholders’ views are heard.

Different recommendations across settings

A particular issue can arise, whereby the same evidence will be interpreted differently in different settings that assess value. A recent qualitative examination of assessments in the oncology area⁴⁴ suggested that the agencies tend to, on the whole, rely on the same studies and published evidence to provide information on efficacy and rates and types of adverse events. This is likely simply a by-product of

⁴¹ Interview with patient groups, May 2010.

⁴² As discussed by other work by EMINet.

⁴³ Interview with PBAC member, end-September 2010.

⁴⁴ Kanavos et al, Euro-Observer, 2010.

the limited amount of high-quality evidence present in the published literature on which the manufacturer submissions rely due to the short time between marketing authorisation and HTA in most cases. Further, the similarities in the evidence cited by the agencies are likely due to the close temporal proximity of the evaluations, precluding the development of substantial additional evidence between the assessment cycles: most of the evaluations for the same compound-indication pairing were conducted within 36 months of each other. The two exceptions were oxaliplatin (mCRC; 38 months), and trastuzumab (mBCA; 80 months).

Yet, the way agencies interpret this evidence often leads to different results, depending on what weight is given to particular elements of the evidence base, as shown on Table 6.2.1. For instance, despite the many concerns with the economic data, the acceptability of the calculated ICER was a strong predictor of whether the compound was approved for reimbursement: there were only 2 cases in which a drug was approved for reimbursement despite high, and otherwise unacceptable, ICERs. These cases concerned two different indications for topotecan, as assessed by NICE: in the case of SCLC, NICE decided to recommend the compound “although the best estimate of the ICER ... was in excess of the normal range for cost-effectiveness for the NHS” (ICER of £33900 per QALY gained), while the compound was also recommended for use in ovarian cancer (despite being dominated by another compound). In these cases, the medicines received recommendation for reimbursement primarily on the grounds of providing important therapeutic alternatives when initial therapies were not tolerated.

Overall, there were cases of insufficient evidence in one case vs special considerations in another (topotecan) leading in a rejection in the first and acceptance with criteria in the second; unacceptable ICER vs good evidence in subgroup analysis (bevacizumab mCRC), leading to rejection in the first case and acceptance with criteria in the second; use of indirect evidence vs inappropriate comparator (gemcitabine mBCA), leading to acceptance in the first case and rejection in the second; subgroup analysis and special considerations vs. unacceptable ICER (pemetrexed MPM), leading to acceptance in the first case and rejection in the second.

These disparities highlight the fact that different value judgments are made by the relevant competent authorities, but at the same time they create confusion to the patient community as to the rationale for acceptance in one jurisdiction and rejection in another. Although these cases are not the majority they seem to constitute a sizeable and ever increasing minority, particularly in therapeutic areas such as cancer, thereby leading to controversy and the phenomenon of cross-border post-code lottery.

Table 6.2.1: Differential coverage decisions and reasons for these in 3 countries (England, Australia and Canada), 2007 - 2009

Drug	Agencies	Outcome	Key Non-pricing Factors impacting differential outcome.						
			Sufficient evidence	Evidence accepted	Appropriate comparator	Use of indirect evidence [1]	Subgroup analysis	ICER acceptable	Special considerations
Gemcitabine mBCA	CED	DNL			No				
	NICE	LWC				Yes			
Panitumumab mCRC	CED	LWC		Yes					
	PBAC	DNL		No					
Topotecan SCLC	CED	DNL	No						
	NICE	LWC							Yes
Trastuzumab mBCA	NICE	LWC				Yes	Yes		Yes
	PBAC	DNL						No	
Bevacizumab mCRC (1 st line)	CED	DNL*						No	
	NICE	DNL						No	
	PBAC	LWC					Yes		
Pemetrexed MPM	CED	DNL						No	
	NICE	LWC					Yes		
	PBAC	L							Yes
Sunitinib malate RCC	CED	DNL*						No	
	NICE	LWC					Yes		Yes
	PBAC	LWC					Yes		Yes

Source: Pomedli and Kanavos 2010.

Notes: ¹ Indirect evidence such as indirect comparison, expert opinion

* = these drugs were approved for reimbursement after a subsequent pricing agreement despite initial initial recommendations not to reimburse.

6.2.2. Access to medicines which have not been explicitly appraised

6.2.2.1 The issue

In the absence of a formal pricing and reimbursement negotiation rule, a situation may arise where the value of a particular technology may not be assessed explicitly. Under these circumstances, the adoption of this technology by the health care system is dependent on individual arrangements by budget holders. If budget holders operate at regional or local level and have the ability to make their own decisions about what can be covered and what not, the outcome can be differential access to these technologies, as some budget holders may approve a technology for use while others may not. The key issues in this respect are, first, the extent to which disparities exist in access to new treatments and, second, the (potential) usefulness

of the technologies subjected to this decision rule. The latter will also be influencing the severity of access problems.

This situation arises, specifically, in the UK because of the value assessments performed on new medicines by the HTA bodies, particularly NICE and SMC and the decentralised nature of the UK NHS, whereby PCTs have competence over funding of new technologies whether these are appraised and recommended by NICE (or SMC) or not. In the latter case, and in the absence of “guidance” from one of the HTA bodies, PCTs may choose not to fund a new technology.

6.2.2.2 Evidence

NICE however does not carry out technology appraisals on all new and existing licensed drugs. Through its formalized ongoing topic selection process, NICE determines which new medications will receive a full appraisal. Subsequently, there exists a group of medicines that have never received a full technology appraisal or an appraisal under a newly licensed indication stemming from a pre-existing marketed molecule. Thus, PCTs are theoretically left without formal NICE guidance on the clinical or cost-effectiveness of these drugs.

Despite the legal obligations to fund NICE approved treatments, PCTs are authorized to manage and control their own budgets and priorities, with oversight and top-line guidance set by relevant Strategic Health Authorities. The vast majority of drug treatment resource allocation decisions are made at the PCT level. The importance of localized decision making is therefore becoming increasingly important in instances where:

- NICE has not reviewed a new or existing medicine because it was not prioritised during the formal topic selection process
- NICE appraisal of a new or existing medicine is currently underway but no decision or guidance has been determined

The lack of NICE guidance could prove to be troubling and contentious partly because PCTs are left to their own devices to develop a set of applicable rules and procedures for determining access and availability to drugs without guidance. If these procedures are not vetted and tested, this could lead to variation in access to drugs across PCTs, a renewal of postcode lottery, inequitable access to life-saving and clinically effective treatments and reduced gains in population health. Recent evidence has suggested significant geographical disparities in the availability of drugs without formal NICE guidance (BBC 2008). A recent survey evaluating local decision making processes for funding new medicines in England reported that 26% of PCTs believed that a postcode lottery was evident in the UK (Adelphi UK, 2009).

This same survey also revealed that on average, 49% of Area Prescribing Committees (APC) – groups established by PCTs to make recommendations on use of new medicines in their localities – spend their time considering medicines not on the NICE agenda or where NICE guidance is pending.

Examination of the top ten retail drug launches between 2007 and 2010 showed that the majority of drugs that captured the highest sales did not attain formal NICE appraisal to date (please see table 6.2.2 for further information). The reason for this is not clearly evident. However, a closer examination of the factors leading up to market launch indicates that most were newly licensed and approved reformulations of their originators, which were nearing patent expiry.

Table 6.2.2 : Leading 10 pharmaceutical retail launches, UK, 2007 – 2010 (in alphabetical order)

Product	Received NICE Appraisal	Drug Profile
BeneFix R	No	BeneFIX(R) Coagulation Factor IX (Recombinant) is an enhancement of the original drug, which was approved in 1997
Requip XL	No	Reformulation of dopamine agonist
Refacto AF	No	Successor product to Refacto. Retains same molecular structure as original but incorporates improved manufacturing process EMEA approval in 2009
Mezavant XL	No	EMEA approval in 2007 Received positive SMC guidance Most recently licensed modified-release mesalazine formulation. Mesalazine, the generic version, is already on the market
Winfex XL	No	Granted marketing authorisation as generic medicines of the original, Efexor
Conversyl Argi Plus	No	European patent expiry of original in 2007. Conversyl Argi Plus combines original active ingredient perindopril with indapamide
Victoza	N/A	EMEA approval in 2009. Received positive SMC guidance NICE final appraisal determination has not been finalised
Seroquel XI	Yes	
Fostair	Yes	
Mircera	Yes	

Source: The authors (from Gbemudu, 2010).

6.2.2.3 Discussion and stakeholder views

It is important to determine what impact the non-appraisal of new medicines is having on patient access to care. Follow-up interviews have taken place in this context with the DH, NICE and individual PCTs in the UK.

The DH has stated that NICE does not exist to “kite mark” all interventions; therefore, it is the responsibility of PCTs to develop “robust and fair processes in place for making decisions on drugs that have not yet been appraised by NICE” (Department of Health 2006c). The DOH published a list of evidence-based sources for PCTs to use, not as substitutes for NICE guidance if and when it becomes available, but as valuable and appropriate alternatives when NICE guidance is unavailable. The suggested sources included (a) Centre for Evidence-based Purchasing, (b) London New Drugs Group (LNDG), (c) London Cancer New Drugs Group (LNCNDG), (d) National Prescribing Centre (NPC), (e) the Scottish Medicines Consortium (SMC) and (f) the United Kingdom Medicines Information Group (UKMi).

From a NICE perspective, it was highlighted that the Institute is required to issue guidance on all new significant medicines including every cancer drug. Defining “significant” was a top priority for NICE. Interviewees estimated that around 200 new drugs or licensed extensions are granted each year. Based on NICE’s capacity, resources and informal collaboration with SMC, they attempt to undertake and publish roughly 50 appraisals a year. This means 150 new drugs are excluded from NICE appraisals. The respondent said that NICE will generally not look at new formulations, orphan drugs, or new indications unless it is costly. They are keen on judging topics against the criteria created to filter out insignificant topics. Interviewees also highlighted the importance of innovation as a component of the criteria and indicated that NICE is not interested in assessing me-toos especially if a generic is already available.

At PCT level, “for products that do not go through NICE, it boils down to the individual PCTs ... the drug and therapeutics committees (D&TCs) and area prescribing committees will call the shots.”⁴⁵ Respondents aligned with medicines management at the PCT level unanimously stated that the APC ultimately determines the outcome of new products, and which ones, especially those that are not NICE reviewed, are added onto the drug formulary. Although the respondents

⁴⁵ Interview with PCTs.

agreed that the APC carries stronger influence in determining which new non-NICE reviewed drugs eventually get introduced in the PCT, it was also made evident that the D&TC yields a great extent of power as well since the first level of decision-making occurs at the hands of the D&TC.

“We choose to hold back from adding or accepting anything new onto the drug formulary unless it has been reviewed by NICE,” according to a Joint head of medicines and management. A prescribing advisor said their “D&TC will not consider medicines that are on NICE’s topic selection list...will wait to hear what NICE has to say before rendering a decision.” Practically all of the respondents acknowledged the legal importance of NICE and said their primary concern was ensuring NICE guidance gets implemented in an appropriate and timely order. This view may imply that they are not heavily bogged down about attending to medicines not prioritised to receive NICE appraisal.

The above suggest that the arrangements for treatments not appraised by NICE can be stringent. Further probing revealed that alternative mechanisms exist – all at local level - to enable such treatments to be covered; these include (a) pass-through payments (PTP), (b) specialised commissioning, (c) use of the IFR process, and (d) using other available HTA information.

It was casually mentioned during an interview with a prescribing advisor that NHS clinicians wanting to use drugs not subject to NICE guidance can seek funding from PCTs through pass-through payment (PTP) arrangements. Application of the PTP is reserved for very strict circumstances, namely, the drugs must be used by limited number of centres, and are of a disproportionately high cost (Ron Pate 2009). These arrangements provide additional payments for use of new drugs, devices, treatments or technologies over and beyond the relevant tariff reimbursement. The additional compensation has to be agreed with commissioners well in advance since the funding may be derived from the PbR (payment by results) pay and price uplift, available to support implementation of NICE guidance and uptake of new secondary care drugs. Drugs funded through the PTP may be subject to a cost and volume contract, managed through monitoring and audit (East of England PCTs, 2009-10). Given the causal nature in which the topic was presented and discussed, it subtly implied that the PTP is hardly utilised by clinicians. However, most PCTs have a set of rules explaining the steps for seeking funding through this channel.

It was mentioned a few times during interviews that specialised commissioning of drugs and services is another avenue in which non-NICE reviewed drugs receive funding. Specialised services are those services provided in relatively few specialist centres to catchment populations of more than 1 million people. These services are commissioned either regionally by Specialised Commissioning Groups or nationally

by the National Commissioning Group (NCG), charged with commissioning very rare and unusual services and treatments, which classically receive orphan drug status. NICE does not appraise orphan drugs. The respondents said that it is quite common NCG provides funding for orphan drugs that never made it past topic selection as long as the drugs pass the NCG's clinical and cost-effective criteria.

As one respondent stated, "the IFR process is used as a stunt gun." An IFR manager in a South East PCT stressed that providers are not allowed to use IFRs as a means to circumvent the PCTs' established processes for approving and commissioning new drugs. However, she concluded that providers are increasingly using the IFR as a gateway for commissioning treatments for a group of patients. These treatments, as she put it, are usually not NICE approved and perhaps not NICE reviewed, and she said they are generally costly but low volume type drugs. It frustrated her that clinicians were ignoring the exceptionality rules and putting the panel in an awkward position of having to deny their requests.

According to the joint head of medicines and management in a Northern PCT, the medicines management team and PCT as a whole are "swayed" by what SMC says when NICE guidance is unavailable. This sentiment was echoed by practically all of the medicines management respondents. The respondents portrayed a hierarchy of information flow, with NICE seating at the helm of this hierarchal pyramid, followed by SMC then NPC then UKMi and the LNDG (see figure one). As a matter of protocol, when NICE guidance is unavailable, these PCTs look to these organisations for recommendations and evidenced-based reviews. Each respondent reacted positively to the work and contribution made by these HTA bodies, especially that of SMC. One respondent said she "sees the value in these bodies since they take a more rigorous and comprehensive review of drugs."

A series of interviews were conducted with leaders of UKMi, LNDG, MTRAC and a regional MI manager in charge of new products in the South West region. This section captures the comments and discussions stemming from the interviews. The respondents explained that over the years their organisations had developed tools to support the medicines management decision-making processes at the local PCT level. For instance, LNDG and UKMi undertake comprehensive horizon scanning to sensitize the NHS and its managers to new drugs coming along. For example, LNDG produces three horizon scanning related outputs. The first is a New Drugs Online program, which is a database of drugs in development as far away as three to five years ahead of market launch. The other tool, which was mentioned by PCT respondents as a highly valuable and essential informational resource used during annual commissioning of drugs and services and D&TC reviews, is Prescribing Outlook. This document, provided confidentially to PCTs alone, lists all new medicines, notably the high costly and resource demanding drugs, coming into

market that PCTs will need to make a decision on. Another Prescribing Outlook version is also jointly produced by UKMi and NPC. Finally, LNDG produces a third document, once again only for PCTs' use, predicting what NICE's decision will be on select drugs. This piece of information is most useful to PCTs, especially D&TC and APC, to allow for effective and accurate budgeting and planning for new introduction of medicines. According to the PCT-based respondents, horizon scanning performed by such bodies as LNDG and UKMi is critical to their work as it enables them to proactively plan ahead of time for new drug entry into their PCTs, whether it is NICE or non-NICE reviewed drugs.

6.2.3. Coverage decisions and access under EPR

6.2.4. The evidence

ERP can become an incentive for pharmaceutical companies to adopt international pricing strategies that, in the end, may have negative impacts on individual country prices and unexpected consequences in countries applying such policies. The main alleged negative effects can be: 1) higher prices in low-income countries that, in the absence of ERP policies, might benefit from lower prices from companies, and 2) delays in the launching new drugs in low-price countries. This was made evident in a recent European Commission report (European Commission, 2009) that asked companies to indicate which countries they preferred to use for launching new drugs. Companies preferred to initiate their product launches in countries with free prices (United Kingdom, Germany, Sweden). In contrast, countries with smaller markets, such as Cyprus or Malta, or with lower disposable income, such as Poland, Bulgaria, Lithuania, Latvia, Estonia, Hungary and Romania, are mentioned last. Considering the relatively small number of new medicines that actually make any substantial therapeutic contribution over existing ones, such delays in marketing might not necessarily be a bad thing.

From a policy perspective, EPR in itself does not restrict access once agreement has been reached but can lead to delays in launch, which, in itself can cause access problems. It can also be the case that manufacturers will not launch in a particular EPR market if they feel that the price they receive from that market is prohibitively low and can threaten their global pricing strategy.

Expensive products may be subject to the usual arrangements via prices collected across a range of countries, but, depending on the value they bring to the table, they can be treated in a slightly different way, notably, be given the opportunity to prove

their value in the local context by enabling local clinical studies, whilst in the meantime, a temporary reimbursement status is granted.⁴⁶

Finally, it is possible that EPR can be combined with additional policy measures for reimbursement purposes in order to deliver a lower price for a particular volume level. It can be further combined with paybacks, should this volume be exceeded. This is one form of risk-sharing that gives the payer the security of capped expenditure in a particular therapeutic class or across the board.

⁴⁶ As was discussed in the context of the Czech Republic.

7. ASSESSING THE VALUE OF INNOVATION

7.1. Overview

Assessment of value of a new therapeutic intervention is an important consideration in determining current and future levels of prices and the treatment of a new therapy from a reimbursement perspective.

7.1.1. Value-Based Pricing

Under VBP considerations, several important elements enter the discussion surrounding value assessment; the first is associated with the uncertainty that exists about the effectiveness of the new treatment, which is also related to the timing at which the assessment is taking place; issues such as whether appraisals ought to take place *ex ante* or *ex post* depending on the type of clinical evidence that is available at launch are at the heart of this debate. The second aspect correlates with the perspective of the assessment and whether a purely therapeutic, health system or a broader societal perspective is used to inform a (pricing) decision. Naturally, as the boundaries are widened from therapeutic to societal, so is the complexity and uncertainty in reaching an evidence-based decision early on. Third, methodological issues, preferences, peculiarities in assessing value, as well as the type of parameters included (e.g. cost types) may influence the outcome of appraisals and the direction in which they are implemented in different countries that – otherwise – implement the same tool. Finally, an additional element enters the debate, namely whether the clinical benefit is the primary focus of the assessment or it is the clinical benefit in relation to cost.

7.1.2. External Price Referencing

In the context of EPR assessment of value is implicitly taken into consideration and this usually materializes through the definition and use of the “basket” of comparator countries and the actions performed within the basket once it has been defined. In defining their basket of comparators, countries may include countries that explicitly recognize value and the “value of innovation”; this is frequently done, for example, through the inclusion of the new treatment’s country of origin. In other cases, care is exercised that the basket includes both high- and low-price countries, or even countries of comparable income level to that of the target country. In terms of actions performed within the basket once it has been defined, it is important to consider whether the basket is used to arrive at the lowest price – and, therefore, the consideration is that of cost minimization – or it is used to arrive at the average price. The frequency of price adjustments and whether EPR is only used to determine launch prices or is also used subsequently to adjust these to price

movements elsewhere also determines whether it is used as a tool to minimize costs or also as a method to indirectly reward innovation.







Both, VBP and EPR, raise important considerations from a stakeholder perspective, particularly in relation to rewarding innovation. These are reviewed in the following sections, alongside the empirical evidence that exists.

7.2. Value of innovation under VBP

7.2.1. The evidence

Valuing innovation in the context of VBP is part of a complex matrix of data, and information as was highlighted in the previous sections. A key limitation of the available data and information at launch is the uncertainty about the effect the new treatment will have. In this context, the available information can be subject to different interpretations by competent authorities that assess value, despite the fact that this information is broadly similar across different settings. The main reasons for individual agency recommendations, following assessment of value are summarised in Table 7.2.1.

Table 7.2.1 : Drug Value Assessment: Main criteria on which recommendations are based across 6 HTA agencies

	 CDR/CEB	 NICE	 PBAC	 HAS	 TLV	 SMC
Clinical efficacy	Non-inferiority/superiority	Non-inferiority vs placebo	Non-inferiority vs comparator	Superiority vs therapeutic comparators	Non-inferiority to comparator	Superiority/non-inferiority vs comparators
	Clinical benefit	✓	✓	✓	✓	✓
	Strength of trial design	✓	✓	✓		
Economic evaluation	Cost-effectiveness (low, certain)	✓	✓	✓	✓	✓
	Cost vs comparators	✓		✓	✓	
	Economic model validity (inputs, methods)	✓	✓	✓	✓	✓
	Value for money	✓				
Need	Budget impact		✓	✓		
	Rx alternatives available/not	✓		✓	✓	
Safety	Population medical need		✓	✓	✓	
	Toxicity/safety profile			✓		✓
	Efficacy/safety ratio (high)				✓	✓

Source: Kanavos et al., Euro-Observer, December 2010.

Qualitative examination of value assessments across indication-treatment pairs drawn from cancer, orphan and CNS indications⁴⁷ suggested that HTA agencies tend to, on the whole, rely on the same studies and published evidence to provide information on efficacy and rates and types of adverse events. This is likely simply a by-product of the limited amount of high-quality evidence present in the published literature on which the manufacturer submissions rely due to the short time between marketing authorisation and HTA in most cases. Further, the similarities in the evidence cited by the agencies are likely due to the close temporal proximity of the evaluations, precluding the development of substantial additional evidence between the assessment cycles. However, some of the differences in reimbursement decisions observed were the result of variations in interpretation of the same key trials, rather than reliance on different evidence per se. Among convergent and divergent outcomes, there were several main factors that influenced the reimbursement decisions of the various agencies.

1) *Use of evidence.* Due to the lengthy time period required to assess long-term outcomes (especially relevant to evaluating survival benefits with cancer therapies) as well as to monitor adverse events, and collect complete economic data, in most cases adequate studies were not available in order to calculate robust estimates of cost-effectiveness, and resulted in high degrees of uncertainty in the ICER. As a result, agencies were faced with a number of options: using sub-group analysis to limit reimbursement to narrower groups or indications for which the estimates were more certain; undertaking indirect comparisons across trials to supplement available evidence; employing expert opinion to reach a decision when the evidence was equivocal; deferral of appraisal decisions until further evidence is developed; or, rejecting reimbursement due to the high level of uncertainty. The agencies seemed to have differing degrees of willingness to employ these different strategies, which likely impacted differences in reimbursement outcomes. For example, in the case of erlotinib (NSCLC), one agency limited its use to patients with EGFR-positive⁴⁸ tumors or tumors of unknown status (LWC), based on putative improved response, whilst another agency considered the subgroup evidence too weak for this type of restriction (L), and a third agency conducted further analysis and concluded that EGFR status was in fact not predictive of response, but still restricted listing based on performance status (LWC).

2) *Special considerations.* Overall, the acceptability of the calculated ICER was a strong predictor of whether the compound was approved for reimbursement, and

⁴⁷ Euro-Observer issue, December 2010.

⁴⁸ Epidermal growth factor receptor, a biologic marker.

there were few cases in which a drug was approved for reimbursement despite a high, and otherwise unacceptable, ICER.⁴⁹ Nonetheless, many cancer indications were given special consideration in the HTAs due to the severity of disease, the relatively few people affected by the specific cancer, lack of other treatment options, or the relative therapeutic benefit that the drug offered. These special considerations appeared to contribute to reimbursement approvals for several compounds, notably sunitinib (renal cell carcinoma) and erlotinib (non-small cell lung cancer) due to lack of alternative effective therapies currently available; and for docetaxel (prostate cancer) and trastuzumab (metastatic breast cancer), for providing significant clinical gains, thereby implicitly rewarding innovation. However, in other instances, even when such extenuating circumstances were considered, this did not always overcome significantly high ICERs, as pemetrexed (malignant pleural mesothelioma) and cetuximab (metastatic colorectal cancer) were initially rejected. It is unclear as to what exactly separates the compounds that, despite their excessive ICERs, receive positive HTA outcomes, and those that do not, when additional criteria are taken into consideration. However, certain considerations may have more weight in this regard (e.g. such as whether an indication has *few* as opposed to *no* effective treatments available).

3) *Pricing*. Through the process of assessing value, the agencies were noted to exert pressure on manufacturers to decrease the pricing of the compound in question in order to improve ICERs and increase the likelihood of reimbursement approval. Similarly, this pressure was also reflected in the development of various forms of risk-sharing agreements, in response to the lack of adequate evidence, requiring the manufacturer to bear a portion of the inherent risk when future costs were uncertain.

4) *Other factors*. The results of an HTA assessment occasionally seemed contingent upon other factors external to the HTA process itself, such as current prices and market authorisation of other comparators, release of new data, and changes in clinical practice. Similarly, while patients often have a consultative role during an HTA, patient preferences for certain aspects of the therapy (e.g. method of administration, frequency of doses, or relative detriments of certain side-effect profiles) played a pivotal role in some instances.

Overall, the agencies tended to approach the use of less-than-ideal evidence with differing strategies: some agencies were likely to reject an application if inadequate evidence was submitted, but also engaged in pricing negotiations to reach positive

⁴⁹ Except for France, which does not consider cost effectiveness evidence.

outcomes; others tended to navigate uncertainty and poor evidence by using indirect comparisons and expert opinion as necessary, along with the development of risk-sharing agreements; finally, others tended to encourage price negotiations and the development of risk-sharing agreements to overcome informational uncertainty.

7.2.2. Discussion and stakeholder perspectives

7.2.2.1 Ex-ante versus ex-post assessment

The question of whether VBP appraisals can take place at launch or when the appropriate evidence that payers require becomes available has received some attention in the literature. Both have advantages and disadvantages, which are intensely debated.

Ex-ante evaluation provides manufacturers with the incentive to invest in gathering the evidence that the health service requires to approve and encourage innovation in areas/therapies where a substantial clinical benefit can be demonstrated. One drawback, however, of the use of ex-ante as opposed to ex-post evidence is that there will be uncertainty surrounding the clinical-cost-effectiveness of the drug outside the RCT setting at the time of launch. Although further ex-post reviews can also be suggested, these may be difficult to ensure as once a pharmaceutical product is approved, the incentive to carry out further trials is diminished and may even be deemed unethical. Nonetheless, a balance between the value of the economic information surrounding the drug and the value of availability of the drug to patients needs to be achieved (as is often emphasised in HTA).

On the other hand, both payers and manufacturers seem to believe that ex-post evidence is as crucial as ex-ante evidence in proving the value of new treatments.⁵⁰ There needs to be acceptance of data obtained in naturalistic settings and methodologies on how best to extract value from such data need to be strengthened. “Avoiding hierarchies of evidence” implying that evidence from RCTs, observational studies, clinical expert evidence, and systematic reviews, serve particular objectives and should all been taken into account, has been mentioned on a number of occasions in the UK and Sweden.⁵¹ Even in the case of the German IQWiG the view that seemed to elevate RCTs to supremacy vis-à-vis all other types of evidence appears to be on the wane with the recent early stage review for new technologies, predicted – among other things - to identify what *additional* data may be required to

⁵⁰ Based on interviews with representatives from 7 manufacturers and the payer/HTA community in the UK, France, Sweden, and Denmark.

⁵¹ Interviews with HTA agencies (NICE, SMC, TLV).

yield an objective value assessment for the technology in question.⁵² Yet, it remains unclear what input or substantive guidance, if any, value assessment agencies provide to manufacturers to enable them conduct ex-post studies that will be instrumental in delivering the appropriate information down the line. As it was put by TLV, “... the expertise or the resource is not available at the moment to provide this level of input to manufacturers, although there are plans for this to change in the near future and enable the agency to provide feedback on methods and expected outcomes to manufacturers”.⁵³

Ownership of data generated from processes outside the context of RCTs is also important, as the cost associated with gathering such evidence is substantial and creating this evidence should provide the scope for collaboration between the payer community and manufacturers. Several interviewees representing manufacturer positions were of the view that more robust methodologies would be needed alongside a wider “European” ownership of the data generated in order for the latter to have wider applicability within the European context.

Ex-post assessment of value can be a key component to VBP, but further reflection and consultation are needed to determine criteria and processes for such appraisals to take place. There may be no sense in requiring ex-post appraisals for all products (even if only applied after a specified starting date). It is likely to be most beneficial where there is either a complex value proposition for a chronic condition (e.g. disease modifying medications for Alzheimer’s disease) or a level of uncertainty related to the evidence available at time of Market Authorisation (MA). Consideration ought to be given to how best to deal with products that might never be able to demonstrate cost-effectiveness e.g. orphan medicines, and to whether products with a very small budget impact should be excluded from ex-post VBP arrangements.

Overall, evidence prior to the launch of a new product is not always available and there may be significant data limitations and concomitant uncertainty. Ex-post assessments may prove instrumental in many cases in determining product value for health services, patients and society, but criteria, methods and processes need to be set up as to which products should undergo these, together with arrangements allowing access to patients in the meantime.

An ex-ante price premium in the case of ex-post assessments would provide a signal to the innovator of the willingness by the payer to reward high risk-taking. Equally, flexibility in pricing arrangements based on the quality of the available evidence

⁵² Interview with IQWiG Board member.

⁵³ Interview with TLV member, December 2010.

should be a highly desirable feature of VBP in that prices could be adjusted downwards as well as upwards depending on the emerging evidence.

7.2.2.2 Implement comprehensive criteria and metrics for a societal perspective

Criteria and metrics from a societal perspective should be considered when assessing drug value and setting pricing/reimbursement levels and ought to include all elements of value. When they do assess value though, pricing/reimbursement systems have frequently chosen to focus on value almost exclusively from the healthcare system (payer) point of view rather than the broader societal or patient/physician (e.g., consider cost offsets to the healthcare system such as hospital stays and/or other drug costs avoided, but not from increased worker productivity or provider efficiency).

One of the few exceptions to this rule seems to be TLV in Sweden, which assesses technologies from a societal perspective. In the UK, the ongoing debate about VBP and its implementation remains a government pledge; to that end, a societal perspective in value assessment has been discussed as the way forward in the post-2014 era, whereby the value of a new technology will be placed on a pathway and will be judged against a broad set of criteria including its contribution to health and social care, but also the contribution to a broader societal well-being⁵⁴.

If a departure from the current norm of health system perspective is desirable, then it is important that appropriate metrics are established for that purpose. The evidence from TLV over the past few years suggests that the following are important in addition to disease severity and equity considerations: (a) humanistic, patient focused benefits such as QoL; (b) longer-term direct cost offsets; (c) indirect system costs that might or might not be covered by payers such as worker productivity, but are nevertheless important in capturing elements of value; (d) benefits to caregivers as well as patients. These considerations highlight the intensity of data and information required to enable an objective value assessment from a “societal” perspective; as we widen the boundaries of value assessment from pharmaceutical to health to societal perspective, the data/information requirements increase significantly (Figure 7.1)

Finally, new standards and tools for more accurately and consistently assessing the more challenging metrics must be developed. Patient groups, for instance, strongly believe that some of the quality of life elicitation tools that national agencies use currently do not capture preferences appropriately. In particular, concerns have

⁵⁴ Interviews with DH and NICE in the UK.

been raised about the ability of the widely used EQ5D tool to capture elements such as fatigue which are important across a number of conditions including brain diseases and oncology. Patients have also mentioned the importance of initiating and widely implementing patient reported outcomes (PROs) in capturing value and outcomes.⁵⁵

7.2.2.3 Foster collaboration between stakeholders

Payers (whether health systems or health insurers), providers, patients and manufacturers must work together, not antagonistically, to establish pilots to investigate new pragmatic ways of managing drug spending and eliciting value taking into consideration inputs from across the spectrum of the stakeholder community.

Agencies such as TLV, NICE or SMC, to mention but a few, have established procedures whereby clinical and patient views are heard and form part of the value assessment process. It is not uncommon to have a well-established programme that provides guidance on patients and patient groups on the type of evidence required in this context and assisting them in fulfilling this requirement.⁵⁶ Against this background, patients widely applaud this opportunity, but, are nevertheless faced with the daunting task of presenting “evidence” on their perception of the disease and the new treatment, before a highly specialized audience. It is felt that “patients and patient organizations do not have the capacity, knowledge or understanding of the relevant jargon to become an active participant in this process; in order to do so they would need to acquire the appropriate skills to be able to participate in a meaningful way”.⁵⁷

A comparable situation arises in reimbursement committees where assessment of value forms an important component of the decision-making process. Although patients have a voice at the table, this is hardly ever used in a constructive manner to inform the process. The feeling is that patients are “overwhelmed and unable to prepare meaningful and technical information that will make a contribution to the case at hand”.⁵⁸

In order to face the challenges, an inclusive process for defining pragmatic, effective changes to drug approval and pricing approaches must be developed, ensuring these are transparent to all as well as ensure that stakeholder participation is meaningful.

⁵⁵ Interviews with patient groups from the CNS and oncology disease areas.

⁵⁶ Interview with the Director of patient programmes at NICE.

⁵⁷ Focus group consensus among 16 patient groups from 12 EU Member States.

⁵⁸ Interview with 3 patient groups in Tallinn in the context of their participation in the national reimbursement committee.

Where appropriate, capacity building may be required to enable interested parties to participate.

7.2.2.4 Varying patent terms in relation to VBP

The duration of a product's exclusivity of supply period is a critical determinant of the price needed to allow financial viability in relation to the marketing of any particular pharmaceutical innovation, particularly those facing niche markets with high prices to recoup high investment costs. If the time taken to develop new medicines is increasing and the number of successful new medicines produced per quantum of resource invested is for whatever reason falling, then one potentially sustainable way of keeping product prices down to VBP defined levels would be to allow variable patent life extensions. Such an approach might also provide a way of addressing 'evidence lag' related concerns to be resolved more elegantly than may be possible via post marketing price increases. This point was raised in meetings with manufacturers⁵⁹, reflecting concerns about clinical development pathways targeting niche areas and moderate willingness to pay by payers.

7.2.2.5 Bridging the gap between regulation and VBP arrangements

Payers continue to be of the view that manufacturers can maximise their effectiveness and increase the probability of a new drug receiving a positive recommendation by designing trials to provide more comparative data, powering trials to indicate superiority rather than only non-inferiority and structuring economic models from both a health and societal perspective, applying the agency preferred methods for discounting and quality-adjusting utility values.⁶⁰

Manufacturers highlight that in the process of eliciting value at an early stage when a product is launched, "there is a knowledge gap, assuming a rising knowledge curve over time; this gap is captured on one hand by the desire to know more about a new technology and its impact on a target patient population and, on the other hand, by the need to enable new technologies to come to market soon enough once safety efficacy and quality have been satisfied given patent term restrictions (Figure 7.2.1). The desire to know more would delay product approval and launch until very late on this knowledge curve (e.g it would occur at point C, when the available evidence would probably satisfy HTA agencies), whereas early access would occur at point B,

⁵⁹ Interviews with senior management at 3 leading manufacturers.

⁶⁰ Summary statements from interviews conducted with NICE, SMC, TLV, SUKL, HAS and the Transparency Commission.

shortly after MA with the resulting uncertainty it implies”.⁶¹ The view of manufacturers is that in the assessment of value payers need to be flexible as the knowledge curve is continuously rising and that there is a clear trade-off between optimal knowledge base and timely introduction. “Assessing value earlier and more rapidly and merging the requirements for MA and HTA/VBP into trial design could help to optimise resource use, maximise health benefits and enhance access and availability to new treatments for needy populations”.⁶²

Patients, on the other hand, are obviously in favour of faster access, particularly for those treatments that can have a significant therapeutic effect, however short-lived this may be. The patient view, however, is that “the current system is totally unfit for purpose given the significant discontinuity between MA requirements and HTA/VBP requirements and that there is great need for this gap to be bridged”.⁶³

A further issue relates to current regulatory practices, particularly around safety. Patients have repeatedly suggested that the probability of positive benefit, however small, can lead to a higher (safety) risk acceptance threshold, particularly in therapeutic areas where uncertainty is very high and there is paucity of available therapeutic options. In this light, a differential risk/benefit ratio could be a likely response. As an interviewee pointed out, “a patient with a life-threatening and potentially lethal condition already lives under tremendous uncertainty and risk; a little more uncertainty and risk would not add much to this.”⁶⁴

⁶¹ Panel discussion with R Bergström (LIF/EFPIA), Mary Baker (EFNA), Hans-Georg Eichler (EMA), Finn Børllum Christensen (EUNetHTA), as part of the HTA Patient Academy, London 15 September 2010.

⁶² Ibid.

⁶³ Ibid.

⁶⁴ Interview with Albert Jovell, Spanish Patient Forum.

Figure 7.2.1 : Spectrum of value in pharmaceutical assessments; from therapeutic, to health system, to societal perspective in value assessment

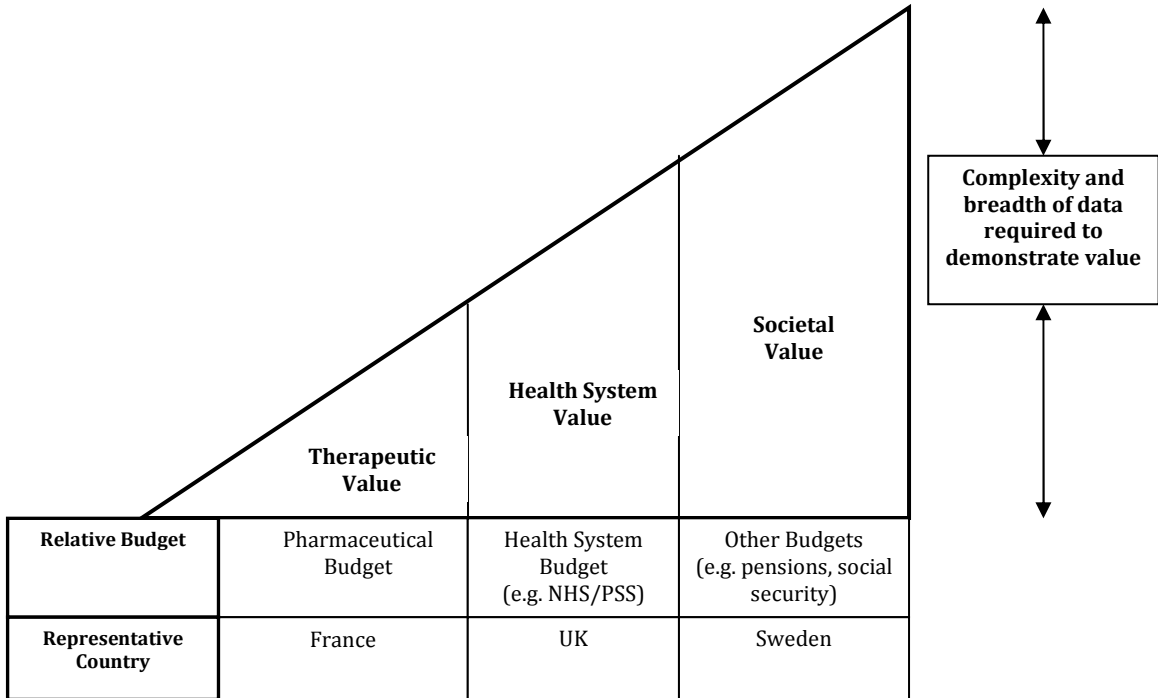
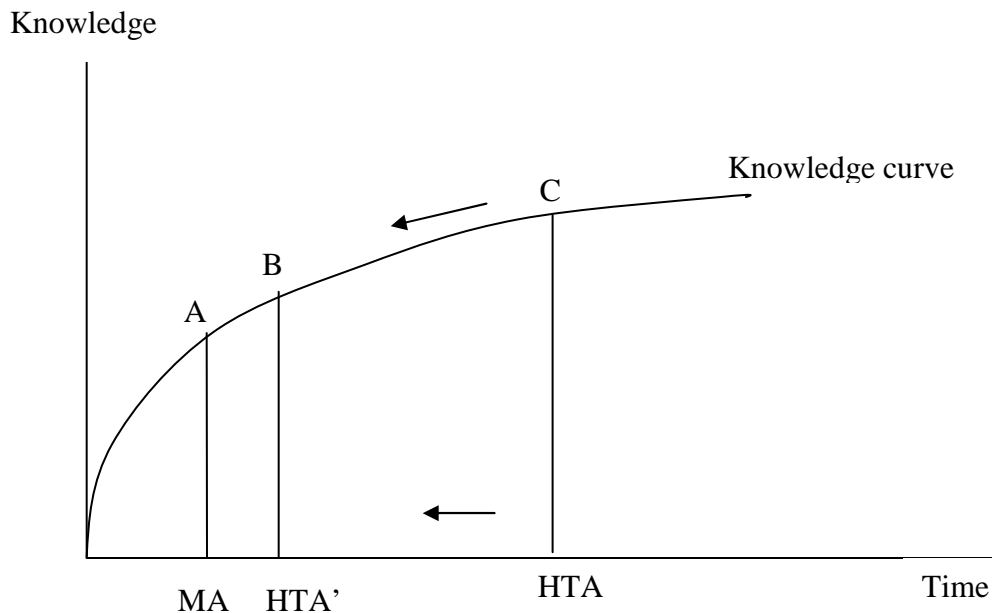


Figure 7.2.2: Knowledge intensity surrounding a pharmaceutical product and the relevance of Marketing Authorisation and Health Technology Assessment in the Knowledge Trajectory



Source: Adapted from a presentation by and discussion with R Bergström, June 2010.

7.3. Value of innovation under EPR

7.3.1. The evidence and stakeholder views

In our interaction with government agencies implementing EPR it is clear that the potential for enabling value assessments, and, therefore, taking into consideration the value of innovation, exists. This can take place in two cases: first, with regard to *new products that do not belong to an existing therapeutic class*, then for the process of reimbursement alternative arrangements can be made other than including these into (internal) reference clusters. These arrangements include the establishment of a new therapeutic category, “if evidence justifies that and is submitted by the manufacturer or is found in the literature or elsewhere.”⁶⁵

The second case is similar to the conundrum faced by HTA agencies in VBP relating to uncertainty. Where medical benefit is not always clearly defined from the available data, then from an EPR perspective, the process is exactly the same as in all

⁶⁵ Discussions with SUKL.

other products, ie taking prices from other countries, based on the basket notion, although there are instances “where very expensive products can be granted temporary reimbursement only, and this can happen three consecutive times only, 12 months at a time”.⁶⁶ If after the three 12-month periods the drug is not eligible for permanent reimbursement, it will come to the market without reimbursement. In the Czech context of EPR, eligibility for reimbursement is defined based on the ability of the manufacturer to prove that the technology is effective within the Czech Republic. What the Czech authorities are looking for in this case, is for the MA holder to set up a registry in the Czech Republic, with a view to proving that the technology is effective and, therefore, confirm the results of RCTs.

There are also instances in which the operation of an EPR scheme does not take into account the value of innovation. For instance, an issue arises when EPR is combined with molecular or therapeutic price referencing, the latter being a frequently-used option setting a reference price across a range of molecules, of which at least one is patent-expired. It is likely that these two effects can be combined and can spill-over across borders. The propagation mechanism for this to take place is differences in patent term dates across countries. Despite EU-wide provisions concerning intellectual property rights protection, patent term dates are not always identical among Member States⁶⁷ and is probably one of the unintended consequences of such differences. Under these circumstances, it is probable that the patent for a product in one country may expire earlier than in others. This would, of course, allow generics to enter in the country where the patent expires and could force the originator price to decline particularly if an internal price reference system is in place. This decline may trigger price adjustment in other countries if the product in question is subject to EPR provisions elsewhere. To that end, such patent term differences across member States can have unintended consequences and lead to cross border price reductions if combined with internal price referencing elsewhere.

This particular phenomenon is not a theoretical case and several situations have arisen in the past: one of them related to price reduction of the originator by about 20% due to patent expiry and subsequent generic entry in one country.⁶⁸ The effect was an immediate price reduction of the same originator in countries referencing the original country.

Overall, EPR systems are not equipped to provide explicit assessments of value of new treatments, but the above evidence suggests that such assessments can take place in particular circumstances. More broadly, if EPR fixes prices at launch only, then there may be no further impact on the value of the product along its life cycle,

⁶⁶ Discussions with SUKL.

⁶⁷ Interviews with manufacturers.

⁶⁸ Interview with manufacturer.

but, frequent adjustments do have an impact because they are usually conducted to take into account price reductions in individual components of the basket or broader adjustments therein.

8. ENCOURAGING AND REWARDING INNOVATION

8.1. Overview

A relevant policy question for both VBP and EPR is whether they in themselves encourage the process of innovation or whether additional incentives are needed to do this. In this section we explore this question bearing in mind that the evidence base to inform this policy question is weak. An implicit assumption is made in this context that price in itself – however important a variable it may be - does not constitute the only criterion for rewarding innovation and that other parameters, both tangible and intangible contribute to that process.

8.1.1. Value Based Pricing

The continuing debate over the pricing of pharmaceuticals has emphasised the relationship of pricing to value. In moving towards VBP, and, hence, a situation where efficiency is –in principle- improved, two aspects of efficiency must be considered; first, *static* efficiency, which relates to the pricing of a product about to enter or already on the market and, second, *dynamic* efficiency which relates to product innovation as applied to future market conditions. Given the tensions in securing static and dynamic efficiency simultaneously there may be an optimal trade-off between the pursuit of both goals. A relevant discussion in this context addresses the factors that decision-makers take into account when considering the value of new technologies and whether a societal perspective can be construed to enhance innovation, or whether the use of low cost alternatives in value assessment provides a disincentive to invest further in innovation. More fundamentally, even if VBP in itself encourages innovation, are additional policies needed to achieve this and if so what are they?

8.1.2. External Price Referencing

Within the context of EPR the relevant factors that could inform whether it encourages innovation, relate to the composition of basket of comparator countries, the price that is taken, the frequency of adjustments, the currencies included in these adjustments, as well as the way that EPR embraces value in light of uncertainty, particularly at the point of a new introduction with incomplete data. In addition, it is important to consider the stability and predictability of the system and, as in the case of VBP, whether additional policies are needed to achieve the objective of encouraging innovation, and, if so, what they are..

8.2. Innovation and Value-Based Pricing

8.2.1. Static efficiency

In the majority of cases VBP uses clinical cost-effectiveness in pricing to pursue a definition of value. In that sense, emphasis therefore moves towards static efficiency with the emphasis on value for money at launch and –potentially- away from dynamic efficiency, ie future innovation.

A number of problems exist in using clinical cost-effectiveness which are pertinent to both existing use and the proposed use to establish VBP. A major issue relates to the use of clinical trial results to establish effectiveness. The objectives of such trials are normally to establish safety, tolerability and efficacy within a tightly controlled population. Such trials are normally short-term and therefore do not establish the long-term health effects required for a comprehensive cost-effectiveness analysis. The results from such trials are currently aimed at a different set of regulatory bodies than those concerned with pricing and reimbursement. Modelling, based on increasingly accepted methods, must therefore be undertaken not only for this reason but also as health economic data on endpoints and resource use are not routinely incorporated within clinical trial studies.

Given that pricing and reimbursement is required on launch an *ex-ante* fast track appraisal method places heavy demands on the evaluation data. This is not impossible to achieve, but is open to uncertainty; hence the combination of *ex-ante* and *ex-post* evaluations.

Health Technology Assessment Agencies performing assessments of value on individual products, require data at launch. This does, in principle, require head-to-head studies or indirect comparisons through some form of meta-analysis of the new product with existing comparator therapy.⁶⁹ It is unlikely that this information would be readily available across the board or that clinical trials, which are increasingly designed with a global perspective, would be tapered to fulfill regulatory criteria in one market for pricing purposes. As shown previously, there may in any case be different standard comparator therapies in different geographical markets.

Therefore, data availability is a major constraint. *Ex-post* risk-sharing is only envisaged as a means of supporting situations where there is not enough available data for an *ex-ante* consideration. The lag time for the implementation of *ex-post* risk-sharing is of obvious interest. Too short a lag will not overcome data constraints and will not provide much incentive to participate; too long could lead to distortion of the perceived gains in static efficiency. While such data constraints are

⁶⁹ Interviews with NICE, TLV, Finnish agency and manufacturers.

not insurmountable they are substantial and have to be faced as an additional investment to secure value for money pricing.

8.2.2. Dynamic efficiency

The impact of VBP has been less discussed with respect to dynamic efficiency. The envisaged regulatory environment is one where manufacturers would pursue investment over a long time frame given that there is a chance of reward based on a product price set in accordance with achieved health benefit.

The envisaged incentive is that manufacturers will invest in areas where the achievable health benefit is greatest. Areas of high disease prevalence combined with unmet medical need offer the obvious highest returns. But if these are also areas characterised by a long lag between research and product development as well as high risks for individual firms, either reason may mitigate against R&D; firms may place smaller value on R&D projects than society in certain areas leading to general under-investment.

Overall, it could be argued that the VBP approach is limited in its ability to deliver on dynamic efficiency and that this is one of its fundamental flaws. Therefore, compensating measures to incentivise R&D will need to be identified and robustly implemented. Further reflection on this particular aspect is offered in section 8.4.

8.2.3. Societal value assessment and innovation

Although few would agree with accepting a price premium for a drug simply because it is innovative, innovation (both breakthrough and incremental) can lead to greater subsequent understanding of the aetiology of a disease (i.e. there could be said to be a positive externality from discovery and use of a new drug), recognition of which is achieved to a certain extent in the French SMR/ASMR system. This may have important dynamic implications for future R&D. In addition, the broader socioeconomic picture has to be considered if there is to be accurate recognition of the benefits that a drug brings.

Within the French SMR/ASMR context, the assessment relates to the value of the drug vis-à-vis a comparator and is done within a strict clinical context. Most countries that have a system of assessing clinical and economic costs and benefits, do so from a health system perspective, taking into consideration those benefits and costs that relate to the health service only. It is not uncommon that “the health service perspective is enshrined into law, thus defining the operational boundaries”

of agencies.⁷⁰ The only country that has so far embraced a societal perspective in health care value assessment is Sweden. “The health economic analysis should be conducted from a social economic perspective. Amongst other things, this means that all relevant costs and revenues for treatment and ill health, irrespective of the payer (county council, local authority, state, patient, relation) should be considered. The information must describe the situation in Sweden.”⁷¹ This is also likely to change in the years to come in the UK, based on the new government’s decision “to implement VBP from a societal perspective”⁷², possibly by “placing a new medicine into the overall disease treatment pathway and considering costs and benefits widely.”⁷³

8.2.4. What comparator is to be used in VBP assessments?

An issue relevant to the discussion of impact on innovation is the comparator used in VBP assessments. This is usually left to the manufacturer with the policy-maker providing guidance on what comparators can be used from a conceptual perspective, e.g. the most widely used treatment. In this context, the use of generic comparators is also controversial and certain views have been expressed with regard to generics being used as comparators in two countries that apply versions of VBP, notably the UK and Sweden. Within the UK context, the views that have been expressed during the Office of Fair Trading (OFT) review of the PPRS are that “the NHS does not have enough flexibility to be generous in this point” (OFT, 2007), although it needs to be seen how this view will be implemented in practice. Equally, in recent changes to its operating model, the Swedish TLV considers “the lowest price generic to be the most appropriate comparator.”⁷⁴

Clearly, this can have an impact from an *ex-ante* perspective and, equally, from an *ex-post* perspective. From an *ex-ante* perspective, there is often flexibility in the choice of comparators, particularly in the context of positioning the new treatment. From an *ex-post* perspective, it may be the case that reviews of the available evidence can lead to a re-assessment of value at therapeutic class level. This was recently manifested with the respective reviews of statins⁷⁵ and anti-depressants⁷⁶ undertaken by TLV and led to de-listing of certain in-patent products.

⁷⁰ Interview with NICE.

⁷¹ Interview with TLV member also confirming the societal approach included in the guidelines for health economic evaluations: <http://www.tlv.se/Upload/English/ENG-lfnar-2003-2.pdf>.

⁷² Interview with UK DH.

⁷³ Interview with NICE.

⁷⁴ Interviews with TLV members.

⁷⁵ <http://www.tlv.se/in-english-old/news/many-millions-wasted-on-unnecessarily-expensive-lipid-lowering-medicines/>

From an ex-post perspective, the use of (the lowest-priced) generics as the most appropriate comparators to drive the discussion on value is somewhat controversial in the context of encouragement of innovation. One possible downside of the VBP model as proposed in the UK and as currently applied by TLV is that it is in effect designed to curtail patent holders' rights to charge a premium for their products during the full life of their patent. While there is a temptation for health systems to consider generic comparators where possible, some consideration may need to be given to the disincentive it provides to the innovator, if the payoff is driven by a generic low cost alternative. "This provides neither short- nor long-term incentives to innovate⁷⁷, whilst at the same time it provides a strong incentive to the innovator to select less risky investment options, which potentially, can lead to less innovation and lower welfare in the future."⁷⁸ Payers on the other hand, wish to understand the value added of individual products within a therapeutic class, in terms of scientific and clinical evidence, quality of life (via validated instruments), improved compliance and cost. This is an area of policy, where both VBP systems and EPR systems seem to be converging.

8.3.External Price Referencing

EPR systems are in principle not designed to reward innovation, but can consider doing so as part of the entire process, particularly for new products, as was discussed in section 7 of the report. In addition, EPR systems could take into account value either through the selection of countries in the basket, (e.g. high price countries) or by considering value in light of uncertainty or both. As is usually the case, such measures can be supplemented with additional incentives elsewhere in the system to fulfil this objective (see also sub-section below).

8.4.Other policies contributing to the objective of (future) innovation

The discussion in the previous two sections highlights the fact that an explicit encouragement of innovation is not necessarily the primary remit of neither VBP nor EPR systems. Many EU Member States do have separate policies in place, whereby biomedical research is encouraged, through a variety of financial and non-financial incentives, which can be targeted to the pharmaceutical sector or can apply

⁷⁶ <http://www.tlv.se/in-english-old/news/the-tlvs-review-of-antidepressants-puts-price-pressure-on-pharmaceutical-companies/>

⁷⁷ Relating to the arguments about static and dynamic efficiency.

⁷⁸ Interviews with manufacturers and EFPIA member; also quoting:
<http://www.efpia.eu/Content/Default.asp?PageID=559&DocID=1351>

more broadly towards innovation; equally, seed funds, such as the Finnish Innovation Fund (SITRA)⁷⁹ or innovation agencies, such as the Swedish VINNOVA.⁸⁰

While it is not within the remit of this report to examine exhaustively national schemes that aim to encourage (bio)pharmaceutical innovation, it is probably worth mentioning in brief two such initiatives, one in the UK and one in Spain. In the UK, the PPRS, which has been in operation in some form or other since the mid-1950s, provides explicit financial incentives for manufacturers to conduct R&D as part of the overall agreement on rate of return regulation.⁸¹ Of course, it has been pointed out that this may be the last ever PPRS agreement (ending 2014), but, nevertheless, it is a mechanism that explicitly links health policy and industrial policy for pharmaceuticals. In addition to the incentives provided by the PPRS, a multi-stakeholder platform (partnership between government, industry, and other stakeholders) exists through the Office for Life Sciences (OLS) that was established in January 2009 with the recognition that more needed to be done to provide a stimulating environment for UK life sciences.⁸²

From a Spanish perspective, the PROFARMA initiative⁸³ aims to accomplish the modernization of the pharmaceutical sector and boost activities that bring fundamental added value to the sector in such way that investments are made in new industrial plants, and new technologies through enhanced R&D. The overall objectives of Profarma relate to (a) an increase in the total level of investments realized in Spain by the firms participating in the PROFARMA program, considering particularly relevant the increase of investments in manufacturing and R&D; (b) a growth in the level of employment for R&D activities; (c) an increase in current R&D spend as a proportion of medicines sales to the Spanish NHS.

8.5. Innovation, VBP and EPR: Discussion and stakeholder effects

8.5.1. Pricing decisions and rewarding innovation: two policy imperatives that can be addressed with one or two rules?

In terms of addressing the policy question we set out to address at the beginning of this section, ie encouragement of innovation, it is important to first of all consider four points: first, both VBP and EPR – the latter more so than the former – are used by decision-makers primarily to inform pricing and reimbursement decisions, in

⁷⁹ <http://www.sitra.fi/en/>

⁸⁰ <http://www.vinnova.se/en/>

⁸¹

http://www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS/DH_090499

⁸² <http://www.bis.gov.uk/ols>

⁸³ <http://www.mityc.es/PortalAyudas/profarma/Descripcion/Paginas/objetivos.aspx>

other words the key policy imperative is pricing and reimbursement; assuming that reward for innovation is a secondary policy imperative, then, in principle, two rules would be needed to satisfy two policy imperatives (reimbursement and reward for innovation). In meetings with HTA agencies it has been pointed out that that manufacturers often do not seem to capture the way HTA agencies work in terms of horizon scanning and early contact, the type of data needed and how it can be generated or sequenced, as well as early stage reviews of the available evidence.

Second, in their deliberation about value and price, decision-makers are often risk averse and potentially unwilling to accept high risks. This is understandable in an environment characterised by ever increasing health care costs, increasing costs of new technologies and higher uncertainty. With this in mind, reward for innovation remains a secondary policy imperative after achieving favourable reimbursement terms.

Third, while industry spends a significant amount of resources in R&D (€26 billion in 2007), an almost equivalent amount has been spent on R&D directly or indirectly by national and supranational sources, indicating a high level of commitment to biomedical research.

Finally, as outlined in previous sections of this report, there are significant challenges to measuring innovation. In the context of VBP the perception of value by the regulator is influenced by factors such as the choice of comparator, the perspective of assessment, or the availability of effectiveness data, among others. In EPR, the way the system is constructed could take indirectly innovation into account.

8.5.2. Societal value assessment

This approach is in itself a positive step towards the inclusion of value elements that can be important from a personal, carer, family and broader societal perspective, but, in itself, this cannot be construed as an approach that rewards future innovation. Additional elements that influence future innovation relate to the overall assessment process, namely, the issue of comparators – particularly generic- either on an *ex-ante* or an *ex-post* basis and whether thresholds are flexible or flexibly interpreted to take into consideration unmet medical need, disease severity, compared with technical efficiency only.

9. ADVANTAGES AND LIMITATIONS OF VBP AND EPR

Both ERP and VBP have advantages and limitations. In this section, we discuss the advantages and limitations of both schemes and present these side by side. Tables 9.1 and 9.2 respectively outline the advantages and limitations respectively.

9.1. Conceptual framework

Value-Based Pricing is associated with a robust conceptual/theoretical framework relating to efficiency in resource allocation. Two definitions of efficiency can apply in this context: the first is *allocative* efficiency⁸⁴, whereas the second is *technical* efficiency. Allocative efficiency implies that in the context of introducing a new technology everyone benefits, whereas technical efficiency seeks to maximize benefit, which can mean that some may lose out. To the extent that the principle of cost effectiveness is underpinned by the concept of technical efficiency, VBP can be associated with benefits for most, but losses for some. This is an element that requires adaptation of the (technical) efficiency framework so that equity, disease severity and the principle of humanity can underscore efficiency arguments.

Contrary to the robust conceptual framework underpinning VBP, External Price Referencing is often criticized not to adhere to a particular conceptual, analytical or theoretical framework. Rather, it relies on a set of seemingly “arbitrary” criteria, relating to the basket of countries, the price taken from that basket, and the intensity of revisions, among others. Yet, the rationale appears to be clear in terms of policy objectives: first, to ensure that countries applying EPR do not overpay for new medicines in relation to (some of) their neighbours particularly in an environment characterized by considerable uncertainty in relation to value; and, second, by aiming to achieve reasonable prices, in relation to their ability to pay, to contribute towards the principle of *macroeconomic* efficiency (overall budget constraint) by means of exerting pressure on price. The above underpin country selection, price taken from the basket and frequency of revisions.

9.2. Capacity to inform decision-making

9.2.1. Value-Based Pricing

VBP clearly has a significant potential to inform rational decision-making in the sense that it evaluates (health) benefits and – in the majority of cases – costs by

⁸⁴ Also known as Pareto optimality.

employing often complex methodologies and drawing on scientific evidence generated by robust designs. Where the assessment of (relative) costs and benefits is subject to uncertainty complex modelling is used to assess relative benefits.

Yet, at a fundamental level the techniques embodied in VBP, as it is currently applied in the HTAs in Member States such as the UK, the Netherlands, Poland, Sweden, Hungary, the Baltic States, Finland and elsewhere, do not always provide robust answers to a number of concerns. There remain a range of methodological and allied limitations relating to the practical application of VBP for medicines, as well as other – higher level – conceptual limitations. They include:

First, the **determination of affordability**: Affordability thresholds are often set in an arbitrary manner. Associated with this there is the fact that in other areas (like maintaining public order and providing care for people considered a danger to the public) such thresholds may be very higher or lower than those used by NICE in relation to the Quality Adjusted Life Year (QALY), or not be taken into account of at all in public policy making and service and product purchasing processes;

Second, the **relative lack of evaluation of additional health benefits**: There may be a lack of evaluation of the additional health related benefits of items such as new medicines for conditions such as dementia. In this instance, models employed by certain payers may not take into account the gains that may be enjoyed by informal carers and family members as a result of better symptom or disease management. Ultimately, the perspective from which the assessment is conducted influences the extent to which these additional health benefits can be included.

Third, **dynamic efficiency and future innovation**: VBP is also not presently charged with evaluating the long-term external benefits that will in time be generating as a result of, for instance, an improved understanding of cancer genomics and/or the provision of high quality research in biomedical sciences. Although it may in this context be argued that other agencies, such as the newly established Office for Life Sciences (OLS) in the UK, or Sitra in Finland or Vinnova in Sweden, may be better placed to take on an industry ‘sponsorship’ role, the arguable reality is that if health systems as the single purchasers of prescription medicines are only willing to pay medicine prices based on immediate individual patient level gains, that will be the *de facto* driver of the overall national system.

Fourth, there are problems associated with the **use of aggregated data** in circumstances where there is substantial variance within populations, and a lack of appropriate provision for identifying and meeting humanely the needs of people who can reasonably be regarded as ‘exceptional cases’.

Fifth, there are **lags between best practice developments and the publication of supportive evidence**. In the oncology context such problems may become apparent because although the effectiveness of anti-cancer drugs is normally first demonstrable in late stage disease treatment, their optimally effective use may be at an earlier stage. If because of an unduly crude application of VBP principles clinically informed logical extrapolations cannot be used in a timely manner to justify new treatment applications, health outcomes can on occasion be impaired.

Sixth, there are **inherent challenges of measuring and comparing utilities** of different types, both within the health sphere and between that and other areas. The possibly special nature of end of life care illustrates this area of concern.

9.2.2. External Price Referencing

EPR by design serves the objectives of decision-making based on pricing information received. However, most EPR schemes are often supplemented with other important information, e.g. clinical and cost-effective evidence, which form part of the submission dossier and, consequently, assist in the decision-making process. EPR has often been criticized as overly simplistic, nevertheless, it is defensible in smaller countries with limited resources to pursue their own regulation and value assessment.

Despite the above, there is an element of “path dependency” characterizing EPR systems in the sense that the information that informs the decision-making process and the way it is arrived at, influence, to a certain degree the final outcome. This is probably more inherent in EPR than it is in VBP. For instance, the type of data required from a particular scheme influence price levels, e.g. country selection, available prices from across the country basket, revision dates. To that end, EPR seems to be relying a lot on external factors influencing pricing (and reimbursement) decisions, without necessarily paying due attention to factors intrinsic to the health care system in which it operates. In addition, the intensity of information required often makes EPR schemes administratively complex.

9.3. Processes

Both VBP and EPR rely on robust processes to inform pricing and reimbursement decisions. Their relative merits are outlined in the following sub-sections.

9.3.1. Value-Based Pricing

VBP relies on a clear analytical framework enabling decisions to be made on health benefits and costs via well-established processes. Indeed, there are elaborate

processes in place outlining the role of the agency that assesses value and whether it is regulatory or advisory, its remit, the type of technologies it appraises and its position within the health care system. Specific issues relating to processes include: (a) assessment procedures and methods (topic selection, data and evidence requirements, analytical design, assessment methods, incl. comparators and dealing with uncertainty); (b) application of evidence to decision-making esp. criteria and timing of assessments; (c) stakeholder involvement: clear provisions for stakeholder engagement in the process; (d) appeals process: a framework to enable stakeholders to appeal against decisions and the independence of that process; (e) a framework exists on Evidence dissemination and implementation.

While elaborate processes have been set up to ensure transparency, clarity, visibility and stability, these are not without limitations, which include: (a) poor timing, as it can take too long to fully appraise the evidence, although this varies and other processes can be in place to ensure appraisal occurs in a timely manner; (b) methods, which from a comparative perspective, are very diverse and this can lead to different decisions for the same treatment (cross-border post-code lottery) across countries and agencies; (c) a decision-making process that allows “value judgements” in decision-making rather than enabling a clear cut decision of whether or not to cover a particular technology; despite the information intensity required, decisions are still based on individual value judgements, although of course, guidance is given to that effect; (d) path dependence, in the sense that decisions depend on inputs and assumptions around them; (e) willingness to pay (WTP), whereby WTP thresholds not transparently set, while the way they are interpreted can vary across settings and can refuse reimbursement based on unclear threshold or unclear interpretation of value; (f) there is no clear framework around affordability and this is usually outside the remit of the Agency appraising the evidence, unless an explicit threshold is used; (g) monitoring of recommendations made usually lies outside the remit of agency conducting value assessment, but could be internalised in order to have better compliance of stakeholders; and (h) the stakeholder involvement is often criticised as unfair among certain stakeholder communities in the sense that it places a great deal of burden and exceeds their capacity to respond adequately.

9.3.2. External Price Referencing

Countries using EPR as the main method of pricing pharmaceuticals have developed detailed, elaborate and robust structures and processes enabling them to undertake the task of pricing based on international prices, informing reimbursement through the same process and examining, among other things, which products require flexibility in the above assessments and on what basis. Important aspects of this

include: (a) the legal framework, which is essential to underwrite transparency; (b) the pricing process, which needs to be in place in order to select a basket of prices to inform prices in the country in question, including the type of prices that will be considered, and whether net prices can be included if not widely available; (c) the reimbursement process, whereby a process needs to be in place to establish product reimbursement; (d) the frequency of price revisions at the request of various stakeholders – both for pricing and for reimbursement; (e) an appeals process, which is important in the overall structure of the system and enable interested parties to have a safeguard against decisions made by the competent authority; (f) procedures for deviating from existing and regulations on pricing and/or reimbursement; these may exist in order to account for cases of medicines which depart from “clear cut” paradigms; (g) procedures dealing with new products with no apparent comparators or in a new therapy class, in which case, provisions are made to review additional clinical or other information that can be instrumental in determining a fair price; (h) dealing with external shocks, e.g. exchange rate depreciations/appreciations and overall volatility; and (i) the frequency of price revisions at the request of various stakeholders – both for pricing and for reimbursement.

It is widely perceived that EPR systems are fairly straightforward, are not administratively complex and do not require a lot of information, since much of what is required is either available at arms’ length, or can be supplied by the manufacturer. Nevertheless, the evidence suggests the opposite: it looks as though EPR systems can be quite complicated and resource intensive in the interests of transparency and stability. EPR systems can be criticized for path dependence (i.e. what inputs feed the system in terms of countries and prices, pretty much determine the outcome) as well as exposure to external shocks, such as excess volatility in exchange rates used.

9.4.Prices, launch prices, launch sequencing and delays

9.4.1. Value-Based Pricing

Across agencies, assessments of value tend to rely on similar studies and evidence in order to inform pricing decisions, but are usually limited by evidence that does not sufficiently address questions of impact on clinical effectiveness, quality-of-life, adverse events or costs, relative to pertinent comparators. Because of this similar core body of evidence, there tends to be reasonable convergence of reimbursement decisions among agencies, although divergence has also been observed (and is increasingly the case) in a number of cases relating to expensive treatments. Divergent outcomes are often the result of varying interpretations in evidence, and

seemingly different degrees of willingness to undertake sub-group analysis, make indirect comparisons, negotiate pricing or innovative reimbursement schemes, or rely on expert opinion, as opposed to outright rejection if adequate data was not available.

This differing willingness to use less-than-ideal types of evidence demonstrates varied responses to the challenging trade-off between using the best available—though incomplete—evidence or simply turning away reimbursement for potentially beneficial (and cost-effective) drugs due to lack of strong evidence. There is no straightforward solution, nor a broad consensus among these agencies: some are likely to reject an application if inadequate evidence was submitted, but also engaged in pricing negotiations to reach positive outcomes; others tend to navigate uncertainty and poor evidence by using indirect comparisons and expert opinion as necessary, along with the development of risk-sharing agreements; others still tend to encourage price negotiations and the development of risk-sharing agreements to overcome informational uncertainty.

Special considerations relating to the life-extending role of specific treatments such as orphan and anti-cancer drugs, as well as the lack of alternative therapies for many conditions (esp. certain types of cancer), tend to favourably impact reimbursement decisions across agencies, and in certain cases, overruled otherwise unacceptable ICERs. Additional factors, such as patient perspectives, market conditions, or the pragmatics of drug use relating to wastage also seem to affect appraisal decisions in a variety of ways.

While some level of uncertainty will always be present, the concern regarding the quality of evidence may be mitigated in part by more transparent guidelines for manufacturers as to the types of data needed by HTA agencies to make rapid, clear decisions on value (subject to constraints present at the time of the value assessment), or by stipulating that certain data requirements must be available at the time of marketing authorisation that fulfil these value assessment needs. This pressure to develop more relevant evidence would potentially improve the overall process of value assessment and expedite the approval of truly clinically- and cost-effective therapies. Unfortunately, the lag between evidence generation and its subsequent use in VBP may still result in data gaps if the methods, data requirements, or market presence or clinical use of relevant comparators change substantially during this lag period.

Clearly clinical- and/or cost-effectiveness drives pricing decisions based on value assessments. In settings where cost-effectiveness is used additional elements or processes can inform pricing decisions. It is, therefore, important to consider the impact of factors such as disease severity, unmet medical need in the indication as

well as human dignity. Put together, these factors can alter and, often, enhance strict cost-effectiveness paradigms by introducing elements of flexibility in its interpretation. This can apply to a variety of treatments including orphans and end-of-life therapies.

Similar situations arise in value assessments from a societal perspective, where stakeholders are in a position to submit information on the new treatment's usefulness not only for the health sector but also for a number of other areas, which were hitherto excluded from impact assessment, such as indirect cost and impact of the treatment on sickness absenteeism, among others.

Because extensive trials have not usually been required for marketing authorisation, historically there has been little incentive for manufacturers to continue trials beyond the point at which safety and minimal efficacy have been demonstrated. Thus the rising prevalence and impact of VBP in the reimbursement process may, through profit-maximising behaviour, encourage pharmaceutical manufacturers to design trials with more appropriate comparators based on current clinical practice, and adopt earlier and more rigorous internal analyses of the predicted economic consequences of the drugs in development to aid "go-no-go" decisions, and to incorporate these economic considerations into net-present-value calculations during the research and development process.

Such considerations would also help pharmaceutical manufacturers set prices at a level more likely to result in fast approvals for reimbursement – and would be more palatable to payers. In short, it is in the manufacturer's advantage in most cases to have the most thorough evidence with appropriate comparators and, because formal VBP processes are still rather new, it may just take some time for the industry to begin developing evidence of this nature.

This generation of evidence by the supply side may be encouraged by increasing adoption of risk-sharing schemes through partnership of healthcare payers and manufacturers, in order to provide early access to innovative therapies, develop robust data, and partially insulate the payer from undue health outcome or financial risk. However, such schemes are not without complications, and must be balanced against the risks of expediting marketing approval. Ultimately, the pragmatics of such schemes will have to be further developed before they can be widely applied to the many new compounds entering the market.

More broadly, and drawing on the sample of assessments examined here suggests that, despite their different locales and contexts, the different HTA agencies generally seek the same types of information regarding clinical and economic consequences of new therapeutics, and encounter the same obstacles during the assessment and appraisal processes. Thus, the formal development of standardised

methodologies for HTA, international harmonisation of data requirements for new therapeutics, and sharing of HTA expertise and results across countries would further develop the field, reduce duplicative effort in collecting and analysing HTA-relevant data, and help address the data gaps that currently persist. While it would be difficult—and likely undesirable and impractical—to create a central HTA agency that would render binding reimbursement decisions, given the differing national agendas and values which impact upon final appraisal decisions (even within an international country bloc such as the European Union), striving for harmonised methods, data collection, and evidence repositories could streamline the HTA process and allow for more complete evidence-based assessments across the health technology spectrum. This would reduce the cross-border post-code lottery that seems to arise particularly in cases where the evidence appears controversial and is viewed differently by different agencies.

Finally, based on a limited number of cases analysed in the context of this report, it appears that the level of innovation, as defined by the payer, is rewarded accordingly. New treatments perceived to be significant innovations receive a substantial price premium in relation to comparators, moderate innovations receive a lower price premium, and those perceived as not adding to existing treatment paradigms achieve –at best– price parity in relation to existing treatments/comparators. Prices of new treatments show little effect of being affected downwards by the outcome of the appraisal process, even if that process results in a negative recommendation in one or more jurisdiction(s), although, as was pointed out during interviews, it could well be the case that pricing decisions had already been shaped prior to the appraisal process, when decisions would need to have been made in connection with comparators that would need to be used in each jurisdiction (and which differ depending on the jurisdiction).

Given the evident disparity in time lapse between MA and HTA recommendation, the diverse criteria (and narrow sub-groups) dictating reimbursement eligibility and inconsistencies in appraisal outcomes across countries, there is a strong indication that an international “postcode” lottery exists in terms of access to medicines. Not only does this have broad repercussions for cost, media attention and public opinion, it also highlights an area of ongoing debate regarding whether citizens with conditions for which treatment is not reimbursed (or not yet assessed) in their home country should be refunded (by their national health system) for seeking care in other EU Member States, or in fact, seek treatment elsewhere, where it may be available.

9.4.2. External Price Referencing

There are a number of consequences of using EPR. First, some evidence points to market launch delays in low-price countries. Second, EPR might produce convergence in international prices because manufacturers could try to impose a single price worldwide and be unwilling to offer lower prices to any country, especially those that are or might be used as a reference by other countries. Consequently, countries that in the past were able to obtain relatively lower prices might not be able to do so in the future. Although the literature provides some evidence on the convergence of international prices of new drugs and marketing delays in low-price countries, it is difficult to assess how far this phenomenon may be due to the expected spillover effects of EPR, to the possibility of parallel trade, or to the fact that these markets are less attractive to suppliers - a set of factors that are often simultaneously present in some countries.

The effects of EPR depend on the specific local details of the practice: number and characteristics of the reference countries, how the national target price is calculated or derived from the prices of the reference countries (minimum price, average, median), and on whether the computed reference price is strictly enforced or simply used as a relatively flexible benchmark. Evidence compiled from meetings with stakeholders and previous experience, suggest that the theoretical reference price often does not become the actual market price, especially in the case of drugs that enjoy a monopolistic position.

An important issue to consider in relation to EPR is whether it has any unintended effects beyond its immediate impact on drug prices, particularly negative effects on the various stakeholders in the country applying it or on other countries. In analysing the effects of EPR as well as other forms of price regulation, two perspectives must be considered: the individual country perspective and the global perspective. Drug regulatory policies are usually a national responsibility, although there are clear trends towards globalisation of some of its aspects, particularly on efficacy and safety standards for market authorisation and intellectual property rights. The pharmaceutical market's globalisation, however, spreads the effects of national P&R regulations well beyond the regulating a country's own national boundaries.

A further unintended consequence of the way EPR operates at times relates to the issue of price revisions and the use of exchange rates for that purpose. In environments where multiple currencies are used and in the presence of exchange rate volatility, the latter can have a significant adverse effect on prices denominated in local currencies, far and beyond what is reflected in actual price movements. If price revisions need to take place and exchange rates be used, then stability and

predictability could be maintained if longer period averages or moving averages are used.

Some of the potential effects of EPR might be the result of strategies adopted by the affected stakeholders, mainly manufacturers, in response to new conditions created by the widespread use of EPR. When a large number of countries began using ERP, companies became aware of spillover effects that stemmed from prices that were being set in a given country. They reacted by designing and implementing appropriate international pricing and marketing strategies to counteract the effects of EPR and maximise global profits under the new conditions. These strategies might affect not only the countries that apply EPR, but others as well, especially those used as reference countries by the former.

The main strategies adopted by manufacturers are, first, trying to set a single international price for their products; second, delaying the launch or even giving up the marketing of new products in countries that try to attain the lowest prices, especially if they are small markets, where the opportunity cost of the strategy is smaller, and if the countries are referenced by other countries with larger markets; and, third, “gaming” the system in order to minimise the likelihood of spillover effects caused by international price differences. Such gaming can take place in a number of ways; for example, by keeping high list prices in the countries used as reference while granting confidential⁸⁵ rebates or discounts to them; i.e. offering a discount or rebate under the condition that it will not be publicised. Companies might also provide a larger number of units than those indicated in the contract, in exchange for maintaining the list price. All these strategies provide manufacturers with a degree of flexibility in satisfying requests for lower prices from country regulators and payers without compromising prices in other countries that take the former as a reference.

EPR is not only distorted by the above strategies, but also by national or regional policies and regulations that affect final prices. Some examples include:

1. the use of payback⁸⁶ as a mechanism through which manufacturers previously agree to return money to public institutions in the form of annual lump-sums ;

⁸⁵ In Germany, confidential discounts between insurers and pharmaceutical companies are very common.

⁸⁶ Payback is a risk-sharing mechanism that requires manufacturers (either individually or collectively, e.g. via their industry association) to return a certain part of their “excess” revenue to a purchaser if sales exceed a previously determined target. This mechanism is used in Hungary, France, Italy, among others.

2. the general discount system used in countries such as Spain (one of the most referenced countries) where manufacturers have to return 1, 2, or 3% of their sales to the Ministry of Health;
3. the profit control system in the UK, whereby manufacturers set the price freely, but when the profit margin from sales of branded medicines to the NHS, exceeds the level granted to the company according to predefined criteria (mainly, involvement in research activities), they have the option of giving a payback or reducing the price the following year;
4. Different risk-sharing agreements (for example, Velcade -bortezomib- in the UK), where the NHS does not have to pay for medicines that do not cure (“outcome guarantee” agreement), but the price listed is the one that applies when medicine works for 100% of the patients.

These policy practices are not directly attributable to EPR, but are certainly more likely to be agreed and accepted as cost-containment policies by the industry since they only affect the country concerned and do not produce spillover effects on other countries via ERP.

9.5.Coverage of and access to new therapies

9.5.1. Value-Based Pricing

The implementation of VBP can, on a number of occasions lead to access problems, although, in principle, a number of safeguards exist for these to be avoided. If the Agency performing value assessments has a mandate to implement its decisions/recommendations, then in the case of “approval” of individual technologies access should be unrestricted. There have been problems of interpretation of this particular policy statement as well as problems of access that have materialised as a result and required clarity. In case the competent Agency does not have a mandate to implement its decisions/recommendations, access problems can indeed arise, particularly in circumstances where the payer is at arms’ length from the Agency, as is the case in some decentralised health care systems. This gap can be bridged either through the competent Agency receiving a mandate or by allowing strong participation of the payer community on the competent Agency’s Board with a view to arriving at decisions combining clinical and/or cost effectiveness and affordability.

For new – and often expensive - technologies approval with criteria and approval with a risk sharing scheme in place can indeed give rise to access problems for the part of the indication population(s) that are not covered, but, on the other hand, both risk sharing and coverage criteria provide the rationale for coverage of such

technologies for certain sub-groups. Enforcing and monitoring these agreements – particularly risk sharing – can be resource-intensive and complex and is usually outside the remit of the agency performing value assessments.

It is increasingly the case that the value of same technology is perceived differently across settings; there have been some, but, alarmingly, increasing phenomena of the same technology being approved in one setting, approved with restrictions in another and rejected in a third. This highlights that the levers decision-makers use to assess value differ significantly across settings, despite the fact that the body of evidence is usually the same. Of course, this is causing distress and confusion to patients particularly in therapeutic areas such as cancer, which are politically sensitive and requires some attention and, possibly, collaboration, by decision-makers.

Finally, value assessments, depending on how they are conducted and what evidence feeds into them, can be time consuming and can lead to significant delays in access, often in excess of one year. Arms' length value assessments usually require significant input, which is often produced and provided independently and is subsequently compared and contrasted with that produced by manufacturers. Clearly, there are significant tradeoffs at this juncture, notably, robustness in evidence base production leading to informed decisions versus timely coverage and access. Rapid reviews can take some of this pressure off combined with ex-post value assessments.

9.5.2. External Price Referencing

EPR does not necessarily restrict access once agreement has been reached but can lead to delays in launch, which, in itself can cause access problems. It can also be the case that manufacturers will not launch in a particular EPR market if they feel that the price they receive from that market is prohibitively low and can threaten their global pricing strategy.

Expensive products may be subject to the usual arrangements via prices collected across a range of countries, but, depending on the value they bring, such products can be treated in a slightly different way, notably, be given the opportunity to prove their value in the local context by enabling local clinical studies, whilst in the meantime, a temporary reimbursement status is granted.

Finally, it is possible that EPR can be combined with additional policy measures for reimbursement purposes in order to deliver a lower price for a particular volume level. It can be further combined with paybacks, should this volume be exceeded.

This is one form of risk-sharing that gives the payer the security of capped expenditure in a particular therapeutic class or across the board.

9.6. Assessment of value

9.6.1. Value-Based Pricing

Ex-ante evaluation provides manufacturers with the incentive to invest in gathering the evidence that the health service requires to approve and encourage innovation in areas/therapies where a substantial clinical benefit can be demonstrated. One drawback, however, of the use of ex-ante as opposed to ex-post evidence is that there will be uncertainty surrounding the clinical-cost-effectiveness of the drug outside the RCT setting at the time of launch. Although further ex-post reviews can also be suggested, these may be difficult to ensure as once a pharmaceutical product is approved, the incentive to carry out further trials is diminished and may even be deemed unethical. Nonetheless, a balance between the value of the economic information surrounding the drug and the value of availability of the drug to patients needs to be achieved (as is often emphasised in HTA).

On the other hand, both payers and manufacturers seem to believe that ex-post evidence is as crucial as ex-ante evidence in proving the value of new treatments. There needs to be acceptance of data obtained in naturalistic settings and methodologies on how best to extract value from such data need to be strengthened but some agencies admit they do not provide any (substantive) guidance to manufacturers on methods, process and likely outcomes. Indeed, further reflection and consultation are needed to determine criteria and processes for such appraisals to take place. Overall, evidence prior to the launch of a new product is not always available and there may be significant data limitations and concomitant uncertainty. Ex-post assessments may prove instrumental in many cases in determining product value for health services, patients and society, but criteria, methods and processes need to be set up as to which products should undergo these, together with arrangements allowing access to patients in the meantime. An ex-ante price premium in the case of ex-post assessments would provide a signal to the innovator of the willingness by the payer to reward high risk-taking. Equally, flexibility in pricing arrangements based on the quality of the available evidence should be a highly desirable feature of VBP in that prices could be adjusted downwards as well as upwards depending on the emerging evidence.

Criteria and metrics from a societal perspective should be considered when assessing drug value and setting pricing/reimbursement levels and ought to include all elements of value. When they do assess value though, pricing/reimbursement

systems have frequently chosen to focus on value almost exclusively from the healthcare system (payer) point of view rather than the broader societal or patient/physician perspective with few notable exceptions. New standards and tools for more accurately and consistently assessing the more challenging metrics may need to be developed. Patient groups, for instance, strongly believe that some of the quality of life elicitation tools that national agencies use currently do not capture preferences appropriately, e.g. capturing fatigue in the EQ5D, or initiating patient reporting outcomes.

Within the above context, payers (whether health systems or health insurers), providers, patients and manufacturers must work together, not antagonistically, to establish pilots to investigate new pragmatic ways of eliciting value taking into consideration inputs from across the spectrum of the stakeholder community. Some agencies have already established procedures whereby clinical and patient views are heard and form part of the value assessment process. It is not uncommon to have a well-established programme that provides guidance on patients and patient groups on the type of evidence required in this context and assisting them in fulfilling this requirement. Against this background, patients widely applaud this opportunity, but, are nevertheless faced with the daunting task of presenting “evidence” on their perception of the disease and the new treatment, before a highly specialized audience. In order to face the challenges, an inclusive process for defining pragmatic, effective changes to drug approval and pricing approaches must be developed, ensuring these are transparent to all as well as ensure that stakeholder participation is meaningful. Where appropriate, capacity building may be required to enable interested parties to participate.

A final issue that deserves greater attention is that payers continue to be of the view that manufacturers can maximise their effectiveness and increase the probability of a new drug receiving a positive recommendation by designing trials to provide more comparative data, powering trials to indicate superiority rather than only non-inferiority and structuring economic models from both a health and societal perspective, applying the agency preferred methods for discounting and quality-adjusting utility values. Manufacturers highlight that in the process of eliciting value at an early stage when a product is launched, there is a significant knowledge gap, assuming a rising knowledge curve over time and contend that in the assessment of value payers need to be flexible as the knowledge curve is continuously rising and that there is a clear trade-off between optimal knowledge base and timely introduction. If the regulatory environment is to evolve and if more complex evidence is required ex-ante, then it might be necessary to re-think intellectual property rights protection or market exclusivity periods. Patients, on the other hand, are obviously in favour of faster access, particularly for those treatments that

can have a significant therapeutic effect, however short-lived this may be, but, at the same time highlight that there is a significant discontinuity between MA requirements and HTA/VBP requirements, which needs to be debated and addressed.

9.6.2. External Price Referencing

From an EPR perspective it is clear that the potential for enabling value assessments, and, therefore, taking into consideration the value of innovation, exist. This can take place in two cases: first, with regard to *new products that do not belong to an existing therapeutic class*, then for the process of reimbursement alternative arrangements can be made other than including these into (internal) reference clusters. These arrangements include the establishment of a new therapeutic category, provided that evidence justifies this.

The second case is similar to the conundrum faced by HTA agencies in VBP relating to uncertainty. Where medical benefit is not always clearly defined from the available data, then from an EPR perspective, very expensive products can be granted temporary reimbursement only with the proviso that additional evidence is generated to prove the benefit claimed by the manufacturer. Governments and payers, including those who operate with an EPR system, are increasingly keen to have local information about health benefit, which often goes through the establishment of a local registry to elicit clinical value in a real setting.

There are also instances the operation of an EPR scheme does not take into account the value of innovation. For instance, an issue arises when EPR is combined with molecular or therapeutic price referencing, the latter being a frequently-used option setting a reference price across a range of molecules, of which at least one is patent-expired. It is likely that these two effects can be combined and can spill-over across borders. The propagation mechanism for this to take place is differences in patent term dates across countries. Despite EU-wide provisions concerning intellectual property rights protection, patent term dates are not always identical among Member States and is probably one of the unintended consequences of such differences. Under these circumstances, it is probable that the patent for a product in one country may expire earlier than in others. This would, of course, allow generics to enter in the country where the patent expires and could force the originator price to decline. This decline may trigger price adjustment in other countries if the product in question is subject to EPR provisions elsewhere.

Overall, EPR systems are not equipped to provide explicit assessments of value of new treatments, but the above evidence suggests that such assessments can take

place in particular circumstances. More broadly, if EPR fixes prices at launch only, then there may be no further impact on the value of the product along its life cycle, but, frequent adjustments do have an impact because they are usually conducted to take into account price reductions in individual components of the basket or broader adjustments therein.

9.7. Encouraging and rewarding pharmaceutical and biomedical innovation

The varying nature and emerging complexity of health technologies, in combination with limited national budgets, has resulted in tensions between delivering cost-effective health care and improving or sustaining a country's manufacturing and research base. As a result, it has become increasingly important to achieve a balance between affordable health care and the use of innovative pharmaceuticals. To that end, considering the value of a new pharmaceutical in clinical and economic terms, is as important as defining who benefits, how the technology diffuses optimally and how it is placed most appropriately in the spectrum of care.

9.7.1. Value-Based Pricing

VBP can address the above challenges by determining which technologies are ineffective versus those with value, and by defining the most appropriate indications for use of the technology (Drummond, 2001). VBP can also serve to validate a new technology and define its role in a health care system. To that end, it provides important benefits by enabling governments to make decisions driven by value, which concurrently supports innovation, and garners patients and physicians with the information needed to make the best treatment choices.

However, the effectiveness of VBP in achieving the above benefits, particularly in terms of encouraging innovation, seems to depend on properly performed assessments and the appropriate implementation and use of subsequent recommendations. VBP can encourage innovation if the assessments are properly conducted, consider a wide range of costs and benefits associated with a new technology (ie adopt a societal perspective), rather than focus solely on acquisition costs. The utility of VBP in encouraging innovation and value-added health care also depends on the assessment process, including when and how a review is performed, the chosen comparators and the resulting decision-making procedures, including implementation.

Whereas from a dynamic efficiency perspective, it is not clear how the currently implemented VBP frameworks incentivise future R&D, from a static efficiency perspective, the requirements placed on data available at launch are substantial (but

not completely insurmountable). Yet, as has been pointed out by several HTA bodies, processes and pathways are available to improve the flow of information, and the quantity and quality of the data and information.

Whereas approaches to VBP reviewed in the context of this report encompass some of the above elements, in practice, it is the case that a number of these elements remain aspirational in most cases, including the perspective of value assessment, and the comparators used from an *ex-ante* and an *ex-post* perspective. More fundamentally, the process of value assessment in relation to encouragement of innovation raises the question of whether changes may need to take place to enable better data to become available at launch. This is clearly an issue that may deserve further exploration and discussion in the very near future, between payers and HTA bodies, regulators (eg EMA) and other stakeholders (manufacturers and patients) and has been raised on several occasions in discussions with key stakeholders in the context of writing this report.⁸⁷

9.7.2. External Price Referencing

External price referencing in itself is not a methodology that explicitly encourages and rewards (future) innovation, or that by design serves this particular objective and the process often leads to a price low from the selected basket of countries. Current innovation may be rewarded in the context of the selected country prices within the basket and if the regulator allows flexibility for the manufacturer to prove its case in particular situations, where high uncertainty does not allow optimal decisions to be taken. Within the context of EPR future innovation can only be encouraged by the approach undertaken by the regulator and the extent to which additional policies exist to foster and encourage R&D investment.

9.7.3. Policies encouraging innovation

“Stimulating, steering and facilitating innovation and innovative research is a proactive policy role. The aim is to create a sustainable R&D environment whereby the likelihood that valuable pharmaceutical innovation reaches the market place is maximised.”⁸⁸ Several countries that implement VBP and/or EPR do have their own innovation policies providing a mix of financial and non-financial incentives directly or indirectly to manufacturers to locate and conduct R&D activities among others.

⁸⁷ This has been raised by several patient groups, manufacturers and their associations and has been recognised by senior executives of the European Medicines Agency (EMA) and some HTA bodies. It has also been raised in discussion with EUNetHTA.

⁸⁸ Belgian Presidency of the EU (2010). “A call to make valuable innovative medicines accessible in the European Union.” Recommendations for a coordinated action to stimulate, measure and valorise pharmaceutical innovation; 2 July.

Implicit in this is the fact that encouraging innovation passes through pricing and reimbursement as well as a wider set of issues underpinning the quality of the science base, research priorities that can create synergies between public and private R&D, and research funding from both the public and the private sector.

9.8. Opportunities for gaming

Despite the relative advantages and limitations of VBP and EPR, they both have a common similarity, namely they present opportunities for “gaming” to manufacturers. These are the result of “regulating” the market, either explicitly (e.g. through the introduction of a set of rules, as is the case is EPR), or implicitly (e.g. by requiring that certain processes are adhered to, as is the case in some elements of VBP).

9.8.1. Value-Based Pricing

Under VBP, such opportunities manifest themselves in (a) explicit thresholds, (b) comparator choice and product positioning, and (c) risk sharing. In the case of explicit thresholds, manufacturers have an obvious incentive to price up to the threshold provided the product in question can potentially justify it. The choice of comparator is very tricky indeed and is influenced, in part, by increasing calls for payers to consider a generic (if this exists) as the most appropriate comparator. In this context, manufacturers will do their best to avoid a genericised molecule as a comparator, even if this means positioning their product as a second or third line therapy. In this case, the comparator is usually an in-patent medicine, the market is smaller and, as a result, the likely payoffs are higher. Finally, in the case of risk sharing, although manufacturers have reservations and fear that such schemes will become the standard for all new drugs, their pursuit is usually associated with maintaining the originally applied price.

9.8.2. External Price Referencing

EPR offers significant opportunities for “gaming” to manufacturers. It can become an incentive for manufacturers to adopt international pricing strategies that, in the end, may have a negative impact on individual country prices and unexpected consequences in countries applying such policies. The main alleged negative effects can be: 1) higher prices in lower income countries that in the absence of ERP policies might benefit from lower prices; and 2) delays in launching new products, or, indeed, no launch of certain products in low price countries fearing spread of their prices more widely. This was made evident in a recent European Commission

report that asked companies to indicate which countries they preferred to use for launching new drugs. Companies preferred to initiate their product launches in countries with free prices (United Kingdom, Germany, Sweden). In contrast, countries with smaller markets, such as Cyprus or Malta, or with lower disposable income, such as Poland, Bulgaria, Lithuania, Latvia, Estonia, Hungary and Romania, are mentioned last. The above have implications for the amplitude and extent of parallel trade. In an environment where opportunities for arbitrage are propagated by (significant) cross-border price differences, any reduction in these works to the manufacturer's benefit, but is unclear whether overall welfare increases as a result.

Table 9.8.1: Comparative presentation of the identified advantages of VBP and EPR

Value-Based Pricing	External Price Referencing
<p style="text-align: center;">Conceptual framework</p> <p>VBP rests on the economic framework provided by economic efficiency (Pareto optimality vs technical efficiency) in resource allocation</p>	<p style="text-align: center;">Conceptual framework</p> <p>No visible conceptual framework outlining choice or size of basket; relies on selection of countries with comparable systems and similar levels of development</p>
<p style="text-align: center;">Capacity to inform decision-making</p> <p>Significant potential to inform rational decision-making by drawing on robust scientific evidence and by comparing the relative benefits (and costs) of different technologies over time, whilst at the same time having the tools to address uncertainty</p>	<p style="text-align: center;">Capacity to inform decision-making</p> <p>Serves objectives of decision-making based on pricing information received; most often supplemented with other important information, e.g. clinical evidence, which form part of the submission and, subsequently, decision-making process</p>
<p style="text-align: center;">Processes</p> <ul style="list-style-type: none"> • Clear analytical framework enabling decisions to be made on health benefits (and costs) • Elaborate processes in place outlining role of agency that assesses value, its remit, the type of technologies it appraises and its position within the health care system. • Assessment procedures and methods (topic selection, data and evidence requirements, analytical design, assessment methods, incl. comparators and dealing with uncertainty) • Application of evidence to decision-making esp. criteria and timing of assessments • Stakeholder involvement: clear provisions for stakeholder engagement in the process • Appeals process: a framework exists to enable stakeholders to appeal against decisions • A framework exists on Evidence dissemination and implementation 	<p style="text-align: center;">Processes</p> <ul style="list-style-type: none"> • Legal framework: In the interests of transparency, the process of pricing and reimbursement regulation is described in legislation • Pricing process: where one needs to have a process in place in order to select a basket of prices to inform the pricing process • Reimbursement process: whereby a process needs to be in place to establish product reimbursement • Prices taken: only published or publicly available to ensure transparency • Appeals process: exists to appeal against decisions • Procedures for deviating from the above rules and regulations • Procedures dealing with new products with no apparent comparators or in a new therapy class • Dealing with expensive products, uncertainty and poor evidence at launch

Pricing	Pricing
<p>Prices and pricing are driven/informed by a variety of factors, enabling informed decisions to be made:</p> <ul style="list-style-type: none"> • Clinical information: this relates to the majority of clinical trial evidence produced by the manufacturer and is supplemented by the new treatment’s safety and tolerability profile; while this evidence is available across settings, value assessments in different settings give more weight to some versus other pieces of clinical/safety evidence and/or clinical endpoints • Cost information: a variety of costs are taken into account, usually from a health system perspective; in cases where value assessment is only related to the new treatment’s clinical profile, a price negotiation can ensue • Health related quality of life (QoL): quality of life data, based on validated instruments, is incorporated in value assessments to enable this aspect of value to be captured • Contact with agency: in order to ensure that the appropriate evidence is produced, most agencies welcome early contact to discuss and/or review data and information and outline their own requirements to manufacturers • Explicit threshold: where it exists, it sets the limits for payers and provides the “revealed” willingness to pay from a payer perspective • Perspective: if a societal perspective is followed, then this allows a broader inclusion of costs and benefits • Launch prices and launch sequencing: usually driven by comparators; choice of stage of the disease (1st line, 2nd line, etc) is critical in (a) selecting appropriate comparator and, as a result (b) informing price • Risk sharing: provides opportunity to 	<ul style="list-style-type: none"> • Simplicity: Thought to comprise a simple and straightforward set of rules • Primarily aiming at macroeconomic efficiency (cost control); this objective drives selection of basket of countries • Path dependence: Price depends wholly on the basket of countries and chosen criteria (e.g. average, lowest, or average of the lowest being selected as the price) • Feasibility: Its implementation is feasible when resources are relatively limited and it provides quick information to regulators and other policy makers. • Transparency: available (list) rather than rebated prices are included

<p>enable access at requested price, if evidence supports this for some sub-groups</p>	
<p style="text-align: center;">Coverage and access</p> <ul style="list-style-type: none"> • Agency performing VBP has mandate: in this case there is a requirement by the system to implement recommendations, whether these are positive, positive with criteria, positive with RS agreements, or negative • Uptake: Early stage value assessment may encourage uptake of new medicines (reflecting increased uptake after positive NICE recommendations), benefiting all stakeholders. • Risk sharing: provides the rationale for inclusion of costly technologies for sub-groups who the evidence suggests can benefit more. 	<p style="text-align: center;">Coverage and access</p> <ul style="list-style-type: none"> • Access: does not per se restrict access once agreement has been reached but can lead to delays in launch, which, in itself can cause access problems
<p style="text-align: center;">Assessment of value</p> <ul style="list-style-type: none"> • Ex-ante assessment <ul style="list-style-type: none"> • Refuses reimbursement for new substances not cost effective; can be combined with risk sharing • Gives better bargaining power for payers • Proof of early stage cost effectiveness assessment may encourage uptake of new medicines benefiting both patients and companies. • Can be ideal for medicines applied in acute conditions where data is easy to collect • Ex-post assessment <ul style="list-style-type: none"> • Continues rapid access to new medicines, beneficial to patients and patients, subject to ex ante risk sharing • Preferred option by industry if combined with ex-ante price premium along with its international ramifications, until case is proven 	<p style="text-align: center;">Assessment of value</p> <ul style="list-style-type: none"> • Value assessments can take place under certain circumstances, namely <ul style="list-style-type: none"> • products that do not belong to an existing therapeutic class provided evidence to that effect is supplied • very expensive treatments for which considerable uncertainty exists and in which case, regulator might award temporary reimbursement status until value has been proven in real life settings • In most cases value assessment is not part of EPR's remit, but can be indirectly inferred by the selection of comparator countries, for instance, by including the country of origin or a balanced selection of prices also from countries that explicitly perform value assessments

<p>Encourage and reward innovation</p> <ul style="list-style-type: none"> • Can encourage innovation if value assessment takes place from societal perspective; currently limited evidence of this taking place (e.g, Sweden and, possibly the UK in the future) 	<p>Encourage and reward innovation</p> <ul style="list-style-type: none"> • Could consider reward for innovation as part of the entire process (e.g. Czech Republic), although this is not always the case in EPR systems
<p>Other</p>	<p>Other</p> <ul style="list-style-type: none"> • Information accessibility: Data easily accessible, however, quality may be questionable • Ease of use: Easy to produce as a starting point in pricing • Visibility: prices are visible across countries and provide some certainty that payers are not overpaying in relation to others

Source: The authors.

Table 9.8.2: Comparative presentation of the identified limitations of VBP and EPR

Value-Based Pricing	External Price Referencing
<p style="text-align: center;">Conceptual framework</p> <p>Despite the strong conceptual framework surrounding it, strict adherence to the principle of “technical efficiency” implies some form of rationing, ie some people may lose out</p>	<p style="text-align: center;">Conceptual framework</p> <p>No visible conceptual or theoretical framework under EPR; the principle of price “importation” applies, which can lend itself to other limitations</p>
<p style="text-align: center;">Capacity to inform decision-making</p> <p>There remain a range of methodological and allied limitations relating to the practical application of VBP, notably,</p> <ul style="list-style-type: none"> • the determination of affordability • the relative lack of evaluation of additional health benefits • the handling of dynamic efficiency and future innovation • the problems associated with the use of aggregated data • the lags between best practice developments and the publication of supportive evidence and • the inherent challenges of measuring and comparing utilities of different types 	<p style="text-align: center;">Capacity to inform decision-making</p> <ul style="list-style-type: none"> • Data difficulties: which dates (for price revisions), which prices, which drugs, which countries • Data handling: data analysis resources (human, material), time lapses between data collection and final presentation, margins, confidential agreements, differences in dosages, form, packaging.
<p style="text-align: center;">Processes</p> <ul style="list-style-type: none"> • Timing: Can take too long to fully appraise the evidence, although this varies and other processes can be in place to ensure appraisal occurs in a timely manner • Methods: from a comparative perspective there is significant disparity, which can lead to different decisions for the same treatment (cross-border post-code lottery) • Decision-making: allows value judgements in decision-making rather than enabling a clearcut decision • Path dependence: decision depends on inputs and assumptions around them • Willingness to pay (WTP): WTP thresholds not transparently set, but does influence perception of 	<p style="text-align: center;">Processes</p> <ul style="list-style-type: none"> • Administration: Can be administratively complex, particularly in relation to checking prices from a variety of countries on a regular basis • Frequency of price revisions: could be kept to a minimum for stability and predictability • External shocks: Needs to take into account external shocks, e.g. exchange rate depreciations/appreciations and overall volatility to provide a stable and predictable environment • Rebated prices: Unable to take into account or accept rebated prices • Other price effects in basket countries: Unable to account for the quantitative effect of different

<p>product and its value</p> <ul style="list-style-type: none"> • Reimbursement: may refuse reimbursement based on unclear threshold or unclear interpretation of value • Affordability: no clear framework and, usually outside the remit of the Agency appraising the evidence, unless an explicit threshold is used • Monitoring: usually lies outside the remit of agency conducting value assessment, but could be internalised • Stakeholder involvement: often criticised as unfair among certain stakeholder communities 	<p>policies (e.g. paybacks, profit returns, etc)</p>
<p style="text-align: center;">Pricing & launch sequencing</p> <p>Prices and pricing are driven/informed by a variety of factors, enabling informed decisions to be made:</p> <ul style="list-style-type: none"> • Clinical information: payers often pay attention to different parts of the new treatment's clinical and/or safety profile. In some cases, safety carries significant weight compared with efficacy, whereas in others, differences exist in the perception of primary and/or surrogate endpoints. • Cost information: a variety of costs are taken into account, usually from a health system perspective; in cases where value assessment is only related to the new treatment's clinical profile, a price negotiation can ensue • Health related quality of life (QoL): quality of life approaches have been criticised on the grounds that (a) they do not provide a comprehensive account of patient-related aspects, e.g. fatigue and (b) some of the metrics involved are methodologically imperfect • Contact with agency: while early contact with agencies is very valuable, it is often difficult to satisfy different agencies' priorities • Explicit threshold: such a threshold can be rigidly applied and, therefore, reject technologies slightly above the threshold. Also provides an incentives for manufacturers to price up to the threshold • Perspective: health system perspective is used in the majority of cases and, although it is a valid option, it frequently excludes (or displays reluctance to accept) valid cost elements • Uncertainty: uncertainty can be addressed 	<p style="text-align: center;">Pricing & launch sequencing</p> <ul style="list-style-type: none"> • Price information: is not always available. Available prices are often heterogeneous (ex-factory, retail, etc) and is not always easy to adjust them to obtain the required type of price • Transaction prices: It is often difficult to find transaction prices; the prices that countries have access to are often not real prices, but virtual list prices; rebates, discounts and clawbacks are in the majority of cases invisible and cannot be included • Availability of products: There is no conclusive evidence about the impact of this practice, although launch delays and non-availability of products (due to decisions not to launch in a particular country) seem to be likely effects • Price convergence: EPR can lead to price (international) convergence as manufacturers try to impose a single price globally and are unwilling to offer lower prices particularly if a country is to be used as a reference country • Exchange rate volatility combined with the lowest price rule can exacerbate the effects of price revisions particularly in environments of frequent price revisions and can be among the unintended consequences of EPR, leading to a race towards the bottom • Launch sequencing and delays: Encourages manipulation behaviour by pharmaceutical industry & launch sequencing: 1st marketing in higher price countries, latter or no marketing in low price countries, publication of public or

<p>with modelling; while this is a valid option for value assessments, disagreements can occur between payers and manufacturers on choice of model/perspective and assumptions made</p> <ul style="list-style-type: none"> • Launch prices and launch sequencing: in many cases, particularly if new treatment pitches to be first line therapy, generic will be the only acceptable comparator; from this perspective it provides a disincentive to manufacturer, who then positions the new treatment as a second or third line therapy 	<p>catalogue prices but not transaction prices which may be confidential; to that end, low price countries can experience significant launch delays</p> <ul style="list-style-type: none"> • EPR can be distorted in a number of circumstances by national regulatory policies which introduce invisibility of net transaction prices, e.g. payback clauses, general discount systems, “excess” profit returns under rate of return regulation, and some risk sharing schemes where the price reflects 100% of utilisation rather than a subset thereof • Knock-on effects: there can be knock-on or spillover effects from international comparisons, especially when countries revise their prices frequently and can lead to downward convergence
<p style="text-align: center;">Coverage and access</p> <ul style="list-style-type: none"> • Lack of Agency mandate: if there is no mandate the risk is that value recommendations won't be implemented • Access: may limit access to new technologies if cost of new technology is higher than the “revealed” willingness to pay • Risk-sharing: in principle good, but often difficult or cumbersome to implement and monitor • Length of review time: long value assessment process can be a barrier to access unless complemented with other measures • International differences: different agencies may place different value judgments on the same technology and based on the same body of evidence, leading to confusion and controversy among patient communities • Products not undergoing value assessments: can lead to a multi-tier system where these products are not necessarily covered by health service, despite being (potentially) available on the private market 	<p style="text-align: center;">Coverage and access</p> <ul style="list-style-type: none"> • Access: can arise in situations where manufacturers do not launch out of strategic considerations (knock-on effects in global pricing) • No launch: price achieved on the market may be prohibitively low for manufacturer to launch out of strategic reasons • Combination with other measures: can be combined with other measures such as price-volume agreements to enable access to a wider patient population
<p style="text-align: center;">Assessment of value</p> <ul style="list-style-type: none"> • Ex-ante assessment <ul style="list-style-type: none"> • Potential for lengthy negotiations between company and reimbursement agency when 	<p style="text-align: center;">Assessment of value</p> <ul style="list-style-type: none"> • Usually, EPR is a cost-minimisation tool that focuses on average or lower-end prices rather than high-end prices

<p>insufficient data available and risk sharing is produced as an option. This approach is likely most applicable in chronic conditions, paediatric applications, cancer and orphan diseases where the population base for trial is minimal and observed outcomes longitudinal.</p> <ul style="list-style-type: none"> • Shifts risk to the manufacturer as there is currently no room for ineffective therapies to be reimbursed by payer • Ex-post assessment <ul style="list-style-type: none"> • Weaker bargaining position of health insurer, as withdrawal of product from the market is a less viable threat (versus ex ante method) • Decision-making: allows value judgements in decision-making rather than enabling a clearcut decision • Path dependence: decision depends on inputs and assumptions around them • Willingness to pay (WTP): WTP thresholds not transparently set, but does influence perception of product and its value • Reimbursement: may refuse reimbursement based on unclear threshold or unclear interpretation of value 	<ul style="list-style-type: none"> • Differential patent protection schemes can have significant spillover effects across countries by combining EPR (the international dimension) with internal price referencing (the national dimension)
<p style="text-align: center;">Encourage and reward innovation</p> <ul style="list-style-type: none"> • Difficult to encourage innovation on its own; needs to have a societal perspective, flexibility in threshold interpretation, appropriate comparators avoiding low cost (generic) alternatives • Needs to be supplemented with additional incentives elsewhere in the system to fulfil objective 	<p style="text-align: center;">Encourage and reward innovation</p> <ul style="list-style-type: none"> • Not designed to serve the objective of encouraging innovation, although can be supplemented to take into account value either through the selection of countries in the basket, (e.g. high price countries) or by considering value in light of uncertainty or both • Needs to be supplemented with additional incentives elsewhere in the system to fulfil objective
<p style="text-align: center;">Other</p> <ul style="list-style-type: none"> • Length of time: Potential for lengthy negotiations between company and reimbursement agency when insufficient data available and risk sharing is produced as an option. • Product selection: VBP is often most applicable in chronic conditions, paediatric applications, 	<p style="text-align: center;">Other</p> <ul style="list-style-type: none"> • Can have a significant global effect • Simplicity: originally thought to be administratively simple with minimal information required, minimal resources needed, and quick outputs, but in practice can require significant resources and be information-

<p>cancer and orphan diseases where the population base for trial is minimal and observed outcomes longitudinal; this depends on type of agency and whether it is “integrated” or at “arms’ length”</p> <ul style="list-style-type: none"> • Data and analysis issues: which data (ex ante, ex post), whose data, longitudinal data, thresholds, measurement of QALY, perspective used • Affordability: no clear framework and, usually outside the remit of the Agency appraising the evidence, unless an explicit threshold is used 	<p>intensive.</p>
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Source: The authors.

10. CONCLUDING REMARK

In this report we have provided a comparative assessment of value-based pricing and external price referencing, two methodologies that are widely used in the EU-27 to inform pricing and reimbursement decisions in the Member States. We have presented the evidence side-by-side to enable a comparison of each method's relative merits and limitations and have drawn widely on available evidence as well as evidence from relevant stakeholders.

The greatest difference between VBP and EPR lies in the fact that the former relies on a combination of scientific judgements (reliability of the evidence base, appropriateness of sub-groups, generalisability, capture of quality of life and handling uncertainty) and social value judgements (severity of the disease, end-of-life interventions [rule of rescue], age and health inequalities) to inform pricing and reimbursement decisions, whereas the latter borrows these indirectly from other countries, provided they are included in the basket. Implicit in this, is the assumption that scientific or/and social value judgements in one particular country or a set of countries are also suited in another.

Beyond their salient features and processes, VBP and EPR have different advantages and limitations and impact key variables such as price/reimbursement, coverage and access, assessment of value and encouragement/rewarding of innovation differently.

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APPENDIX

Case study of Erlotinib (TARCEVA®), 150mg

Erlotinib (TARCEVA®) is indicated for advanced and metastatic non-small-cell lung cancer (NSCLC) (as a second-line treatment), to treat patients when at least one previous chemotherapy has failed, and for which doctors have weighed the chance of survival before prescribing the treatment.

Generally, it has received a positive HTA recommendation in all study countries (UK, Scotland, Sweden, France), but with restrictions in some. In Scotland, the drug was first rejected because the economic case was not demonstrated; it then received a positive appraisal upon resubmission restricted to patients who would otherwise be eligible for treatment with docetaxel, the current standard option of care. In the UK, it is restricted as an alternative treatment to docetaxel provided that the treatment overall costs are the same as for docetaxel, on the basis that it has not proved to be clinically equivalent to docetaxel, but has the advantage of being an oral treatment (versus an injection for docetaxel) and having a favorable toxicity profile. Similarly, in Sweden the possible lower clinical benefit was balanced by the higher quality of life to the patient compared to pemetrexed and docetaxel. An ASMR rating level V was granted, because no direct comparisons with pemetrexed and docetaxel, the other existing treatment alternatives, were presented.

Table A1. Comparators used in HTA appraisals.

comparators	NICE	TLV	HAS	SMC
Docetaxel	best supportive care	second-line treatment alternative	second-line treatment alternative	second-line treatment alternative
Pemetrexed		second-line treatment alternative	second-line treatment alternative	second-line treatment alternative

From the above, it can be generally concluded that erlotinib is considered as a drug with a low level of innovation, where its efficacy is most likely to be lower than its comparators while it has a favorable toxicity profile and way of administration.

Figure A1. Erlotinib 150mg – indexed prices across EU countries

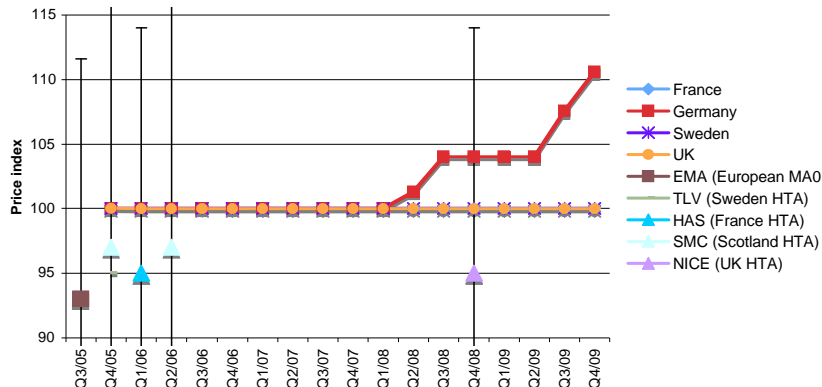
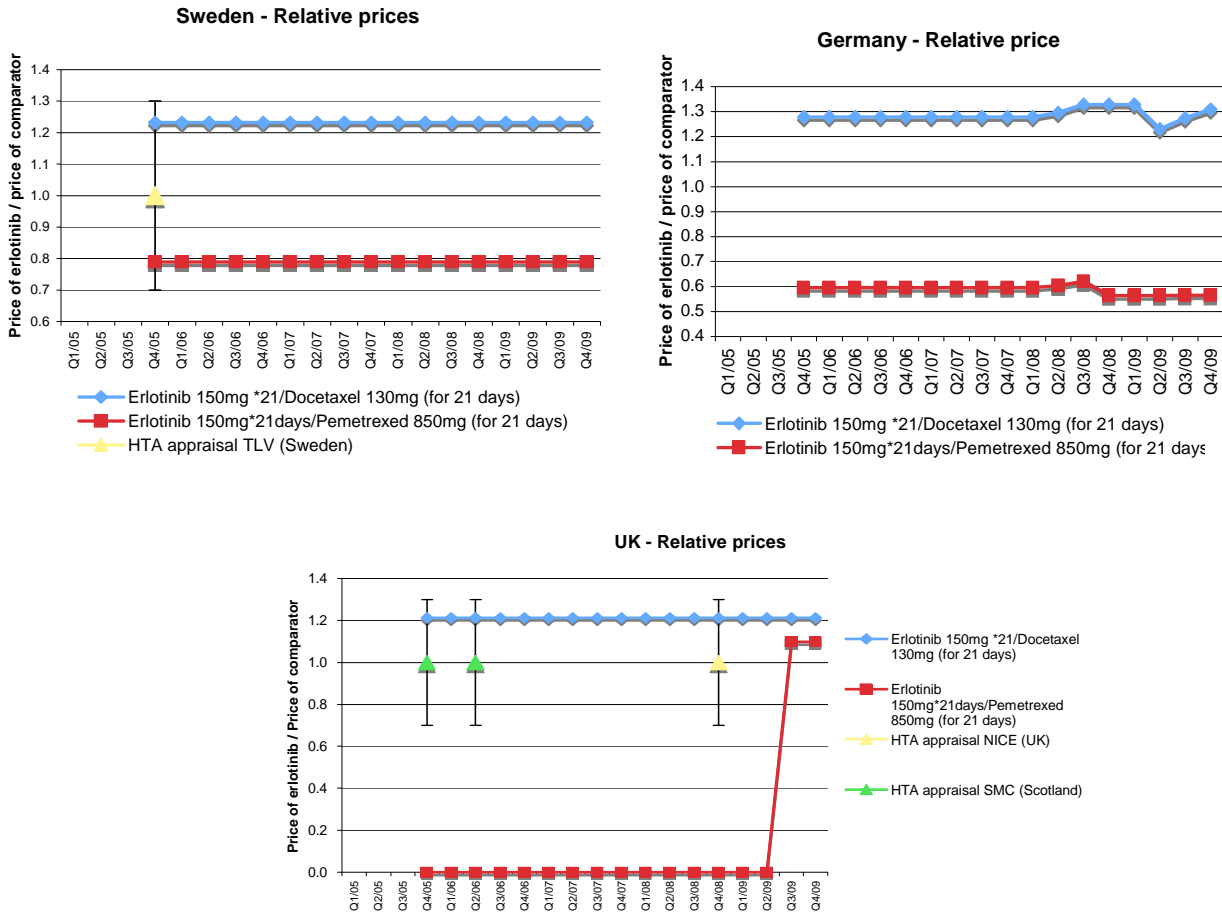


Figure A1 illustrates EMA’s market autorisation (MA) date, as well as the HTA appraisal dates for France, UK, Scotland, and Sweden. All prices are stable across time, except for the price in Germany, which rises prior and again right after the appraisal by NICE, which restricted the use of erlotinib to a limited population.

The three figures below (Figure A2) illustrate the relative prices of erlotinib against its two comparators, docetaxel and pemetrexed⁸⁹. In all three cases, the price of erlotinib is set slightly higher than docetaxel (between 1.21 and 1.278 times higher). Similarly, the price of erlotinib is set at a slightly lower than or equal to pemetrexed (between 0.595 and 1.098). All relative prices are stable, with the exception of the German prices, which appear to fluctuate in favor of erlotinib as of Q2 2008, slightly before the appraisal by NICE. No pricing data for France was available in this case.

⁸⁹ The comparative dosages are the following :
 Erlotinib 150mg daily for 21 days = Docetaxel one injection of 75mg/m² (for 21 days) = Pemetrexed one injection of 500mg/m² (for 21 days).
 The assumption of m² is 1.7m² per patient, based on the appraisal from SMC.

Figure A2. Relative prices of erlotinib and its comparators (in euros)



In summary, erlotinib has been valued as a drug with a low level of innovation by all agencies. NICE has issued the most restricted HTA appraisal of all 4 agencies. Overall, the prices have shown to be stable across time, and the price premium over its comparators is close to zero. The most surprising observation is the price increase in Germany shortly before and after the appraisal by NICE.

This raises the question whether the restrictions implemented by NICE, most likely having a negative effect on the level of sales, are intentionally compensated in other countries, such as in Germany, where free pricing applies.

Case study of Bortezomib (VELCADE) – 3.5mg powder for intravenous injection

Bortezomib received a market authorization from the EMA in April 2004 for the treatment of multiple myeloma as 1) monotherapy (2nd line treatment/3rd-line treatment), in patients whose disease is progressive and who have failed to respond to at least one other treatment and have already had, or cannot undergo, bone marrow transplant; 2) in combination with melphalan and prednisone (1st line treatment), in patients who have not been treated before and are not suitable for high-dose chemotherapy with a bone marrow transplant.

Monotherapy treatment (second-line treatment) with bortezomib is recommended by NICE and limited to patients who respond (partially or fully) to the treatment after a first cycle of 4 weeks. In the contrary case, the manufacturer agrees to reimburse in full the treatment costs (risk sharing agreement). In Scotland, bortezomib was rejected twice because the economic case was not demonstrated, and was accepted upon the second resubmission in October 2009 with a Patient Access Scheme that improves the cost-effectiveness of bortezomib (the patient access scheme is the same as in the NHS, where costs are covered when the response rate is superior to 50%). In France, bortezomib received different ASMR ratings (Table A2). As monotherapy (second-line treatment), it was first issued a level V rating because of the already existing therapeutic alternatives and of the mode of administration, and after a second resubmission with additional evidence on its efficacy, a level IV rating was given. As third-line treatment (after at least failure to respond to two treatments), it received a level II rating because of the treatment's efficacy. Finally, as an add-on therapy (first-line therapy) to melphalan and prednisone, it was granted an ASMR III rating. In Sweden, bortezomib is recommended as both second and third line treatment.

Table A2. Indications of Bortezomide

Indications	NICE	TLV	HAS	SMC
Multiple Myeloma	x	x	X	x
1st line treatment In combination with melphalan and prednisone - in patients who have not been treated before and who are not suitable for high-dose chemotherapy with a bone marrow transplant.			ASMR III 10.06.2009	
Second line treatment Monotherapy - in patients whose disease is progressive and who have failed to respond to at least one treatment and have already had, or cannot undergo, a bone marrow transplant.	LWC 10.2007	L 20.02.2007	ASMR IV 12.04.2006 28.07.2007	LWC 04.08.2006 06.07.2007 09.10.2009
the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and is continued in patients with complete or partial response, and	x			x
3rd-line treatment Patients having received at least 2 anterior treatments, and whose disease was progressive in at least the last treatment		L 12.10.2004 20.02.2007	ASMR II 26.04.2004	
Risk-sharing agreement/Patient access scheme	x			x

Many alternative treatments exist for which the choice depends on many factors and the stage of the disease progression. For first-line therapy, usually the patient will receive an aggressive course of action with a combination of treatments, followed by a bone marrow transplant. For comparability reasons, the first line treatment

alternatives are not used in this case study, since it has only been appraised in France.

For second and third-line therapy, different treatment options exist and are presented in table A3. The main comparator is dexamethasone, which may be considered the most common option.

Table A3. Treatments options and comparative doses for 2nd and 3rd line treatment of multiple myeloma

Regimen	Doses	Cycle length
Bortezomib	1.3mg/m ² d1, 4, 8, 11	21 days
Vincristine Doxorubicin Dexamethasone	0.4mg iv daily D1-4 9mg/m ² iv daily d1-4 40mg po daily d1-4 and d12-15	21 days
Dexamethasone	40mg po daily d1-4, 9-12, and 17-20	28-35 days
Melphalan Prednisone	7mg/m ² po d1-4 40mg po d1-4	28 days
Cyclophosphamide	300-500mg/m ² po or iv weekly	21-28 days
Human body surface: 1.6m ²		

Source: SMC appraisals for bortezomib

Pricing

Figure A3 illustrates the indexed prices of bortezomib across a range of European countries as well as the market authorisation and HTA appraisal dates. The price of bortezomib in Sweden and in the UK remains stable across the observation period. In contrast, the price in Germany appears to increase slightly and then remains stable, and at Q2 2009 another increase occurs (right after the appraisal in France for first-line treatment). The most interesting case is in France. The price decreases slightly after an ASMR level IV is issued to bortezomib for the second-line treatment, and again slightly after an ASMR III is issued for bortezomib as first line treatment.

This may be due to the fact that sales are expected to increase, thus having a downward pressure on prices.

Figure A3. Indexed prices of bortezomib 3.5mg powder for IV

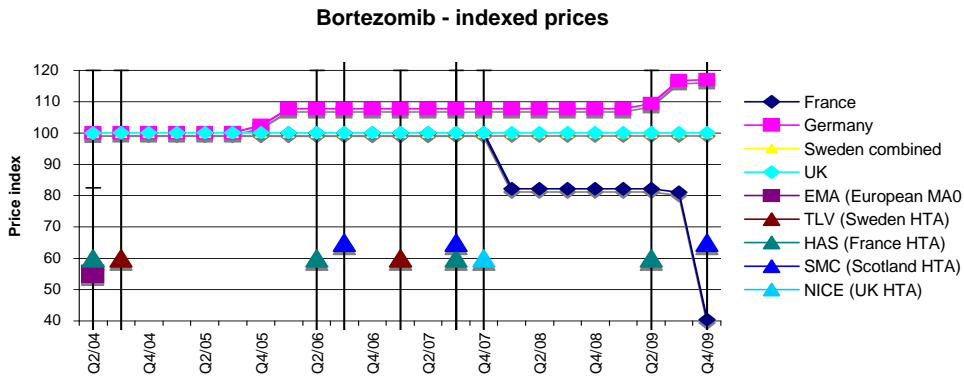


Figure A4. Relative prices of bortezomib 3 doses (3.5mg for IV)

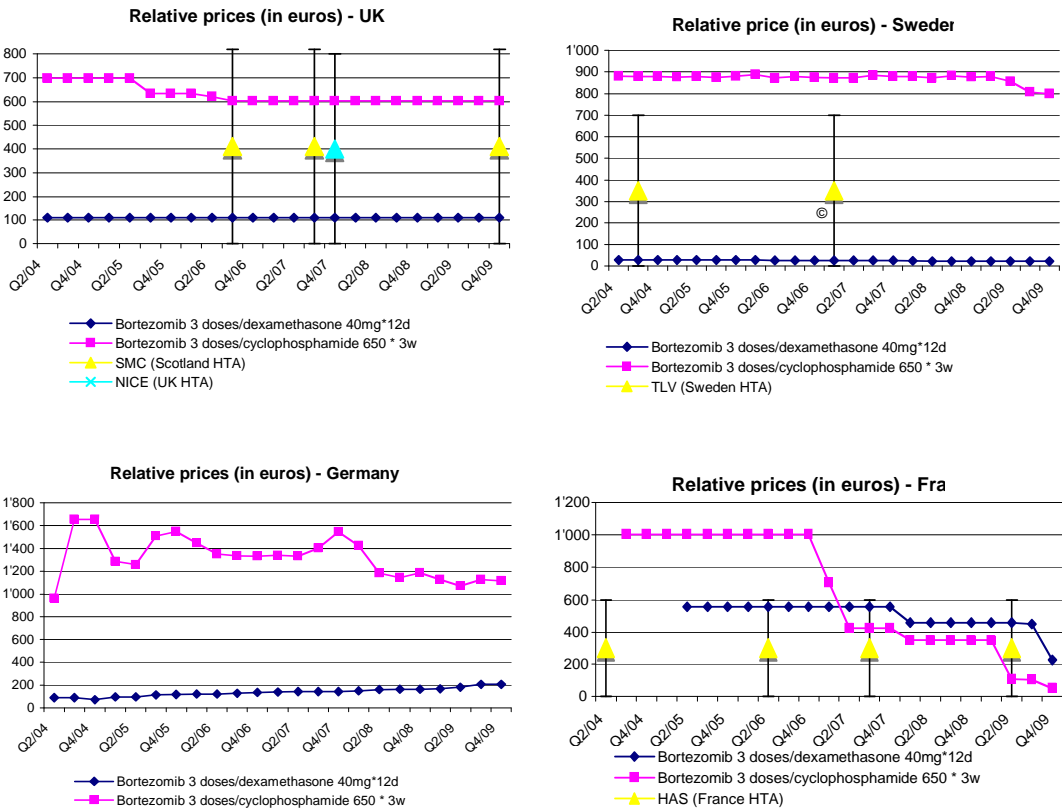


Figure A4 illustrates the relative prices of bortezomib and two comparators (dexamethasone and cyclophosphamide) according to the doses in table A3. The most relevant comparator is dexamethasone, for which a direct comparison with bortezomib was presented in the HTA appraisals. The relative prices of bortezomib vary between 28, 90, 109, and 555 times higher respectively in Sweden, Germany, UK, and France than dexamethasone. It then increases in Germany (because the price of bortezomib increases, and the price of dexamethasone decreases). In contrast, the relative price decreases in France, mainly due to the price decrease of bortezomib.

Initially in France, bortezomib received an ASMR level II, which can justify that the price at launch was 555 higher than dexamethasone. Then, as it receives approvals for other indications at lower ASMR levels (V, IV, and III), its price appears to decrease accordingly. In the UK, the relative price remains very high compared to dexamethasone, most likely because it has demonstrated its superiority in terms of efficacy. Moreover, a risk sharing agreement and patient access scheme guarantees that only the patients with partial and complete response are covered, thus increasing the “value” of the treatment for this population, which can justify this higher price. In contrast, in Sweden, the price is set at a lower level than dexamethasone compared to the other countries (28 times higher than its comparator). This is due to the fact that the price of dexamethasone in Sweden is higher as the pricing data of only different doses of dexamethasone were available. Finally, in Germany, the price is set 90 times higher than dexamethasone, similarly to the price level given in the UK.

Bortezomib is on average 1000 times more expensive than cyclophosphamide. However, it may be slightly less interesting to analyze, as often used in combination to other treatments. NICE for example doesn't even mention this treatment option in its appraisal.