Impact of Health Technology Assessment (reimbursement) on considerations for international regulatory strategies

Wissenschaftliche Prüfungsarbeit

Thesis

zur Erlangung des Titels

to obtain the degree

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

at the Faculty of Mathematics and Natural Sciences,

Rhenish Friedrich-Wilhelms-University Bonn (Germany)

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Bonn 2010

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1 Case setting

The CEO of an EU-based international pharmaceutical company has requested a short presentation from the core project team of “FUTURA” The presentation should provide sufficient information on the European clinical development strategy to assess whether development should be pursued further in respect of return of investment. “FUTURA” is an innovative drug currently in phase 2 clinical trials for a broad indication for that other pharmaceutical treatment options exist. The technical development team is envisaging a more convenient delivery mode for “FUTURA” than available for other drugs approved for this indication. In addition, “FUTURA” has also shown potential in phase 1 studies in some indications with low prevalence and high medical need that may qualify for orphan designation.

The international regulatory manager as member of the core project team is required to provide relevant regulatory input on the clinical development programme. As the team recognises the growing importance of the “fourth hurdle” for successful pharmaceutical development, it has requested a joined recommendation from the regulatory and market access managers regarding endpoints, study population, design and acceptability of clinical data by regulatory competent authorities (CAs) and Health Technology Assessment (HTA) bodies in order to gain regulatory approval plus reimbursement in Europe.

The regulatory manager is thus far not familiar with HTA requirements and the market access manager not with regulatory requirements. This document aims to provide them with an overview to this respect to guide their discussions and to develop a joined recommendation.

2 Table of Content

Table of Figures

3 List of Abbreviations

ANDA	Abbreviated new drug application
BfArM	German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
BLA	Biologic license application
CA	Competent authority
CADTH	Canadian Agency for Drugs and Technologies in Health
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDR	Common Drug Review
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
CURE	Clopidogrel in Unstable angina to prevent Recurrent Events
EC	European Commission
EFTA	European Free Trade Association
EMA (previously: EMEA)	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EUnetHTA	European network for HTA
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HLPF	High Level Pharmaceutical Forum
HPFB	Health Products and Food Branch
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICH	International Conference on Harmonisation
INAHTA	International Network of Agencies for Health Technology Assessment
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (German Institute for Quality and Economic Efficiency)
ISPOR	International Society For Pharmacoeconomics and Outcomes Research
ITT	Intension-to-treat
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MPA	Medical Products Agency (Läkemedelsverket, Sweden)
NDA	New drug application

NICE	National Institute for Health and Clinical Excellence (UK)
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
PP	Per-protocol
QALY	Quality-adjusted life-year
RCT	Randomised clinical trial
SBU	Swedish Council on Technology Assessment in Health Care
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
TGA	Therapeutic Goods Administration (Australia)
TLV	Swedish Dental and Pharmaceutical Benefits Board (Tandvårds- och läkemedelsförmånsverket)
UK	United Kingdom
US	United States
USA	United States of America

4 Executive summary

In an environment of increasing healthcare costs, policy makers and payers try to protect healthcare budgets mainly by cost containment measures regarding prices of medicinal products whilst considering their (legal) responsibility to provide access to innovative medicines. For active substances that have run out of patent, a healthy generic competition serves to regulate prices. Costs of innovative medicines particularly in areas of high need such as oncology or orphan diseases are, however, raising and consequently increase the relative budget spent. Therefore, during the development of an innovative medicinal product, not only quality, safety and efficacy need to be considered but also pricing and reimbursement requirements. Pricing and reimbursement is, also in the EU, a national responsibility as it is influenced by national processes and value judgements that are partially determined by national factors. Conditions are either negotiated prior to market or after market entry.

The costs of innovative medicines are mainly driven by increasing development costs partially due to higher regulatory requirements but also marketing spent. Premium prices are paid increasingly only for substantiated added therapeutic value, a major but not the only determinant of which are clinical and patient-relevant benefits compared to standard therapeutic intervention. Added therapeutic benefit can arise from increased efficacy/effectiveness, lesser side effects, improved applicability, convenience or quality of life. It is the task of health technology assessment (HTA) organisations to review data related to added therapeutic benefit in order to inform policy decision makers and payers in their considerations of pricing and reimbursement. Data to determine at least initially the added therapeutic benefit of an innovative medicinal product could be obtained from phase III registration studies. However, the design of these studies needs to accommodate requirements of both, regulatory competent authorities and HTA organisations regarding endpoint selection, comparators, study duration (longer follow-up) and population as well as statistical approaches and hence impacts the overall regulatory strategy.

This master thesis provides a brief overview of regulatory approval procedures, pricing and reimbursement systems and HTA approaches that need to be taken into consideration when discussing regulatory and HTA-relevant strategy within a development project team of an international company. The focus of this work is on European systems and developments relating to innovative medicinal products whilst occasionally looking towards relevant ex-EU countries. The potential impact of HTA requirements on the design of regulatory phase III studies to yield useable (relative) efficacy and effectiveness data is analysed. Furthermore, interaction and information exchange interfaces between regulatory competent authorities (CAs) health technology assessment (HTA) organisations and companies are discussed. Attention has been

given to specific issues related to the effectiveness assessment of orphan drugs and new delivery modes.

In conclusion, policy decision makers, payers and companies are increasingly aware of the need of (relative) efficacy/effectiveness data and a harmonised approach to their assessment to support national pricing and reimbursement decisions. To avoid duplication of development programmes, phase III clinical studies need to be designed to meet the joint requirements of HTA and regulatory review. Early and continuous dialogue between regulatory competent authorities, HTA organisations and pharmaceutical companies is required to shape the clinical strategy suiting both purposes.

5 Introduction including aim of the thesis

The resources of any healthcare or health insurance system are limited. With increasing prices of healthcare and drugs, healthcare policy makers have to protect budgets by cost cutting measures. The direct and indirect costs of the healthcare system are produced by many different sources, such as:

- Cost of medical care / healthcare professionals
- Cost of administration (such as health insurances)
- Cost medicinal products
- Cost of devices and equipment
- Cost of hospitals and medical practices
- Cost of distribution

Although the cost of medicines appears not to be the largest but nevertheless growing segment of most healthcare budgets (in Germany, France and UK less than 20% during the past 15 years)[1], cost cutting measures currently focus on the cost of medicinal products, including innovative products. It appears debatable why policy maker currently pay less attention to cost cuttings measures in other segments.

In Europe, about 75% of medicinal products and devices are reimbursed from public funds[2]. The rising costs of medicinal products contribute to the pressure on health budgets and result in the challenge how maximise “public health” for a given healthcare budget. For medicines, this translates into how best to provide access to effective but also to innovative medicinal products at an affordable cost to the public.

In Europe, pricing and reimbursement are national responsibility whilst regulatory approval can be gained by Centralised, Mutual Recognition or National procedures. The price of medicinal products can be controlled at various steps in the manufacturing and distribution chain, such as ex-factory, wholesale and pharmacy level[3]. In the current discussions and for the purpose of this thesis, price control and negotiation at ex-factory level is the critical one.

In making decisions regarding which innovative medicinal products should be reimbursed and at what price, international healthcare policy makers are increasingly turning to HTA. HTA provides effectiveness and cost-effectiveness analysis (CEA) of medical technologies including the impact and value of an innovative medicine to relative to the existing, cheaper drugs on the market. The current discussions focus on how the HTA and regulatory requirements can be aligned and harmonised to be covered by one single clinical development programme.

As such, discussions are ongoing which (clinical) studies and data (endpoints/populations) are required to support the economic evaluation of medicinal

products. Already pharmaceutical companies include economic endpoints in registration studies and/or conduct post-approval studies to show added therapeutic benefit. However, there is some evidence showing that pharmacoeconomic studies funded by pharmaceutical industry are more likely to return positive conclusions than those funded by non-profit organisations[4,5,6], suggesting errors and bias in industry-sponsored design and/or interpretation of pharmacoeconomic calculations and studies.

The presented master thesis attempts to discuss the current and potential future evidence base required for health technology assessment (HTA) and resulting pricing and reimbursement decisions in relation to considerations regarding regulatory strategy with focus on Europe. It is likely that regulatory phase III registration studies yielding relative efficacy data will in future become even more important as evidence base for initial relative effectiveness conducted by HTA organisations to support pricing and reimbursement decisions. As a consequence, HTA requirements will greatly influence the design of phase III (registration) studies, and hence regulatory strategies of pharmaceutical companies. Harmonisation of some key requirements for HTA and regulatory review is required. To achieve this, information exchange and interactions between regulatory and HTA specialists on governmental and industry side need to be improved.

6 Registration requirements

The key role of regulatory competent authorities is the approval of medicinal products by evaluating their pharmaceutical quality, preclinical and clinical data based on the registration dossier. Furthermore, regulatory authorities provide guidance throughout the drug development process including scientific consultations and/or meetings and authorise and inspect clinical studies for validity and GCP-compliance of source data. Post-approval, regulatory authorities are concerned with review of variations/amendments to the registration dossier and collection and review of safety data.

Although due to the ICH approach, the overall format and structure of the registration dossier (Module 2 to 5) and the approach to quality, safety and efficacy is more or less harmonised in key regions, the particular requirements regarding content in terms of quality data and clinical studies still vary between regions. The requirements for preclinical safety studies are somewhat more harmonised.

In view of reimbursement, randomised clinical trials (RCTs) constitute the most important and also most expensive part of pharmaceutical development and hence registration dossiers. Pivotal phase III studies are frequently referred to as “registration studies”.

Registration studies are designed to show the efficacy and safety of a therapeutic intervention. In addition, they need to adhere to ICH and regional (regulatory and indication-relevant) and as well as therapeutic guidelines. The requirements set out in the detailed guidance significantly shape the design of RCTs conducted to achieve evidence-based approval with respect to:

- Primary and secondary endpoints
- Study population
- Study duration
- Statistical analysis
- Compliance with Good Clinical Practice (GCP), Good Manufacturing Practice and Good Laboratory Practice

Regulatory requirements for, and the assessment of, clinical studies regarding the risk/benefit balance may differ between regions. For global drug development programmes, such differences in requirements constitute a major challenge regarding the design of international registration studies and strategies.

In theory, once approved, medicinal products could be marketed. However, many countries have introduced a system of pricing & reimbursement negotiations, partially based on HTA or reference pricing prior to market entry. This process is frequently termed the “fourth hurdle”, meaning the fourth requirement to be fulfilled in addition to acceptability of quality, safety and efficacy of the medicinal product (see section 7).

Regulatory Competent Authorities (CAs) carry out the scientific assessment of the registration dossier independent of pricing & reimbursement considerations. Approval based on the scientific assessment is granted without pricing considerations/HTA, an approach that may be challenged in the light of greater demand for generation of HTA-relevant data. It has been criticized that, due to the nature of data currently frequently provided with the regulatory dossier (non-inferiority versus another treatment rather than superiority), granting a marketing authorisation (MA) instigates the wrong impression of a treatment having shown added therapeutic value because. Non-inferiority or equivalence could also mean lesser outcomes regarding efficacy or safety as long as the data are within the predefined inferiority margins[7].

6.1 The European regulatory system

In the European Union, national CAs such as the German Federal Institute for Drugs and Medical Devices (BfArM), UK Medicines and Healthcare products Regulatory Agency (MHRA) and the Swedish Medical Products Agency (MPA) co-exist alongside an EU-spanning European Medicines Agency (EMA). The legal basis for development and registration of medicinal products is set out in European pharmaceutical law, particularly Directive 2001/83/EC as amended, which has been adapted and implemented by all Member States into national law. Depending on the nature and development path of the medicinal product, a MA can be based on the following legal basis set out in Directive 2001/83/EC as amended:

- According to Article 8(3), assessment and approval of (innovative) medicinal products requires a full dossier (quality, safety, efficacy). With respect to clinical data, depending on the target indication usually 2 phase III RCT preferably conducted versus comparator are required. The assessment is based on the summary data submitted by the applicant with the dossier, but not the source data.
- According to Article 10(1), for the approval of generic drugs quality, but no preclinical data and only human bridging data are required
- According to Article 10(3), in case of an extension application (e.g. the medicinal product can not be considered a generic or bioequivalence can not be shown or a new indication is targeted), results of appropriate clinical studies are required for approval
- According to Article 10(4), for the approval of similar biological medicinal products appropriate preclinical and clinical data must be submitted
- According to Article 10a, for approval of products with well-established use a bibliographic dossier may suffice
- According to Article 10b, for approval of fixed combinations of known substances quality, and only preclinical and clinical data regarding the combination not the single active substances are required
- According to Article 10c, for approval of doublets of identical, already approved products informed consent to cross-reference data is sufficient

These differences in approval requirements are reflected in pharmaceutical development costs, with approval according to Article 8(3) being the most cost-intense. Consequently, any pricing discussion needs to take into consideration the legal basis and hence regulatory requirements particularly regarding clinical development of a particular medicinal product.

During the development process, all European CAs offer Scientific Advice in form of meetings or written consultation to the applicant to discuss approaches to, and details of, the planned development programme.

One of the key tasks of the CAs is the review of the registration dossier submitted to support the MA application. MAs can be obtained via different approval pathways:

- National MAs granted by individual national CAs resulting arising from:
    - National procedure
    - Mutual recognition procedure according to Article 28 of Directive 2001/83/EC[8]
    - Decentralised procedure according to Directive 2004/27/EC amending Directive 2001/83/EC[8]
- European MA via Central Procedure according to Regulation 726/2004/EC[9] granted by the European Commission (EC) based on the recommendation of the EMA; not all medicines are eligible for the Central Procedure. Within the framework of the centralised procedure, special procedural pathways (exceptional circumstances, accelerated assessment or conditional marketing authorisation) could be applicable.

Review time tables of the centralised procedure and the MRP/DCP part of procedures are set by guidelines. The time to national approval after the MRP/DCP procedure should be 30 days according to Article 28 of Directive 2001/83/EC as amended[8]. However, at present this timing is however not kept by many Member States. National procedures do not adhere to any particular time table.

In case of national MAs, the summary of product information (SmPC), labelling and patient information for any particular product can somewhat vary between Member States depending on which procedure was chosen, the centralised procedure results in identical labelling texts across the entire EU.

Whilst according to Regulation (EC) 726/2004[9] to date only selected classes of medicinal products are legible for review via Centralised Procedure, all products with orphan drug status are mandatory reviewed via Centralised Procedure to further the accessibility of such drugs across the EU. To be awarded orphan designation and as a consequence to become legible to a set of incentives, medicinal products under development have to fulfil a number of criteria (Regulation 141/2000[10]), most importantly

they have to show potential in a disease which affects less than 5 in 10,000 people in Europe. Most orphan drugs are authorised according to Article 8(3); other legal basis is however possible. However, due to the small patient group available for studies, exceptional or conditional approval as laid out in Article 14 of Regulation (EC) 726/2004[9] could become applicable based on less complete sets of clinical efficacy data.

An ever growing number of European Directives, Regulations, detailed guidelines and Points to Consider etc supplement Directive 2001/83/EC[8] and need to be taken into consideration during drug development. Regulatory assessment is carried out independently and thus far in ignorance of any needs regarding HTA-data. Subheading 13 of Directive (EC) 726/2004[9] setting out details for the centralised procedure states that assessment of the MA dossier should be independent of economic considerations: *"In the interest of public health, authorisation decisions under the centralised procedure should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations."*

In case of centralised procedure, an EU-wide binding MA is granted by the European Commission. However, market access may still depend on previous completion of national pricing negotiations. National MA procedures (including MRP/DCP) may be accompanied or followed by pricing & reimbursement negotiations.

7 Healthcare systems and reimbursement

The specifics of price negotiation objectives and reimbursement of treatments in any society depend on how a particular national health system is funded as well as the legal situation regarding the patient's right to access to medicines and healthcare as well as political agenda.

Most countries have social health insurances or public health services in place, which aim to distribute the risk and cost of healthcare among the broader population. In each society, health insurances (also referred to as payers) have a limited budget available for healthcare including cost of medicines. The actual budget of any particular health insurance/health service depends on the number and demographics of people contributing to the fund, contributions and availability of additional resources (additional governmental or employer funding).

Whilst single-payer (universal) social healthcare systems exist for example in Australia (Medicare), Canada (Medicare), China and the United Kingdom (National Health Service), other countries such as Germany and the US have multiple-payer healthcare systems[11]. As social health insurances or services frequently cover the majority of population, they have a high impact and extensive authority, especially in the domain of fee and price negotiations[12]. Examples are the Czech Republic, France and Canada. In

other countries such as the US and Switzerland large parts of population are covered by private insurers. Private health insurers can also compliment the social health insurances and systems such as in Australia, Germany and the UK.

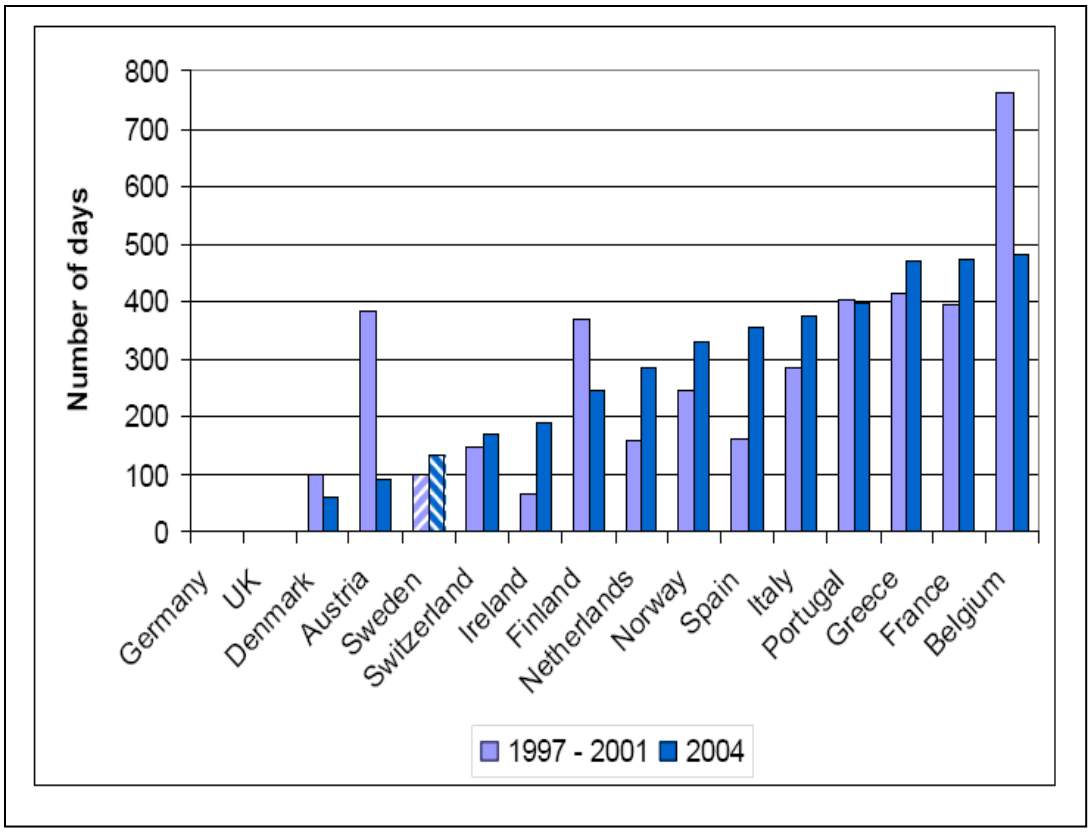
The more diverse the healthcare situation in any country, the more complex is the pricing and reimbursement landscape between suppliers and payers. Even within one country, different insurances and systems may take different positions regarding pricing and reimbursement of treatment to patients (full reimbursement versus reimbursement of a specific percentage of the cost of the medicinal product) and hence negotiate different prices. In general, due to higher income per capita, private insurers may frequently be less restrictive in their reimbursement policies.

There is an obvious conflict of interests: suppliers including pharmaceutical industry aim to maximise profit and, in case of innovative medicines, recover development costs as fast as possible, whilst the objective of the payers is to protect their budget and pay as little as possible for the maximal impact on public health. Naturally, physicians want to provide, and patients expect to get, the best healthcare possible regardless of cost.

With respect to reimbursement particularly of premium priced innovative medicines, some insurances/health systems restrict reimbursement to a selected “positive” list and/or reimburse only part of a medication to protect their overall budget. The price control policies and decision criteria of which medicines are included on a positive list or what percentage is reimbursed vary significantly between countries[13]. Ideally such decision criteria should include HTA as at least one of the elements. Frequently, pricing policies are also politically motivated[14] in respect to different indications or bias towards domestic pharmaceutical industry[13].

Price negotiations clearly can delay market entry post regulatory approval and hence access to medicines, as can also be deducted from in Figure 1:

Figure 1: Average time from pricing and reimbursement application to reimbursement[15]



Ultimately, pricing and reimbursement negotiations aim to control the healthcare budget and to maximise the benefit of healthcare and subsequently medicines for as many patients as possible. In a landscape of oversupply of different medicinal products for the same indication, partially targeting the same mechanism of action and with many high-selling and well-established drugs running out of patent, generic competition is a very effective tool for decreasing prices. Mainly due to high development costs, for innovative medicinal products pharmaceutical industry anticipates premium prices. However, on the background of limited resources, any long-term added therapeutic value such innovative medicines may provide to the patient and society compared to existing treatment needs to be proven to payers in order to obtain an acceptable premium price and equally important, a reimbursement recommendation. It is one of the tasks of HTA to determine the effectiveness of innovative medicines and to provide relevant reports to decision makers among the payers.

7.1 Pricing and reimbursement situation in the EU

Decisions and negotiations of the ex-factory and/or reimbursement prices of medicinal products are generally made on a national or, depending on the healthcare system, even individual health insurance level.

Article 4(3) of Directive 2001/83/EC as amended clearly states that *"The provisions of this Directive shall not affect the powers of the Member States' authorities either as regards the setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes, on the basis of health, economic and social conditions."* Consequently, management of healthcare budgets and price negotiations are a national responsibility. Member States increasingly include assessment of the added value of innovative medicinal products by using health technology assessment (HTA) as one of the criteria in pricing and reimbursement negotiations. In addition to an (ideally internationally accepted) HTA approach, national social, budgetary and ethical factors have to be taken into consideration[16,17].

Council Directive 89/105/EEC[18], also referred to as Transparency Directive, states general requirements for pricing and reimbursement regarding processes and transparency within the EU to ensure free movement of goods, however does extend to national policies. This Directive states that Member States in which medicinal products can only be marketed after agreement on price must take the decision regarding pricing and reimbursement within 90 days of the pricing submission by the company. Furthermore, in the event of refusal of market entry of the medicinal product at a given price they ought to provide the reasons for this decision.

The High Level Pharmaceutical forum (HLPF) was set up by the European Commission to promote the sustainable availability and delivery of medicines to all European markets. Its Working Group on Pricing has issued recommendations such as guiding principles for good practices implementing a pricing and reimbursement policy, assessment of the innovative value of medicines and improving access to orphan drugs[19,20,21] however, these are not binding and have only advising character only.

According to the Guiding Principles for Good Practices implementing a pricing and reimbursement policy as published by the Pricing Working Group of HLPF, in setting prices and reimbursement rules, each of the member states aims to fulfil three goals[20]:

- Optimal use of resources to maintain sustainable financing of healthcare
- Access to medicines for patients
- Reward for valuable innovation

Each Member State uses different tools and approaches to achieve these goals.

Valuable innovation as expressed in benefit in the areas therapeutic/clinical benefit, quality of life benefit or socio-economic benefits should be rewarded. Therapeutic or

clinical benefit is considered the highest ranking benefit[19] (PF innovation). Criteria to assess the added therapeutic value:

- Efficacy/effectiveness
- Side effects
- Applicability
- Convenience
- Experience
- Quality of life

Efficacy/effectiveness and side effects are considered to be the most important criteria contributing to benefit. As stated in the final report of the HLPF[22], convenience leading to improved compliance is only considered a valid criterion when this translates into an overall clinical benefit.

Overall, pricing and reimbursement policies and approaches differ greatly between EU Member States and consequently, the price for a particular medicinal product varies significantly between countries[23]. These price differences are exploited by parallel trading industry, which influences pricing, regulatory and marketing strategy.

There appear to be three or four main methods that are being used in EU Member states to exercise cost-containment in pharmaceutical expenditures[2,24]:

- Fixed pricing/price control (direct control or indirect control via generic substitution)
- Profit control
- Cost-effectiveness pricing
- Reference pricing

In some of the EU Member States the overall pricing and reimbursement status is associated with classification of medicinal products according to the degree of innovation and added therapeutic value or therapeutic need and/or a negative/positive list[13].

7.1.1 Belgium

In Belgium, medicinal products are classified into Class 1 relating to medicinal products with added therapeutic value for which a premium price can be negotiated or Class 2 relating to medicinal products without added therapeutic value including generics, which will be priced equally or less than similar drugs already on the market. For Class 1 drugs, pharmacoeconomic data are requested[19].

The actual price and reimbursement level (ranging from 30% for contraceptives or migraine medicines to 100% for life saving medicines) is decided by the Ministry of Social Affairs and Public Health upon a recommendation of the Medicines Reimbursement Commission. This commission makes their recommendation after consideration of the added therapeutic value, a maximum price set by the Ministry of

Economic Affairs, the price proposed by the manufacturer, therapeutic and social needs, budgetary implications, the cost/effectiveness ratio and prices in other EU Member States[13].

7.1.2 France

The French healthcare system is primarily managed at national level by the government and the parliament. The system of pricing and reimbursement is rather complex and arbitrary; thus far it is independent of any real cost-effectiveness considerations although it considers clinical and therapeutic benefits[13,19]. As soon as an MA is granted, the company has to apply for positive reimbursement listing to obtain funding by the mandatory health insurance. Initially the Medicines Evaluation Commission (Commission d'Evaluation des Médicaments) decides which medicinal products are reimbursable and for which indication based on medical benefit and improvements versus existing alternatives[25]. Reimbursable drugs are classified according to reimbursement level (from 0 to 65%) into 5 categories by the Transparency Commission (Commission de Transparence). The actual drug prices, which are also binding for private prescriptions, are set by the Pricing Committee (Comité Economique du Médicament) according to a scale of improvement and negotiations with the company. Prices have to be aligned with those in Spain and Italy and should not exceed prices in Germany or the UK. Companies have to submit expected sales information which are part of pricing considerations and are penalised when exceeded. Companies are also required to fund post-marketing studies assessing real life effectiveness or drug utilisation[25].

7.1.3 Germany

In Germany, 90% of population are covered by one of over 200 social health insurances and 10% by private insurances. At present no "fourth hurdle" is in place for medicinal products and in principle, companies are free to set the price of medicinal products which are automatically reimbursed after regulatory approval. Germany is often used as international reference price country by other Member States, which particularly motivates companies to achieve the highest price possible. According to § 35 of the German Social Law Book V maximal reimbursement prices can be set for generic drugs, drugs with a similar structure or a similar therapeutic action to already approved drugs ("me too's")[26]. The Federal Joint Committee (Gemeinsamer Bundesausschuss), a governmental body, is tasked with classification of drugs into reimbursement categories (therapeutic class reference pricing system). The actual reimbursement price is set by the Association of Social Health Insurances (Spitzenverband der Krankenkassen) that is represented in the Federal Joint Committee. The reference price is apparently calculated by regression models based on a standard-pack (usually the most sold drug package in this group of medicinal products). Considerations in price setting also include provision of a sufficient, useful, economic feasible healthcare of high quality.

Innovative drugs with proven cost-efficiency or for which no therapeutic alternative exists are currently excluded from any price fixation according to § 31 of the German Social Law Book V[26] (SGB V). For all other medicinal products excluded from the therapeutic class reference pricing system, the Association of Social Health Insurances can establish a maximal reimbursement price. This price should be based on cost-effectiveness information. In January 2011, a new pharmaceutical law (Arzneimittelneuordnungsgesetz[27]) will come into force, which requires the company to supply pharmacoeconomic evidence supporting any added therapeutic value and effectiveness as well as ex-factory prices in other EU Member States and expected sales volume as basis for price negotiations with the Association of Social Health Insurances. The pharmaceutical company is free to set a price for a new or innovative medicinal product in the first year of marketing, afterwards the reimbursement price is determined in negotiations based on cost-effectiveness assessment.

The Institute for Quality and Economic Efficiency (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) provides the Federal Joint Committee with cost-effectiveness assessments as basis for pricing considerations. According to the new pharmaceutical law coming into force in 2011, the IQWiG will have the entitlement to access regulatory dossiers as one of the sources for its effectiveness evaluation. Evaluation of evidence should be completed within 3 months of regulatory approval. A reassessment of the cost-effectiveness based on new data can be requested by the company after 1 year at the earliest[27]. Companies can request advice meetings with the Federal Joint Committee to agree on the nature of the requested pharmacoeconomic data.

Private insurances in Germany do not adhere to the therapeutic class reference pricing system and reimburse cost of drugs usually in full.

7.1.4 Sweden

In Sweden, pricing and reimbursement procedures for new drugs have been revised in 2002 to incorporate a requirement for data on cost-effectiveness. The joint pricing and reimbursement decisions as part of the national Pharmaceutical Benefit Scheme are made by the Dental and Pharmaceutical Benefits Board (Tandvårds- och läkemedelsförmånsverket, TLV) and are based on HTA and societal perspectives[28,19]. Whilst for new drugs, the company has to initiate the reimbursement review, TLV initiates the review process for older drugs that received reimbursement status prior to October 2002. A pharmaceutical company has to apply for reimbursement of a new medicinal product at a freely set price with a supportive dossier including clinical and cost-effectiveness evidence based on a health economic model. The reimbursement decision of the TLV, which is targeted to be available within 120 days of submission, is supported by HTA assessment by the Swedish Council on Technology Assessment in Healthcare (SBU), together with recommendations from the National Board of Health

and Welfare and the MPA. In case a submission based in the initial price is rejected, the manufacturer can resubmit with a different price or with new evidence[28].

However, even if a medicinal product is not reimbursed on a national level, individual counties can still decide to fund reimbursement of such drug based on specific locally-set criteria e.g. if a cost-effective drug fulfils an unmet need, in a severe disease, where there are only a few patients who have no other treatment alternatives.

7.1.5 United Kingdom

The UK healthcare system is primarily publicly funded, with 80% of funding coming from taxation, 12% from national insurance[29]. At present, prices of medicinal products in the UK are still set freely by pharmaceutical companies although the current government aims to abolish the free price setting[19]. Generic competition and parallel import are affecting price. Reimbursement is regulated via 2 negative lists. Economic evaluation is carried out by the National Institute for Health and Clinical Excellence (NICE) that was established in 1999 and re-mandated in 2005. The Department of Health selects drugs that are to be assessed by NICE regarding reimbursement recommendation, not pricing. Guidance issued by NICE is binding; in case a medicinal product is not recommended, it will not be reimbursed by NHS at all. Private health insurances however may reimburse such drugs.

Overall, the more diverse the health insurance situation in any country, the more complex is the pricing and reimbursement landscape between industry/suppliers and payers. Germany, for example, has a multifaceted reimbursement structure with multiple social and private health insurances and insurance networks in place and discounts are negotiated with a particular network.

There have been discussions about a central EU pricing and reimbursement agency[30]. However, pricing and reimbursement is not covered by the EU treaty and, as stated above, Directive 2001/83/EC also confirms national authority in this area. Therefore, in the foreseeable future, the establishment of such centralised EU pricing and reimbursement agency is highly unlikely. Member States would have to align on the following aspects if a harmonisation of pricing & reimbursement across the EU were ever to take place[30]:

- Economic evaluation guidelines
- Decision making process
- Willingness to pay for health technologies & value judgements

As discussed above, at present there are significant differences in the approaches to reimbursement between EU Member States. Amongst the three listed aspects, harmonisation of economic evaluation guidelines appears the most likely aspect to be

achievable although even here enormous obstacles have to be overcome. Harmonisation of HTA approaches may be one of the steps in this direction.

7.1.6 Pricing of Orphan drugs

Premium prices should only be awarded to real innovative medicinal products with added benefit developed for indications with high medical need. There are still many areas of unmet medical need with no meaningful standard therapy available, especially in orphan indications. As for regulatory approval, the requirement to provide robust clinical and economic data exists in principle also for orphan drugs. However, here EMA and many HTA organisations accept a higher degree of uncertainty of (where feasible: relative) efficacy and effectiveness data reflected in smaller study populations, use of surrogate endpoints and effect size[31,32] and economic evaluations. Some countries such as Belgium do not even request economic evaluations for orphan drugs[33]. As intended by Regulation (EC) 141/2000, industry has put significant efforts into the clinical development of orphan indications. However, there is usually a steep premium price (€ 6,000 – 300,000 per year) attached to these medicinal products[33,34,35] and a forceful patient advocacy lobbies payers to reimburse orphan drugs even at this premium price[36]. To be legible for orphan status, the target indication has to have a prevalence of less than 5 in 10,000 people. Considering the small number of patients, willingness to pay in orphan indications is high, making them a worthwhile target for the industry. Nevertheless, due to the high cost and increasing number of approved orphan drugs, the relative budget spent on orphan drugs is increasing compared to drugs for larger indications. As a results, payers become will be more demanding regarding effectiveness data supporting premium prices of orphan drugs[33,34,35], especially if the respective medicinal product is also approved for larger indications.

8 HTA as decision criterion in pricing and reimbursement considerations

Increasingly, decisions on pricing and reimbursement include or are based on effectiveness and cost-effectiveness information.

The final report of the EU HLPF "*Acknowledges the distinction between the scientific assessment of the relative effectiveness of medicinal products and health-economic assessments of their costs and benefits. Endorses the aim of relative effectiveness assessment to compare healthcare interventions in daily practice and classifying them according to their added therapeutic value*."[22]

Health Technology Assessment (HTA) aims to provide a systematic review of the impact of therapeutic interventions and services including medicinal products regarding safety, effectiveness, in addition to social, legal and ethical aspects and regarding cost in

comparison to the benefit. This assessment usually feeds into pricing and reimbursement negotiations[16].

HTA comprises outcome or effectiveness research (evaluates the effect of healthcare interventions on patient's well-being including clinical outcomes, economic outcomes, and patient-reported outcomes) and pharmacoeconomics (health economics, consideration of costs)[37]. HTA is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner[38].

The key role of health technology assessment is to provide health policy decision makers with a scientific basis for their reimbursement and pricing decisions, particularly of innovative medicinal products. More particular, the objectives of HTA include[16]:

- Evaluation of health benefits and optimisation of the health system
- Supply of information with the objective to improve the health status of the population and to distribute the financial resources more effectively
- Supply of information as a basis for decisions on the different levels of the health system
- Examination of established procedures and assessment of new technologies
- Identification of scientific and of research deficits
- Support concerning the prioritisation of future research activities.

The first national agency for HTA in Europe was established in Sweden in 1987. As first country, Australia in 1993 introduced guidelines on cost-effectiveness evidence to be included in the reimbursement submissions to the Pharmaceutical Benefits Advisory Committee (PBAC)[39]. Presently, an increasing number of countries include cost-effectiveness considerations, the so-called "fourth hurdle", in the reimbursement process prior to market access after having passed the three regulatory hurdles of providing convincing evidence for safety, efficacy and quality[40].

8.1 Methodologies of HTA

HTA-organisations use an array of different methodologies in the assessment of (relative) effectiveness, and subsequently cost-effectiveness. Although it is not the focus of this thesis, some of the more common expressions of effectiveness and cost-effectiveness are described here in brief.

One of the accepted but also highly disputed effectiveness measures is the quality-adjusted life-year (QALY), which equals the number of (additional) years of life gained following a therapeutic intervention weighted by a utility value of the relative quality of life experienced[41]. The QALY adds considerations regarding the short-, medium- and long-term costs and savings of added therapeutic benefits of a therapeutic intervention.

In the assessment of quality of life a great variety of factors are considered such as the level of pain, mobility, general mood and side effects of treatment. A year in perfect health is considered equal to 1.0 QALY, death is equal to 0 QALY. A year in ill health would be discounted and depending on the severity of impediments expressed as for example 0.5 QALY.

Comparing gains or losses in QALY following alternative interventions yields in expression of relative effectiveness: the QALY obtained with standard therapy is subtracted from them QALY obtained with the innovative therapy[42]. Some HTA agencies claim that the QALY can be used to compare different therapeutic interventions across different indications; however this is disputed by others.

Once the difference in QALY with an innovative versus a standard treatment has been established, the extra cost of one extra QALY (as one extra year of perfect health provided to one person or more likely an increment of better health provided to many people) with the innovative therapy is determined as measure of cost-effectiveness.

A cost-effectiveness analysis (CEA) is performed when the costs are measured in monetary units and outcomes are measured in non-monetary units, e.g. reduced mortality or morbidity[41]. Another form of cost-effectiveness analysis is the cost-utility analysis (CUA), in which costs are measured in monetary units and outcomes in terms of their utility, usually to the patient, e.g. using QALYs[41]. Other approaches are cost-of-illness analysis, cost-minimisation analysis, cost-consequence analysis and cost-benefit analysis. The results of these analyses yield in recommendations regarding whether an innovative drug should be reimbursement or not at a particular price.

It is difficult and controversial to put a particular monetary value against health outcomes as there is a societal, indication and patient perspective included and there is no real consensus or threshold on what is considered to be cost-effective[43,44]. However, according NICE, innovative medicinal products in the UK that cost more than £20,000-30,000 per extra QALY are usually not considered cost effective[45].

In the QALY and cost consideration, some quite important factors such as differences between life expectation and quality of life depending on age or indication are neglected, or taken into account (value judgement) by adjustment calculations. One of such approach is discussed by Pinto-Prades[46], who calculates that a value between €20,000 to 40,000 per QALY can be cost-effective depending on assumptions for the willingness to pay. It should be noted that there are national differences in value judgement.

The incremental cost-effectiveness ratio (ICER) is defined as additional cost of the more expensive intervention compared with the less expensive intervention (standard therapy) divided by the difference in effect or patient outcome between the interventions[41]. Often,

the change in effects is measured by the number of quality-adjusted life years gained by the intervention.

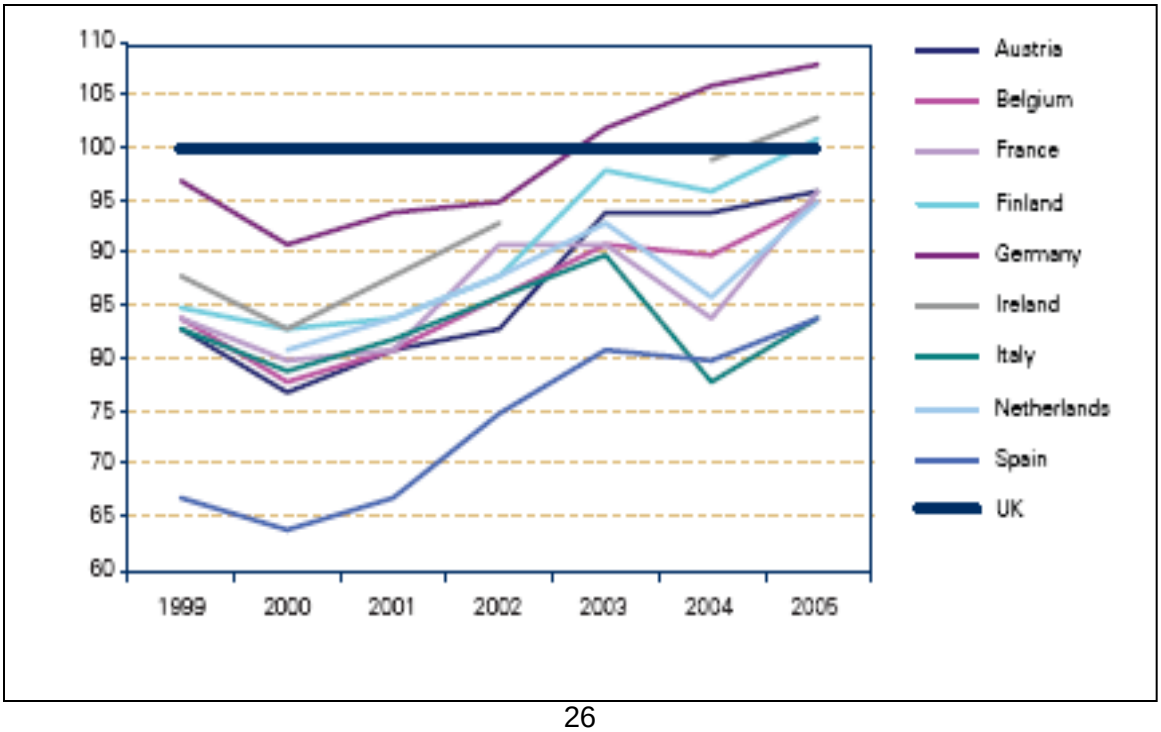
There are now are a few large scale clinical trials ongoing or completed comparing the effectiveness of treatments in large indications such as heart disease. One of them, the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial conducted between 1998 and 2000 included 12,562 patients in 28 countries and yielded in addition to multiple publications regarding cost-effectiveness. Long-term (average 9 months) effectiveness and cost-effectiveness calculations based on ICER conclude that use of clopidogrel plus aspirin is both effective and cost-effective compared to aspirin alone in patients with acute coronary syndrome[47]. This result was mainly due to reduction in hospitalisation cost when adding clopidogrel despite its higher ex-factory costs.

The discussion of efficiency, which describes the extent to which the maximum possible benefit is achieved out of available resources, is of importance to payers but is outside the scope of this thesis.

8.2 HTA in Europe

In Europe, about 75% of medicinal products and devices are reimbursed from public funds[2] . The rising costs of medicinal products (see Figure 2) contribute to the pressure on health budgets and result in the challenge of how maximise “public health” for a given healthcare budget. For medicines, this translates into how best to provide access to effective but also to innovative medicinal products at an affordable cost to the public.

Figure 2: Cost of medicinal products in Europe 1999 – 2005[48]



At present, HTA approaches feeding into pricing & reimbursement decisions of the individual Member States are handled at national level and no European harmonisation/central HTA body exists. All Member States are currently carrying out relative effectiveness assessments and each Member States carries out its own assessments resulting in a great diversity of approaches and outcomes regarding recommendations[49]. However, the evaluation of added therapeutic value is considered scientific work whose results can be used by all interested Member States. Pricing and reimbursement shall remain a national responsibility and it is appreciated that a relative effectiveness and cost-effectiveness assessment is most likely to be meaningful at national level due national difference in willingness to pay and other value factors. However, Member States could benefit from work- and best practice sharing in HTA[50].

The EC HLPF has established a Relative Effectiveness Working Group, which has published some documents on core principles, data requirements and networking in HTA[49,50,51]. Overall, two different phases of data generation for effectiveness assessment are distinguished:

- Before market authorisation (MA) ("MA data"), usually arising from phase III registration studies or other RCTs
- After market authorisation has been granted and the decision on price and reimbursement is taken ("Access to market data"), arising from real-life/post-marketing information, such as observational studies, registries and medical claims data

It was found that the majority of studies produce efficacy and not effectiveness data, and only few studies directly address relative efficacy of different therapeutic interventions. Although it is acknowledged that most registration studies have frequently a suboptimal design for assessment of effectiveness based on (relative) efficacy, evidence from such studies is valued significantly higher than that from "access to market data". Key criticism of phase III registration studies was the lack of a suitable active comparator, choice of endpoints and study duration.

In the core principles it is clearly stated that assessment of relative efficacy is the first step to the assessment of relative efficiency[50]. Relative efficacy data are usually contained in the registration dossier and hence, also due to an increase in products authorised by the centralised procedure, most Member States have equal access to these data, providing a common starting ground for evaluation of relative effectiveness. It was also agreed that the assessment processes for relative effectiveness should remain separate from product market authorisation procedures (which does not mean that they are necessarily performed by different organisations). Furthermore, it was strongly recommended to include both regulatory agencies and EMA, in some form, in networks that deal with issues related to relative effectiveness. However, there are also

legal issues concerning data confidentiality and sharing as well as access to data of registration dossiers in some countries.

From 2006 to 2008, governmental HTA organisations from EU Member States, EEA and EFTA countries and a large number of relevant regional agencies and non-for-profit organisations that produce or contribute to HTA had organised at European level in EUnetHTA. This organisation aimed to further collaboration between HTA-bodies in Europe to facilitate efficient use of resources, knowledge sharing and to promote good practice in HTA methods and processes[38]. However, EUnetHTA has advising character only and no powers of implementation.

Since 2010 until 2012, based on the work of EUnetHTA and the HLPF, a EUnetHTA Joint Action programme is underway which also includes establishment of contact with key stakeholders in HTA including the EMA.

In the following, selected, well-developed national HTA systems and organisations are described briefly to understand some of the differences in national approaches to HTA.

8.2.1 United Kingdom

In the UK, different local HTA agencies are feeding into NHS daily practice[37]:

- National Institute for Health and Clinical Excellence (NICE)
- Scottish Medicines Consortium (SMC)
- All Wales Medicines Strategy Group
- National Coordinating Centre for Health Technology Assessment

The best know is NICE, which undertakes appraisals of health technology and publishes binding guidelines for England to support the cost-effective use of NHS resources in three areas[42]:

- The use of health technologies including innovative medicinal products and interventional procedures
- Clinical practice
- Guidance on health promotion and ill-health avoidance

The clinical and health technology guidance is applicable in England, Wales and Northern Ireland and the public health guidance in England only. Clinical guidelines are usually reviewed every three years or earlier if substantial new evidence emerges. The SMC provides HTA information for Scotland but collaborates with NICE and some of the NICE health technology guidance are also applicable in Scotland.

NICE health technology appraisals are focussed primarily on evaluations of efficacy and cost-effectiveness versus standard therapy based on QALY and CUA in various circumstances. The appraisals investigate the following questions regarding a specific health technology:

- Is it likely to result in a significant health benefit across the NHS when given to all relevant patients
- Is it likely to result in a significant impact on other health related government policies (e.g. reduction in health inequalities)
- Is it likely to have a significant impact on the resources of the National Health Service
- Will the guidance add value in a controversy of interpretation or significance of the available evidence on clinical and cost effectiveness

The Department of Health refers selected, but not all, health technologies including medicinal products for appraisal to NICE. The sponsoring company is invited to provide an evidence submission.

Assessment reports serving as basis for appraisals are produced by independent academic centres. Relevant stakeholders such as patient groups, organisations representing healthcare professionals and manufacturers (also of active comparators) are invited to take part in the appraisals or act as commentators. Following consolidation of comments, the evaluation report is reviewed by an independent Appraisal Committee which also considers verbal testimony from clinical experts, patient groups and carers. The final technology recommendations (to date nearly 200) are published as guidance and contain recommendations according to four categories:

- Recommended
- Optimised
- Only in research
- Not recommended

Technology appraisals can focus on single or multiple technologies or indications and different data sources and procedures are used for these two approaches. Single technology assessment focuses on a single innovative therapeutic intervention targeting a single indication or on already marketed technologies that have been developed for a new indication. Single technology assessment is primarily based on data submission by the company. For areas with high need, a fast-track appraisal system is in place.

NICE offers advice to pharmaceutical companies during the product development (usually during phase II and prior to III studies) for health technologies that may be referred for a technology appraisal to allow the company to shape their clinical development programme to fit their acceptance criteria[52]. On the clinical site NICE will provide advice on study population, duration, endpoints, comparator and type of the study. NICE will also provide feedback on economic evaluation design, methodological issues and insights from existing models.

The Scottish Medicines Consortium aims to provide rapid HTA for reimbursement decisions in Scotland for all newly approved medicinal products including major new

indications of already marketed medicines based on submissions[53]. The documentation to be submitted by the company includes economic evaluation and budget impact (usually CUA based on QALY). Submissions are initially reviewed to verify that all requested information has been provided, followed by detailed review by the SMC's New Drugs Committee. Reviewers will identify comparators considered to be clinically relevant to the NHS in Scotland which may differ from those identified by the company. The use of comparators has to be according to the UK or EU summary of product characteristics (SmPC), however for the final recommendation is based only on studies that are carried out according to the UK SmPC.

For orphan drugs, SMC will accept a greater level of uncertainty in the economic case. Additional factors, such as whether the medicinal products is indicated for a life threatening disease; substantially increases life expectancy and/or quality of life, can reverse, rather than only stabilise, the condition, or bridges a gap to a "definitive" therapy, will also be considered in assessing both the level of uncertainty and cost per QALY which is acceptable.

SMC aims to provide the review of relative efficacy/effectiveness and cost-effectiveness within 18 weeks of submission which should occur within 3 months of receipt of MA. SMC does not appraise vaccines, branded generics, non-prescription-only medicines, blood products, plasma substitutes and diagnostic drugs. In contrast do NICE, SMC recommendations are not binding although it is expected that the Scottish NHS takes them into account in reimbursement decisions.

8.2.2 Germany

In 2004, the IQWiG was set up with the task to assess the evidence-based effectiveness or (in future) cost-effectiveness according § 35b of the German Social Law Book V[26]. The IQWiG is a governmental-implemented independent scientific HTA institute, which carries out HTA for innovative or already marketed therapeutic interventions upon requests from the Federal Joint Committee or upon its own initiative. The scope of its work includes scientific effectiveness or cost-effectiveness reports and fast-track reports on medicinal products, devices, procedures and clinical treatment guidelines and disease management programmes. The recommendation are reviewed and considered by the Federal Joint Committee in the pricing and reimbursement process. The IQWiG reports are based on a systematic search for, and analysis of, published studies which provide sufficiently reliable results[54]. IQWiG then produces a synthesized benefit analysis from these results.

The key steps in the preparation of an IQWiG report as follows[55:]

- Formulation of the research question
- Preliminary report plan
- Written public consultation

- Final report plan
- Systematic review of literature
- Scientific assessment
- Preliminary report
- External quality review
- Written public consultation including external commentators
- Presentation to Federal Joint Committee and other stakeholders
- Consolidation of comments
- Final report

To ensure the highest level of certainty of results, only high-quality studies with high internal validity complying with the following criteria are included in the benefit/effectiveness analysis[32]:

- Only RCTs (against active comparator or placebo) are considered as these provide data with the least bias, unless otherwise justified
- Ideally double-blinded studies
- Intention-to-treat (ITT) analysis
- Use the (innovator) medicinal product according to German SmPC unless otherwise justified
- Comparator needs to be licensed in Germany and used to German SmPC unless otherwise justified
- RCTs need investigate "hard" endpoints (mortality or morbidity) and/or patient-relevant endpoints and not surrogate endpoints

The use of non-randomised or observational studies requires particular justification. Surrogate endpoints are not accepted as they are judged to be "unreliable" and "misleading" unless the causality of these surrogate endpoints with patient-relevant or "hard" endpoints has been convincingly shown in interventional studies[32]. Subgroup analysis is usually not accepted. However, the IQWiG accepts studies that are in line with the duration requested by regulatory guidelines. With this approach many possibly informative studies are excluded from the start. The IQWiG praises its scientific evidence-based approach, however this has been also criticised for being too selective as there are very few "ideal" studies for effectiveness considerations. The IQWiG stated to this respect: *"Great certainty of results and proximity to everyday conditions do not exclude one another, but only require the intelligent combination of study type, design, and conduct. […] . Such studies are being discussed at an international level ("real world trials", "practical trials" or "pragmatic trials")"* [32]. The IQWiG considers itself as close the SMC with respect to HTA approach.

The IQWiG reports draw the following conclusions[32]:

- *"Proof of a(n) (additional) benefit or harm exists.*
- *Indications of a(n) (additional) benefit or harm exist.*

- *Proof of the lack of a(n) (additional) benefit or harm exists.*
- *Indications of the lack of a(n) (additional) benefit or harm exist.*
- *No proof and no indication of a(n) (additional) benefit or harm exist."*

For an therapeutic intervention to be qualified as showing "proof" of an benefit or harm requires[32]:

- Either that a meta-analysis of studies shows statistically significant difference between interventions regarding this outcome-related effect (with low uncertainty)
- Or at least two independent studies show convincing statistically significant difference between interventions regarding this outcome-related effect (with low uncertainty) and there are not additional studies showing controversial results
- An exception only one study shows statistically significant difference between interventions regarding this outcome-related effect can be accepted, however this study has to confirm to specific requirements

In case studies included in the meta-analysis show a high uncertainty of results, they can only support "indication" but not "proof" of an effect. From the above, the final conclusion is drawn that a therapeutic intervention has either a "benefit potential, a "harm potential" or a "weighting of benefit and harm". For cost-effectiveness analysis, which so far have not been produced, the IQWiG intends to use the methodology of "efficiency-frontier" presented by graphs[56].

The approach and study selection used by the IQWiG has the potential to lead to a re-assessment of the same studies as used for regulatory assessment. Due to the different objectives, this can result in contradictions in conclusions between regulatory and HTA assessment; the consequences of which remain legally abstruse and lead to uncertainties amongst physicians and patients.

It should be noted that for evaluation of therapeutic interventions for orphan indications, the IQWiG still requires the highest level of evidence (comparative RTCs) but is prepared to accept a meta-analysis of smaller studies, surrogate endpoints and a higher level of uncertainty (usually 5 % but for orphan indications 10 %) where justified[32].

According to the revision of the German pharmaceutical law coming into force in January 2011, for any new or innovative medicinal product a pharmaceutical company has to supply latest with market entry a cost effectiveness dossier to achieve long-term reimbursement of premium prices. This dossier needs to compare cost-effectiveness of the medicinal product with that of other relevant therapeutic approaches available for this indication. Data to support this dossier should usually be obtained from regulatory phase III studies or where necessary additional pharmacoeconomic studies. The data requirements including endpoints, comparators and study design can be discussed upfront with the Federal Joint Committee or the IQWiG in early advice meetings well ahead of dossier submission. It is targeted to have a cost-effectiveness analysis

available within 3 months of regulatory approval. In case no cost-effectiveness dossier is submitted, it is assumed that no added therapeutic value exists and reimbursement will be according to the therapeutic reference class system.

8.2.3 Sweden

The SBU, established in 1987, has the government remit to comprehensively assess healthcare technology from medical, economic, ethical, and social standpoints. The SBU conducts its own research which can, but does not have to, be considered by TFL in addition to the submissions by the company during pricing and reimbursement negotiations[28].

In its HTA assessment, SBU focuses on the following questions[102]:

- Which treatment options are most effective?
- How can we diagnose problems most accurately?
- How can we use healthcare resources to achieve optimum benefits?

The HTA reports prepared by SBU are based on systematic literature reviews and include data that present the best available scientific evidence on the benefits, risks, and costs associated with different therapeutic interventions. Assessment is based on QALY. Depending on the scope of the individual project, SBU review may take several years.

SBU published three classes of reports:

- Yellow reports: a comprehensive report in a whole subject are, not just an individual medicinal product for a specific indication. These reports are externally and internally reviewed and approved. Examples of these reports are “Dyspepsia and Gastro-oesophageal Reflux (2007)” or “Patient Education in Managing Diabetes (2010)”.
- White reports: provide initial information on therapeutic interventions or other healthcare topics which may trigger a “yellow report”.
- Alert reports: early assessment of a single therapeutic intervention under development based on systematic literature review. These reports approved.

Similar to the IQWiG process, much emphasis is given to the definition of research topic, definition of criteria of studies selection, collection and selection of relevant studies and finally weighting of results. Only high quality, relevant studies will be included the in the assessment unless otherwise justified. The evidence used in the review is classified according to the GRADE system of evidence levels[57,58]:

- Strong scientific evidence is equivalent to a high quality of the body of evidence according to GRADE (further research is very unlikely to change the confidence in the estimate of effect).
- Moderately strong scientific evidence is equivalent to moderate quality of the body of evidence according to GRADE (further research is likely to have an

important impact on the confidence in the estimate of effect and may change the estimate).
- Limited scientific evidence supported is equivalent to low quality of the body of evidence according to GRADE (further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate).
- Insufficient scientific evidence is equivalent to very low quality of the body of evidence according to GRADE (any estimate of effect is very uncertain in case no studies meet the quality and relevance criteria).

If studies of equal quality and relevance have generated contradictions in scientific evidence, no conclusion is drawn.

In summary, each EU Member State has somewhat different approaches to HTA and a harmonisation of at least parts of the process is desirable to make HTA assessment more comprehensible and transparent, and ideally effectiveness assessments useful to other Member States.

9 Registration requirements, reimbursement and HTA in selected countries outside Europe

Although the main focus of this thesis resides in the discussion of European systems and relations between regulatory CAs, HTA and pricing and reimbursement organisations and processes, in the light of globalisation it is of interest to also briefly describe and discuss the situation in other key countries such as the USA, Canada and Australia.

9.1 Australia

The Therapeutic Goods Act of 1989 establishes the legal basis for the Therapeutic Goods Administration (TGA), the sole regulatory authority in Australia. With respect to approval of innovative drugs, new indications or dosage forms, the TGA bases rejection or approval on the resolution of the Australian Drug Evaluation Committee. The Australian requirements for data supporting the regulatory dossier are mainly based on those required by EU regulations and guidelines. For phase III clinical studies, active comparator studies are not mandatory.

The review of regulatory dossiers for new drugs takes 255 days but the overall process on average 13 to 15 months. For generic drugs, abbreviated procedure applies with a review timeline of about 45 days[59]. Approval of regulatory dossiers is independent of pharmacoeconomic evaluations and pricing and reimbursement negotiations.

Australia has extensive cost-containment measures in place leading to very low prices for medicinal products. Post TGA approval, the Pharmaceutical Benefits Pricing

Authority makes decisions about the reimbursement of therapeutic interventions based on comparative cost-effectiveness appraisals provided by the Pharmaceutical Benefits Advisory Committee (PBAC)[60]. The company has to submit pharmacoeconomic dossiers for pricing and reimbursement negotiations.

The PBAC was established in 1954 and is the oldest HTA organisation advising on the effectiveness and cost of a proposed benefit of a medicinal product compared to alternative therapies. Formal consideration of cost-effectiveness started in 1993 with companies having to provide pharmacoeconomic dossiers. Assessment relies on the QALY concept, cost minimisation or an acceptable ICER but requires only relatively basic analyses. PBAC receives input from the Economic Sub-Committee mainly consisting of academics, which advice the PBAC on cost-effectiveness following appraisal of the pharmacoeconomic dossier submitted by the company[60]. As a result, PBAC recommends unrestricted listing, restricted benefit, authority required (the equivalent of prior approval), or do not list[60].

9.2 Canada

The legal basis for the work of Health Canada's Health Products and Food Branch (HPFB) is the Canadian Health and Food Act. The review is based on Canadian and ICH guidelines. Standard review target time for a new drug is 345 days, for abbreviated and priority review 20 - 225 days, however usually takes longer. HPFB is available for scientific consultations during the development process. In Canada, regulatory approval is independent of pharmacoeconomic evaluations and pricing and reimbursement negotiations.

All hospital medicinal products are fully funded by the public health care system with no co-payments. About 90% of Canadians have an insurance cover for outpatient prescription medicinal products. Pricing and reimbursement evaluation is not part of the initial licensing process but is managed by separate agency post-licensing (strong focus on effectiveness and health economic justification). The Patented Medicine Prices Review Board reviews prices of medicinal products under patent protection and classes them into 3 categories according to the degree of improvement they offer[62].

To date, each of the 18 individual provinces makes its individual decisions regarding reimbursement, making the Canadian system rather complex[17]. However, all provinces use in their decision process recommendations of the Common Drug Review (CDR).

The Canadian Agency for Drugs and Technologies in Health (CADTH) heads up the CDR process. This consists of a systematic review of the clinical evidence based on an independent literature search and a critique of the detailed pharmacoeconomic dossier submitted by the company. The submission made by the company has to include tabular listings of all published and unpublished clinical studies that are and are not part of the

submission dossier[101]. These listings bear some resemblance with the tabular listings included in the ICH Common Technical Document. Furthermore, the company submission needs to include CEA or CUA based on the primary outcomes cost per life year gained, cost per QALY or cost per event avoided. Innovative medicinal products should be compared with standard therapeutic intervention in Canada. Patient group input and feedback from the company are taken into consideration during the review process. The review takes between 94 to 124 days. Companies may request a pre-submission meeting to clarify requirements. Based on the HTA review, the Canadian Expert Drug Advisory Committee eventually issues non-binding recommendations as to medicinal product to be listed, be listed with criteria or conditions, not be listed, or states a recommendation may be deferred pending clarification of information.

9.3 United States

In the US, the Food and Drug Administration (FDA) is the single regulatory authority for the approval of claims for medicinal products, in the US referred to as “drugs” or “biologics”. Review of regulatory dossiers of small molecules and antibodies is carried out by the Center for Drugs Evaluation and Research (CDER), and for (most) biologics and blood products by the Center for Biologics Evaluation and Research (CBER).

The legal basis for the assessment and approval of drugs is the Code of Federal Regulations. The work of CBER has its foundation in the Federal Food, Drug and Cosmetic Act and that of CBER in addition by the Public Health Service Act. The regulatory review is based on ICH and US-specific guidelines.

Similar to the European situation, the FDA gives advice in form of meetings and feedback to clinical studies to guide the pharmaceutical development process. The data requirements for the regulatory dossier depend on the nature of the drug under review:

- Approval of (innovative) drugs via new drug application (NDA) and biologic license application (BLA) requires a full dossier (quality, safety, efficacy). Usually 2 pivotal (confirmatory) phase III RCT are required conducted versus placebo in the same population. Depending on the degree of innovation or medical need, fast track approval, priority review or accelerated approval could be applicable. External review and opinion is frequently provided by Advisory Committees.
- Approval of generic drugs via abbreviated new drug application (ANDA) only requires quality data and demonstration of bioequivalence.

In contrast to European CAs, the FDA requests submission of original clinical data that are used to re-analyse and verify study results and interpretations submitted by the applicant with the regulatory dossier.

No specific time table but target evaluation times are available for the review of dossiers and the time required for review depends on the nature of drugs:

- The average standard review time for NDAs and BLAs for first cycle review is about 10 months, and for second cycle review 16 to 28 months. Priority review should take 6 months.
- The ANDA review process is relatively fast and according to federal law should be concludes after 180 days, however in 2009 took on average 26 months[63].

FDA grants approval independently of any pricing or HTA considerations, however current discussions seem to indicate that it may in future take a role in effectiveness assessment.

The US Orphan Drug Act 1983 regulates the requirements for orphan designation (disease that affects less than 7,5 in 10 000 people in the US) and related incentives.

Pricing and reimbursement systems in the USA are multifaceted. About half of the Americans are insured privately, one third via governmental programmes such as Medicare and Medicaid, and about 15% are thus far uninsured although the latter will change based on the recent US healthcare reforms[64]. The prices of innovative medicinal products available on prescription in the United States are the highest in the world. About 70% of prescription drugs are reimbursed, the other 30% are paid by patients. Reimbursement and pricing is handled at the level of the individual healthcare insurances. Thus far, the government was legally not allowed to directly set prices for prescription medicinal products; however this is being changed with the Medicare Prescription Drug Price Negotiation Act of 2010.

Many individual health insurances request clinical and economic evidence from pharmaceutical and biopharmaceutical manufacturers as a condition for reimbursement[40]. The majority of them have adopted the submission format developed by the Academy of Managed Care. Review of HTA data is carried out by a broad variety of external organisations, such as Blue Cross and Blue Shield Association Technology Evaluation Center.

The comparison of the US, Canadian and Australian situations to that in Europe further highlights the broad spectrum of approaches to HTA and consequently pricing and reimbursement. Interestingly, Clement et al. and Lexchin et al. compared the cost-effectiveness and effectiveness recommendations by NICE, PBAC, and CDR, and SMC, PBAC and CDR, respectively[17,61]. They found considerable variations regarding recommendations between countries even when considering the same medicinal products, which appear to be based on differences in pharmacoeconomic evaluations reflecting discrepancies between countries and health systems. Furthermore it was found that over 40% of dossiers contained significant uncertainty around clinical effectiveness data, usually resulting from inadequate study design or the use of inappropriate comparators and unvalidated surrogate endpoints that hampered the

effectiveness analyses. In a global market some harmonisation of processes and requirements would be of real advantage.

10 Generation of data for HTA of innovative medicinal products

HTA organisations aim to produce evidence-based systematic reports on effectiveness and/or cost-effectiveness; however the strength of this evidence depends heavily on the availability and selection of data as well as modelling and assessment methods. Although international standards and guidelines have been developed and promoted by organisations like ISPOR[37], EUnetHTA, the International Network of Agencies for Health Technology Assessment (INAHTA), the AGREE collaboration[65] or the EU Pharmaceutical Forum[19], the level of evidence that is included in HTA considerations, assessment methods and cost attributes differ between countries[49,51]. Particularly the appreciation of benefits (including societal factors) that are considered to provide added value and the willingness to pay for them vary between countries based on national value judgements. For these reasons pricing and reimbursement but also HTA currently remain currently a national responsibility.

It appears important to clarify some terminology. According to INAHTA, (clinical) effectiveness is the evaluation of benefit to risk of a therapeutic intervention under ordinary (real-life) circumstances as measured by mainly patient-relevant outcomes (e.g. less adverse events, ability to do daily activities, longer life, response rate, rate of hospitalisation, hospitalisation duration etc.). In contrast, efficacy parameters obtained in RCTs describe the effects that are achieved under ideal (controlled) conditions.

Relative effectiveness is the comparison of different therapeutic interventions under ordinary (i.e. real-life) circumstances in order to classify them according to their practical therapeutic value that may differ nationally depending on the specifics of the healthcare system[50]. It differs from relative efficacy in that here the effects are achieved under normal rather than controlled conditions.

For innovative medicines, HTA assessment usually focuses on the assessment of the added therapeutic value compared to standard therapy, e.g. relative effectiveness. The US Department of Health and Human Services refers not to relative effectiveness, but comparative effectiveness[66]; although there are some distinct differences between the definition of relative and comparative effectiveness, for the purpose of this thesis they are considered equivalent.

Here it should be noted that the term “added therapeutic value”, although widely used, is not concisely defined. A definition mentioned by Eichler et al., 2010, was used Bureau Européen des Unions de Consommateurs when working with the European Medicines Agency Working Group with Patient Organisations80:

- *"A new medicinal product can be said to have added therapeutic value if sound clinical data show that it offers patients better efficacy, and/or better safety and/or simpler administration, than existing alternatives"*

However, this could relate to "added therapeutic value" in an experimental setting (e.g. RCTs) or similarly to "added therapeutic value" under ordinary circumstances. The same appears also to apply to the term "benefit".

Ideally, HTA organisations require relative effectiveness data or at least relative efficacy data obtained from an active comparator study with full access to the source data. This would be the case where clinical data have specifically been generated for the purpose of HTA, usually funded by governmental sources. Presently, HTA organisations search publicly available data such as scientific publications, European Public Assessment reports (EPARs), product information/labelling, clinical databases and/or specific health-economic dossiers submitted by the company as basis for their assessment. Clearly, depending on source it is difficult to check the validity and completeness of these data. Furthermore, there is a lag-time between data generation and their public availability for HTA report generation.

HTA-relevant data should be available prior to, or around, regulatory approval for the purpose of pricing and reimbursement and to facilitate fast access to the (innovative) medical product at a justified price based on initial HTA reports. Additional data that become available later may trigger a review of the assessment and subsequent re-negotiation of pricing & reimbursement conditions where applicable.

10.1 Data requirements for HTA

HTA aims to assess the relative effectiveness of therapeutic inventions in a real-life setting based on positive and negative causal effects of a therapeutic intervention compared with an alternative active treatment[32]. So what are they data requirements?

Measurement of relative effectiveness in an experimental setting requires collection of clinical data from a large patient population under relatively uncontrolled conditions that equate to ordinary circumstances. At least two active treatments have to be tested for superiority. For effectiveness assessment, inclusion of objective and patient-relevant endpoints as well as long-term data is of high relevance. This means long(er)-term data collection in costly, large-scale clinical trials with very relaxed eligibility criteria. It is certainly questionable if it is necessary and can be assured that such studies also adhere strictly to GCP criteria and clinical trials standards.

One example for a recent effectiveness study is the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) trial in schizophrenia conducted and funded ($42.6 million) by the US National Institute of Mental Health Institute[67]. This study included 1,400 participants recruited from a wide range of patients with various treatments at 57 sites

around the US and lasted 18-month duration. CATIE was conducted as a randomised double-blind cross-over study: initially patients were randomised to one of five treatments (olanzapine, perphenazine, quetiapine, risperidone or ziprasidone). The design anticipated a 3-phase study, whereby the first two phases are blinded (with exception of clozapine, which was a treatment option in phase 2 and 3 only) and the third phase is conducted in an open-label setting[68]. The primary outcome, which is a very different endpoint to those used in regulatory efficacy studies, was time to treatment failure (all-cause treatment discontinuation) measured by switch of medication as an expression of comparative effectiveness. The majority (three quarters) of patients switched later from their first treatment to another study medication highlighting the overall low effectiveness of the study medications. The data from the first phase of the CATIE study showed a significantly better effectiveness of one of the medications (olanzapine) over three other study medications but not the fourth, however this relatively small effectiveness advantage was counterbalanced by increased side effects of olanzapine[69]. In addition, a vast array of secondary endpoints including reasons for discontinuation, safety parameters and quality of life questionnaires were collected from the CATIE study and subsequently published, essentially showing positive and negative outcomes for all medications tested. The overall conclusion from this study is that treatment in must be tailored to individual patient needs.

There is a lot of controversial discussion of the CATIE results, starting with the appropriateness of the selection of medicinal products tested, the inclusion of an open-label arm, comparability of dosing, chosen statistical approach. This also highlights some of the issues with larger-scale cross-over effectiveness studies.

Any clinical trial delivers information that resides within a spectrum/scale between (relative) efficacy and effectiveness. Usually registration studies tend to deliver information that is more to the (relative) efficacy side of the spectrum[51].

Thus far, effectiveness studies, also referred to as “pragmatic or practical clinical trials” are an exception[70,71]. Furthermore, it is unrealistic to expect such data to be available prior to or even at regulatory approval, hence HTA has to draw on other sources available as part of EPARs or medical reviews or publications, especially for initial effectiveness evaluation:

- RCTs
- Observational studies including registries
- Meta-analyses

Ideally, studies to be used for HTA-purpose are also longer-term, have broader eligibility criteria and include active comparators and patient-relevant endpoints.

Especially for initial HTA review, the first step in assessing relative effectiveness is assessment of relative efficacy obtained from head-to-head or other RCTs. However, even this appears to be not a simple task. With time, information from other, usually post-marketing studies will contribute to a growing HTA-relevant data basis and facilitate re-assessment of relative effectiveness of a therapeutic intervention.

10.1.1 Randomised clinical trials for registration

The first data that will become publicly available for a new medicinal product and therefore could serve as basis for HTA are relative efficacy data from randomised clinical trials submitted for regulatory approval. Therefore it is of importance to discuss differences between regulatory phase III trials and pragmatic trials that are the ideal data source for HTA to find potential areas of overlap and harmonisation to support initial HTA review of newly approved medicinal products.

Phase III efficacy studies that are the basis of regulatory submission dossiers are likely to have a quite different focus compared to pragmatic clinical trials regarding:

- Endpoints
- Study population
- Duration
- Study design
- Statistical analysis
- Comparators

Endpoints

For most indications, there are clear regulatory guidelines as to which primary and secondary endpoints need to be tested to obtain approval of a specific claim in a given indications. These endpoints supporting the claim include “hard” clinical relevant endpoints as well as validated surrogate endpoints that in literature have shown to be correlated to clinical endpoints. In the setting of rheumatoid arthritis this would for example be the clinically relevant endpoint reduction of signs and symptoms as for example measured by the number of tender and swollen joints or the American College of Rheumatology scoring system and the surrogate endpoint prevention of structural damage as measured by X-ray[72,73]. In oncology, mortality as measured by overall survival is considered a “hard” endpoint, whilst tumour response is an endpoint that is not correlated with an improvement in quality or duration of life. Nevertheless, as concluded by Apolone et al. many cancer treatments have been approved on the basis of tumour response as validated surrogate endpoint[74]. Other controversial endpoints in oncology are progression-free survival and time-to-progression that are considered by EMA as surrogate endpoints.

HTA focuses particularly on patient-relevant endpoints, which in addition to the clinically relevant “hard” endpoints (mortality and morbidity) include quality of life endpoints[32].

Side effect profiles are of high relevance. Surrogate endpoints are usually not accepted by HTA unless they are validated to be causally linked to a patient-relevant outcome[32,75].

Interestingly, as progression-free survival is judged to have quality of life attributes, HTA recognises this endpoint as patient-relevant endpoint and not as surrogate[75].

Study population

In regulatory RTCs efficacy is demonstrated under ideal circumstances, meaning that patients randomised into this study are selected to show the maximal effect. This is achieved by a vast number of rather strict eligibility criteria. In a real-life setting, patients presenting to the physician will not undergo as many checks and analyses to evaluate if they are most suitable to benefit from a medicinal product. As a consequence, pragmatic clinical trials trying to capture effects under ordinary circumstances have more relaxed eligibility criteria. Thus, regulatory RCTs have a lower external validity than pragmatic clinical trials.

Furthermore, at present many innovative therapeutic interventions especially in chronic conditions such as rheumatoid arthritis or cancer are being studied as second- or third line or add-on treatments for initial regulatory approval. As a result their effectiveness may be underestimated in such relapsing or refractory patient populations. From an effectiveness point to view, it may be worthwhile to investigate them in a first-line setting as provided convincing relative efficacy is shown this subsequently could save the cost for other upfront treatments. However, there are ethical considerations that also need to be taken into account. As post-marketing effectiveness studies usually investigate “on-label” use of a medicinal product, potentially useful interventions may otherwise not be investigated and reimbursed when used first line[75].

Duration

Depending on the indication (chronic versus acute), demonstration of endpoints after few months will usually suffice for regulatory approval: The required observation time depends of course on the indication and nature of endpoints. As an example, evidence of reduction of sign and symptoms after 6 months is usually sufficient in rheumatoid arthritis[72,73], however for radiological endpoints an observation period of 12 months is required. Treatment of bacterial infections will usually last less than 2 weeks, and studies are required to follow patients four to six weeks post –treatment[76]. According to ICH guideline – Topic E1[77] for approval of medicinal products intended for long-term treatment of non-life-threatening conditions safety data after 6 months of treatment suffice to support approval, although 12-months data are favoured and should be submitted as soon as they become available.

For HTA purpose, the overall long-term or even life-long effect of a treatment for chronic disease is of importance even after patients have stopped receiving the medicinal

product under observation[32]. In the life-threatening indications in oncology, non-responders immediately move on to another therapeutic intervention. This of course interferes with the evaluation of the effect of any medicinal product on long-term overall survival as it is not clear which of the therapeutic interventions has contributed to the effect[75]. The same situation arises for other chronic conditions when patients are to be followed much beyond receiving the study medication.

Study design

Pivotal RCTs supporting a regulatory dossier are usually prospective, randomised, double-blind, controlled studies; there are some exceptions such as in orphan diseases. All regulatory studies are conducted according to ICH guideline – Topic E3[78] compliant with GCP requirements and especially phase III studies are frequently audited to this respect to verify the validity of source data. Pragmatic clinical trials may not necessarily adhere to such strict criteria and standards and hence have a much lower internal validity.

Regulatory studies are often carried out in cross-over design allowing intra- and inter-group comparisons and for some conditions, cross-over studies are a regulatory requirement. In cross-over trials, treatment phases can be switched more than once and more than two treatments can be compared with each other. Analysis of patients in their originally assigned study groups can dilute any observed effect[75].

Comparators

To obtain regulatory approval it is of importance to demonstrate a maximal effect of a medicinal product. According to ICH guideline – Topic E10[79] it is important to distinguish in clinical studies between assessment of efficacy and/or safety and assessment of relative efficacy, safety, risk/benefit relationship or utility of two treatments. As mentioned by Eicher et al.[14] it is the former that is the focus for regulatory approval. Use of placebo is best suited to investigate the maximal effect and also the adverse event profile of an innovative therapeutic intervention.

Hence, and as requested by FDA, regulatory studies are frequently run against placebo rather than an active comparator. Directive 2001/83/EC as amended describes the preference, but not absolute requirement, for studies conducted versus an active comparator, or placebo and an active comparator "*In general, clinical trials shall be done as 'controlled clinical trials' if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified […] ; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo*".

In addition, the revised World Medical Association Declaration of Helsinki requests conduct of clinical studies against gold-standard treatment rather than placebo with some exceptions, as stated in principle 32 of the Declaration[80]:
"The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- *The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or*
- *Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option."*

As stated, it is not always possible to show an effect against an active comparator. This is for example the case for some orphan indications for which no standard treatment exists. Furthermore, as also described in ICH guideline – Topic E10, comparators should be acceptable to the region for which the data are intended.

As companies seek to establish global development programmes, they frequently decide on superiority studies against placebo as comparator to gain acceptance of the studies in the US and in Europe. However, for use of regulatory studies as basis for extrapolation of relative effectiveness using modelling approaches[32], direct demonstration of relative efficacy in head-to-head studies against an active comparator aiming for the same endpoints is preferred. It is of cause a question which comparator is the most acceptable: for HTA considerations, this should be the "gold standard" intervention in a particular indication and country (approved or not approved, although the latter is not reimbursed), whilst another rationale would be (and is frequently used by companies) to use the medicinal product with the closest mode of action to the one under investigation.

Eichler et al. reviewed the publicly available information of 42 and 47 new molecular entities authorised between 01 January 2007 to 31 December 2008 by the FDA and EMA, respectively[14]. Of these, 17 (40.5%) and 24 (51.1%) included trials against active comparators in the US and Europe, respectively.

Van Luijn et al.. reviewed publicly available information (European assessment reports, Medline and Embase) of 122 new medicinal products approved via centralised procedure in the EU between 1999 and 2005[81]. They found that at the moment of market authorisation, 48% of them had been studied in RCTs in comparison to existing medicines however. Significantly less RCTs against active comparator were available for medicinal products with a new mechanism of action, most of which were orphan drugs and/or biologics. Overall, only one-third of these trials were published and publicly

available at the moment of marketing authorisation, therefore precluding evidence-based assessment of any added therapeutic value. Even if an active comparator is used in a registration RCT, this is not always the "gold-standard" as recommended by current (national) clinical treatment guidelines and usually required for assessment of relative efficacy as basis for (modelling of) relative effectiveness. Furthermore, there is the risk of downward-drift of efficacy when subsequent trials use different comparators and not one "gold standard" within one indication / class of drugs[14]. Therefore, the best design would be a 3-arm trial including placebo and the "gold-standard" active comparator, as required by Directive 2001/83/EC.

Statistical analysis

The patient numbers included in regulatory RCTs are calculated to show a statistically significant difference in a primary endpoint of clinical relevance. For regulatory approval, usually and as per FDA/EMA guidance replication of results in a second study in a similar patient population is required to minimise the possibility of a first class error [82,83]. Pragmatic clinical trials usually include large patient populations, have a long duration and hence and not replicated.

Although it is a requirement that all patients are included in the statistical analysis of regulatory phase II and III studies (ITT), significant weight is placed on the results derived from patients that have been treated per-protocol (PP) as the effects they experience are most likely due to the medicinal product when administered at a given schedule[83]. Therefore, it is an aim to keep as many patients as possible on treatment as per protocol. PP analysis however can mask effects caused by the study medication and has a potential to overestimate differences.

In a real-life setting, patients who do not respond to treatment are being switched to another one. Furthermore, due to a misunderstood underlying reason that could be treatment-dependent or -independent patients may decide to drop out of the study protocol at any time point. For HTA this information is most useful as it suggests effectiveness of a prescription that may or may not be realised. Therefore, to reduce attrition bias, for HTA analysis the statistical strategy is always to evaluate clinical data as per ITT including all patients. In fact, in the highly debated CATIE clinical effectiveness trial in schizophrenia switch to another medication has been used as the primary endpoint[69].

Of particular importance is the decision on type of statistical comparison, either to demonstrate superiority, non-inferiority or equivalence of a therapeutic intervention versus a comparator group. The majority of industry-sponsored pivotal registration studies are presently superiority studies versus placebo or are non-inferiority or equivalence studies versus an approved medicinal product in a given indication. Eichler et al. concluded that only one of 42 (2.4%) US and 10 of 47 (21.3%) European

registration studies had shown superiority against an active comparator[14]. Nevertheless, such superiority studies would provide the best evidence for added therapeutic value, which payers are prepared to pay for more than for existing drugs. However, it requires larger patient populations to detect a significant difference in superiority studies compared to non-inferiority or equivalence studies.

Furthermore, the risk of failure to demonstrate superiority against an active comparator is higher than to show non-inferiority or equivalence. Showing non-inferiority or equivalence could however also mean a new medicinal product performed somewhat worse than the established comparator since such finding would be masked as long as the data remain within the pre-defined margins of non-inferiority or equivalence of the limit[7].

It may, however, not be always possible to show superiority. For example, in orphan indications patient numbers available for recruitment into a superiority trial may not be sufficient to show superiority. Furthermore, it might be a stiff task to show superiority in a setting when medicinal products with the same underlying mechanism of action are compared, as for example B-cell inhibition. Another challenge is posed by indications and drug classes where standard treatment has already reached the therapeutic ceiling. In the latter case the attempt of showing a statistically significant difference would mean inclusion of very large patient numbers, reflecting in inflation of development costs and consequently target price. Except possibly for orphan indications, companies might than have to accept being classified as “me too’s” without proven added therapeutic value and consequently moderate or reference pricing and reimbursement conditions.

Taken together, most phase III RCTs currently conducted to support a registration dossier do not provide the optimal relative efficacy data that could be for extrapolation of relative effectiveness data, for example using multifactorial regression modelling. However, common grounds could be defined for future phase III trials to serve both, regulatory and HTA needs.

10.1.2 Observational studies

Observational studies are non-interventional, uncontrolled studies, which record therapeutic intervention (exposure) as decided upon by the physician in relation to the effects on the patient and his health status. The clinical trials Directive 2001/20/EC defines a non-interventional study as follows[84]:
“…a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring

procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data."

As such, they can be used to evaluate correlations between the approved therapeutic intervention and patient-relevant health events. Since such studies have very relaxed eligibility criteria and patients are not randomised according to a set of rules, they are prone to bias and hence have a low internal validity. However, observational studies can be carried out prospectively as well as retrospectively and can include a large number of patients at relatively low cost[14]. Databases of public or private insurers or institutions provide a good source for observational studies. Due to their non-interventional nature, these studies reflect the "real-life" situation and can therefore provide useful information for HTA although one has to remain considerate of the level of evidence. Of note, non-interventional studies do not have to adhere to the EU clinical trials and GCP Directive 2001/20/EC.

Since observational studies including registries do record exposure in a real-life physician's practice and only approved medicinal products are used, HTA-relevant data from observational studies becomes only available later in the lifecycle of a medicinal product; well after approval.

10.1.3 Meta-analyses

According to the definition put forward by the IQWiG[85], a meta-analysis is a statistical technique used to summarise quantitatively the results of several studies on the same question to an overall result. Eichler et al. refer to a specific methodology of meta-analyses also as "common reference indirect comparison based on RCT information"[14], which in the absence of head-to-head RCTs may be the next best approach to the assessment of relative efficacy as basis for relative effectiveness. Inclusion of different RCTs investigating a common therapeutic intervention increases the certainty of results compared with the consideration of an individual study. The validity of meta-analyses depends on the statistical methodology used but even more on the quality, quantity and compatibility of source data. Meta-analyses can only be performed later in the lifecycle of a medicinal product once sufficient data has been accumulated. Usually publication and clinical databases are used as basis for meta-analyses, such as Pub Med, The Cochrane Library, Center of Reviews and Dissemination (CRD), HTA Databases, Cihnal. The completeness and quality of data used in a meta-analysis can not really be checked with the originator. Hence, they provide a lower level of evidence for HTA reports.

However, considering most randomised clinical trials are currently still run against placebo or therapeutic interventions other than what is considered the "gold standard" within any particular country, meta-analyses allow to generate relative effectiveness data by inter-study comparison.

One goal of using HTA information is to support the use of premium priced medicinal products only where a real benefit has been shown in a defined population of patients in indications with high medical need. In this respect, an increasing number of Member States have set up interesting risk sharing practices and conditional pricing depending on emerging effectiveness information[86]. The Netherlands, for example, exercises conditional reimbursement of innovative medicines in hospitals over a period of 3 years. During this period information regarding added therapeutic value and some insight in cost-effectiveness based on outcome research can be gained. These data are evaluated regarding cost-effectiveness in a re-appraisal procedure at the end of the conditional reimbursement period. The outcome of this evaluation subsequently determines the decision regarding future reimbursement. There is some discussion as to who will conduct the outcome research and who will pay for it.

Another approach is used in the UK, whereby effectiveness research has been funded the by NHS: Several medicinal products have been studied over a period of 10 years to investigate if they meet a predefined cost-effectiveness value. In case this value is met, the pricing & reimbursement status is maintained, if a medicine turns out to be above this value, the (reimbursement) price is cut and if it is below it could be increased.

In conclusion, initial effectiveness calculations could be carried out based on intelligently designed head-to-head registration studies that try to satisfy the needs of regulators and payers. It has to be reiterated that this might not always be possible (see above). Later in the life cycle of a medicinal product these effectiveness calculations should be revised and complemented with data from pragmatic clinical trials, observational studies or registries.

11 Opportunities for collaboration of regulatory authorities and HTA bodies

11.1 Networking

The argumentation outlined above highlights the need for collaboration between regulatory authorities and HTA bodies to define areas of overlap and agree on some areas of harmonisation of requirements for regulatory approval and (initial) effectiveness / cost-effectiveness assessment. Such collaboration is necessary to sustain the national healthcare systems by paying premium prices only for added therapeutic value and to ensure the competitiveness of the pharmaceutical industry by cost-containment in development. By now this is also appreciated by policy makers around the world including Europe, where as an expression of this debate the HLPF was established in 2005 by the European Commission. In its final report[2]2, the HLPF recommended to: "*Promote the exchange of information on relative effectiveness assessments in order to improve the data availability and transferability*". Subpoints of this recommendation will be discussed below. In the US, the $ 1.1 billion CER programme signed by Congress in

2009, has triggered comparative effectiveness activities, which are also likely to impact the FDA[87].

The report "Development of networking and collaboration" published by the relative effectiveness working group of the HLPF includes the following recommendations: *"It is strongly recommended to include both regulatory agencies and EMEA, in some form, in networks that deal with issues related to relative effectiveness."* This recommendation has been taken up in the Work programme 2010 of the EMA as well as the EMA draft Roadmap to 2015[88,89]. In 2010, the EMA has started a series of meetings with EUnetHTA.

11.2 Public Assessment Reports

Another very important step is the improvement of information exchange between regulators and HTA organisations. Most important vehicles in this process are the European Public Assessment Report (EPAR) or National Public Assessment Reports. This is in alignment with the final report of the HLPF[22], which recommended "*Member States, with the involvement of the European Medicines Agency, should continue their efforts to consider how European Public Assessment Report and the National Public Assessment Report can further contribute to relative effectiveness assessments.*" Van Luijn et al. found that only 27% of results of RCTs submitted as part of a dossier in a centralised procedure were published at time of MA, highlighting the importance of timely availability of EPARs as data source for HTA[81]. It is intended to review and standardise the format of the EPAR to make it more accessible and usable to HTA reviewers[89]. Particular emphasis will be on increasing the transparency of scientific review process including the rationale for the decision and quantitative aspects of the benefit/risk assessment to better support relative effectiveness assessments. Furthermore, to obtain an at a glance overview of up to date clinical data it may be useful expand the original EPAR, rather than issuing separate post-authorisation scientific discussions following Type II variations. It may also be worthwhile to consider if, for the purpose of HTA, data from non-regulatory studies such as observational of phase IV studies should be integrated into the evolving EPAR, however this is currently outside the remit of the EPAR. As EPARs are by nature public documents, no legal and confidentiality issues can arise from their use for HTA.

EPARs are also helpful in ensuring the validity of effectiveness assessment: in contrast to HTA organisations which thus far rely mainly on publications, the regulatory CAs have the legal means to inspect or check the source data they use as basis for their assessment. Hence, data included in a regulatory review and subsequent EPAR have a high internal validity.

In addition to the EPAR, it could also be considered if it may be (legally) possible to share post-marketing safety information contained in the periodic safety update reports

with HTA organisations as some this information may impact the (re-)assessment of safety benefits of a therapeutic intervention and hence associated quality of life. As for the EPARs, it may be feasible to consider a restructuring of the PSUR to suit the HTA organisations needs.

Such initiative would also conform with the following recommendation of the final report of the HLPF[22] to "*increase the understanding among those involved in relative effectiveness assessments of the possibilities and limitations in the generation of data that can be used for relative effectiveness assessments during and after the granting of marketing",* which is also reflected in the EMA Roadmap to 2015: *"Maintaining the dialogue with HTA bodies especially in the post-authorisation phase is very important in view of the vast amount of data which are obtained through post-authorisation collection."* Nevertheless, it was also recommended that the processes of relative effectiveness assessment should remain separate from market authorisation procedures[50].

11.3 Scientific advice

Furthermore, the HLPF advised that *"National authorities and companies should also consider ways of having early dialogue during product development to improve the generation of appropriate data as far as possible.*"

According to the EMA draft Roadmap to 2015[89], EMA will investigate how best to engage with HTA organisations from early development throughout the lifecycle of the medicinal product including post-authorisation phase to align on data requirements and information exchange.

The need for early consultation between HTA organisations and companies has been addressed by some Member States such the UK and in future also Germany who offer advice meetings. A very interesting development is taking place in Sweden and the UK, where in pilot projects the regulatory CA is offering voluntary parallel or joint scientific advice in conjunction with the HTA organisation[90,91].

The UK pilot project started in 2010 and to date procedures have been requested but not completed[92]. The pilot offers at present parallel (two sets) and not joint (one consolidated) scientific advice. With the parallel advice, also based on experience made with FDA/EMA parallel scientific advice, there is the possibility that the two organisations may diverge at certain points. However, as MHRA and NICE due to the parallel process will have insights into each others thinking and standpoints, it should be expected that no significant contradictions will occur in these two set of advice given to the company[93]. This is also facilitated by joint pre-meetings, joint meetings with the sponsor and exchange of draft advice letters between MHRA and NICE[92]. The Swedish pilot project offering joint scientific advice from MPA and TLV (note: not SBU) started in 2009[91]. To

date no public information is available on the overall outcome and perception of these pilot projects.

For the purpose of streamlining the development process of medicinal products to simultaneously suit the needs of regulatory CAs and HTA organisations, joint advice would be of much greater benefit than parallel advice. However, this would require regulators and HTA assessors to agree on common view points and requirements for phase III registration studies and possibly also preclinical studies, a position that based on the considerations above has not been reached as yet (see also section 12).

Establishment of a continuous consultation process between regulatory CAs and HTA organisations during the entire lifecycle of a medicinal product would help to reduce extra cost and development time due to avoidance of duplication of studies with somewhat different endpoints, study populations etc. However, it needs to be clarified which legal and data confidentiality hurdles may hamper such close exchange of information.

Furthermore, clear and early communication of requirements for regulatory approval and relative effectiveness assessment to the company could avoid contradiction in assessment outcomes of the same set of registration data by regulatory CAs and HTA organisations. In turn, this will help to avoid unnecessary investment and failure of success in taking the “fourth hurdle”.

11.4 Establishment of a European HTA organisation?

Besides the discussions about a central EU pricing and reimbursement agency as outlined above[30], there have also been considerations regarding a harmonisation of the HTA process in Europe including the usefulness of an “Euro NICE”, which apparently is a legally feasible option[94]. Such possibility or the extension of the remit of the EMA to include relative effectiveness assessment but not cost-effectiveness was for example discussed at the annual general assembly of the European Federation of Pharmaceutical Industries and Associations in June 2010[95].

It is also a requirement on the industry side that regulatory affairs and market access/HTA experts work closely together in the process of study planning to define areas of overlaps and divergence with the ultimate aim of gaining approval and reimbursement. Although the requirements for effectiveness assessment are not yet harmonised, some of them can be anticipated or discussed with the relevant CAs and HTA organisations in individual or joint scientific advices.

11.5 Effectiveness dossier

With the increasing demand for submission of HTA dossiers, it seems sensible to work towards a harmonised structure of at least the effectiveness part of such dossier similar

as achieved by the ICH process for regulatory dossiers. Furthermore, it is of uppermost importance that the industry increases transparency regarding data that may be feasible for inclusion in efficiency assessment and hence provides a full overview of all clinical studies conducted in the HTA dossier, such as already implemented in Canada. One could speculate if the existing CTD structure could just be expanded to include a module on relative effectiveness assessments, however harmonisation of other requirements is needed first before such discussion should be taken up. Furthermore, depending on the process and organisations involved in the review of such dossier, legal and confidentiality challenges may have to be resolved first.

In conclusion, it would be appreciated if regulatory CAs and HTA organisations at least in Europe but ideally also worldwide could align on the requirements regarding clinical data for effectiveness and regulatory assessment. A more integrated process of guiding clinical development and possibly also review of data will achieve harmonisation of HTA outcome as scientific basis for national pricing and reimbursement negotiations.

12 Potential impact of HTA requirements on registration studies and consequences for (international) regulatory affairs

Requirements of regulatory CAs (efficacy, safety and quality assessment) regarding clinical studies differ from those of HTA organisations (effectiveness and cost-effectiveness assessment). It is, however, inevitable that organisations HTA and regulatory CAs need to work together to achieve the aim of a timely effectiveness assessment in close proximity to regulatory approval. This in turn will impact the regulatory strategy and HTA strategy of the companies developing innovator medicinal products regarding the design of phase III clinical programme and likely also post-marketing studies and data collection.

International companies ideally aim for one single world-wide clinical development programme (with some regional bridging studies to extrapolate results) for a particular medicinal product in a given indication. This is a prerequisite for containment of pharmaceutical development time and costs, which would be hugely inflated when even more large(r)-scale clinical studies would be requested. Due the efforts of the ICH significant harmonisation has been achieved of some of the regulatory requirements, however, such process has not even started intrinsically for HTA. To avoid duplication of development efforts by requesting one set of clinical data for regulatory approval and another set of clinical data as basis for effectiveness assessment, harmonisation of requirements is urgently needed. In Europe, the starting collaboration between EunetHTA and the EMA is a first step in this direction. However, this harmonisation process is likely to take many years. Nevertheless, considering the lead times of pharmaceutical development especially for phase III, companies are already required to anticipate how clinical studies could be tailored to meet the requirements of regulatory CAs and HTA organisations simultaneously.

12.1 Expected impact of harmonisation of requirements on study design

For an international pharmaceutical company with focus on Europe it seems appropriate to contemplate how the European regulatory and HTA requirements may develop Although it is unlikely that full consensus will be achieved in all areas, efforts have to be made to find agreement on a set of requirements in some of the key areas for phase III registration studies that are acceptable for the purposes of both, regulatory and HTA organisations, at least to enable the latter to perform initial effectiveness assessment. Below is briefly discussed, how such harmonisation may impact key elements of the phase III study design and planning.

12.1.1 Endpoints

For each indication, a clear set of "hard" and "patient-orientated" acceptable endpoints could become available to guide the clinical strategy of registration studies. Combined endpoints may distort results in favour of one medicinal product over the other and may not reflect their real value[96], hence simple clean endpoints should be used. Agreement needs to be reached which endpoints have to be targeted as primary and which are acceptable as secondary endpoints. There maybe inclusion of a set of secondary endpoints that specifically answers cost-effectiveness questions. It seems likely that also for orphan drugs more emphasis will be placed on "hard" endpoints. More research may support the validity of surrogate endpoints to support their future use in HTA.

12.1.2 Study population (efficacy or effectiveness measurements):

The eligibility criteria for phase III studies could be required to be less stringent without compromising effect size. This is likely to come at the cost of increased patient numbers, which has a financial and time impact and may also not be possible for all indications, including orphan diseases. Furthermore, depending on ethical considerations, a shift towards investigation of innovative interventions as first- or second line rather than third line treatment may occur to demonstrate maximal effect. Care has to be taken in the selection of study population regarding potential genomic differences (such as slow metabolisers, regional genetic differences) that may affect efficacy and safety, as also discussed in ICH guideline – Topic E5.(R1)[97].

12.1.3 Duration of studies

It is likely that the duration of registration studies will remain dictated by regulatory requirements to avoid further delay of pharmaceutical innovation; however follow-up of patients might be extended outside of the regulatory requirements to yield longer-term effectiveness information. This requires extra funding and organisational considerations.

12.1.4 Study design

The design of a phase III registration study is likely to be dictated by regulatory requirements. However, for large indications it is likely that there will be a strong request for 3-arm phase III studies, including the innovative therapeutic intervention, standard therapy (active comparator) as well as placebo where feasible. Again, this will increase clinical development costs and times.

12.1.5 Choice of comparator (relative efficacy/effectiveness; standard therapy or placebo)

Agreement on a globally (or at least regionally) acceptable specific active comparator ("gold standard") per indication could be reached on the payer/governmental side (see also below). In the absence of such agreement the company needs consider carefully which markets are of particular importance and ideally find a common standard treatment that is acceptable to all of them. It seems appropriate to plan for 3-arm studies including active comparator and placebo (as smallest common denominator) to decrease the risk of regulatory failure due to non-acceptance of the comparator (see below). Standard therapy must not necessarily mean a medicinal product but could also refer to a surgical procedure or a medical device. The acceptance of global development programmes with comparator studies is likely to be increased based on current discussions indicating that the legal basis in the US may to shift for towards the request of active comparator studies to support relative effectiveness assessments[98].

12.1.6 Statistical analysis

At present, ITT analysis is already applied to most phase III studies. Depending on the targeted price (premium versus reference) and indication and mechanism of action of the medicinal product, an overall increase in superiority studies could be expected where premium prices are targeted. Therefore, when planning a phase III study for an innovative intervention, superiority studies and not non-inferiority studies have to be considered. This may also trigger a further shift of pharmaceutical development towards areas of unmet need were superiority can be shown, a move that would be welcomed by policy makers. For non-inferiority and equivalence studies it seems likely that limits will be tightened and will have to be thoroughly justified. Use of a globally/regionally accepted common comparator would help to avoid a downward-drift of efficacy in non-inferiority and equivalence studies.

12.2 Impact on regulatory strategy of the company

So how could the current debate regarding dual use of phase III registration studies for regulatory (safety and efficacy) and HTA (effectiveness and relative effectiveness) assessment impact on the regulatory strategy? At the outset of planning a clinical phase

III programme for an innovative intervention, the company has to carefully consider the target reimbursement price in relation to the target claim (area of unmet need?, first or second line treatment), mechanism of action, data from phase II studies and business case to shape a programme that suit the business expectations.

12.2.1 Premium price targeted

In case there is an established standard therapy for this indication, superiority studies versus active comparator are likely to be required (see above). In the likely situation of lack of a globally accepted standard therapy, the company has to select the most appropriate alternative treatment option that is accepted in most key markets. This is a major challenge even within Europe, as HTA organisations like the IQWiG only accept studies with comparators if they are used according to local medical practice or SmPC, which can vary between countries unless a suitable comparator is centrally approved.

Furthermore, it is important to consider differences or comparability of dose levels, route of administration and dosing regimen when selecting an active comparator. In case where no standard therapy exists such as for orphan diseases, studies against best supportive care may have to be conducted.

Data from phase II studies need to be clearly dissected to extrapolate which may endpoints may be targeted to demonstrate superior outcomes over standard therapy. For Europe, requirements for a superiority claim are best described in Commission Regulation (EC) No 847/2000[99]. Although this regulation is primarily targeted at similar orphan medicinal products, the aspects of clinical superiority are likely to be transferable:

- Greater (relative) efficacy as measured by clinically meaningful endpoints, other endpoints including surrogated may be used
- OR: Greater safety in a substantial portion of the target population(s)
- OR: In exceptional cases, another major contribution to diagnosis or to patient care can be acceptable. Convenience or patient compliance may feature here.

Ideally, the primary endpoint should be a simple, well accepted “hard” efficacy endpoint that will be globally acceptable for HTA. The phase III studies should be tailored to meet the (meaningful) superiority endpoints, but additionally endpoints that provide a rounded picture of the “added therapeutic value” of the innovative medicinal product including safety. Although this is outside the scope of gaining approval, post-marketing trials or observational studies supporting longer-term added therapeutic benefit should be planned for.

Under the perspective of a new, more convenient delivery mode compared to other medicinal products for the same indication, a patient-relevant primary endpoint convincingly showing a clinical relevant benefit resulting from that delivery mode such as increased compliance needs to be targeted. Only if such endpoint is met, it will be able to support premium prices at launch based on HTA considerations. It needs to be

considered if the medical product under development is likely to show significant superiority in endpoints in addition to that related to the mode of delivery. Should this not be the case, it may also be a feasible strategy to launch at reference price and obtain patient compliance data from post-marketing observational studies to support a later revision of reimbursement decision to obtain premium price.

Overall, it is highly advisable for the regulatory and HTA company experts to seek joint or individual scientific advice on the matters of superiority, comparator and feasible endpoints supporting the target claims and request of a premium price.

12.2.2 Reference price acceptable

Non-inferiority or equivalence studies are sufficient for this scenario. However, the choice of comparator needs to be carefully considered (see above) and non-inferiority margins to be defined and justified. Scientific advice is recommendable here as well.

12.2.3 Regional differences in population

With respect to endpoints for a product that is intended for international markets, the regulatory strategy has to consider if there are (genetic) population differences in the key target markets that may influence outcomes (including those with patient relevance) of a study. Examples for this would be slow metabolisers that are more frequent in Asian populations. Studies need to be conducted in relevant markets, or bridging studies planned.

12.2.4 Orphan indication

In case it is intended to develop the innovative medicinal product for several indications, it needs to be considered if and how the target prices per indications influence may each other (e.g. premium price for the orphan indication, reference price for the large indication or same price across indications). This may dictate the sequence of indication development. Should for example a differential pricing policy be intended, development of somewhat different products regarding dose levels, route of administrations and regimens to be investigate may be attempted.

However, payers grow increasingly alert of the increase in relative budget spent on orphan drugs and therefore are in future less likely to be willing to pay steep premium prices unless there are convincing effectiveness data supporting them[33]. In addition, some orphan indications such as idiopathic thrombocytopenic purpura become quite competitive targets. Therefore, the company really has to investigate and predict the competitor, expected efficacy and pricing and reimbursement landscapes before starting phase III investments into such project. Although at present HTA organisations are slightly more lenient regarding their requests towards orphan drugs, it is likely that in future more emphasis will be place to substantiate efficacy and effectiveness data with

long-term follow-up data[21]. Suggestions from the HLPF include setting up collaborations between Member States regarding scientific assessment of the clinical added value that could lead to non-binding common clinical added value assessment reports to facilitate national pricing and reimbursement decisions. Furthermore, conditional pricing and reimbursement agreements could be considered until more data become available. Companies should therefore include relevant pharmacoeconomic endpoints in pivotal clinical studies of orphan drugs and plan for post-marketing trials or observational studies to produce high-quality data to support the added therapeutic benefit. EURODIS has requested to be set up an EMA working party for the scientific assessment of the clinical added value of orphan drugs, which as may also provide input on the requirements regarding endpoints and data via involvement in Scientific Advices[100].

12.2.5 Sequence of MAs

In case the centralised procedure is not used for European approval, due to reference pricing and parallel import across countries the regulatory strategy should also to be matched with the pricing and reimbursement strategy regarding sequence of approval and also launches. Hence, it appears likely that a sponsoring company would try to achieve approval and market access first in highly priced reference country, such as Germany and the UK before attempting approval in lower-priced countries.

12.2.6 Scenario planning

Company project teams should also discuss and plan how to deal with the data and the project in case the target is missed (i.e. superiority can not convincingly be shown, would this lead to termination of the project). Fall-back scenarios for both should be considered. The company should also contemplate involvement in risk sharing activities such as described in the HLPF document on risk sharing practices[86].

13 Conclusion and outlook

In an environment of raising costs of innovative medicines and budget constrains, payers are increasingly taking HTA recommendations regarding relative effectiveness into account for pricing and reimbursement negotiations. Premium prices will be paid mainly for innovative medicinal products showing added therapeutic value as measured by clinical and patient-relevant endpoints. Added therapeutic benefit can arise from better efficacy/effectiveness, lesser side effects, improved applicability, convenience or quality of life compared to standard of care.

The cornerstones of HTA are relative effectiveness and cost-effectiveness assessment. Whilst the cost element will remain a national item, (relative) effectiveness can be deducted from clinical RCTs, observational studies and meta-analyses. At present, many different approaches to effectiveness and cost-effectiveness assessment are being used and data requirements vary. There are specific challenges to the

assessment of orphan drugs. However, initial steps are being undertaken to achieve some harmonisation of the effectiveness evaluation and, although this will remain a national issue, increase the transparency of the cost-effectiveness assessment. In Europe, the High Level Pharmaceutical Forum has provided some first recommendations to this respect, however looking beyond Europe, an international process similar to ICH would be helpful.

Especially in close timely proximity to MA approval, there are some overlaps in data requirements of HTA organisations with that of regulatory CAs. Relative effectiveness can be calculated using efficacy data from RCTs; ideally relative efficacy data. To obtain suitable data, two approaches could be chosen: request of two separate clinical development programmes separately aiming to provide data for a) regulatory approval and separately for HTA/pricing and reimbursement decisions or b) simultaneous for both purposes by merging the requirements within one programme. In the light of cost containment it is acknowledged that a pragmatic approach is necessary and regulatory and (initial) HTA requirements need to be amalgamated to suit one joint clinical (phase III) development programme. This is highly likely to impact on the design of the phase III studies regarding endpoint selection, comparators, study duration (longer follow-up) and population as well as statistical approaches and hence overall regulatory strategy. Regional (EU) and international harmonisation of acceptable endpoints, comparators and approaches to HTA would be of significant help in designing such dual-purpose phase III studies within an international clinical development programme. It seems, however, likely that local differences in requirements for HTA (and regulatory) data will continue to point at least some local bridging studies.

With the changing joint requirements towards the phase III clinical studies, interactions and communication between regulatory and HTA specialists on payer/governmental side and companies need to be improved. A first European step in this direction is being undertaken by EMA and EunetHTA. To achieve early exchange and alignment of requirements, joint (HTA and regulatory) scientific advice appears to be a suitable platform that is currently being piloted in few European countries. As European and national public assessment reports/summaries contain an extensive listing and review of all available clinical data they, in a restructured format, provide an ideal vehicle to share clinical data submitted for regulatory review with HTA organisations. Later integration of post-marketing data into EPARs and subsequent relative effectiveness re-evaluations need to be discussed.

It could be expected that in future most or all countries will request submission of a HTA / pricing & reimbursement dossier alongside, or shortly after, regulatory review and approval of innovative medicinal products. Therefore, a harmonisation of requirements and also structure of the dossier would be of advantage. The responsibility for review of such HTA dossier remains to be determined. It may be worthwhile considering if the

review of relative efficacy/effectiveness data should be tagged on to the review of the regulatory dossier and carried out by the same organisation, as this may become the case in the United States. Such approach would also prevent controversial outcomes of a regulatory and HTA review.

Considering the existence of a single market throughout the EU and the increase of centralised regulatory review of innovative medicines establishment of a central European HTA organisation may be of benefit. Based on the current EU treaty, relative effectiveness assessment by such putative central agency would nevertheless still have to be translated into national pricing and reimbursement decisions.

In summary, requirements of different regulatory CAs and HTA organisations needs to be taken into account for strategic considerations in the design of a phase III clinical programme for an innovative medicinal product. In Europe, only the first steps towards harmonisation of requirements within HTA (effectiveness) and between regulatory CAs and HTA organisations have just recently been initiated. Early consultation with regulatory CAs and HTA organisations may help to avoid duplication of development costs by combining requirements in one set of phase III (registration) studies. Fast progress in the harmonisation of HTA requirements across Europe and alignment with regulatory requirements is needed. A global harmonisation approach would be welcomed.

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Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Unterschrift