



IS THERE A
COMMONALITY ACROSS
THE STRUCTURED
DECISION FRAMEWORKS
USED BY HTA AND
REGULATORY AGENCIES?

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WORKSHOP REPORT

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A COMMONALITY AMONG DECISION FRAMEWORKS USED BY REGULATORY AND HTA?

Section 1: Executive Summary

Background to the Workshop

Over the last five years a number of programmes have been initiated by regulatory agencies and companies to develop benefit-risk methodologies, all of which have a number of common elements. At the CIRS annual benefit-risk Workshop in Washington DC in 2012, there was a consensus from those who are developing benefit-risk methodologies for assessing medicines that there were four key stages to benefit-risk decision-making; Framing the decision; Identifying the benefits and risks; Assessing the benefits and risks; and Interpretation and Recommendation.

Underpinning these was an overarching eight-step framework characterised by; 1. decision context; 2. building the value tree; 3. value tree refinement; 4. assessing relative importance; 5. evaluating options; 6. evaluating uncertainty; 7. concise presentation of results – visualisation and 8. final recommendation.

These steps are explicitly or implicitly part of all the methodologies for benefit-risk assessment currently being developed by regulators and companies. This overarching framework provides the basis for common agreement and discussion of the benefit-risk assessment of medicines by regulatory agencies and other relevant stakeholders.

In addition to these approaches, other groups such as those agencies undertaking health technology assessments (HTA) of new medicines have also developed methodologies to aid them in making benefit/risk/value decisions. As the roles of both licensing bodies and HTA agencies become aligned in terms of data requirements and timing of decisions, can the two groups learn from each other's methodologies?

This Workshop was designed to bring together the various stakeholders to address the question "Is there a commonality across the structured decision frameworks used by HTA and regulatory agencies?" It is well understood that decision

context is different between the two bodies but the ability to use the same decision frameworks would enable the articulation of the decision made by HTA and regulatory agencies to be transparent.

Workshop Objectives

- **Discuss the similarities and differences** between the decision frameworks used by regulatory and HTA agencies
- **Further the thinking** as to what can be learnt from evaluating different methodologies used by both HTA and regulatory agencies for making their benefit-risk decisions explicit
- **Identify the common elements** across methodologies and discuss how to achieve a consensus on a scientifically acceptable framework for making decisions that are broadly applicable to these stakeholders

Introduction

CIRS Executive Director, Lawrence Liberti welcomed participants to the Workshop, where they would attempt to uncover ways in which structured frameworks could be used to bring continuity to decisions regarding new medicines made by regulators and health technology assessors. He suggested that the some of this work might centre on three of the basic components of decision making; that is, the ability to provide a rationale for a decision, the integration of various viewpoints in a structured but flexible way and the communication of the outcome in a clear and cogent manner.

Much progress has been made over recent years in the development of structured frameworks for benefit-risk decision making but **Day 1 Chair, Professor Hubert Leufkens**, *Chairman, Medicines Evaluation Board, The Netherlands* pointed out that significant work has yet to be accomplished. In bridging the decisions of regulators and HTA assessors who must evaluate the same data in different contexts, Prof Leufkens

proposed the consideration of the sometimes significant uncertainty that is still present at the time of regulatory decision making and the disconnect among regulators and HTA assessors, both of which may cause the lack of reimbursement for approved products and reduce access to needed medicines by patients.

Key points from presentations

SESSION 1: ALIGNING DECISION FRAMEWORKS FOR BENEFIT-RISK ASSESSMENT BETWEEN HTA AND REGULATORY AGENCIES: IS THIS PRACTICAL?

Patients, caregivers and prescribing physicians are worried less about the methodologies that are used to explain benefit-risk decision making regarding medicines than they are about the availability of those medicines. **Jean Mossman**, *Policy Lead, European Brain Council, UK* explained that when it comes to the regulation of medicines, patients want to know if the drug being considered will improve public health. They also would like to find out if it is safe and effective in all patients or only in some and the level of certainty that exists regarding its safety and efficacy. When it comes to the evaluation of medicines by health technology assessors, patients still want to understand the thought process used by HTAs to assess similar aspects of the medicine. In addition they want to know how much it costs and if it can be afforded by all patients or just by some.

When a regulator approves a new medicine, the approval is based on the population to be treated, the comparator used in clinical trials and the product's overall benefit-risk profile. However, health technology assessors may disagree with the selection and evaluation of any of these parameters. How can patients then be expected to understand the rationale for these divergences? Furthermore, misalignment can occur among all stakeholders; that is, regulators, HTA agencies, patients, payers, healthcare professionals and government policy makers may all wish to measure different things for different populations using divergent methodologies and rationale. **Lars Brüning**, *Head of Global Market Access, Bayer Healthcare Pharmaceuticals, Germany* proposed that the fulfilment of four criteria; however, may enable alignment of all of these stakeholders: involved and educated patients; transparent processes and common criteria and language; early parallel dialogue with regulatory and HTA agencies and public-private partnership approaches.

Dr David Lyons, *Senior Medical Officer, Irish Medicines Board* (now the Health Products Regulatory Authority) concluded that it may be difficult for regulatory and HTA authorities to use a common instrument for the evaluation of benefit-risk because of the major differences between the remits of the two groups and their evaluation criteria, especially criteria for benefit. However, with improved interaction between the two bodies the regulatory evaluation could be made much more user friendly to health technology assessors, both in general and in specific cases with dialogue facilitated by applicants' advance notification to regulators of elements in the evaluation of a marketing application that may be of particular concern to health technology assessors.

The context, perspective and language for decision making differ in some ways among regulators, who must consider the needs of the public and health technology assessors, who must consider the perspective of the payer. Regulators employ a benefit-risk decision-making framework that uses the parameters of quality, safety and efficacy, whilst health technology assessors think in terms of benefit-cost; that is, they wish to maximise benefit per cost unit and they use a framework that allows them to allocate scarce resources. Regardless of the framework that is used, Professor **Angela Timoney**, *Chair, Scottish Medicines Consortium*, reminded Workshop participants that patients need to understand the contexts of both regulatory and HTA decision making and transparency and an aligned decision framework may support their understanding and engagement.

The goal of the European Network for Health Technology Assessment (EUnetHTA) Work Project 4 was to develop the Core HTA model, a "generic methodological HTA framework based on current best practices". **Dr Kristian Lampe**, *Senior Medical Officer, FINOHTA, National Institute for Health and Welfare, Finland (THL); Coordinator, EUnetHTA WP8* explained that in the development of a Core HTA model, the relevance of each assessment element is considered and translated into one or more practical research question(s), which are answered using typical research methodologies. The result is a structured collection of HTA data in which information on a particular issue can be found at a standard location within the Core documentation. The Core HTA model is intended to primarily serve as a scientific basis for local, national and regional reports and enable sharing

of information due the standard structure.

Professor Hans Georg Eichler, *Senior Medical Officer, European Medicines Agency* posited that there could be commonalities across structured decision frameworks used by regulators and health technology assessors, especially in the consideration of benefits, harms and uncertainty. Publicly clarifying the benefit-risk asymmetry that is part of many regulatory decisions through use of a structured framework may add clarity and transparency, potentially improve the 'light to heat ratio' in public debate and even ultimately provide feedback that can influence regulatory decisions. Patient involvement and framing decisions to patients as risk-risk rather than benefit-risk may be needed to overcome the sometimes conservative risk aversion expressed by some decision makers. Addressing uncertainties, however, may be the biggest challenge in the development of frameworks for decision making.

Regulatory review and health technology assessment can be seen as two similar processes with different perspectives. Regulatory review focuses on safe, effective and acceptable quality of new medicines, whilst health technology assessment centres on the effectiveness of that medicine. **Barbara J Sabourin**, *Director General, Therapeutic Products Directorate, Health Canada* explored the differences in benefit-risk assessments of Health Canada and the Canadian Agency for Drugs and Technology in Health (CADTH) using public information for two new active substances. Results of the comparison indicated that there was overlap in the data presented to both agencies and both reviews were dependent on the data available based on the designs of the clinical trials, which may enable the use of a similar benefit-risk template. Additionally, advance conversations with HTA colleagues about their requirements might allow regulators to present information in a manner that avoids duplication of effort and expedites patients' access to medicines.

Providing the counterpoint to Ms Sabourin's presentation, **Dr Chander Sehgal**, *Director, Drug Review Programs, Canadian Agency for Drugs and Technologies in Health* said that contextual differences between regulatory and health technology assessment might result in substantial hurdles and potential limitations for alignment between regulators and health technology assessors. Practical concerns include different goals and drivers, legal issues, how each group addresses societal values such as

balancing innovation with sustainability, review capacity and resource restrictions. However, there are good opportunities and potential approaches to regulatory-HTA interactions; early engagement would allow the alignment of data requirements and create opportunities for novel approaches such as adaptive licensing designs.

Although regulatory and health technology assessment requirements differ because they are each constructed for the purpose of answering specific questions, whether used by regulators or health technology assessors, the structured decision making approaches used to assess these data requires clarity regarding who decides what and when and about the rules employed in their decisions. For regulatory review, these questions are does a new drug have a clinical effect under controlled conditions and is it safe? In other words, what is the drug's benefit-risk balance? For HTA the questions are how effective is a new drug compared with existing treatments in routine clinical practice and is the new drug cost effective? In other words, what is the drug's value? **Dr Elizabeth George**, *Associate Director, Centre for Health Technology Evaluation, NICE* said that where decisions may be difficult based on the available evidence, NICE will continue to work at enhancing its use of a deliberative and inclusive process of evaluation and a transparent explanation of that process and its outcomes to its healthcare stakeholders.

As part of her doctoral research programme, **Dr Iga Lipska**, *Senior Research Fellow, CIRS* sought to determine the correlations between the regulatory approval process and health technology assessment recommendations in European countries. The results of her studies indicated that the number of negative or restrictive HTA recommendations correlated positively with EMA approval time; longer approval times were an indicator of dossier complexity. All of the correlations had marginally significant tendencies; however, it remains unknown if EMA approval time is an appropriate surrogate of potential issues at registration.

Trastuzumab emtansine (T-DM1, Kadcyla®) was recently approved in the US and Switzerland for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer (mBC) who previously received trastuzumab and a taxane, separately or in combination. Although clinical trial results indicated that this drug demonstrated a significant improvement in progression-free

survival over capecitabine plus lapatinib, **Dr Jens Grueger**, *Vice President, Head of Global Pricing and Market Access, Roche, Switzerland* explained that the number of events did not cross the efficacy-stopping boundary in the scheduled interim overall survival analysis and European HTA has consistently ruled that progression-free survival is not a valid surrogate for overall survival. Whilst EU regulators consider progression-free survival for regulatory approval, they require demonstration that there is no detriment in overall survival. After informal engagement with regulatory and HTA stakeholders it was determined that an unplanned, second interim analysis of overall survival after 50% of events would be considered. After this analysis showed a 32% reduction in mortality hazard, the drug received positive CHMP recommendation; however, the effect of subgroup analyses on HTA in Europe remains unknown.

Before designing its development programme for tofacitinib, a novel inhibitor of the JAK

inflammation pathway, Pfizer sought HTA scientific advice on a number of relevant domains. **Dr Indranil Bagchi**, *Vice President and Head, Payer Insights & Access, Pfizer, USA* reported, however, that the resulting scientific advice received from four countries was extremely divergent in terms of the study designs and economic evaluations that would be required. Significant actions are possible to reduce differences among local HTA reports and guidance including transparent guidance and definition of incremental medical benefit that rewards innovation and that is applicable across a range of jurisdictions. Alignment in recommendations from regulatory and HTA agencies in relation to comparators and endpoints for development programmes and standardisation of the supportive briefing book and consultation formats will enhance the predictability of process in industry efforts to provide international access to innovative medicines.

Recommendations from across the Syndicates

1. Further examine which common elements could be communicated by regulators to facilitate health technology assessment; identify issues addressed in the UMBRA benefit-risk framework vis a vis the nine core domains of HTA.
2. Retrospectively apply an example of a health technology assessment to the UMBRA framework, starting with the common elements of benefits and harms.
3. Based on the outcome of recommendation 2, CIRS should prospectively map assessments to the UMBRA framework – involving industry and regulatory and health technology assessment agencies.
4. Regulatory and HTA agencies should reach out to the general public to better communicate about their systems.
5. Regulatory agencies should create assessment reports more suited to patient needs, engage more with healthcare professionals and better manage the balance between required expertise and conflicts of interest.
6. HTA agencies should educate stakeholders about the role of HTA, communicating more effectively about requirements, criteria and recommendations and discuss listing or reimbursement and access.
7. Industry should work collaboratively with patient groups in a therapeutic area and give these patients information about trial outcomes.
8. CIRS should include more healthcare professionals (HCPs) in their Workshops.
9. CIRS should provide a systematic overview of recent regulatory decisions, HTA recommendations and reimbursement and pricing decisions.

- 10. CIRS should identify HCP and patient information needs and the kinds of knowledge they seek on regulatory and HTA and decision-making processes.**
- 11. To address the diversity in HTA methodology and requirements and the mismatch with regulatory needs: CIRS should**
- Develop a review paper outlining the challenges from an industry, regulatory and HTA agency and patient perspectives; defining activities that are currently occurring in this area and discussing gaps and opportunities
 - Convene a Workshop focussing on how to move forward and including all key stakeholders
 - Form a coalition of a small group of HTA agencies to pilot a common review template on an international scale, potentially with regulatory and patient input, observe how this would work in practice, compare to existing processes and to potentially expand from there
- 12. To address inefficiencies and diversity of disease-specific guidelines: A review should be conducted of existing guidance for drug development and HTA and current activities in this area should be reviewed for their impact and methods for the further development and enhancement identified.**
- 13. To address inefficiencies and diversity of disease-specific guidelines: A demonstration pilot with key stakeholders should be developed**
- An initial survey to identify key topics to address (eg, EQ5D, PFS, 6 min walk) and a review of the identified topic should be conducted
 - A multi-stakeholder workshop should be convened to address the issue
 - A demonstration pilot to show feasibility of cross-agency guidance should be established through a neutral third party such as the Institutes of Medicine or the Innovative Medicines Initiative
- 14. To resolve the need for improvement in parallel scientific advice processes: An international and independent group should evaluate the strengths and challenges of different early advice procedures, studying the impact of early advice on development and outcome, identifying the areas for further improvement and moving to greater alignment, building upon the EMA early advice workshop held in November 2013.**
- 15. To resolve the need for improvement in parallel scientific advice processes: an organisation such as INHATA should establish a training process to improve in-meeting discussion.**
- 16. To resolve the need for improvement in parallel scientific advice processes: CIRS should develop an international best-practice framework.**

Workshop Programme

DAY 1: 1 OCTOBER 2013	
SESSION 1: ALIGNING DECISION FRAMEWORKS FOR BENEFIT-RISK ASSESSMENT BETWEEN HTA AND REGULATORY AGENCIES: IS THIS PRACTICAL?	
Chairman's welcome and introduction	Prof Hubert Leufkens , <i>Chairman, Medicines Evaluation Board, The Netherlands</i>
How important is it for patients that licensing bodies and HTA agencies can explain their respective benefit-risk decisions by utilising an aligned overarching framework?	
Patients viewpoint	Jean Mossman , <i>Policy Lead, European Brain Council, UK</i>
Industry viewpoint	Lars Brüning , <i>Head of Global Market Access, Bayer Healthcare Pharmaceuticals, Germany</i>
Regulatory viewpoint	Dr David Lyons , <i>Senior Medical Officer, Irish Medicines Board</i>
HTA viewpoint	Prof Angela Timoney , <i>Chair, Scottish Medicines Consortium</i>
Methodologies to build structured approaches to decision making in the context of licensing and in relation to HTA: What can be learnt?	
The core HTA model: What is it and how does this aid a structured decision-making process?	Dr Kristian Lampe , <i>Senior Medical Officer, FINOHTA, National Institute for Health and Welfare, Finland; Coordinator, EUnetHTA WP8</i>
A structured benefit-risk framework: more clarity and transparency?	Professor Hans Georg Eichler , <i>Senior Medical Officer, European Medicines Agency</i>
Canadian perspective	Barbara Sabourin , <i>Director General, Therapeutic Products Directorate, Health Canada</i> Dr Chander Sehgal , <i>Director, Drug Review Programs, Canadian Agency for Drugs and Technologies in Health</i>
A perspective from NICE	Dr Elizabeth George , <i>Associate Director, Centre for Health Technology Evaluation, NICE</i>
SESSION 2: BENEFIT-RISK DECISION MAKING	
Chairman's introduction	
Assessing HTA and regulatory approval decisions: A cohort study	Dr Iga Lipska , <i>Senior Research Fellow, CIRS</i>
Assessing HTA and regulatory approval decisions – Two company case studies showing different aspects of alignment or transparency of the benefit-risk decision between HTA and regulators	
Case study one	Dr Jens Grueger , <i>Vice President, Head of Global Pricing and Market Access, Roche, Switzerland</i>
Case study two	Dr Indranil Bagchi , <i>Vice President and Head, Payer Insights & Access, Pfizer, USA</i>

Syndicate sessions	
Syndicate session 1: Mapping HTA frameworks onto UMBRA	<p>Chair: Prof Robert Peterson, Executive Director Drug Safety Effectiveness Network, Canadian Institutes of Health</p> <p>Rapporteur: Eddie Reilly, Vice President, Head of Global Regulatory Affairs, GlaxoSmithKline Vaccines, Belgium</p>
Syndicate session 2: Communicating regulatory and HTA benefit-risk decisions to patients	<p>Chair: Dr Thomas Lönngren, Independent Strategy Advisor, Pharma Executive Consulting, UK</p> <p>Rapporteur: Dima Samaha, Advisor- Innovation and External Affairs, INESSS, Canada</p>
Syndicate Session 3: Collaboration between HTA and regulatory in the development space — how could this improve alignment?	<p>Chair: Dr Linda Harpole, Vice President Global Health Outcomes, GlaxoSmithKline, USA</p> <p>Rapporteur: Dr Franz Pichler, Director, Global Public Policy, Eli Lilly and Company, UK</p>
DAY 2: 2 OCTOBER 2013	
SESSION 3: SYNDICATE SESSIONS AND FEEDBACK	
Chairman's introduction	Professor Hans-Georg Eichler , Senior Medical Officer, European Medicines Agency
Feedback of Syndicate discussion and general discussion	
Panel discussion	
Communication and transparency of decisions: How good is the presentation and documentation of decisions made by licensing and HTA organisations?	
A perspective on HTA decisions	Dr Jan Mueller-Berghaus , Paul Ehrlich Institute, Germany
A perspective on licensing decisions	Dr Wim Goettsch , Project Leader EUnetHTA WP5 on Relative Effectiveness Assessment of Pharmaceuticals and Medical Devices. Health Care Insurance Board, The Netherlands
Industry perspective	Dr Jens Grueger , Vice President, Head of Global Pricing and Market Access, Roche, Switzerland
A patient's perspective	Dr Mary Baker , President, European Brain Council

Section 2: Syndicate Discussions

Syndicate Discussion A

Mapping HTA frameworks onto UMBRA	
Chair	Prof Robert Peterson , <i>Executive Director Drug Safety Effectiveness Network, Canadian Institutes of Health</i>
Rapporteur	Eddie Reilly , <i>Vice President, Head of Global Regulatory Affairs, GlaxoSmithKline Vaccines, Belgium</i>

Background

At the 2012 annual CIRS Workshop there was an agreement that there are four key stages in the benefit-risk assessment of medicines for the purposes of submission to and review by licensing authorities: framing the decision; identifying the benefits and risks; assessing the benefits and risks and interpretation and recommendation. An overarching eight-step framework underpins these stages (Figure 1).

All the methodologies currently being developed by pharmaceutical companies and regulators explicitly or implicitly incorporate these steps (Figure 2). In addition to these approaches, other groups such as those agencies undertaking the health technology assessment (HTA) of new medicines have also developed methodologies to aid them in making decisions such as the core dossier in Europe (Figure 3). These overarching frameworks provide the basis for common ground and

agreement on the principles for assessment and the type of questions HTA and regulatory agencies have to consider in the evaluation of a medicine.

As the roles of licensing bodies and HTA agencies become aligned in terms of data requirements and timing of decisions, can each group develop learnings from the discussions and methodologies being used by the other? Although it is well understood that HTA and regulatory decision contexts differ, the ability to use similar decision framework would enable the transparent articulation of their respective decisions.

Objectives

The objectives of this Syndicate group were to:

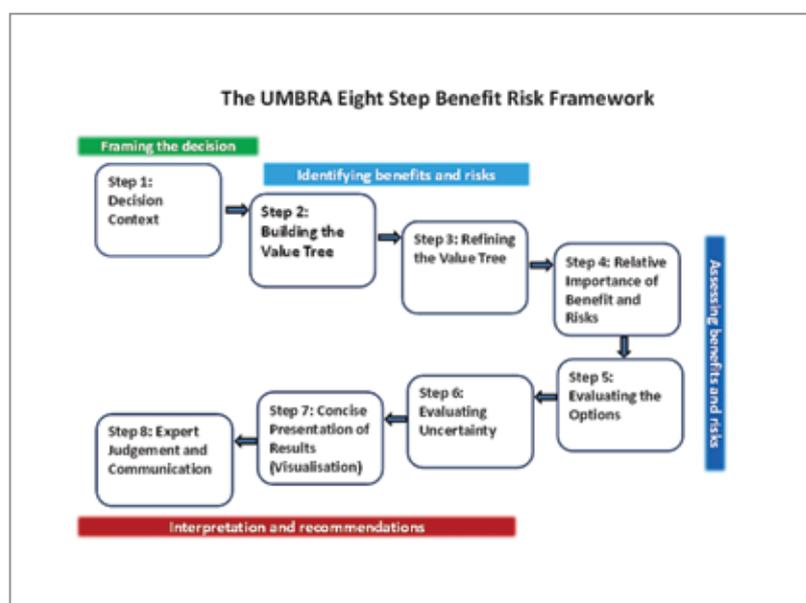
- Identify the common elements of regulatory and HTA evaluation and begin to map HTA assessments to the elements of the UMBRA framework where possible
- Discuss the key challenges and potential opportunities for improved transparency, decision making and communication through the use of a common framework for decision making across HTA and regulatory agencies
- Make recommendations on the commonalities and possible approaches to achieve a consensus on a scientifically acceptable framework for making decisions that are broadly applicable to these stakeholders

Questions for consideration

It was hoped that this group would provide feedback on:

- What are the common elements between HTA and regulatory agency decision making with regard to benefits and harms?
 - Discuss how different HTA approaches

Figure 1. The overarching UMBRA Eight-Step Benefit-Risk Framework underpins the four stages of benefit-risk assessment.



Mapping the Principles of key initiatives to the UMBRA Benefit-Risk Framework

Groups	Framing the Decision		Identifying Benefits and Risk		Assessing Benefits and Risks		Interpretation and Outcome		
Framework	Step 1: Decision Context	Step 2: Building the Value Tree	Step 3: Refining the Value Tree	Step 4: Assessing Relative Importance	Step 5: Evaluating the Options	Step 6: Evaluating Uncertainty	Step 7: Concise presentation of results: Visualization	Step 8: Final Recommendation	
FDA	Analysis of conditions Unmet medical need	Clinical Benefits & Risks		Evidence and uncertainties			Words: Telling the Story	Conclusions and Rationale Risk Management Plans	
EMA	Nature & Framing of the Problem	Objective: Favourable & Unfavourable Effects		Options to be evaluated & the Consequences	Trade off: Benefit/ Risk Balance	Evaluating Uncertainty	Effects Table Risk tolerance	Consistency of Decisions (Linked Decisions)	
BRAT	Define Decision Context	Identify Outcomes Build Value Tree	Customize framework: Refine Value Tree	Assess relative importance of different outcomes: Weighting or Ranking Other Stakeholders		Evaluating Uncertainty?	Display & Interpret Key BR metrics Validate Results	Decision & communication of BR Assessment	
CIRS	Decision Context	Building the Value Tree All Benefits All Risks	Rationale for Benefits & Risks in overall BR assessment	Weighting of Benefits & Risks	Valuing or Scoring of Options		Visualization	Expert Judgement & Risk Management	

Figure 2. Methodologies developed for benefit-risk assessment incorporate implicitly or explicitly the UMBRA Eight-Step Framework.

could be mapped to the different UMBRA steps. Note: As in all decision-making processes, this is an iterative procedure; the activity rather than the actual order is important.

- What are the main challenges and opportunities for aligning language and frameworks between HTA and regulatory agencies?

Critical issues

A decision-making framework that is common to both regulators and health technology

Figure 3. The core elements of health technology assessment in Europe.

Domains of HTA

- Identified in previous EU projects, particularly EUR-ASSESS and ECHTA/ECAHI
- Promote the multidisciplinary nature of HTA

Health problem and current use of technology
Technical characteristics
Safety
Clinical effectiveness
Costs and economic evaluation
Ethical analysis
Organisational aspects
Social aspects
Legal aspects



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assessors would enable a transparency of process including the determination of the criteria for assessment and their weighting as well as the communication of outcomes. For example, the framework might provide a means for conveying the bases of differing regulatory and HTA decisions based on the same data.

In addition to these reasons for a common framework, there may be other opportunities for synergies and efficiencies resulting from alignment; however, differing contexts that result from the evaluation of varying elements such as efficacy versus effectiveness may represent an obstacle.

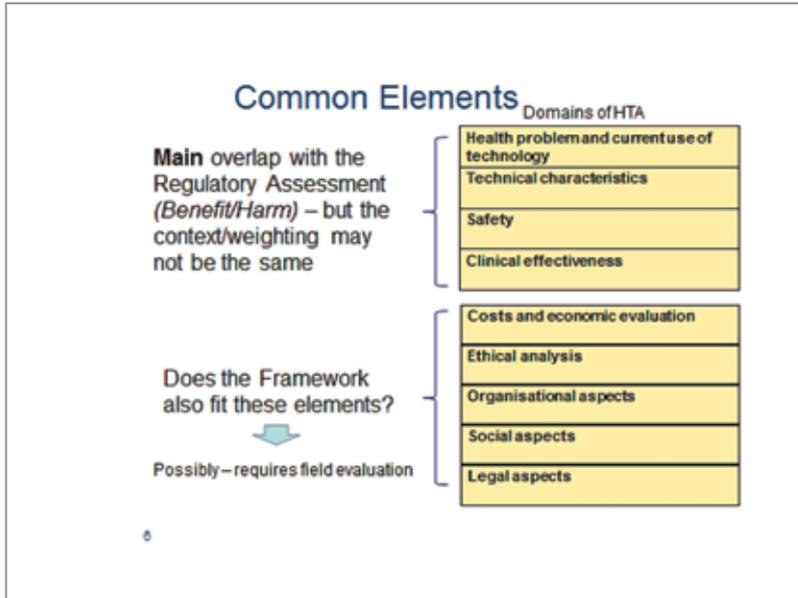
There is overlap between the core elements of health technology assessment and elements examined by regulators; that is, the health problem and current use of technology, the technical characteristics, safety and clinical effectiveness. The other elements within the core domains of the HTA might possibly fit a framework used by regulators but this issue may require field evaluation for a final determination (Figure 4).

The UMBRA framework is a step-wise approach to benefit-risk decision making in which the steps are important but their sequence is not critical. In principle, the UMBRA framework can work for HTA; however there are some challenges, including the fact that HTA is very broad and may examine a therapeutic class rather than an individual product. It should be determined if a framework will be applied to only benefits and harms or to all of the core elements of health technology assessment and indeed, perhaps the more limited perspective should be considered as a first step.

Additionally, there is variability of remit among national HTAs; that is, whether they are called to provide decisions or advice. Ultimately, the value of a common decision framework will lie in its ability to make regulatory and HTA recommendations more transparent and easier to communicate and help explain potential differences, find efficiencies in common elements and reduce duplication of effort.

Strategies

If it is determined that there is a future desired state in which regulation and health technology assessment are more integrated, a standard output must be determined for the use of the framework in health technology assessment and a strong interface that includes a common lexicon must be developed. Elements should



Recommendations

1. Further examine which common elements could be communicated by regulators to facilitate health technology assessment; identify issues addressed in the UMBRA benefit-risk framework vis a vis the nine core domains of HTA.
2. Retrospectively apply an example of a health technology assessment to the UMBRA framework, starting with the common elements of benefits and harms.
3. Based on the outcome of recommendation 2, CIRS should prospectively map assessments to the UMBRA framework – involving industry and regulatory and health technology assessment agencies.

Figure 4. There is overlap between some elements of the core HTA assessment and the elements of regulatory review.

be identified that could be generated by the regulators and reused by health technology assessors. Finally, questions generated by the HTA process could be mapped to the UMBRA benefit-risk framework.

Syndicate Discussion B

Communicating regulatory and HTA benefit-risk decisions to patients	
Chair	Dr Thomas Lönngren , <i>Independent Strategy Advisor, Pharma Executive Consulting, UK</i>
Rapporteur	Dima Samaha , <i>Advisor- Innovation and External Affairs, INESSS, Canada</i>

Background

Once a company has developed a new medicine, two decision makers (regulatory and HTA agencies) have to be satisfied regarding its benefits and harms prior to patients gaining access. However, a survey conducted by CIRS in 2013 indicated that patient groups found that the benefits and harms of new treatments are poorly communicated by these agencies.

HTA systems are set up by governments and health ministries to assess the value of a medicine but the potential difference between the regulatory and HTA agency assessment can cause confusion to many stakeholders. This may be exacerbated by patients' lack of understanding of the terminologies and methodologies employed by the different decision makers.

This Syndicate was asked to discuss the current ways of communicating regulatory and HTA decisions to patients and what the challenges are for clear and unambiguous communication regarding differences in decisions and why the differences have occurred.

Objectives

The objectives of this Syndicate group were to discuss:

- Company and agency (regulatory and HTA) perspectives regarding the current quality of communication of the two decisions
- The challenges to providing patient-friendly information on decisions
- Recommendations as to how patient communication of regulatory and HTA decisions could evolve to ensure clarity

Questions for consideration

The Syndicate was asked to provide feedback on:

- Current approaches to communicating regulatory and HTA decisions to patients
- The perspective of different stakeholders as to whether current communications are fit for

purpose

- What patients are looking for in terms of the detail of communication
- The main challenges to providing patient-friendly information
- Future approaches to communicating with patients in terms of the decisions being made on benefits and harms by the agencies – would an aligned overarching framework enable this process?

Critical issues

Current approaches for patient communication include newsletters, publicly available reports, executive summaries in lay terms, information campaigns such as the EMA campaign regarding black triangles for medications under surveillance, website sections dedicated to patients, product leaflet information (although these mainly lists adverse events) and academic outreach efforts such as the London School of Economics patient education programme. It may, however, be worthwhile to consider communication to the public as opposed to communication to patients and increase the amount of preventative information that is provided.

It was the consensus of this Syndicate that despite strong effort, most of these communications are not fit for purpose because public perception is that products are solely beneficial as patients do not truly understand the concept of benefit-risk and healthcare professionals are not particularly well-educated about how to assess or communicate this topic. Even when information is available, patients do not necessarily know it exists and they have little understanding of the regulatory and health technology assessment systems.

Patients have specific needs regarding the details of communication including learning about the benefits as well as the risks associated with medicines and the rationale behind agency decisions and recommendations. They seek information tailored to their needs and their

particular context; that is, it should be adequate, available, comprehensible, relevant and timely.

There are obvious challenges to the provision of patient-friendly information. It is a resource-intensive process and patients and agencies have yet to speak the same language. It is necessary to communicate effectively without frightening patients, using familiar vocabulary and striking a balance between promotional and meaningless information. In addition, few patients are actually involved in the development of patient information and trust issues remain as a barrier. There is a lack of understanding of the roles of the different stakeholders. The differences in regulatory and HTA perspectives are not understood by patients and health technology assessment tends to be perceived as a barrier to access.

Strategies

Information needs to be made readily available to patients, healthcare professionals and the public and the roles, processes and rationales underlying decisions need to be more transparent and comprehensible. Agencies should use the cascade of information, providing information to member states who will communicate with patients allowing the information to trickle down to the general public.

Healthcare professionals must assume a central role, acting as vectors of information between agencies and patients. However, they must be better educated in benefit-risk as well as regarding agency processes and decisions or recommendations. Patients need access to reliable information. Patient education should be readily available that incorporates visual tools and workshops, help lines and informal forums where patients and healthcare professionals can discuss the risks, benefits and uncertainty of medicines would be ideal. Ultimately, patients should be involved in the decision-making process; that is, in the scoping and drafting of recommendations and patient advocacy groups have a critical responsibility in this area.

Recommendations

1. Regulatory and HTA agencies should reach out to the general public to better communicate about their systems.
2. Regulatory agencies should create assessment reports more suited to patient needs, engage more with healthcare professionals and better manage the balance between required expertise and conflicts of interest.
3. HTA agencies should educate stakeholders about the role of HTA, communicating more effectively about requirements, criteria and recommendations and discuss listing or reimbursement and access.
4. Industry should work collaboratively with patient groups in a therapeutic area and give these patients information about trial outcomes.
5. CIRS should include more healthcare professionals (HCPs) in their Workshops.
6. CIRS should provide a systematic overview of recent regulatory decisions, HTA recommendations and reimbursement and pricing decisions.
7. CIRS should identify HCP and patient information needs and the kinds of knowledge they seek on regulatory and HTA and decision-making processes.

Syndicate Discussion C

Collaboration between HTA and regulatory in the development space - how could this improve alignment?

Chair	Dr Linda Harpole , <i>Vice President Global Health Outcomes, GlaxoSmithKline, USA</i>
Rapporteur	Dr Franz Pichler , <i>Director, Global Public Policy, Eli Lilly and Company, UK</i>

Background

Incorporating regulatory and HTA requirements into companies' development programmes and achieving the necessary collaboration between the two types of agencies to attain this incorporation is challenging. These challenges can be due to many factors such as differences in the remit, scope and evidence requirements of each agency and the level of resources and time required. In addition, within Europe there are many HTA agencies, processes and procedures to consider. However, the commonality that all stakeholders share is the desire to encourage innovation and have effective new medicines to treat unmet medical needs.

As the timing for HTA assessment is now either in parallel or just after the regulatory agency assessment, the evidence generated in the development phase has become critical to both decisions. The task for this Syndicate group was to evaluate whether closer collaboration between HTA and regulatory agencies in the development space could help improve alignment in the decision phase. The group was asked to discuss both if and how collaboration between these agencies could best be achieved and to identify the challenges and opportunities.

Objectives

The objectives of this Syndicate group were to:

- Identify possible areas for collaboration between HTA and regulatory agencies that could occur in the development phase, which would enable better alignment for decision making in companies and HTA and regulatory agencies
- Enumerate the challenges and opportunities for companies and HTA and regulatory agencies
- Make recommendations as to which areas would be the most important for collaboration to enable alignment and how this collaboration could be best facilitated

Questions for consideration

The Syndicate was asked to provide feedback on:

- What opportunities are there for better collaboration between HTA and regulatory agencies in the development phase?
 - Please consider the opportunities and benefits to companies, HTA and regulatory agencies, patients and healthcare systems
- What are the critical areas and mechanisms for collaboration between HTA and regulatory agencies that would improve alignment of decisions?
 - For example, study design, use of endpoints, use of comparators, quality-of-life studies; scientific advice, both parallel and joint
- What are the main challenges for closer collaboration between HTA and regulatory agencies and how could these be best overcome?

Critical issues

This Syndicate agreed on several overriding critical issues in collaboration between HTA and regulatory agencies in the development space.

- The patient's voice is often missing. That is, patient input tends to come in as part of the regulatory and HTA review component but is generally missing from development phase, where patients may be best suited to define unmet needs and to establish patient-relevant endpoints.
- Incentives for decision making are misaligned. All of the stakeholders are trying to improve public health and yet at the individual product assessment level there is a disconnect such that potentially useful technologies are sometimes blocked due to entrenchment of locally focused positions.
- There is real and perceived lack of trust among all parties: While this has improved significantly over the past five years, there is still a considerable improvement needed.

- The timeliness for getting many new medicines to patients should be improved. Sequential processes and inefficiencies in development and review due to conflicting and/or diverse requirements are barriers to timely patient access.

Issues addressed by Syndicate

The Syndicate specifically addressed issues in three key areas: 1) The diversity of HTA methods and requirements and the mismatch with regulatory needs; 2) inefficiencies and diversity of disease-specific guidelines; and 3) the need for improvement in parallel scientific advice processes.

Issue: The diversity in HTA methodology and requirements and the mismatch with regulatory needs

Strategies

Industry is faced with incredible diversity in the methodologies and requirements that are used by health technology assessment agencies and must decide whose advice, requirements and methods will be followed. Although much work is being done to harmonise these components, it may be useful meanwhile to classify the archetypes of HTA and to identify key agencies that represent broader communities and create a core document for HTA submissions to these agencies. This may have the additional effect of enabling communications and data exchange among the HTA agencies within these communities and potentially with regulatory agencies as well. If industry and HTA agencies combined efforts to create this core dossier or template, issues surrounding methodologies and data may also be resolved in the process. However, it should be realised that there will always be limits to alignment based on local context-dependent environments.

Issue: Inefficiencies and diversity of disease-specific guidelines

Strategies

Multiple, unlinked HTA and regulatory guidelines for disease treatment currently exist. Although there is some existing stakeholder guidance for the use of these guidelines it does not appear to have created an impact. Patients should be engaged around the development of disease treatment guidelines, helping to define patient-relevant components, unmet needs, risk tolerance and clinical trial endpoints. To achieve efficiency in establishing the patient voice, patients should ideally present viewpoints to regulatory and HTA agencies simultaneously. Existing fora and activities such as the Green Park Collaborative and EUnetHTA Work Package 7 should be assessed for their potential to be accelerated.

Issue: the need for improvement in parallel scientific advice processes

Strategies

Parallel scientific advice from regulatory and HTA agencies remains disjointed. There has been a limited attempt to reach a consensus and meeting minutes remain separate and non-standard. Moreover, some agencies may be unaware of the limited practical feasibility of their advice. Recognising that this is somewhat early in the evolution of shared advice, it should be recognized that pre-advice preparation by all parties is critically important. Governance should be developed around appropriate funding for the development of a process to ensure independence and credibility for agencies. The process should outline what is reviewed and when it is reviewed to optimise resource allocation. It should also be understood that the timing of advice is important and the advice itself needs to be flexible and impactful.

Recommendations

1. To address the diversity in HTA methodology and requirements and the mismatch with regulatory needs: CIRS should
 - Develop a review paper outlining the challenges from an industry, regulatory and HTA agency and patient perspectives; defining activities that are currently occurring in this area and discussing gaps and opportunities
 - Convene a Workshop focussing on how to move forward and including all key stakeholders
 - Form a coalition of a small group of HTA agencies to pilot a common review template on an international scale, potentially with regulatory and patient input, observe how this would work in practice, compare to existing processes and to potentially expand from there
2. To address inefficiencies and diversity of disease-specific guidelines: A review should be conducted of existing guidance for drug development and HTA and current activities in this area should be reviewed for their impact and methods for the further development and enhancement identified.
3. To address inefficiencies and diversity of disease-specific guidelines: A demonstration pilot with key stakeholders should be developed
 - An initial survey to identify key topics to address (eg, EQ5D, PFS, 6 min walk) and a review of the identified topic should be conducted
 - A multi-stakeholder workshop should be convened to address the issue
 - A demonstration pilot to show feasibility of cross-agency guidance should be established through a neutral third party such as the Institutes of Medicine or the Innovative Medicines Initiative
4. To resolve the need for improvement in parallel scientific advice processes: An international and independent group should evaluate the strengths and challenges of different early advice procedures, studying the impact of early advice on development and outcome, identifying the areas for further improvement and moving to greater alignment, building upon the EMA early advice workshop held in November 2013.
5. To resolve the need for improvement in parallel scientific advice processes: an organisation such as INHATA should establish a training process to improve in-meeting discussion.

Panel Discussion of Syndicate Results: Key points

Dr Wim Goettsch, *Project Leader EUnetHTA WPS on Relative Effectiveness Assessment of Pharmaceuticals and Medical Devices. Health Care Insurance Board, The Netherlands*

- In an examination of the potential of EPARS (European Public Assessment Reports) to be used in HTA assessments in 2010 by MEDEV/EUnetHTA, a number of issues were raised including the presentation of clinical trial results using prose rather than data, the absence of justifications for benefit-risk analyses, possible inconsistencies between data treatment in figures and text and between data provided and final conclusions and evidence standards.
- In the EPAR improvement project, conducted as a collaboration between the EMA and EUnetHTA, three EMA - EUnetHTA meetings were convened in 2010 and 2011 in which

the adaptation of the assessment report template in line with comments from MEDEV/EUnetHTA were discussed. From August to November 2011 ten EPARS using the new template were evaluated by ten HTA organisations with the same questionnaire used by the EMA to assess EPARS and on 22 February 2012 in Paris there was a presentation of the outcome of the parallel EPAR review by EMA and EUnetHTA. Positive comments were made by both HTA and regulatory reviewers of the template and the results were scheduled to be published shortly after this Workshop.

- EUnetHTA conducted a comparison of pilot assessments of relative effectiveness for pazopanib and zostavax and an assessment of canagliflozin was in progress at the time of this Workshop to determine what elements were similar and different to (EPARS) and the reasons for differences. Possible issues uncovered include the use of surrogate

endpoints vs clinical endpoints, the use of progression-free survival versus overall survival and the use of composite endpoints. It was noted that more strict definitions are required and differences persist in the use of direct and indirect comparisons.

Dr Mary Baker, *President, European Brain Council*

- We are an aging society: thanks to good science, a fine pharmaceutical industry and excellent clinicians, two thirds of the people who have lived to be 65 are alive today. However, this is associated with significant challenges including the lack of representation of the elderly in clinical trials.
- We must transfer some of the responsibility for society's health and the prevention of disease to society. In the UK, in addition to the comorbidities of ageing, infertility, teenage pregnancy, smoking and drug and alcohol abuse consume a significant portion of the national health funds before the treatment of serious disease can be addressed.
- Patients must move from approaching regulators and health technology assessors with passion and emotion to having helpful interactions grounded in science and economics. Efforts have been made by institutions like the London School of Economics to provide patients with some of the necessary education and tools and efforts have been funded by industry. Equal efforts must be made to extend education to clinicians, who in some cases may understand even less about regulatory and HTA issues than some patients.
- EMA may wish to consider using patient advocate networks and clinicians to communicate with patients regarding the safety and effectiveness and the benefits, risks and uncertainties of new medicines that have been approved for marketing. Information needs excellent communication vehicles including the broader use of a special vocabulary that patients understand.

Dr Jan Mueller-Berghaus, *Paul Ehrlich Institute, Germany*

- In Germany, HTA and regulatory decisions are not systematically compared, as it was intended by German legislation that G-BA and IQWiG operate within a very narrow frame of responsibilities and thus far their procedures have been kept separate, even though they may operate under the same ministry. Interestingly, the HTA methodology

is very close to a regulatory benefit-risk assessment with the exception that HTA are now looking at added benefit compared to a standard therapy that they define in their own deliberations.

- Currently, the only interaction between German regulators and health technology assessors happens during early advice before phase three, where there is a legal provision for regulatory involvement. This should be advanced because we need to come to a common understanding of how clinical trials that satisfy the needs of both parties can be developed.
- G-BA and IQWiG communications regarding their assessment strive to be clear and transparent. Criteria are published and all the results are accessible on the web. However, their methodologies do not seem to apply to all situations; for example, the thresholds for relative benefit were established without providing a detail of the rationale or the opportunity for multi-stakeholder discussion.

Dr Jens Grueger, *Vice President, Head of Global Pricing and Market Access, Roche, Switzerland*

- We have reached quite a high level of transparency regarding the processes that underlie regulatory and HTA decisions. There are general principles common to both groups, clarifying the context for the decision, ensuring the quality of the data, criteria and weights are established and deciding how you will evaluate the different options. Although as Dr Goettsch pointed out there are a number of science-related differences such as the use of surrogate endpoints vs clinical endpoints, the use of progression-free survival versus overall survival and the use of composite endpoints, great strides in transparency and scientific consistency have been made.
- The question is do we accept without further question diverging decisions that come out of this transparent process? Patients may wonder why they cannot obtain medicines that have been approved for marketing and which are available in a nearby jurisdiction but this diversity is driven by the fact that some countries invest a large portion of their gross domestic product on healthcare, whilst other countries have a fixed envelope of funds that necessitates difficult choices. We must accept the rules of the system, or change that system. The communication has to be more about the context.

Section 3: Presentations

How important is it for patients that licensing bodies and HTA agencies can explain their respective benefit-risk decisions by utilising an aligned overarching framework?

Jean Mossman

Policy Lead, European Brain Council, UK

Patients, caregivers and prescribing physicians are worried less about the methodologies that are used to explain benefit-risk decision making regarding medicines than they are about the availability of those medicines. Ms Mossman, who works primarily with patients with cancer, observed this reality most recently when a young woman with metastatic melanoma, who, as she watched her treatment options disappear, knew that there were treatments in the industry pipeline that might have been effective against her disease that she could not access. It is those people, the patients, who should give us the framework for thinking about the alignment of regulatory and reimbursement decisions.

Patients do have questions for regulators and health technology assessors regarding the

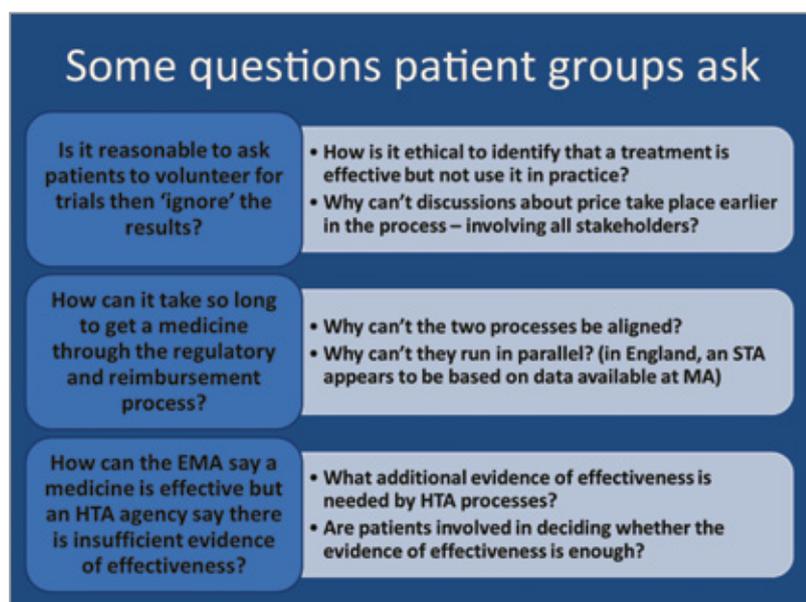
ethics and rationale for not only approving but also for the delay and denial of patient access, such as whether it is reasonable to ask patients to volunteer for clinical trials and then poorly communicate the results of those trials; what the reasons are for the lengthy wait for medicines to be approved by both regulators and HTA assessors and why regulators agree that a new medicines is effective while HTA assessors decide that there is insufficient evidence for effectiveness (Figure 5).

When it comes to the regulation of medicines, all stakeholders want to know if the drug being considered will improve public health. They also would like to determine if it is safe and effective in all patients or only in some along with the level of certainty that exists regarding its safety and efficacy. Some regulators have publicly acknowledged that patients may be more willing to accept the risks associated with effective medicines than regulators are prepared to accept. Many patients understand that benefit and risk are a part of any healthcare system.

In addition they want to know how much it costs and if it can be afforded by all patients or just by some. The question from the patient perspective is who decides the cut-off point for a medicine's affordability and why is this not discussed more publicly? Patients would like health technology assessors to know that value of a medicine does not equal its price but rather what that medicine brings to patients' quality of life and to society in general, who must consider making that patient fit to participate in the workforce and to support and care for his or her family. Ultimately, it is a question as to how heavily the patient perspective will be weighted by regulators and how these opinions will impact decisions for society.

Patients should be part of the decision-making process for medicines and their participation should begin with identifying the important questions for clinical trials and to help with designing study endpoints to ensure that what is being measured is important to the people who will take the medicine. However, patients are rarely asked directly about important clinical questions such as the nature of the unmet need or invited to be involved in defining trial endpoints.

Figure 5. Patients' questions for regulators and health technology assessors largely surround the barriers to timely access to medicines.



Patients should also be involved during the regulatory and reimbursement processes. However, most patients know very little about the regulatory process. Only a few are formally involved in the process and the issue surrounding the potential for conflict of interest in patient participation in the process must be resolved. And although some patients are familiar with the HTA process, in some jurisdictions, many see it as a barrier to access.

Certain assumptions are made regarding the perspectives of stakeholders; that is, that those of regulators, payers and prescribers are evidence-based, rational and objective whereas those of patients and patient organisations are passionate, emotional and subjective. But that is not to say that the viewpoints of patients are not valid nor that patient organisations cannot be assisted in providing objective, rational evidence to the decision-making processes. However, it can be difficult for patients to achieve the understanding of outcomes that is necessary to inform the decision-making process in the face of complex or obfuscating terminology (Figure 6).

HTA processes are neither straightforward nor easy to navigate. The challenge is for patients to learn the language of reimbursement and for HTA assessors to learn the language of patients. In the book *The Norm Chronicles: Stories and Numbers About Danger*, Spiegelhalter and Blastland try help the public to understand statistics and risk, explaining that for the individual patient, benefit and risk are a binary

... for the individual patient, benefit and risk are a binary situation; that is, a medicine will or will not benefit or harm them.

situation; that is, a medicine will or will not benefit or harm them. "Can risk claim to be true to the numbers and to you at the same time? ... It can't. For people, probability doesn't exist."¹ Working with the London School of Economics, Ms Mossman and Dr Mary Baker, President of the European Brain Council have developed a toolkit to help patients and patient organisations understand health technology assessment. This system, which has been translated into several languages, is available at <http://www.htai.org/index.php?id=744#c2840>

Ms Mossman concluded that it is important that regulatory and reimbursement decisions are consistent, especially since they are often based on the same data. It is confusing for patients to be told that a medicine works but does not work well enough to be reimbursed. Patients, regulators and HTA agencies working together and finding the paradigms that would allow alignment might help avoid the perception that the role of HTA is purely rationing, as in the end, all stakeholders want the same thing: getting the right drug to the right patient at the right time.

As for the original question on which this presentation was based: how important is it for patients that licensing bodies and HTA agencies can explain their respective benefit-risk decisions? It is very important and the use of an aligned overarching framework for that explanation can facilitate alignment of these decision makers.

Reference

1. Spiegelhalter DJ, Blastland M. *The Norm chronicles: Stories and numbers about danger*. London, UK: Profile Books, 2013.

Figure 6. The use of complex terminology to describe treatment outcomes may serve to remove patients from decision-making processes.

Understanding outcomes for patients

- Survival
- Mortality
- PFS
- Time to disease progression
- TWIST
- RECIST
- Relative risk
- Absolute risk
- Hazard ratio
- Kaplan Meier Curve
- Forest Plot
- Waterfall Plot
- Fountain Plot
- Tornado Plot
- Conjoint analysis

Regulatory and HTA alignment: An industry perspective

Lars Brüning

Head of Global Market Access, Bayer Healthcare Pharmaceuticals, Germany

When a regulator approves a new medicine, the approval is based on the population to be treated, the comparator used in clinical trials and the product's overall benefit-risk profile. However, health technology assessors may disagree with the selection and evaluation of any of these parameters. How can patients then be expected to understand the rationale for these divergences? Furthermore, misalignment can occur among all stakeholders; that is, regulators, HTA agencies, patients, payers, healthcare professionals and government policy makers may all wish to measure different things for different populations using divergent methodologies and rationale. The fulfilment of four criteria; however, may enable alignment of all of these stakeholders: involved and educated patients; transparent processes and common criteria and language; early joint dialogue with regulatory and HTA agencies; and public private partnership approaches.

1. Involved and educated patients

Industry is challenged on multiple fronts in their efforts to incorporate patient viewpoints and experience into drug development. Patients

are not homogeneous in their views; that is, individual experience matters and has an impact, leaving industry to determine whether the views of advocates, expert patients or a diverse patient population should be sought.

It has come to be understood that patients should be included in early clinical programme development to help shape outputs to more accurately reflect patient needs but industry has yet to determine the best methodology to bring the patient into the process in a structured way. Qualitative and quantitative approaches to capture patient views, preferences and needs are being used increasingly, but industry would like to be certain that regulators and HTA agencies accept these methodologies in principle. Additionally, although patient input is needed at the Scientific Advisory Group level to ensure that the patient experience is being captured, understood and valued, patients first need to be educated so that they can be confident in their involvement.

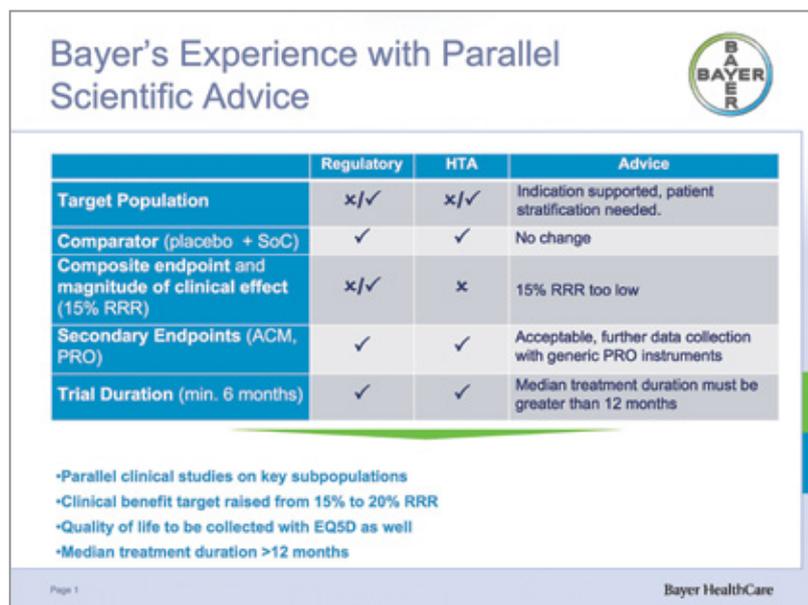
Bayer has already taken the first steps in patient involvement. There is early engagement of patients in clinical development; burden of illness and patient preference studies are being conducted and joint patient/payer advisory boards are being convened. In the future, it is envisioned that patients will become industry partners in shaping clinical programmes at Bayer, providing early input into benefit-risk perceptions, a systematic qualitative analysis of patient benefits and regular patient contributions into the market access process.

2. Transparent processes and common criteria and language

There are many programmes looking at developing a robust and transferrable benefit-risk framework and methodology but the format and language to be used is not yet fully aligned across regulatory agencies. Although common elements have been found to underpin benefit-risk frameworks, agencies have used different methodologies to capture data. The EMA have developed a table to list the favourable and unfavourable effects and their uncertainties in their benefit-risk evaluations. The FDA benefit-risk framework displays evidence and uncertainties for an analysis of a condition, unmet medical need, benefits and risks and risk management of new drugs. The Consortium for Benefit-Risk Assessment (COBRA), comprising the health authorities of Singapore, Switzerland, Australia, and Canada and facilitated by the Centre for Innovation in Regulatory Science

WORKSHOP REPORT

Figure 7. Anonymised example of Bayer's experience with parallel regulatory/HTA scientific advice.



Qualitative and quantitative approaches to capture patient views, preferences and needs are being used increasingly, but industry would like to be certain that regulators and HTA agencies accept these methodologies in principle.

– CIRS, developed the Proforma as common assessment report template.

Guidelines have begun to emerge through the European Network for Health Technology Assessment (EUNetHTA) that give some direction to the way HTA agencies may assess benefit-risk but these are not yet aligned to regulatory requirements. There is hope, however, that these two worlds will come together in the EU. The EMA and EUNetHTA have developed a three-year plan and are working closely to facilitate drug development by cooperating in giving advice to pharmaceutical companies. In fact, EUNetHTA is piloting joint early dialogue with a number of national HTA agencies alongside the EMA scientific advice programme to guide companies in the design of trials that will generate evidence that is appropriate for regulators and HTA assessors. Additionally, because it was felt that European public assessment reports (EPARs) required refining to better address the needs of HTA organisations, the collaboration between HTA groups and regulators has already resulted in a series of improvements to the EPAR template.

Figure 8. True joint relative effectiveness assessment across HTA agencies would eliminate the need for multiple, parallel relative clinical effectiveness assessments, expedited access and lowering costs.

3. Early joint dialogue with regulatory and HTA agencies

Success factors for industry engagement with

agencies have been established as earliness, transparency, precision, mutual trust and a non-binding nature of the advice. Bayer has had positive experience with early parallel regulatory / HTA advice. In one particular instance, there was commonality in the resulting advice, with both regulators and HTA evaluators advising patient stratification. Bayer was able to draw significant conclusions from the session that strongly enhanced the development programme (Figure 7).

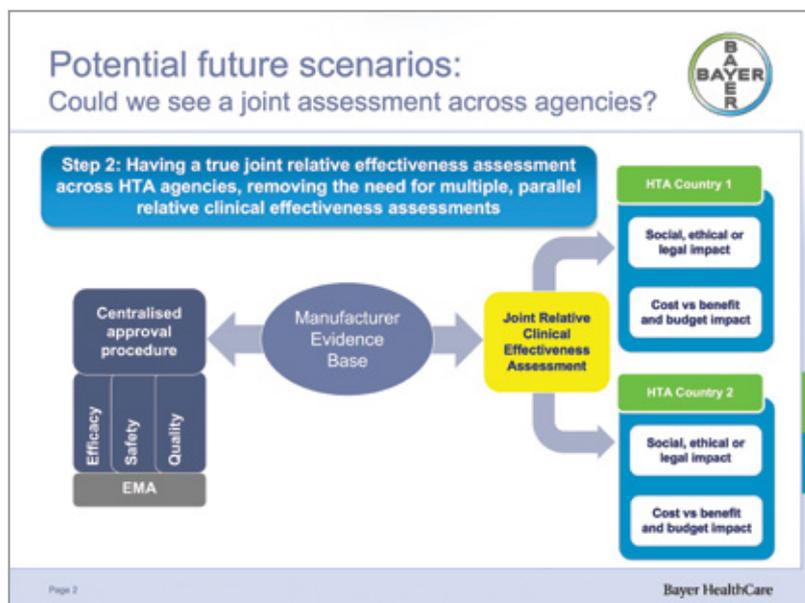
Currently, although companies have one view of their product and can submit one dossier into the central approval process of the EMA, they currently must submit multiple overlapping analyses of the same clinical benefit-risk profile to the HTA authorities of different countries, a time-consuming process that delays patient access and increases cost. By first gaining alignment on the frameworks, criteria and methodology of the clinical effectiveness assessment and then having a true joint relative effectiveness assessment across HTA agencies, the need for multiple, parallel relative clinical effectiveness assessments would be removed, access would be expedited and costs lowered (Figure 8).

4. Public/Private partnership approaches

Public/Private partnerships will allow us to pilot ideas and test methodologies and contribute to the alignment across regulators HTAs and industry. These include - funded through the Innovative Medicines Initiative (IMI) - the European Patient Academy on Therapeutic Innovation (EUPATI) patient education efforts to become true partners in the R&D process, the work of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) group to develop tools to evaluate the benefits and risks of new medicines and the Safer and Faster Evidence-Based Translation (SAFE-T) group, which is creating methods to improve personalised medicine.

Conclusions

Despite the fulfilment of these four criteria for alignment among healthcare stakeholders, alignment between regulatory and HTA agencies on methodological issues as on the use of randomised clinical trials versus pragmatic and observational studies and models and real world data may remain to be significant challenges to all stakeholders. However, alignment on other aspects such as the rising importance of quality of life and on the risks to particular population may be closer at hand and easier to achieve.



How important is it for patients that licensing bodies and HTA agencies can explain their respective benefit-risk decisions by utilising an aligned overarching framework?

Dr David Lyons

*Senior Medical Officer, Irish Medicines Board (now the Health Products Regulatory Authority)**

How the regulator sees benefit-risk analysis

Regulators around the world employ diverse approaches to analyse the benefit-risk balance of new medicines but they must all distil sizable marketing applications that can run to 100,000 pages into assessment reports that are a fraction of that size, summarising the quality, efficacy and safety of the medicine. Regulators do not examine the cost of a medicine and in that respect they can function somewhat removed from certain real world considerations. Health technology assessors, on the other hand, attempt to work within constrained healthcare costs and to obtain the best medical value for society's money.

The functions of regulators and health technology assessors may be logically divided for several reasons; that is, they may be separate in order to provide regulators with a second opinion and perspective; to avoid granting the power to both license and set the price for new

regulatory evaluation could be made much more user friendly to health technology assessors . . . with dialogue facilitated by applicants' advance notification to regulators of elements in the evaluation of a marketing application that may be of particular concern to health technology assessors.

medicines to a single agency and to properly utilise the knowledge of local conditions and the expertise that health technology assessors have developed that is necessary to perform these evaluations. However, the pure regulatory review of a medicine can be considered artificially limited as each product is considered in isolation, with little contextual comparison. This separation of the regulatory and HTA functions of assessment has extended the time required for the availability of medicines.

Improving the process

In 2006, the EMA/CHMP formed a Working Group to improve and standardise the benefit-risk evaluation process. The assessment overview of this process "forces" the reviewer to evaluate benefits and risks and the uncertainties surrounding those parameters to develop an overall conclusion. Although the Working Group concluded that benefit-risk evaluation cannot be "mathematicised," they have constructed an Effects Table to facilitate the development of quantitative or semi-quantitative evaluations that list the new medicine's effects and their importance (Figure 9).

In a pilot project conducted in the first quarter of 2013, the EMA distributed eight live assessments with Effects Tables to CHMP delegates and alternates for comment. Reviewers indicated that there was a huge variability in the standards employed in the tables that ranged from incomprehensible and too lengthy to the very helpful instances that allowed a semi-quantitative evaluation of the new medicine at a glance. The evaluation also revealed that the use of the template was very dependent on the evaluator's editing skills and that there were some problems with the template, which may be easily amended. The project was to be continued for a further six-month period and then re-evaluated.

Dr Lyons has participated in joint EMA/HTA meetings for qualification advice. This type of

Figure 9. The EMA Effects Table lists the favourable and unfavourable effects of a medicine and their clinical relevance.

Effect	Importance
Improved cardiac output	Quite important but poor symptomatic benefit
Increased liver enzymes	Important but no clinical hepatitis

meeting does not concern advice regarding a medicinal product but rather, for the fitness of a metric that will be used to evaluate a medicine; for example, a surrogate marker, electronic patient diary or statistical modelling. In this experience, however, the applicants' questions were addressed to regulators or to health technology assessors with little overlap and therefore did little to advance alignment. Meetings for joint scientific regulatory and HTA advice for medicines have been convened in some countries.

Regulatory hurdles

In 1987, P Slovic investigated the influence of the risk-seeking or risk-avoidance behaviours of reviewers on the assessment process and found that older reviewers were more likely than younger colleagues to take risks¹. This finding is an example of an uncontrollable element of regulatory benefit-risk evaluation. By avoiding the use of technical jargon, regulators can ensure that their communications are transparent and clear to all stakeholders.

Regulatory benefit-risk evaluation is further complicated by seeking to address the uncertainty around the so-called "unknown unknown" risks. For example, the non-steroidal anti-inflammatory drug valdecoxib was eventually found to be associated with three times as much sulphur-related toxicity as

celecoxib, a similar NSAID that also contained a sulphur atom and tolcapone, a catechol-o-methyltransferase inhibitor that was suspended due to unforeseen hepatotoxicity, while entacapone a similar drug of the same class was found to be much less hepatotoxic.

Conclusions

Dr Lyon concluded that it is doubtful that regulatory and HTA authorities can use a common instrument for the evaluation of benefit-risk because of the major differences between the remits of the two groups and their use of specific evaluation criteria, especially criteria for assessing benefit. However, with improved interaction between the two bodies the regulatory evaluation could be made much more user friendly to health technology assessors, both in general and in specific cases with dialogue facilitated by applicants' advance notification to regulators of elements in the evaluation of a marketing application that may be of particular relevance or concern to health technology assessors.

**The material in this presentation is the personal opinion of the presenter and is not endorsed by EMA/CHMP/IMB.*

Reference

1. Slovic P. Perception of risk. *Science*.1987; 236:280-285.

Aligning decision frameworks for benefit-risk assessment between HTA and regulatory agencies: Is this practical? How important is it for patients?

Professor Angela Timoney

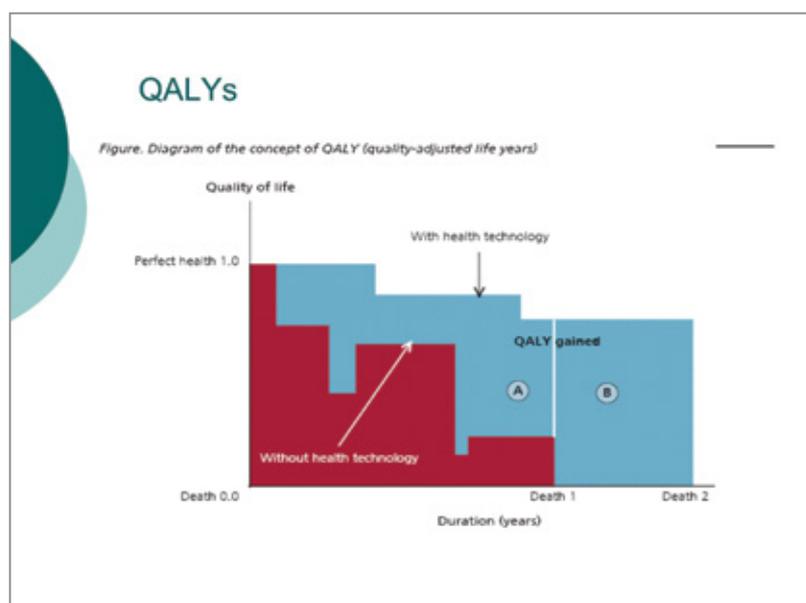
Chair, Scottish Medicines Consortium

Differing roles and frameworks

The context, perspective and language for decision making are entirely different among regulators, who must consider the needs of the public and health technology assessors, who must consider the requirements of the payer. In addition to these differences, the identity of the various stakeholders involved in the specific assessment process must be clearly established in the context of every decision. That is, is the payer who is the focus of the health technology assessment the person with a healthcare budget, or the person who contributes to the budget? Is the public all citizens, their democratically elected representatives or even the media who voice a public view?

The benefit-risk decision-making framework that uses the parameters of quality, safety and efficacy, is primarily the domain of regulators. Health technology assessors, on the other hand, think in terms of benefit-cost; that is, they wish to maximise benefit while minimising cost

Figure 10. In a cost utility analysis, outcomes are measured in terms of quality adjusted life years (QALY); that is the quantity of life adjusted for the quality of life in that period.



... patients need to understand the contexts of both regulatory and HTA decision making and transparency and an aligned framework may support their understanding and engagement.

impact and they use a framework that allows them to efficiently allocate scarce financial resources. It is legitimate and important that both these points of view are part of the decision making for new medicines, however, their differences make the use of one all-encompassing decision framework unlikely.

Health Technology Assessment tools

Health technology assessors accept the regulators' evaluation of the safety and efficacy of a new medicine. They do not consider its affordability but rather its cost-effectiveness by measuring its costs, benefits and unfavourable effects. The types of economic evaluation used can vary among HTA agencies.

- In a cost utility analysis (CUA), the outcomes are measured in terms of quality adjusted life years (QALY); that is the quantity of life adjusted for the quality of life in that period. Treatment options are compared in terms of the cost per QALY ratio (Figure 10).
- In a cost-benefit analysis, treatment outcomes are measured in terms of monetary units and health outcomes such as survival are translated into money by asking about the willingness to pay for the benefit. The result is expressed in terms of excess of benefit over cost; that is, the willingness to pay being greater than the cost.
- A cost-effectiveness analysis (CEA) compares interventions that resulted in different degrees of the same outcome (for example 10% and 20% increased survival) on the cost per unit of effect; for example, the cost per life year gained or the cost per case detected.

Professor Timoney explained that the Scottish Medicines Consortium prefers to use cost utility analyses. The National Health Service does not have a QALY threshold but medicines with a QALY of less than £20,000 are usually considered readily acceptable, while those with QALYs of £30,000 or more must be more carefully justified.

The patient perspective at Scottish Medicines Consortium

The SMC has incorporated the views of patient

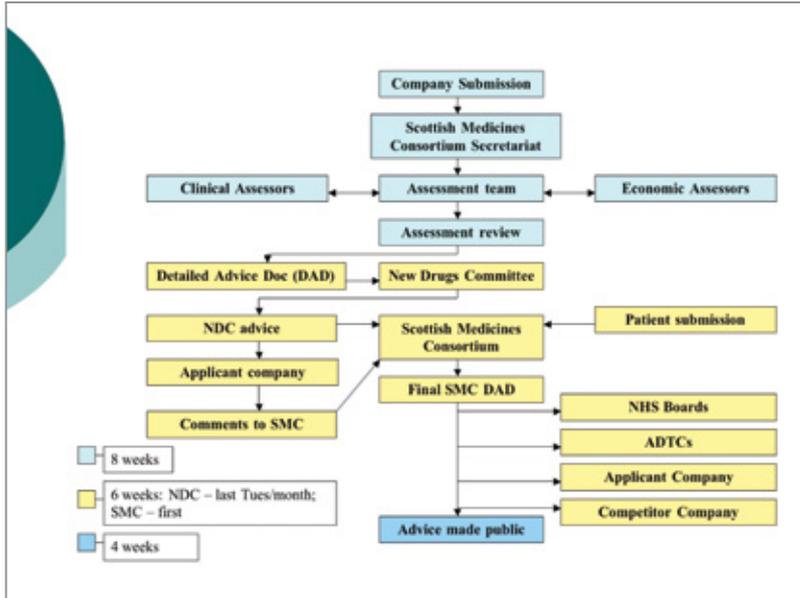


Figure 11. Patient submissions are a part of the process used to evaluate the majority medicines by the Scottish Medicines Consortium.

interest groups (PIGs) since its inception but the integration of public interest in the form of patient and public interest group (PAPIGs) is a newer phenomenon. The SMC encourages PIG submissions, in which patients and their advocates can testify as to what it is like to live with a particular disease in Scotland and what they are looking for in terms of improved therapeutic options.

SMC membership is geographically widespread and multidisciplinary, including doctors, pharmacists, economists, chief executives, stakeholders in the NHS, representatives from the Association of the British Pharmaceutical Industry (ABPI) and patient representatives.

In fact, patient representatives are an integral part of the organisation and patient interest submissions are a formal part of the review process for approximately 70% of new medicines that have gone through initial clinical and scientific evaluation and have been passed onto the New Drugs Committee (Figure 11.) Ensuring that the patient perspective is reflected in accurate and scientifically correct advice has been a challenging but important aspect of the work of the SMC. As an indication of the importance of these contributions in elucidating patient priorities, the SMC has initiated a pilot of these interactions in informing its advice.

An aligned framework?

The steps employed in the Universal Methodology for Benefit-Risk Assessment (UMBRA) framework: (1. decision context; 2. building the value tree; 3. value tree refinement; 4. assessing relative importance; 5. evaluating options; 6. evaluating uncertainty; 7. concise presentation of results – visualisation and 8. final recommendation), which are used by regulators, may also be appropriate for use in health technology assessment. However, the framework lacks the element of cost-effectiveness and the context in which the costs and benefits of a medicine are extrapolated for consideration in a lifetime of use in NHS Scotland.

Regardless of the framework that is used, patients need to understand the contexts of both regulatory and HTA decision making and transparency and an aligned framework may support their understanding and engagement.

The HTA Core Model

What is it and how does this aid a structured decision-making process?

Dr Kristian Lampe

Senior Medical Officer, FINOHTA, National Institute for Health and Welfare, Finland (THL)
Coordinator, EUnetHTA WP8

The goal of the European Network for Health Technology Assessment (EUnetHTA) Work Project 4 was to develop a “generic methodological HTA framework based on current best practices (Core HTA model)”¹. The key aims of this project were to capture the shareable “core” of HTA, to enable production of structured HTA information and sharing the acquired knowledge to support joint and local HTA assessments. The HTA Core model that has been developed consists of three components: the ontology, which defines the set of questions that HTA should answer; methodological guidance, which describes how to answer those questions; and a reporting structure that outlines how to present the answers.

Ontology

The ontology of the HTA Core model is the formal representation of the information contents of a health technology assessment,

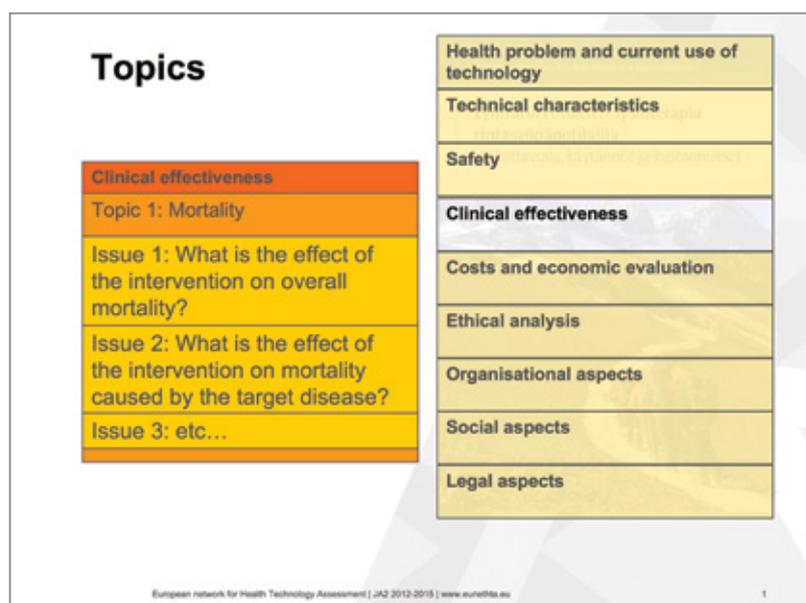
The Core HTAs are intended to primarily serve as a scientific basis for local, national and regional reports . . . Local jurisdictions can easily use the pool of structured information that is contained within the Collections as project platforms . . .

for example, the effect of the technology on the reduction of symptoms. The assessment elements can be viewed as building blocks, with each element providing information on certain aspect of the technology. These elements are defined by nine broad domains.

The nine common domains of health technology assessment, which reflect the multidisciplinary nature of HTA, had been previously identified in EU-funded HTA projects, particularly EUR-ASSESS and The European Collaboration for Assessment of Health Interventions and Technology (ECHTA/ECAHI). These domains are 1) the health problem and current use of technology, 2) the technical characteristics, 3) safety, 4) clinical effectiveness, 5) cost and economic evaluation, 6) ethics and 7) organisational, 8) social and 9) legal aspects.

For each of the nine domains, topics were identified for more specific areas of investigation; for example, the domain clinical effectiveness could be divided into topics that would include morbidity and mortality. Issues, or practical questions were then devised that would uncover the effect of the technology on that topic; for example, “what is the effect of this technology on the mortality caused by the target disease?” (Figure 12)

Figure 12. Issues, or practical questions uncover the effect of a technology on a given topic within a domain.



Methodological guidance

The methodological guidance included in the model assists in finding answers to the questions defined by the ontology. The guidance exists on the levels of domains, the individual assessment elements and the whole model. To avoid duplicative efforts, domain-level guidance mostly consists of reviews of state-of-the-art methodology and links to detailed guidance. There are different strengths of guidance; that is, there are tips, recommendations and standards that must be met.

Reporting structure

The reporting structure for the Core model provides a standardised format for reporting the HTA information. This has been developed in the form of Collections, or general texts that

may include a domain description, discussion of the methodology, introduction and summary. Result cards within the collections each contain a succinct answer to questions defined by one assessment element. Supplementary text such as evidence tables can be described in an Appendix. It is important to remember that EUnetHTA Collections do not contain recommendations, because their aim is to provide a contextual format for information that is then locally interpreted and used.

Use of the reporting structure results in the development of Core HTA information; that is, any HTA information produced using the HTA Core Model and published within the HTA Core Model Online. *Core HTA* is defined as an extensive assessment of a new technology with all domains included, whereas *Rapid HTA* is a fast assessment that includes a selection of domains. In the development of a Core HTA, the relevance of each assessment element is considered in the context of the technology being evaluated. If an element is relevant, the generic issue is translated into one or more practical research question(s) but any possible non-relevance of an element is also recorded in the report. Relevant questions are answered in the Core HTA using typical research methodologies. The result is a structured collection of HTA information in which information on a particular issue can be found at a standard location (whether in paper or electronic form). The assessment elements are coded with specific identifiers and users of the system can easily search and merge information from different collections.

The Core HTAs are intended to primarily serve as a scientific basis for local, national and regional reports. They enable distributed production of HTA; in for example, different domains by separate research groups and easy sharing of information due to their standard structure. Local jurisdictions can easily use the pool of structured information that is contained within the Collections as project platforms, choosing among official EUnetHTA collections such as the Core HTAs and Rapid HTAs or from other collections (Figure 13).

Existing applications of the HTA Core model include projects for medical and surgical interventions and diagnostic technologies conducted between 2006-2008 and projects for screening technologies and the rapid relative effectiveness assessment of pharmaceuticals that were part of the EUnetHTA Joint Action from 2010-2012. Ongoing work in EUnetHTA Joint Action 2 that will continue until 2015 will seek to harmonise and update existing applications and also to develop a new application for the full assessment of pharmaceuticals, which unlike the Rapid model, will contain all assessment domains.

Benefit-risk

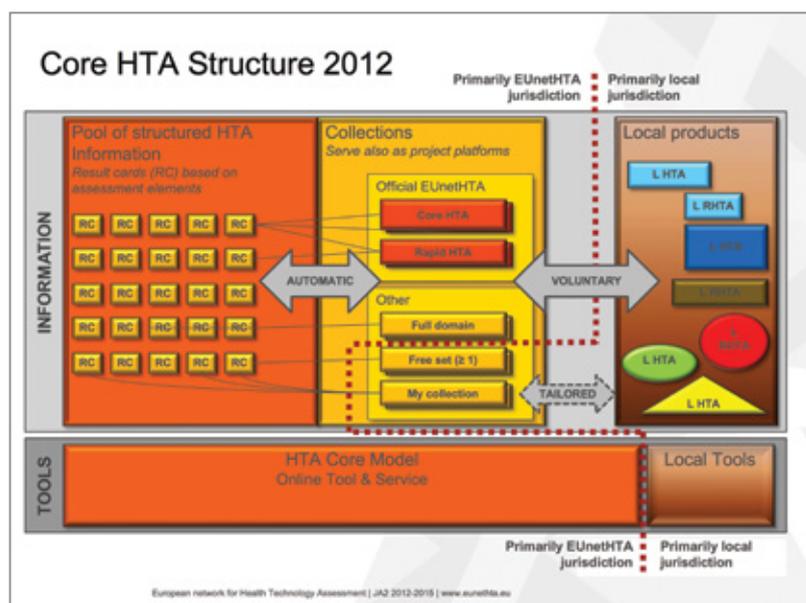
Benefits and risks are included as concepts in several of the nine domains but primarily as separate questions and not combined under specific headings. For example, the safety domain topics might include patient safety, occupational safety and environmental safety and safety risk management and in the clinical effectiveness domain, topics might include mortality, morbidity, function, health-related quality of life and patient satisfaction.

Enhancements to the ethical analysis domain are currently in development and may include questions such as

What are the benefits and harms for patients and what is the balance between the benefits and harms when implementing and when not implementing the technology? Who will balance the risks and benefits in practice and how? Can the technology harm any other stakeholders? What are the potential benefits and harms for other stakeholders, what is the balance between them? Who will balance the risks and benefits in practice and how?

The Collection summary is also being revised to contain a standard table listing the consequences of using or not using the technology. Whilst the Core Structure can

Figure 13. Local jurisdictions can choose Core HTA collections of structured information to act as platforms for their evaluations.



provide the data that can be used to make benefit-risk decisions, a more advanced analysis of benefit-risk is considered a local responsibility.

Moving forward

As part of Work Package 7, EUnetHTA is developing a template for evidence submission, taking into account evidence requirements and the HTA Core Model. To develop a common ontology among decision makers other than health technology assessment agencies, including regulators and the industry, stakeholders may wish to consider the organisation of information used in

evaluations. Similarly, other stakeholders may wish to consider using the Core Model of HTA information in processes other than HTA and linking the HTA Core Model or the adaptation features of HTA Core Model Online with benefit-risk assessment information and tools. Finally, feedback from national and regional users of Core HTA information on specific drugs and the different reimbursement decisions for that drug from different countries would assist future users.

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A structured benefit-risk framework: more clarity and transparency?

Professor Hans Georg Eichler

Senior Medical Officer, European Medicines Agency

There are some common elements between the structured frameworks that regulators and health technology assessors use to evaluate new medicines, particularly those that address benefits, harms and uncertainties. The primary decision rule employed by regulators, however, is do the benefits outweigh the risks and is the degree of uncertainty around a benefit and risk estimate acceptably low?

Benefit-risk and regulatory decisions

Does a structured framework add clarity and transparency?

The Effects Table that is currently being explored by the EMA as a benefit-risk decision-making framework clearly and transparently communicates to other stakeholders the favourable and unfavourable effects of medicines that the regulator considers important. The Effects Table, however, does not quantify the importance of these effects as does a slightly more complex framework such as a decision tree, which employs probabilities and weighting and this quantification may be an important clarifying factor in explaining benefit-risk decisions.

O'Brien and colleagues found that there is an asymmetry in the amount of benefit the average person must expect to gain compared with

the amount of money they are willing to spend to experience that benefit.¹ Nobel winning decision-analyst D Kahneman attributes this asymmetry to the psychological principle of risk aversion; that is, the utility of losses weighs heavier than gains and he sets the ratio at 2:1.²

In considering health outcomes rather than financial costs, that ratio can be further skewed. A survey of value judgements among practicing hospital physicians found that on average, "four or five additional lives had to be saved by better treatment of the disease for each additional death caused by the treatment itself." This may lead to the conclusion that most physicians view death attributable to disease as a more acceptable outcome than death attributable to iatrogenesis.³ This level of risk aversion is not in the best interest of public health nor of the enlightened patient who wishes to maximise their health utilities.

A regulator or an HTA body, or even a patient who is maximally risk tolerant might approve drugs that are useless or dangerous, which is a type I error. On the other hand, if those stakeholders are maximally risk averse, no new treatments would be approved and medical progress would come to a standstill, which is a type II error.⁴ Although the risk aversion of regulators and physicians may arise from an understandable wish to avoid criticism when

Patient involvement and framing decisions to patients as risk-risk rather than benefit-risk may be needed to overcome the risk aversion of decision makers.

treatment results in negative health outcomes, the art in regulatory science requires that the middle ground between risk tolerance and aversion be reached.

Could a structured framework influence a decision?

There are some studies that seem to indicate that patients do not have this strong asymmetry and are in fact more willing to experience risk for the possibility of benefit than are physicians and perhaps regulators. Publicly communicating the benefit-risk asymmetry that is part of many regulatory decisions through use of a structured framework may add clarity and transparency, potentially improve the 'light to heat ratio' in public debate and even ultimately influence regulatory decisions. This may require patient involvement in decision making and the judicious framing of benefit-risk or risk-risk trade-offs to patients.

Uncertainty and regulatory decisions

Uncertainty is not to be confused with risk. Some sources of uncertainty such as effect size can be quantified. There are, however, many sources of "unknown unknowns" and the potential for bias towards these factors cannot be quantified. All decision frameworks should address uncertainty but decision makers may find it difficult to adequately describe this.

A recent editorial in the *New England Journal of Medicine* said that uncertainty "may cause psychological discomfort in patients who find uncertainty disconcerting"⁵ Some decision makers are more sensitive to uncertainties than

others. A recent publication pointed out that countries using economic assessments with sensitivity analyses may reject new medicines more often, as these processes highlight uncertain outcomes more than point estimates.⁶

Conclusions

There could be commonalities across structured decision frameworks used by regulators and health technology assessors, especially in the consideration of benefits, harms and uncertainty. The use of structured frameworks will likely add clarity and transparency, improve the light-to-heat ratio of public discourse and may also affect the outcome of the decisions. Patient involvement and framing decisions to patients as risk-risk rather than benefit-risk may be needed to overcome the risk aversion of decision makers. Addressing uncertainties, however, may be the biggest challenge in the development of frameworks for decision making.

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The Canadian perspective from the regulatory side

Barbara J Sabourin

Director General, Therapeutic Products Directorate, Health Canada

Assessment of new drugs at Health Canada and CADTH

Canada, the eighth largest pharmaceutical market in the world, is an observer of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and its regulatory dossiers are based on the ICH Common Technical Document. Canada has participated in several working groups to develop these standards and has memoranda of confidentiality with many jurisdictions, allowing information sharing and discussion of challenging product dossiers. Canada has a priority review process for files with substantial evidence of significant benefit that significantly reduces review time without changing process.

Health Canada's review process for new medicines can be mapped to the Universal Methodology for Benefit-Risk Assessment (UMBRA) eight-step process; that is, examining the decision context, building and refining the value tree, evaluating the relative importance of the benefits and risks, assessing the different options, evaluating uncertainty, potentially creating a visualisation or a concise presentation of the results and employing expert judgement and communication.

Generally, after a new drug has been authorised for marketing by Health Canada, in order for it to be included in provincial formularies (except for the Province of Québec), sponsors prepare dossiers for submission for Common Drug Review through the Canadian Agency for Drugs and Technology in Health (CADTH).

Health Canada and CADTH benefit-risk assessment: case studies

Ms Sabourin explored differences in benefit-risk assessment between Health Canada and CADTH using public information for two new active substances. Regulatory information was obtained from the Summary Basis of Decision for each product and HTA information was derived from the Common Drug Review process. As cost assessment is unique to health technology

assessment, this process was not explored.

Dificid (fidaxomicin)

Fidaxomicin is a macrocyclic antibiotic used to treat *Clostridium difficile*-associated diarrhoea in adults. Priority review status for fidaxomicin was granted at Health Canada on the basis of the drug's potential to reduce infection recurrence. A complete data package was provided that was based on two pivotal randomised clinical trials. Although Health Canada does not require a risk management plan, one was provided for this submission. Priority review status was also provided at CADTH. In addition to the same complete data package describing the two pivotal studies, CADTH also reviewed patient and Canadian Drug Expert Committee (CDEC) panel input and cost-utility studies.

Health Canada concluded that fidaxomicin had an acceptable safety profile was effective for the treatment of *Clostridium difficile* infection (CDI) and was not inferior to vancomycin. There was no efficacy claim for recurrence and a Notice of Compliance was granted. CADTH concluded that based on evidence from the randomised clinical trials, fidaxomicin achieved similar clinical efficacy when compared with vancomycin. However, it was not recommended for listing due to cost issues.

In this case, overlapping but somewhat different packages of information were reviewed by Health Canada and CADTH for different purposes. There was concurrence by the two agencies on the main efficacy conclusions from the randomised clinical trials but divergences regarding the evaluation of CDI recurrence. CADTH also considered the off-label use of metronidazole as treatment for CDI in its evaluation.

Victrelis (boceprevir)

Submission for the Hepatitis C virus (HCV) protease inhibitor boceprevir was made to Health Canada within the priority review category. A full data package included the results of the two main randomised clinical trials, SPRINT-2 and RESPOND-2.

CADTH made two separate assessments of boceprevir. The first complete data package included three randomised clinical trials, SPRINT-2, RESPOND-2 and PO5689. An additional data package was submitted for the second review that included an updated literature search on non-invasive methods to assess liver fibrosis and on the use of the protease inhibitor

in special populations. Patient input was also received.

Health Canada issued a Notice of Compliance for use of boceprevir in combination with peginterferon alpha and ribavirin. Peginterferon alpha 2b was used in the randomised clinical trial but there was a supplementary filing for use with peginterferon alpha 2a and ribavirin. CADTH listed boceprevir for the treatment of chronic HCV infection genotype 1 in patients with compensated liver disease in combination with peginterferon alpha and ribavirin for patients with the clinical criteria of detectable levels of HCV RNA in the last 6 months and fibrosis stage of F2, F3 or F4. Listing was conditional for a reduced price and one course of treatment only.

There was concurrence between the two agencies regarding their evaluations of efficacy based on the randomised clinical trials and there were similar recommendations for response-guided therapy. Health Canada specified that boceprevir was for use in combination with ribavirin and interferon alpha 2b. The agency did not consider the results of study PO5689, which at the time were supplied by the sponsor in poster format only. The CADTH evaluation included comments on use of methods to assess liver fibrosis and included a recommendation for the use of erythropoietin for treatment of anaemia in their assessment of the cost associated with therapy. CADTH also commented on the concomitant use of boceprevir with HIV drugs in HCV-HIV-co-infected patients, who were excluded from the randomised clinical trials.

Discussion and conclusions

There was general concurrence on the clinical assessments made by Health Canada and CADTH for fidaxomicin and boceprevir. Health Canada approvals were based on the pivotal randomised clinical trials that were submitted and no off-label use was considered for the final recommendation.

For fidaxomicin, Health Canada's evaluation considered the facts that metronidazole is not indicated for CDI and previous oral vancomycin data for the indication were extremely limited. The lack of effect of fidaxomicin on recurrence in the NAP1/BI/027 *Clostridium difficile* strain was taken into consideration, resulting in the non-approval of the drug for CDI recurrence.

Additional advance conversations regarding HTA requirements might allow regulators to present information in a timely and supportive manner, avoiding duplication of effort and expediting patients' access to medicines.

There was also a significant overlap in the clinical data presented for boceprevir to both Health Canada and CADTH; however, there was a second evaluation of the drug's benefit-risk profile completed by CADTH.

Clinical evaluation of the methods for liver biopsies and use of boceprevir in HIV/HCV-co-infected patients were considered by CADTH and the agency also took data obtained from additional sources (patient input) into account and accepted clinical results (study 5685) from a poster for review. The CADTH benefit-risk assessment included cost-benefit analysis and results were expressed in quality-adjusted life years (QALYs). The Health Canada assessment resulted in a Notice of Compliance and market access but comparative effectiveness to existing products is not assessed prior to issuance of an NOC by Health Canada.

Regulatory review and health technology assessment are two similar processes with different perspectives. Regulatory review focuses on safe, effective and acceptable quality of new medicines, whilst health technology assessment centres on the effectiveness of those medicines. Using publicly available information, it cannot easily be determined if either Health Canada or CADTH performed their assessments in these two cases specifically following the eight-step UMBRA methodology. However, there was overlap in the data presented to both agencies and both reviews were guided by the data available based on the designs of the clinical trials, which may enable the use of a similar benefit-risk assessment approach. Additional advance conversations regarding HTA requirements might allow regulators to present information in a timely and supportive manner, avoiding duplication of effort and expediting patients' access to medicines.

HTA-Regulatory interaction: Where to start?

Dr Chander Sehgal

Director, Drug Review Programs, Canadian Agency for Drugs and Technologies in Health

The CADTH process

Stakeholders in the review of new medicines in Canada include industry as the sponsors, Health Canada as the regulators, the Patented Medicine Prices Review Board as the price setters of the ceiling price (non-exclusive), the Canadian Agency for Drugs and Technologies in Health (CADTH) as the assessors of health technology and finally, patients and healthcare professionals as the ultimate users.

Attributes of the optimal regulatory process, transparency, timeliness, quality and predictability of process are also desirable in health technology assessment. However, because of the different goals of the two processes and the different contexts not only between regulation and health technology assessment but within different regions, predictability of outcomes can be challenging,

A structured, predictable process is employed in each CADTH review. Using scientific oversight and continuous quality improvement, CADTH moves the assessment of new medicines from uncertainty to funding recommendations

through planning, prioritisation, production and knowledge mobilisation. After a submission is deemed adequate, a review team is assembled that consists of two or more clinical reviewers, two economic reviewers, a clinical project owner and economic project owner, a project manager, an information specialist and one or more clinical experts. This team conducts clinical and economic reviews and the resulting clinical and economic reports are submitted to the Canadian Drug Expert Committee (CDEC) for their use in developing recommendations.

Structured decision making using the CDEC deliberative framework may be mapped to the UMBRA eight-step process and involves presentations by the assigned discussants, open discussion amongst CDEC members, CDEC member deliberation on the evidence and the unmet patient needs and finally choosing a recommendation option through a voting process. There are four categories of CDEC recommendations: list, list with clinical criteria and/or conditions, do not list at the submitted price or do not list, each with its own considerations (Figure 14)

Patient evidence

Seventy-five Canadian patient groups have provided input to CADTH between 2010 and 2014. Evidence received from these groups is summarised by CADTH and is included in the materials provided to the CDEC. For example, the patient input information summary included in the ivacaftor recommendation document.

- Outcomes of importance to patients include improved survival, improved quality of life, elimination or reduction in the need CF therapies and delaying the need for lung transplantation.
- Patients and their caregivers can be substantially impacted emotionally, psychologically, physically and financially by CF. In addition, a considerable amount of time (two to seven hours per day) is spent on airway clearance activities to maintain lung health. In the event of acute pulmonary exacerbations, patients can spend at least two weeks in hospital.

At the CDEC level, patient input is presented, used in deliberations and is reflected in recommendations. CADTH strives to share the outcome and impact of patient input with all stakeholders, particularly with those who provide the input. In fact, patient input was cited as one of the reasons for a positive recommendation

Figure 14. The four categories for CDEC recommendations; these considerations are still evolving.

Recommendations Options	
Options	Description and Considerations
List	Drug demonstrates comparable or added clinical benefit and acceptable cost/cost-effectiveness relative to one or more appropriate comparators.
List with clinical criteria and/or conditions	Drug demonstrates comparable or added clinical benefit and acceptable cost/cost-effectiveness relative to one or more appropriate comparators in a subgroup of patients Drug demonstrates added clinical benefit, but the cost/cost-effectiveness relative to one or more appropriate comparators is unacceptable
Do not list at the submitted price	Drug demonstrates comparable clinical benefit, but the cost/cost-effectiveness relative to one or more appropriate comparators is unacceptable.
Do not list	Drug does not demonstrate comparable clinical benefit relative to one or more appropriate comparators.

for ivacaftor: "Patient groups identified unmet need in the treatment of CF that CDEC concluded could potentially be met by ivacaftor."

Parallel Health Canada – CADTH submissions

From 2010 to 2012, CADTH accepted submissions for health technology evaluation before regulatory approval (called pre-NOC submissions) was received for medicines that were designated as priority review. Beginning in November 2012, sponsors were permitted to make these parallel submissions regardless of a medicine's priority status and currently, approximately one third of submissions to CADTH are made before regulatory approval is received.

Issues in alignment

The contextual differences between regulatory and health technology assessment (Figure x) result in substantial hurdles and potential limitations for alignment. These include the fact that clinical trials are designed by industry,

Figure 15. Contextual divergence between regulatory and health technology assessments.

Regulatory Assessment	HTA Assessment
First hurdle to access	Typically follows regulatory approval Parallel Reviews (pre-NOC)
More Predictable processes	Transparency and interaction evolving
Economics not included	Value for money drives HTA
Greater harmonisation among different regulators (FDA, EMA, HC)	Similarity but lack of harmonisation (Canada: CDR, pCODR, INESS)
Greater interaction with the applicant	Limited interaction with the applicant
Benchmarking exists	Benchmarking ?
Cost recovery programs common	Cost recovery programs evolving



Early engagement would allow the alignment of data requirements and create opportunities for adaptive licensing design.

primarily in consultation with regulators, with outcomes narrowly defined and typically with a short follow-up duration. There is a general lack of external validity or generalisability with the results of these trials and often limited opportunity for direct patient input.

Multiple practical concerns surround the potential harmonisation of regulatory and health technology processes such as different goals and drivers, legal issues, societal values such as balancing innovation with sustainability, capacity and resource restrictions. There is a question as to whether health technology assessment can be benchmarked in the same way as regulatory processes and if there is even a need to do so. The sequential review process in which health technology assessment follows regulatory approval, takes additional time.

There is more Health Canada-industry interaction than there is interaction between industry and CADTH, but more formal input from patients to CADTH compared with the regulatory agency. There is currently no interaction between CADTH and Health Canada regarding parallel submissions. However, there are opportunities and potential approaches to regulatory-HTA interactions. Early engagement would allow the alignment of data requirements and create opportunities for adaptive licensing designs. Parallel reviews such as those of pre-Notice of Compliance submissions for Canadian Common Drug Review reduce the time between regulatory approval and CDEC recommendations. Therefore, the opportunities for harmonisation of structured decision-making frameworks for regulatory and HTA bodies remain to be elucidated.

Is there a commonality across the structured decision frameworks used by HTA and regulatory agencies? A perspective from NICE

Dr Elisabeth George

Associate Director, Centre for Health Technology Evaluation, NICE

Whether used by regulators or health technology assessors, structured decision making requires process, methodology and criteria; that is, it must specify who decides what, when they decide it and what the rules are for their decisions. However, regulatory and health technology assessment requirements differ because they are each constructed for the purpose of answering different questions. For regulatory review, these questions are *does a new drug have a clinical effect under controlled conditions and is it safe?* In other words, what is the drug's benefit-risk balance? For HTA the questions are *how effective is a new drug compared with existing treatments in routine clinical practice and is the new drug cost effective?* In other words, what is the drug's value?

By maintaining important procedural principles such as scientific rigour, inclusiveness, transparency and timeliness, the National Institute for Health and Care Excellence (NICE) is able to develop preliminary recommendations between 4 and 4.5 months after market

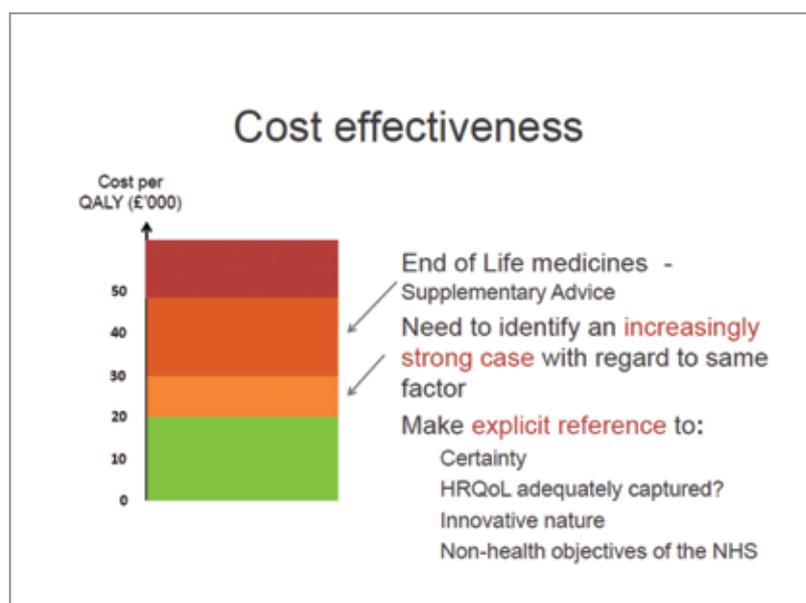
authorisation. The rules for NICE appraisal have been established in its *Guide to the Methods of Technology Appraisal*, which was first published in 2004 and updated several times since then, most recently in its third edition in April 2013. Within the Guide, the rules or reference cases for each element of health technology assessment are clearly described. Cost-effectiveness limits are also transparently detailed; medicines costing less than £20,000 per quality-adjusted life year (QALY) gained are usually recommended, whilst those with a cost per QALY gained between £20,000 and £30,000 may require supplementary information such as the medicine's additional effects on health-related quality of life, or, in exceptional circumstances equality-related factors or non-health-related objectives (Figure 16). For medicines with costs above £30,000 per QALY gained, value factors need to represent an increasing impact, up to a boundary of £50,000 or more per QALY gained, which NICE has allowed for end-of-life medicines.

In 2011, in response to internal and external input, NICE conducted a Workshop to evaluate the use of multi-criteria decision analysis in its decision making. It was determined that there were several potential advantages to the use of this more structured approach including improved transparency, accountability and consistency. It was additionally thought that the use of this type of decision making would provide an opportunity for NICE to obtain public "buy-in" regarding the rationale for difficult choices and help to direct future research and development by providing clear signals to industry regarding aspects of innovation that are highly valued.

Accordingly, NICE considered which criteria might be included; how performance could be measured and scored; how weights could be assigned to each of the criteria; how costs and opportunity costs of achieving an improvement in a composite measure of benefit should be considered and how the transparency of the deliberative process could be improved. Ultimately, however, it was decided that the use of multi-criteria decision analysis was not appropriate for NICE, as the methodology had not yet been determined for the manner in which best to assign weights to those criteria in a way that would be acceptable to all healthcare stakeholders.

The following new text indicates the position on the use of multi-criteria decision analytic techniques

Figure 16. Medicines with a cost below £20,000 per QALY gained are typically recommended by NICE, whilst those with a higher cost per QALY gained require additional evidence or special circumstances, or are not recommended.



6.2.21 “[...] Techniques exist to consider the trade-off between health benefits and non-health benefits quantitatively. These techniques require that all relevant criteria are identified in advance, quantified and then weighted to reflect aspects of social value in a way that can be regarded as legitimate by all stakeholders. At present the introduction of such techniques into the Committee’s decision-making is considered unsuitable. Therefore the Committee will take non-health objectives of the NHS into account by considering the extent to which society may be prepared to forego health gain in order to achieve other benefits that are not health related.”

In 2010, the Department of Health published their plans to establish value-based pricing of medicines in the UK. It was envisioned that this plan would employ QALY weighted to the burden of illness and incorporate consideration of severe conditions whose treatment affects patients, caregivers and society and the use of society’s resources (Figure 17).

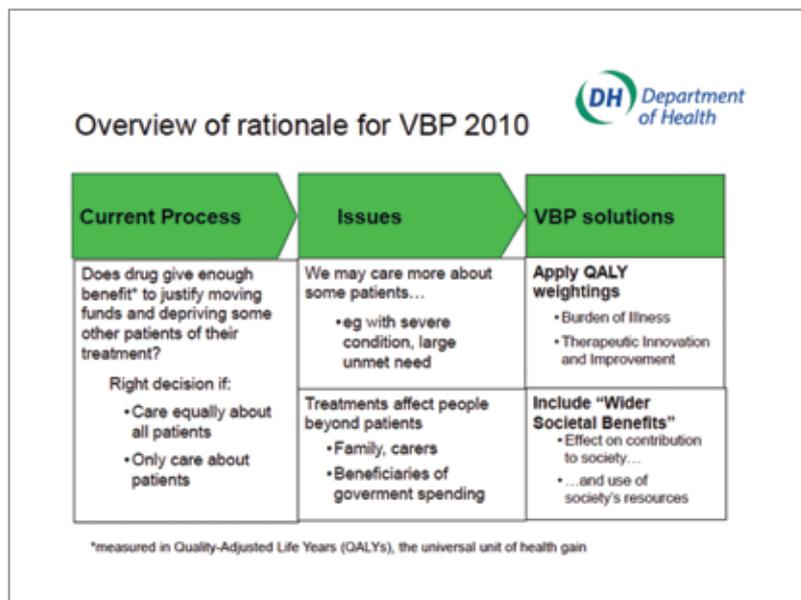
Considerable work in this area has been

... structured decision making requires process, methodology and criteria; that is, it must specify who decides what, when they decide it and what the rules are for their decisions.

accomplished since 2010 including the exploration of a definition of the burden of illness, the conduct of a technical workshop and the development of a framework by the Department of Health as well as academic research into severity, societal benefits, end-of-life therapies and evidence requirements for technology appraisal. In 2013, the Department of Health announced that NICE would play a central role in the development of value-based pricing and since then the NICE Decision Support Unit has reviewed the methodological development work for the plan, a Working Party was formed to provide advice to NICE Board, and it was planned that the NICE Board would approve an addendum to the *Guide to Methods of Technology Appraisal 2013*, which was to be used in appraisals starting in January 2014. At the time of this presentation, there were a number of elements still to be finalised for the value-based pricing process including the cost-effectiveness threshold, the topic selection, the status of medicines in the Cancer Drugs Fund, potential patient access schemes and evidence requirements.

Dr George concluded her presentation by reiterating that although structured decision making for both regulators and health technology assessors requires clarity regarding who decides what and when and about the rules employed in their decisions, requirements for these stakeholders are fundamentally different. In decisions lacking sufficient evidence, NICE will continue to work at enhancing its use of a deliberative and inclusive process of evaluation and a transparent explanation of that process to its healthcare stakeholders.

Figure 17. The Department of Health established a Value-Based Pricing plan for medicines in 2010.



Assessing HTA and regulatory approval decisions: A cohort study

Dr Iga Lipska

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Background

Currently, there appears to be areas of overlap for regulatory approval and HTA recommendations in terms of timing and requirements. In addition, there are several ongoing European initiatives to draw these two processes closer together, including the Transborder Healthcare Directive, which describes patients' rights in choice of cross-border healthcare. In addition, the EU Transparency Directive, scheduled for legislative review in 2014, applies to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of public health insurance systems. According to the requirements of this directive, HTA pricing decisions must be made within 90 days and reimbursement decisions within 180 days and these decisions must be based on objective and verifiable criteria and open to judicial appeal at the national level. Several approaches have been proposed to decrease the timing of HTA review to meet the timing requirements of the directive, including informal price negotiations before market authorisation, the non-reassessment of the elements on which

regulatory authorisation is based; that is, quality, safety and efficacy, and data sharing between regulatory and health technology assessment agencies. Finally, beginning 26 June 2013, upon request of the European Commission, the European Medicines Agency may participate in meetings of the HTA network and its working groups.

Doctoral research

As part of her doctoral research programme entitled *The quality of industry health technology assessment (HTA) submissions for medicines and their review by HTA agencies*, Dr Lipska sought to determine the correlations between the regulatory approval process and health technology assessment recommendations in European countries, specifically to find the association between duration of the process of marketing authorisation (MA) approval at European Medicines Agency (EMA) and health technology assessment recommendations in European Union countries. The hypothesis underpinning the study was that an increase in EMA approval time correlates with an increase in the number of HTA negative recommendations, as longer approval process timing might be an indicator of complexity and potential issues in the dossier.

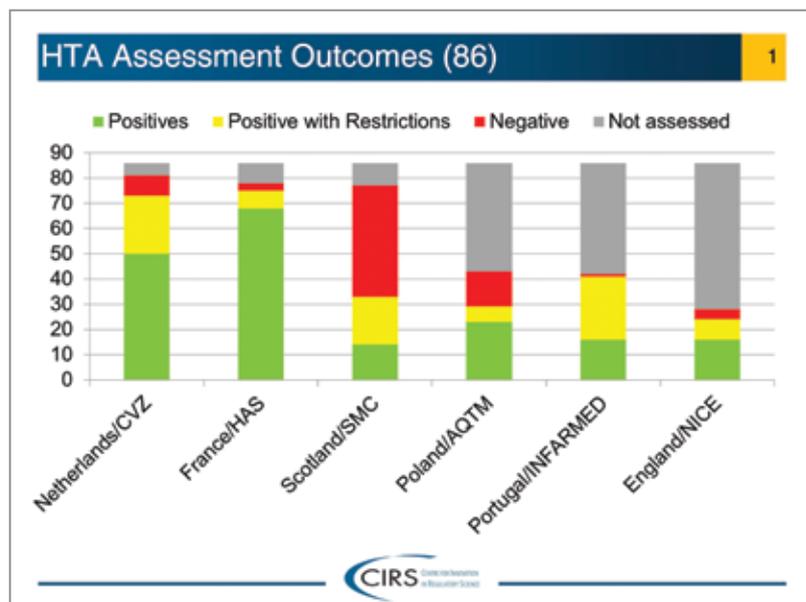
Methods

EMA MA timing for new active substances (NASs) during 2007-2010 were analysed based on information publicly available in sources such as European Public Assessment Reports. In addition, analysis was made of first HTA recommendations issued by HTA agencies in six European jurisdictions: SMC in Scotland, HAS in France, CVZ in the Netherlands, AOTM/AHTAPol in Poland, NICE in England and INFARMED in Portugal (Figure 18). Analyses were performed per country because although EMA decisions are centralised, HTA recommendations are taken independently by EU member states.

A cohort of 86 drugs that met defined inclusion criteria and that were approved by the EMA from 2007 through 2010 were evaluated. For purposes of this study, EMA approval time from submission date to approval date and number of cycles of review were taken as surrogates of complexity and potential issues in the dossier.

The number of EMA review cycles was considered and HTA recommendations were categorised using three specific scales. For the first categorisation scale, a detailed analysis was performed of the reasons behind nine

Figure 18. HTA recommendations from six HTA agencies from 2007-2010 were analysed.



WORKSHOP REPORT

subgroups of HTA recommendations:

- Negative for other reasons; negative for clinical and economic reasons, negative for clinical reasons, negative for economic reasons
- Positive with clinical and economic restrictions, positive with clinical restrictions, positive with economic restrictions, positive with minor restrictions
- Positive

The second categorisation scale contained three subgroups:

- Negative
- Positive with restrictions
- Positive

The third categorisation scale contained four subgroups and differentiated between two levels of restrictions:

- Negative
- Positive with major restrictions
- Positive with minor restrictions
- Positive

For graphic representations herein, the second scale was used.

Both a quantitative approach, in which cycles, approval time and number of HTA recommendations were considered and a qualitative approach, in which the reasons for

... a longer EMA review time resulted in a greater number of negative HTA recommendations. ... All of the correlations had marginally significant tendencies.

HTA recommendations were considered were used in Dr Lipska's evaluations. Two correlations were tested: EMA approval time and total number of negative recommendations and EMA approval time and total number of negative recommendations without the category "negative for other reasons". All three scales were coded using an ordinal scale, with higher numbers indicating a more beneficial HTA recommendation.

Results

For these 86 drugs, the median approval time at the EMA was 410 days (n = 33) in 2007; 421 days (n = 18) in 2008; 482 days (n = 23) in 2009 and 432 days (n = 12) in 2010.

The number of negative recommendations correlated positively with EMA approval time and this correlation was statistically significant, resulting in the conclusion that a longer EMA review time resulted in a greater number of negative HTA recommendations. There were negative correlations between HTA recommendations and approval time in the UK, no matter which coding was used. Approval time also correlated negatively with HTA recommendations in the Netherlands for the second and the third coding. The third coding revealed also negative correlation between approval time and total indicator of HTA recommendations. All of these correlations had marginally significant tendencies (Figure 19)

There were some limitations to the study including the fact that it remains unknown if EMA approval time is an appropriate surrogate of potential issues affecting registration. In addition, only drugs reviewed by HTA agencies were part of the study. Orphan drugs were part of this research and re-submissions were not, both of which may have exerted confounding effects on results. Finally, the effect of the analysis of recommendations of different HTA organisations, each with varying scopes and processes is uncertain.

Figure 19. Marginally significant tendencies were observed in the correlation between regulatory approval time and HTA recommendations.

Approval time v. categorisation of HTA/stats 2

Spearman's rho correlation coefficients between approval time and HTA recommendations.

Country	The first coding			The second coding			The third coding		
	rho	p-value	n	rho	p-value	n	rho	p-value	n
Scotland	-0.072	0.267	76	-0.113	0.165	77	-0.113	0.163	77
Poland	-0.097	0.267	43	-0.069	0.330	43	-0.069	0.330	43
Netherlands	-0.159	0.111	61	-0.191 #	0.070	61	-0.175 #	0.089	61
France	-0.070	0.271	78	-0.071	0.270	78	-0.070	0.271	78
England	-0.273 #	0.080	28	-0.315 #	0.052	28	-0.315 #	0.052	28
Portugal	-0.253	0.106	26	-0.253	0.106	26	-0.253	0.106	26
Total	-0.144	0.095	84	-0.143	0.098	84	-0.156 #	0.078	84

rho – Spearman's rho correlation coefficient; p – value – statistical significance; n – number of drugs assessed ; # - p<0.1



Assessing HTA and regulatory approval decisions: Case study trastuzumab emtansine (T-DM1)

Dr Jens Grueger

Vice President, Head of Global Pricing and Market Access, Roche, Switzerland

Trastuzumab emtansine

Trastuzumab emtansine (T-DM1, Kadcyla®) was recently approved in the US and Switzerland and received positive CHMP recommendation for approval for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer (mBC) who previously received trastuzumab and a taxane, separately or in combination. Filing for trastuzumab emtansine was based on results from EMILIA, an international, phase III, randomised, open-label study comparing trastuzumab alone to lapatinib in combination with capecitabine in 991 patients with HER2-positive locally advanced breast cancer or mBC who had previously been treated with trastuzumab and a taxane chemotherapy.

Trastuzumab emtansine is an antibody-chemotherapy conjugate in which trastuzumab binds to the HER2 receptor on cancer cells, triggering the release of the cytotoxic emtansine. The drug had been tested in two phase II trials in patients whose cancer had progressed on previous trastuzumab and/or taxane therapy with overall response rates of 26% and 35%.^{1,2} Capecitabine plus lapatinib was selected as a comparator because heretofore, this combination had elicited the best progression-free survival rates in this patient population.

The primary endpoints for the EMILIA study were progression-free survival by independent review, overall survival and safety. Key secondary endpoints included progression-free survival by investigator, overall response rates, duration of response and time to symptom progression. Stratification factors for patients were world region, number of prior chemotherapy regimens for mBC or locally advanced breast cancer and presence of visceral disease.

A hierarchical statistical analysis was performed in a pre-specified sequential order. A final analysis of progression-free survival by independent review was made after 508 observed events. Interim analyses were

performed for overall survival and using predetermined efficacy stopping boundaries and number of deaths observed. A final analysis of overall survival was made after 632 events.

Trial results: US/EU and regulatory/HTA differences

Results indicated that trastuzumab emtansine demonstrated improved efficacy over capecitabine plus lapatinib including a significant improvement in progression-free survival (hazard ratio = .65; $P < .0005$). Interim overall survival data favoured trastuzumab emtansine but the number of events did not cross the efficacy-stopping boundary (hazard ratio = .621; $P = .0005$). The US FDA was informed of these results and they were then presented at the Annual Meeting of the American Society for Clinical Oncology in 2012.³

The FDA subsequently advised Roche that trastuzumab emtansine qualified for priority review in the US, that the trial results were sufficient for regulatory approval and that the company should consider allowing patients in the capecitabine plus lapatinib treatment arm to cross over to trastuzumab emtansine therapy. This, course of action, however, presented Roche with a dilemma. European health technology assessment has strictly and consistently ruled that progression-free survival is not a valid surrogate for overall survival and is not considered an appropriate endpoint to demonstrate relevant patient benefit. Although EU regulators consider progression-free survival for regulatory approval, they require demonstration that there is no detriment in overall survival. Therefore, Roche informally engaged with regulatory and HTA stakeholders to determine if there would be support to conduct an unplanned, second interim analysis of overall survival after 50% of events had occurred. The consensus of opinion was that although this course of action would not be optimal, it would be considered.

Accordingly, Roche implemented this plan for an unplanned interim analysis of overall survival in alignment with regulatory authorities and the results were presented at the Annual Meeting of the European Cancer Congress/European Society for Medical Oncology in 2012, showing a 32% reduction in the hazard for mortality ($P = .0006$).⁴ Additionally, trastuzumab emtansine was associated with improvements in safety profile and key secondary efficacy endpoints, including time to symptom progression. The final analysis of overall survival is expected to be completed in

the middle of 2014.

The FDA approved trastuzumab emtansine in February 2013 and the CHMP granted a positive opinion for the drug in February 2013. The effect of subgroup analyses on health technology assessment for trastuzumab emtansine in Europe, however, remains unknown. Whereas regulatory agencies conduct benefit-risk analyses on total populations, health technology assessors commonly look at results in subgroups separately. In the case of trastuzumab emtansine, few patients with non-visceral metastases were included so that results in this subgroup were not statistically significant. Moreover, approximately 30% of patients in the trial had not been treated with previous anthracycline therapy as specified in some countries treatment guidelines.

Conclusions

Roche experienced a positive regulatory/HTA interaction regarding their clinical trial analysis strategy in order to accelerate patient access to innovative therapy with significant benefit. However, there appears to be an increasing trend in health technology assessment to subdivide trial populations in order to challenge incremental benefit or the lack of use of an appropriate comparator in subgroups.

Roche experienced a positive regulatory/HTA interaction regarding their clinical trial analysis strategy . . . However, there appears to be an increasing trend in health technology assessment to divide trial populations in order to challenge incremental benefit . . .

References

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Assessing HTA and regulatory approval decisions – A company case study showing different aspects of alignment or transparency of the benefit-risk decision between HTA and regulators

Dr Indranil Bagchi

Vice President and Head, Payer Insights & Access, Pfizer, USA

Xeljanz (tofacitinib)

Tofacitinib is a novel inhibitor of the JAK inflammation pathway with the potential to address a large unmet medical need across multiple inflammatory indications such as rheumatoid arthritis, psoriasis and ulcerative colitis, with activity observed when administered orally.

Before designing its development programme,

[HTA advice] helped to develop plans to address potential gaps in evidence and facilitated interaction with internal stakeholders on the rationale for inserting specific elements in the development programme.

Pfizer sought HTA scientific advice on a number of relevant domains for tofacitinib. Advice was solicited, including the required comparisons for assessment of comparative effectiveness, the adequacy of proposed comparisons by lines of treatment, the design of the comparative effectiveness research (superiority, non-inferiority, non-inferiority margins and active control) as well as the relevance of indirect comparisons. Endpoint advice was requested including primary comparisons of interest and health-related quality of life and work and functional outcomes. Cost and economic evaluation input was sFinally, Pfizer also sought advice on economic evaluation including patient population of interest, the type of model, types

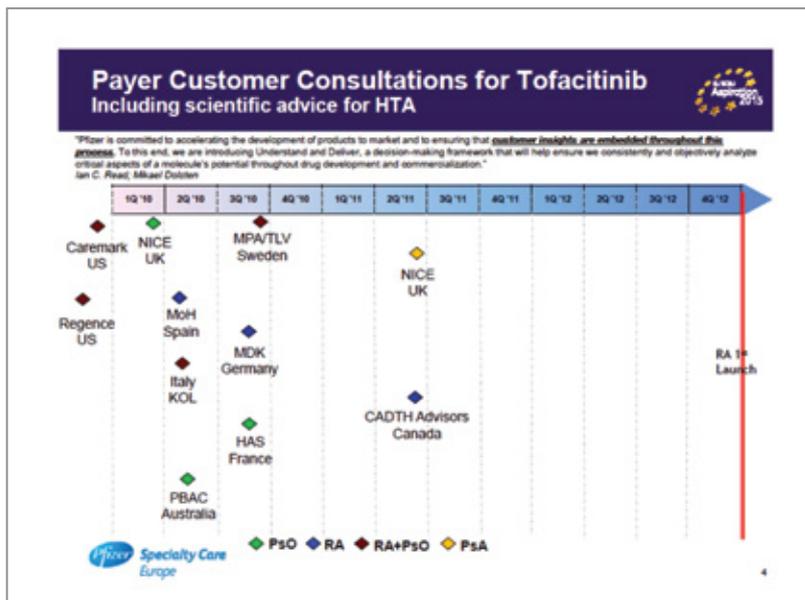


Figure 20. Pfizer sought comprehensive HTA advice in the US and in Europe for tofacitinib.

of cost considered and utility assessment (Figure 20).

The resulting scientific advice received from four countries regarding two proposed indications for tofacitinib was extremely divergent in terms of the study designs (suggested endpoints and comparators) and recommended methods for economic evaluation (population of interest, types of costs considered and utilities; Figure 21).

Figure 21. Pfizer received divergent scientific advice from HTA agencies in four different countries.

After receiving this advice, Pfizer designed one of the most comprehensive clinical trial programmes in the history of the therapeutic class, which included six randomised controlled

	Country A	Country B	Country C	Country D
Study Design				
Comparative Effectiveness	HQH study with Biologic A preferred	HQH comparison with Biologic A required	HQH study with Biologic B preferred	HQH study with Biologic A preferred
Design	At least non-inferiority	Superiority for additional benefit assessment	Active Control only	Active Control only
Indirect Comparisons OK?	Yes	No	Required for ICER only	Not required
Endpoints	Standard	Patient relevant and included in label	Standard	Standard but for sub-groups
Economic Evaluation				
Type	ICER and CMA if efficacy deemed similar	Frontier analysis preferred for pricing negotiation only	ICER for regions only	Not evaluated for reimbursement
Type of costs	Work and disability costs are relevant	Only drug costs	Work and disability costs are not required	Work and disability costs considered
Utility	Mapping derived is ok	Not relevant	Direct preferred	Direct preferred

phase III trials, with the result that tofacitinib was approved by the US FDA in 2012 and the Japanese PMDA and Swissmedic in 2013. However, it was not approved by the EU EMA, despite a subsequent appeal. After regulatory approval, because of the drug's ability to address a serious unmet medical need, market access was quickly achieved in Japan and Switzerland and it is currently on 80% of formularies in the US.

Lessons learned

The advice received shaped the clinical development programme for tofacitinib, helped to develop plans to address potential gaps in evidence and facilitated interaction with internal stakeholders on the rationale for inserting specific elements in the development programme. However, individual consultations were time and resource intensive and limited guidance was provided on the expected content of the briefing books for the agencies. In addition, there was a lack of consistency among HTA recommendations and a lack of alignment in technical recommendations for comparators from regulatory and health technology assessment agencies.

Pricing and reimbursement decisions and criteria for appraisal are and will remain country specific. The cost of care, the medical care continuum, preference for site of care and clinical comparators are highly variable across national jurisdictions. Furthermore, the perspective of budget holders is highly dependent on funding sources for healthcare and differs across national jurisdictions. However, significant actions are possible to reduce differences among local HTAs. Transparent guidances and a definition of incremental medical benefit are required that rewards innovation, sustains incentives for maintaining future investments in innovation and that is applicable across a range of jurisdictions. Alignment in recommendations from regulatory and HTA agencies in relation to comparators and endpoints for development programmes basic and a scientifically valid rationale, together with the standardisation of the elements of the briefing book and consultation formats will enhance the predictability of process in industry efforts to provide international access to innovative medicines.

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Appendix: Workshop Attendees

Regulatory agencies		
Dr Michael Berntgen	Head of Section: Rheumatology, Respiratory, Gastroenterology and Immunology	European Medicines Agency, UK
Dr Claus Bolte	Head – Clinical Review	Swissmedic
Prof Sir Alasdair Breckenridge	Former Chairman	Medicines and Healthcare Products Regulatory Agency, UK
Dr Petra Dörr	Head of Management Services and Networking	Swissmedic
Prof Hans-Georg Eichler	Senior Medical Officer	European Medicines Agency
Rosmin Esmail	Director, Knowledge Translation	Alberta Health Services, Canada
Dr David Lyons	CHMP Member	Irish Medicines Board
Dr Jan Mueller-Berghaus	Clinical Assessor	Paul-Ehrlich-Institut, Germany
Dr Clarice Alegre Petramale	Director of Department of Health Technology Incorporation	Ministry of Health, Brazil
Barbara Sabourin	Director General, Therapeutic Products Directorate	Health Canada
Dima Samaha	Advisor – Innovations and External Affairs	INESS, Canada
Dr Vania Cristina Canuto Santos	Deputy Director, Department of Health Technology Incorporation	Ministry of Health, Brazil
Health Technology Agencies		
Dr Elizabeth George	Associate Director – Technology Appraisals	National Institute for Health and Care Excellence, UK
Dr Wim Goettsch	Project Leader EUnetHTA WP5 on Relative Effectiveness Assessment of Pharmaceuticals and Medical Devices	Health Insurance Board, the Netherlands
Dr Mirjana Huic	Assistant Director and Head of Department for Development, Research and Health Technology Assessment	Agency for Quality and Accreditation in Health Care and Social Welfare, Croatia
Dr Kristian Lampe	Senior Medical Officer	National Institute for Health and Welfare, Finland
Anne Lee	Chief Pharmaceutical Adviser	Scottish Medicines Consortium
Prof Hubert Leufkens	Chairman	Medicines Evaluation Board, the Netherlands
Gintarė Mikšienė	Head of Medical Technologies Division	State Health Care Accreditation Agency, Lithuania
Prof Robert Peterson	Executive Director	Drug Safety and Effectiveness Network, Canadian Institutes of Health Research
Dr Chander Sehgal	Director, Common Drug Review and Rapid Response	Canadian Agency for Drugs and Technologies in Health
Prof Angela Timoney	Chair	Scottish Medicine Consortium
Patient representatives		
Dr Mary Baker	President	European Brain Council
Jean Mossman	Policy Lead	European Brain Council, UK
Pharmaceutical companies and consultancies		
Dr Indranil Bagchi	Vice President and Head, Payer Insights & Access	Pfizer Inc, USA
Neil Branscombe	Director of Health Economics	Les Laboratoires Servier, France
Lars Brüning	Head of Global Market Access	Bayer Healthcare Pharmaceuticals, Germany

Mike Chambers	Director of Health Economics	GlaxoSmithKline, UK
Dr Judith Creba	Head EU Liaison & Policy	Novartis Pharma AG, Switzerland
Robin Evers	Vice President, WRS Primary Care	Pfizer Ltd, UK
Gilles Fontan	Senior Director, Regulatory Affairs	Celgene R&D, Switzerland
Dr Ann-Katrin Gonschior	Head of Center of Excellence HE&OR	Boehringer Ingelheim GmbH, Germany
Dr Jens Grueger	Vice President, Head of Global Pricing and Market Access	F. Hoffmann-La Roche Ltd, Switzerland
Dr David Guez	Director of R&D Special Projects	Institut des Recherches Internationales Servier, France
Dr Sanjay Gupta	Executive Director and Head of Health Economics and Outcomes Research	Daichi Sankyo, USA
Linda Harpole	Vice President, Global Health Outcomes	GlaxoSmithKline, USA
Tara Hutton	Regulatory Affairs Strategy, Associate Director	Biogen Idec, UK
Dr David Jefferys	Senior Vice President, Global Regulatory	Eisai Europe Ltd, UK
Dr Katarina Jelec	Senior Regulatory Project Manager	Novo Nordisk A/S, Denmark
Angelika Joos	Head, Regulatory Policy EU and Most of World	Merck Sharp & Dohme (Europe) Inc, Belgium
Dr Hiroki Kato	Director	Zeria Pharmaceutical Co Ltd, Japan
Dr Eric Klein	Senior Director, Regional HO and HTA	Eli Lilly and Company, USA
Dr Thomas Lönngren	Independent Strategy Advisor	Pharma Executive Consulting, UK
Dr Carsten Möller	Strategic Access Manager	Bayer Pharmaceuticals AG, Germany
Dr Robert O'Donnell	Vice President, Global Regulatory TA Head – Neuroscience	Janssen, UK
Taisa Paluch-Kassenberg	Senior Regulatory Affairs Manager	Astellas Pharma Global Development, The Netherland
Dr Franz Pichler	Director, Global Public Policy	Eli Lilly and Company, UK
Dr Leo Plouffe	Vice President and Head of Risk Management, Global Pharmacovigilance	Bayer HealthCare, USA
Eddie Reilly	Vice President, Head of Global Regulatory Affairs	GlaxoSmithKline Vaccines, Belgium
Dr Ronald Robison	Vice President, Regulatory Affairs, Medical Services and Research & Development	AbbVie, USA
Dr Joseph Scheeren	Head of Global Development Asia and Head of Global Regulatory Affairs	Bayer Healthcare Company Ltd, China
Dr Isabelle Stoeckert	Head, Global Regulatory Affairs, Europe/ Canada	Bayer Pharma AG, Germany
Christopher Walker	Executive Director, Regulatory Affairs	Amgen Limited, UK
Dr Robert Waters	Senior Director, European Regulatory Affairs	Allergan Ltd, UK
Academic institutions		
Mike Chambers	Professor of Physiology and Pharmacology	University of Namur, Belgium
Dr Judith Creba	Assistant Professor, Division of Pharmacoepidemiology and Clinical Pharmacology	Utrecht University, The Netherlands
Robin Evers	Director, Centre for Socioeconomic Research	Cardiff University School of Pharmacy and Pharmaceutical Sciences, UK

Centre for Innovation in Regulatory Science (CIRS)	
Lawrence Liberti	Manager, Communications
Executive Director	Executive Director
Nicola Allen	Research Fellow
Magda Bujar	Research Analyst
Patricia Connelly	Manager, Communications
Art Gertel	Senior Research Fellow
Dr Iga Lipska	Senior Research Fellow
Dr Neil McAuslane	Director