



UNDERSTANDING
HTA AND COVERAGE
DECISION-MAKING
PROCESSES:
THE KEY TO FACILITATING TRANSPARENT
ACCESS TO MEDICINES

28-29 SEPTEMBER 2011
SURREY, UK

WORKSHOP REPORT

Workshop authors

Franz Pichler, PhD

Lawrence Liberti, MSc, RPh, RAC

Patricia Connelly, BA, ELS

The Centre for Innovation in Regulatory Science (CIRS) mission is to identify and apply scientific principles for the purpose of advancing regulatory and HTA policies and processes in medicines development.

CIRS is an independent UK-based subsidiary company, forming part of the Intellectual Property and Science business of Thomson Reuters. It is governed pursuant to constitutional documents that assure it is operated for the sole support of its activities. CIRS has its own dedicated management and advisory boards, and its funding is derived from membership dues and related activities.

Centre for Innovation in Regulatory Science
The Johnson Building, 77 Hatton Garden, London, EC1N8JS, UK

Email: Centre@cirsci.org

Website: www.cirsci.org

UNDERSTANDING HTA AND COVERAGE DECISION-MAKING PROCESSES:

The key to facilitating transparent access to medicines

Section 1: Executive Summary

Background to the Workshop

In general, countries want to improve their population's health by providing medicines that are safe and effective in a timely and efficient manner. Most jurisdictions take a broadly similar approach to providing access to new medicines, whereby the first requirement is the receipt of market authorisation from the regulatory authority based on meeting safety, efficacy and quality criteria. Following market authorisation, a coverage decision is often required to determine how payment for the medicine will be reimbursed. Increasingly, Health Technology Assessment (HTA) is being used to evaluate new medicines and to inform coverage decision making about the added benefits to populations covered, while sometimes also determining whether the new medicine represents added value for money.

There is considerable diversity between countries in the requirements of, the processes for and the extent of transparency in HTA appraisal and coverage body decision making. There is increasing interaction between different HTA agencies to begin to align their requirements and methodologies and also between regulatory agencies, HTA and coverage bodies in defining how to measure relative efficacy, provide shared early advice and otherwise coordinate their activities. The diversity of process and transparency represents a challenge to agencies as they try to learn from one another's strengths and capabilities and can hinder understanding and trust between the stakeholders involved.

This Workshop addressed the central question: given the diversity in the processes of HTA evaluation, coverage decision making and reimbursement between countries, how can the activities of such different systems be compared?

Workshop Objectives

- **Determine if the different HTA and coverage systems are comparable**
 - For comparisons to be valid it is important to know on what basis they are made and to understand that the HTA and coverage bodies operate within very different frameworks.

- Can a systematic approach to mapping the processes from regulatory approval to reimbursement provide an understanding of where each process fits into the organisations and healthcare systems, the nature of the organisations and hence the meaningfulness of cross comparisons?

- **Ascertain if there is value in developing HTA-related industry benchmarking**

- Companies routinely use internal targets to drive performance, but can comparison between companies in terms of the inclusion of HTA requirements into clinical development and the outcome on the following rollout be used to provide an understanding of the influence of HTA on development plans and rollout?
- Can such benchmarking provide insight into predictability of time or success across jurisdictions?

- **Establish whether there is value in developing performance indicators for HTA and coverage bodies**

- Such indicators could be used for the purpose of measuring ongoing reforms and change, identifying existing procedural facilitators and obstacles and for learning by comparison with peer agencies.
- Is it possible to develop an international set of performance indicators, or should such comparisons be best conducted by region or by similarity of organisation?

Key points from presentations

Day 1 Chairman, Prof Bengt Jönsson, *Professor of Health Economics, Stockholm School of Economics, Sweden,* initiated the Workshop by remarking that as health technology assessment has evolved over the past several decades to become increasingly important in both policy development and reimbursement decision making, seeking methods to compare and assess diverse international processes has become critical not just for purposes of efficiency and predictability but to stimulate and foster innovation and quality.

SESSION: TRANSPARENCY IN EVALUATING NEW MEDICINES FOR COVERAGE DECISIONS SHOULD BE A COMMON GOAL

Published in 2010, the *Rx&D International Report on Access to Medicines* revealed a wide diversity in public coverage for new medicines among the 34 member countries of the Organisation for Economic Cooperation and Development, which ranged from 88% to 19% of new medicines.¹ Although all HTA and coverage agencies are unique and the decisions they make are dependent on a variety of factors, **Dr Brian O'Rourke**, *President and CEO, Canadian Agency for Drugs and Technologies in Health, Canada* said that benchmarking their diverse principles, processes, methods and timelines could lead to more consistency and predictability in performance, transparency, value and ultimately, patient access. However, he cautioned that to yield the best results, the benchmarking process should be kept as simple and collaborative as possible.

While **Greg Rossi**, *Vice President, R&D Payer Evidence, AstraZeneca, UK* agreed that transparency and harmonisation in assessments among HTA agencies is possible, current variance in mandates and criteria for assessment will continue to lead to different reimbursement decisions. Nevertheless, the innovative pharmaceutical industry looks to HTAs, that these may facilitate an appropriate benefit for innovation and with the hope that together both stakeholders can build trust in each others' data and rigorous decision-making processes and ensure a clear understanding of the value that innovative products bring to a target population. Harmonisation and transparency among HTA agencies are achievable when assessing the potential effectiveness for new medicines, but transparency and harmonisation in consideration of real-life effectiveness and value are still being debated.

SESSION: HOW ARE TRANSPARENCY, QUALITY AND PREDICTABILITY BUILT INTO DIFFERENT REVIEW SYSTEMS?

Recognising that health outcomes are significantly affected by disparities in clinical judgement and skill and adherence to evidence-based medicine, **Dr Marc Berger**, *Executive Vice President & Senior Scientist, OptumInsight, UnitedHealth Healthcare Group (UHG), USA*, explained that his organisation has been able to positively impact health outcomes through a two-tiered approach of changing clinical behaviour in the treatment of commonplace

conditions and ensuring quality treatment through experienced "centres of excellence" for patients with rare, complex conditions. Using information in their data warehouse UHG is able to benchmark performance; analyse practice variation and identify higher quality, higher efficiency providers; provide actionable information to patients and target appropriate patients for care management and referrals to those centres of excellence.

Regulatory agencies have benefitted from the identification of common benchmarking approaches and have used the results of independent assessments to identify and implement best practices. For example, since 2006 Swissmedic has successfully met stakeholder expectations for increased efficiency, transparency and consistency with the assistance of external benchmarking and internal indicator systems such as the Advanced Planning and Scheduling System. **Dr Petra Dörr**, *Head of Management Services and Networking, Swissmedic, Swiss Agency for Therapeutic Products* explained that in addition to increased efficiency, flexibility and adherence to target times, it is expected that this system will optimise transparency in terms of project status and resource utilisation. Experience from the regulatory agencies suggests that a similar approach to benchmarking could be applicable to the activities of seemingly diverse HTA agencies.

SESSION: CASE STUDIES OF PERFORMANCE INDICATORS FOR A NATIONAL HTA AGENCY

According to **Prof Lloyd Sansom**, *Emeritus Professor, Division of Health Sciences, University of South Australia*, because of international differences in legally available public information, benchmarking HTA processes from public domain data may be challenging. However, readily available performance indicators for the Pharmaceutical Benefits Advisory Committee (PBAC) of Australia demonstrate that approximately 90% of new drugs are recommended for coverage in Australia within 5 years of first submission to the agency. These data indicate that for many drugs, however, multiple resubmissions and data reanalyses are required and PBAC is committed to using the results of this type of benchmarking project to enhance international dialogue and cooperation with all stakeholders to optimise the efficiency and effectiveness of the HTA process.

Since its beginnings in March 2000, the National Institute for Health and Clinical Excellence (NICE)

has issued guidance on 232 new medicines.

Nina Pinwill, *Associate Director, Centre for Health Technology Evaluation, NICE, UK* explained that during that time, NICE has adjusted its processes and methods to meet the expectations of a broad group of shareholders, and this adaptation will continue with the implementation of value-based pricing for new medicines beginning in January 2012. Although significant changes are underway in the National Health Services, NICE is expected to continue to remain at the centre of new policies to improve access and innovation in medicine.

SESSION: CAN COMPARISON, PERFORMANCE INDICATORS AND BENCHMARKING BE USED TO ENABLE SHARED LEARNING?

In 2008, the International Working Group for HTA Advancement published *Key principles for the improved conduct of health technology assessment for resource allocation decisions*.² Day 1 Chair **Prof Bengt Jönsson**, *Professor of Health Economics, Stockholm School of Economics, Sweden*, reported that a subsequent investigation into the use of and support for those principles showed that while no health technology organisation implemented all fifteen of the principles, support for this approach is positive among European agencies.³ Publications on HTA benchmarking and principles for comparative effectiveness research are currently underway.

Because member companies of the CIRS HTA Programme indicated that CIRS could add value by undertaking a programme to determine the impact of HTA requirements on the development of new products, CIRS has initiated a pilot for a benchmarking database that tracks individual products through their development and rollout. Although assessing the comparison of the impact of diverse HTA systems represents a significant challenge, **Dr Franz Pichler**, *Manager, HTA Programme, CIRS*, detailed the preliminary results derived from observations on twelve products across eight jurisdictions that support the feasibility of the proposed CIRS benchmarking process, provided an indication of individual insights to come, identified new areas of investigation and highlighted the need to contextualise the results.

Day 2 Chairman, Prof Adrian Towse, *Director, Office of Health Economics (OHE), UK* introduced the second day's presentations by remarking that the process developed for and lessons learned from the ongoing benchmarking of regulatory agencies in Europe can and should be successfully translated for use in an HTA context.

SESSION: BUILDING QUALITY THROUGH CREATION OF A COMMON TECHNICAL DOCUMENT FOR HTA

As *Director of the Secretariat, European Network of Health Technology Assessment (EUnetHTA)* **Prof Finn Børlum Kristensen** reported on the development and implementation of good practice principles for assessing relative effectiveness based on the EUnetHTA HTA Core Model, a pool of structured information categorised into nine chapters or "domains" which permit a consistent presentation of information deemed necessary to inform an HTA decision. The core model has been developed as an online tool. Dr Kristensen noted that although there are more similarities than differences underlying the scientific assessment of relative effectiveness across jurisdictions, in EUnetHTA's development of the framework for a common European methodology, both the differences between countries and the context for those differences are considered.

SESSION: TIMELINESS, QUALITY, PREDICTABILITY AND TRANSPARENCY IN HTA/COVERAGE: A VIEW FROM OTHER KEY STAKEHOLDERS

Considering how transparency and comparison of systems will benefit HTA-regulator interaction, **Prof Hans-Georg Eichler**, *Senior Medical Officer, European Medicines Agency, (EMA), UK* stated that because the move toward increased transparency by regulators is unavoidable and independent comparisons of regulatory activities are already underway, HTA organisations should work towards facilitating open discussion about the scientific basis for their decisions especially when diverse coverage decisions for the same new medicine occur across jurisdictions. Approaches can include the alignment of methodology and evidence standards, the explanation of divergent decisions on the basis of credible differences in regional healthcare environments and the anticipation and management of high-profile variances in decision outcomes.

Speaking on behalf of industry stakeholders, **Ed Godber**, *Vice President, Access to Medicines Centre of Excellence, GlaxoSmithKline, UK* suggested four concepts that can help optimise innovation through health technology assessment; predictability of the value of a new medicine can be best attained through linking the assessment to the medicine's performance in the health system; transparency through a commitment to review the product's performance through

the use of sound scientific approaches; quality through “value mapping” the evidence-generation process ensuring precision to address evidence throughout the product’s life cycle and timeliness through an ongoing dialogue and scientific exchange to support the alignment of evidence with public and patient value expectations.

References

1. Wyatt Health Management. *The Rx&D International Report on Access*

to Medicines. Available at http://www.patientscomefirst.ca/inc/pdfs/RxD_InternationalReport_2010_en.pdf; accessed October 2011.

2. Drummond MF, Schwartz J, Jönsson B. Key principles for the improved conduct of health technology assessment for resource allocation decisions. *Int J Technol Assess Health Care*. 2008;24:244-258.
3. Neumann PJ, Drummond MF, Jönsson B. Are key principles for the improved conduct of health technology assessment supported and used by Health Technology Assessment organizations? *Int J Technol Assessment Health Care*. 26: 71–78.

General Recommendations From Across Syndicates

1. Streamline the list of parameters to benchmark and focus on the assessment.
2. Make use of the more efficient existing models for HTA evaluation.
3. Examine HTA performance, especially at interim milestones.
4. Find mutually acceptable solutions and seek gradual improvement in the quality of HTA methods, assessments, and decisions processes.
5. CIRS should assist with the continuance of ongoing work on the development of a global common HTA lexicon that has been initiated by multiple groups.
6. Taking the current EUnetHTA core model pilot into consideration, CIRS should also assist in the development of a “non-common” HTA submission framework – a generic process map and tool that can serve as the flexible basis for global HTA submissions. This framework could also serve as a guide for companies not only for submission but also for points to consider in early and mid development, and could give guidance for the types of data to be developed for particular countries or regions. It should include links to reference documents and ideally be supported by a dynamic database of guidance documents with a search engine such as could be provided by the International Drug Regulatory Affairs Compendium (IDRAC).
7. Support a dialogue and effort on pharmacoeconomic models and create and publish a consensus where possible.
8. Based on its ongoing mapping and benchmarking activities, CIRS should investigate methods for additional HTA process time savings to improve patient access.
9. Use the Quality Scorecards system developed by CIRS for the regulatory field to assess the quality of dossier submissions and their reviews in the context of HTA.
10. Assess HTA quality in the context of internationally accepted principles.
11. Refine the definition of quality in the context of HTA as specified by Syndicate 3.
12. Establish the elements of a quality dossier and a quality review as also enumerated by Syndicate 3.

Workshop Programme

DAY 1: 28 September 2011	
Welcome	Lawrence Liberti , <i>Executive Director, CIRS</i>
Chairman's introduction	Prof Bengt Jönsson , <i>Professor of Health Economics, Stockholm School of Economics (SSE), Sweden</i>
Session: Why transparency in the process of evaluating new medicines for coverage decisions should be a common goal	
Value drivers of performance and the assessment of new technologies: a US coverage plan perspective	Dr Brian O'Rourke , <i>President and CEO, Canadian Agency for Drugs and Technologies in Health (CADTH), Canada</i>
Why innovators want greater HTA clarity and predictability	Greg Rossi , <i>Vice President, R&D Payer Evidence, AstraZeneca, UK</i>
Session: Comparing different healthcare systems: how is transparency, quality and predictability built into review systems	
Progressing the benefit-risk framework – What is getting in the way – methodology, culture or some other factor?	Dr Marc Berger , <i>Executive Vice President & Senior Scientist, OptumInsight, UnitedHealth Group, USA</i>
Improving regulatory agency performance: measuring time, performance and quality	Dr Petra Dörr , <i>Head of Management Services and Networking, Swissmedic, Swiss Agency for Therapeutic Products</i>
Session: Case studies of performance indicators for a national HTA agency	
Activity indicators for the Pharmaceutical Benefits Scheme	Prof Lloyd Sansom , <i>Emeritus Professor, Division of Health Sciences, University of South Australia</i>
Performance indicators for NICE	Nina Pinwill , <i>Associate Director, Centre for Health Technology Evaluation, National Institute for Health and Clinical Excellence (NICE), UK</i>
Session: Learning from each other: how can comparison, performance indicators and benchmarking be used to enable shared learning?	
Identification of good practice when using HTA for resource allocation decisions.	Prof Bengt Jönsson , <i>Professor Emeritus, Health Economics, Stockholm School of Economics (SSE), Sweden</i>
Benchmarking pilot study of HTA impact on industry	Dr Franz Pichler , <i>Manager, HTA Programmes, CIRS</i>

Syndicate Sessions	
Syndicate 1: Can milestones be identified to allow for meaningful comparison between different systems, HTA or coverage bodies?	
Chairman	Prof Bruno Flamion , <i>Chairman, Belgian Committee for Reimbursement of Medicines</i>
Rapporteur	Pierre Sagnier , <i>Vice President, Development Projects, Global Market Access, Bayer Health Care Pharma, Germany</i>
Syndicate 2: Removing barriers to equitable patient access to new medicines	
Chairman	Katrine Frønsdal , <i>Senior Researcher, Norwegian Knowledge Centre for the Health Services (NOKC), Norway</i>
Rapporteur	Angus Grant , <i>Vice President, Business Development and Global Strategic Alliances, Celgene Corporation, USA</i>
Syndicate 3: Beyond benchmarking time and process: can we assess quality?	
Chairman	Barbara Sabourin , <i>Senior Executive Director, Therapeutic Products Directorate (TPD), Health Canada</i>
Rapporteur	Dr Iga Lipska , <i>Senior Research Fellow, CIRS</i>

Day 2: 29 September 2011	
Chairman's introduction	Prof Adrian Towse , <i>Director, Office of Health Economics (OHE), UK</i>
Session: Building quality into the application dossier through creation of a standard submission template: a common technical document for HTA	
Development and implementation of good practice principles for relative effectiveness based on the EUnetHTA core HTA model	Prof Finn Børllum Kristensen , <i>Director, European Network of Health Technology Assessment (EUnetHTA)</i>
Session : What is the view from other key stakeholder on comparison of timeliness, quality, predictability and transparency in HTA and coverage?	
How increased transparency and the ability to compare systems will benefit HTA-regulatory interactions	Prof Hans-Georg Eichler , <i>Senior Medical Officer, European Medicines Agency, (EMA), UK</i>
What does industry want to see from HTA agencies in terms of time, quality, predictability and transparency?	Ed Godber , <i>Vice President, Access to Medicines Centre of Excellence, GlaxoSmithKline, UK</i>
Panel discussion	<p>Dr Jens Grueger, <i>Vice President, Head Global Market Access, Pfizer Primary Care Business Unit, UK</i></p> <p>Dr Thomas Lönnngren, <i>Director Pharma Executive Consulting</i></p> <p>François Meyer, <i>Advisor to the President, Assessment Division, Haute Autorité de Santé, (HAS), France</i></p> <p>Barbara Sabourin, <i>Senior Executive Director, Therapeutic Products Directorate (TPD), Health Canada</i></p>
Chairman's summary	Prof Adrian Towse
Conclusion of workshop	Lawrence Liberti

Section 2: Syndicate Discussions

Three Syndicate groups were asked to discuss three different aspects of benchmarking quality in HTA and coverage processes,

provide strategies to address the critical issues outlined in their discussions and to arrive at recommendations for change.

Syndicate 1	
Chair	Professor Bruno Flamion , <i>Chairman, Belgian Committee for Reimbursement of Medicines, Belgium</i>
Rapporteur	Pierre Sagnier , <i>Vice President, Development Projects, Global Market Access, Bayer Health Care Pharma, Germanys</i>
Syndicate 2	
Chair	Katrine Frønsdal , <i>Senior Researcher, Norwegian Knowledge Centre for Health Services</i>
Rapporteur	Angus Grant , <i>Vice President, Business Development and Global Strategic Alliances, Celgene Corporation, USA</i>
Syndicate 3	
Chair	Barbara Sabourin , <i>Senior Executive Director, Therapeutic Products Directorate, Health Canada</i>
Rapporteur	Iga Lipska , <i>Senior Research Fellow, CIRS, UK</i>

WORKSHOP REPORT

Syndicate 1: Can milestones be identified to allow for meaningful comparison between different systems, HTA or coverage bodies?

Background

This Syndicate was asked to address the topic of how to meaningfully compare HTA and coverage bodies across jurisdictions and what key elements should be included in such a comparison. The group was asked to make recommendations on how to structure such evaluations, what milestones and processes are meaningful for comparison, and what key performance indicators could be measured across agencies. A quantitative focus on process, time and resources was suggested.

Accordingly, the Syndicate focussed on issues including the identification of which HTA and payer organisations to benchmark and the dimensions on which comparisons should be made. Additionally, the expectations, goals, and incentives of the different stakeholders, the Donabedian framework¹ and the 15 principles for quality improvement and time and timeliness indicators were also discussed.

Critical issues

What and whom to benchmark? The scientific and technical aspects of HTA assessment should be mapped and understood for purposes of comparison and benchmarking. These maps must be explicit and fully transparent with the goal of using the visualised process to recommend best practices aimed at reducing unintentional random variations among processes. Although the societal values implicit in appraisals, pricing, and reimbursement decisions should also be mapped and understood, they are not yet amenable to benchmarking. Rather, the foundation must be laid for a stepwise, bottom-up, long-term convergence of decision-making processes (Figure 1). Members of this Syndicate recommended benchmarking not only individual agencies but also the entire HTA and payer system. With self-improvement as a goal, these stakeholders were advised to initiate a circle of voluntary mutual comparisons leading to procedural enhancements, before financially pressed local governments intervene. The focus in this process should be on identifying value-added steps, improving process efficiency and identifying dimensions such as medical need

that can be compared across countries.

Expectations, goals and incentives of different stakeholders: In addition to efficiency and speed, the pharmaceutical industry seeks predictability and consistency from HTA and payer agencies in their dealings with scientific evidence. For their part, healthcare decision

Figure 1. The foundation for benchmarking must be laid for a stepwise, bottom-up, long-term convergence of decision-making processes.

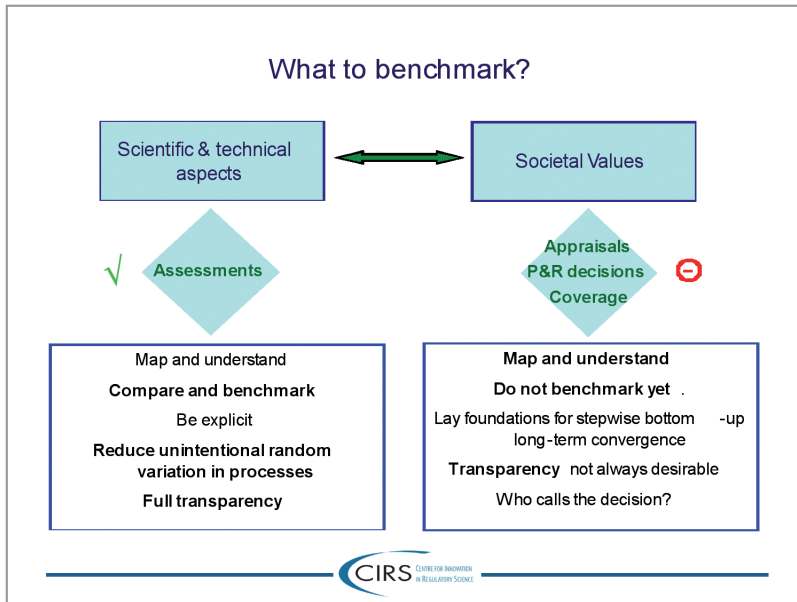
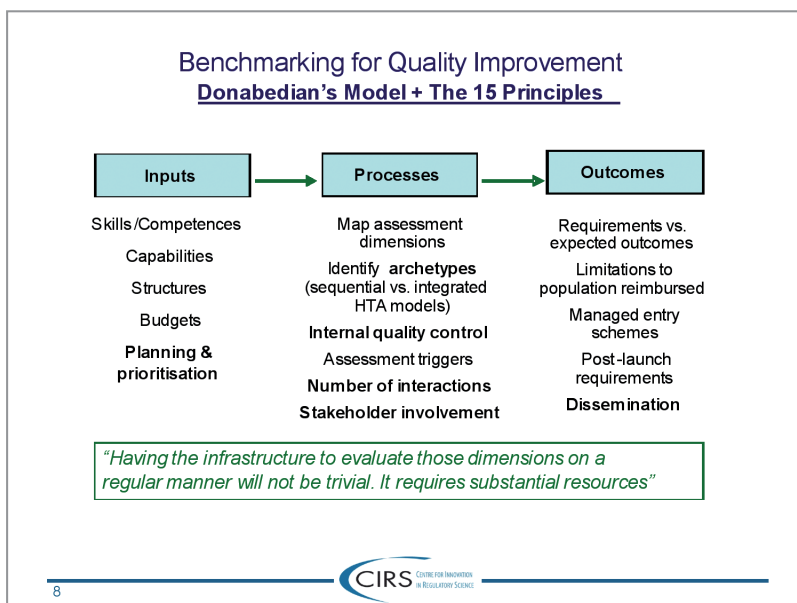


Figure 2. The Donabedian model of examining the input, process and outcome of a system specially to evaluate healthcare services.

makers want accountability, affordability, equity, value for money and to some degree, synergy between the approaches of HTA and payer agencies. Total quality improvement of the decision making process and improved patient



access to medicines are shared but still distant goals, with healthcare system inefficiencies and budget silos often acting as negative incentives.

Strategies

The Donabedian framework and the 15 principles for quality improvement:

It was this group's consensus that the combination of the well-established "Donabedian model" of examining the input, process and outcome of a system specially to evaluate healthcare services¹ together with the 15 key principles for the improved conduct of health technology assessment cited by Professor Bengt Jönsson in his presentation could serve as a foundation for HTA process enhancement (Figure 2). Of the input aspects of the model, the Syndicate identified agency planning and prioritisation as particularly key; consolidating the common elements of HTA models was deemed an essential process and the planned and thoughtful dissemination of results was identified as one of the most important aspects of HTA outcomes. It was recognised, however, that the infrastructure to evaluate those dimensions on a regular basis would require substantial resources.

Dimensions and efficacy: To avoid redundancy in efforts to establish the various elements of efficacy in HTA assessment such as identifying appropriate comparators, seeking the optimal use and design of pharmaco-economic studies and developing disease-specific guidelines, the Syndicate advocated synergies through the use of existing models by the various groups examining HTA improvement such as the International Network of Agencies for Health Technology Assessment and the European Network for Health Technology Assessment.

Time and timeliness indicators: The Syndicate suggested that although the total timing is important, an examination of the time to achieve interim milestones would likely be of more practical utility, and the trade off between the timing and quality of HTA-sponsor interactions is a vital consideration.

Recommendations

1. Streamline the list of parameters to benchmark and focus on the assessment.
2. Make use of the more efficient existing models for HTA evaluation.
3. Examine HTA performance especially at interim milestones.
4. Find mutually acceptable solutions and seek gradual improvement in the quality of methods, assessments, and decision processes.

Syndicate 2: Removing barriers to equitable patient access to new medicines

Background

This Syndicate examined the question of why different patient populations vary in their ability to gain access to new medicines. They also considered whether there are aspects in the system to either encourage industry to submit earlier to different jurisdictions or to encourage agencies to reduce administrative barriers – potentially via development of standardised submission templates.

It was the aim of this Syndicate to explore both barriers and solutions from agency and company perspectives and to suggest processes, procedures and practices that could be put in place to encourage earlier submissions to HTA agencies.

Key questions to be answered included

- What are the practical barriers that delay submission to HTA?
- Is reformatting submissions based on the same dataset causing delays to HTA submissions?
- Should there be development of standardised submission templates?
- What are the benefits and challenges to doing this?
- Could a common HTA dossier format be widely accepted?
- Does the EUnetHTA core model give us the starting point?
- Could this be used internationally, or are there limitations?

- Would such an approach be of benefit to both companies and agencies?

Critical issues

National barriers: It was this group's consensus that barriers to patient access include inter-country differences such as specific legislation and related bureaucratic complexities, regional social philosophy, economic limitations, regional treatment practices, clinical trial endpoint preferences, societal expectations of benefit-risk (clinical benefit and comparative or relative effectiveness) and the influence of patient-relevant outcomes on HTA decision-making processes. Company strategy for the international rollout of medicines likely also presents a barrier to speedy access in certain regions.

Strategies

Aligning regulatory requirements among key jurisdictions was in large part formalised through the widespread acceptance of the Common Technical Document (CTD) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and for the Centralised Authorisation procedure of the European Medicines Agency; however, these approaches took more than a decade to develop and refine. This Syndicate suggested that the impetus now provided by the rapid speed of innovation could facilitate faster acceptance of common HTA standards and processes. It was further anticipated that the work of the European Network for HTA, CIRS and other HTA organisations will contribute to the recognition of the benefits of aligning processes and procedures that support HTA decision making.

Dialogue, that is, the effective communication and collaboration among stakeholders, was determined to be the key to HTA enhancements that would ultimately result in process changes that could accelerate patient access to medicines. A common lexicon is already being developed and its continued thoughtful development will be necessary for this communication to grow across jurisdictions. Industry should communicate, through publications and other media, the learnings in both process and outcomes from parallel submissions to multiple HTA bodies and from HTA and regulatory agencies. Stakeholder consensus on pharmacoeconomic models should also be published. All of these communications should be enhanced by

engagement with patients or patient advocates.

With these factors in mind, the Syndicate reformulated its discussion focus questions to

- What can be done to improve the HTA landscape that may ultimately improve patient access to new medicines?

and

- How can CIRS contribute to the dialogue?

Recommendations

1. CIRS should assist with the continuance of ongoing work on the development of a global common HTA lexicon that has been initiated by multiple groups.
2. Taking the current EUnetHTA core model pilot into consideration, CIRS should also assist in the development of a “non-common” HTA submission framework – a generic process map and tool that can serve as the flexible basis for global HTA submissions. This framework could also serve as a guide for companies not only for submission but also for points to consider in early and mid development, and could give guidance for the types of data to be developed for particular countries or regions. It should include links to reference documents and ideally be supported by a dynamic database of guidance documents with a search engine such as could be provided by the International Drug Regulatory Affairs Compendium (IDRAC).
3. Support a dialogue and effort on pharmaco-economic models and create and publish a consensus where possible.
4. Based on its ongoing mapping and benchmarking activities, CIRS should investigate methods for additional HTA process time savings to improve patient access.

Syndicate 3: Beyond benchmarking time and process: can we assess quality?

Critical issues

Quality in the context of HTA: The Syndicate developed a working definition of quality as “meeting expectations”; in this case, the expectations of the companies in relation to the quality of an HTA review and of the agencies in relation to the quality of the HTA submission. The group discussed other factors included in the determination of quality, including the stakeholder’s unique perspective, the transparency and timeliness of the process, and the manner in which to best present and consider relevant information; furthermore, there was consensus that the quality of submissions directly relates to their solid scientific content. Ultimately, however, it was agreed that a complete and comprehensive definition of quality as it relates to HTA processes would require further analysis and refinement.

Elements of a quality dossier and review:

Listed by the Syndicate in order of importance, the quality of a dossier to support a submission for HTA depends upon the robustness of the data that supports the reimbursement decision and the inclusion of all relevant information. The integrity of the data within the dossier is also critical; that is, the data must be consistent between tables and text and between clinical effectiveness analysis and economic evaluation or budget impact analysis. Finally, the physical dossier should be a logically structured, well-written compilation using a clear format.

Also named in order of importance, a quality review of an HTA submission must be transparent, scientifically sound, and scientifically consistent, that is, the same as for other drugs within the same therapeutic area, legally consistent by jurisdiction, address relevant needs such as societal values, be procedurally predictable, and within time targets.

Strategies

The measurement of quality: According to this Syndicate, of inputs, processes and outputs, quality is most easily measured in processes. Tools to ensure quality or to support good quality process such as internal and external peer-reviews, audits, the use of standard operating procedures and procedures for learning and feedback should be in place and followed.

The continuous improvement of quality:

The Syndicate agreed that the impact of HTA decisions should be evaluated and built into future decision-making paradigms. Furthermore, quality HTA systems should be flexible and responsive, for example, to new data and evidence standards and should become even more adaptable in light of the growing prospect of international information exchange.

Transparency: Documents related to HTA submission and review should be available in the public domain although confidentiality, particularly as it relates to patient-level data may be an issue. In the course of involving all stakeholders in dialogue all conflicts of interest should be disclosed.

Reference

1. Donabedian A, Wheeler JRC, Wyszewianski L. Quality, cost, and health: An integrative model. *Medical Care*, 1982;20:975-992.

Recommendations

1. Use the Quality Scorecards system developed by CIRS for the regulatory field to assess the quality of dossier submissions and their reviews in the context of HTA.
2. Assess HTA quality in the context of internationally accepted principles.
3. Refine the definition of quality in the context of HTA as specified by this Syndicate.
4. Establish the elements of a quality dossier and a quality review as also enumerated by this Syndicate.

Section 3: Presentations

Learning From Shared Experience

Dr Brian O'Rourke

President and CEO, Canadian Agency for Drugs and Technologies in Health (CADTH), Canada

The Canadian Agency for Drugs and Technologies and Health (CADTH) assesses drugs, medical devices, surgical procedures and diagnostic tests for the purpose of providing recommendations and advice to the payers who decide which products should be listed and funded through the Canadian public healthcare system. In his presentation, Mr O'Rourke discussed why benchmarking of CADTH and other health technology assessment (HTA) agencies should take place, what should be measured and how such measurement might be implemented.

Why benchmark HTA agencies?

HTA has become truly a global phenomenon (Figure 3), and external organisations, associations and the media have already begun to benchmark international pharmaceutical reimbursement activities, and by extension, HTA processes. The annual report from the Canadian pharmaceutical industry lobby association, Rx&D, recently reported on public coverage for 150 drugs treating 181 indications among countries in the Organisation for Economic Cooperation and Development (OECD). This report indicated

that internationally, the average percentage of reimbursement for these drugs was 64%. The country reimbursing the highest percentage of available drugs was the United States at 88%, whilst the country with the lowest percentage of reimbursement was Poland, with 15% of drugs reimbursed. At 51%, Canada ranked 23 out of 29 countries studied.¹

One of the challenges in benchmarking the many international agencies lies in their uniqueness. Mr O'Rourke quoted O'Donnell and colleagues in their report of international HTA, "If you have seen one HTA system, you have seen one HTA system."² Despite the differences among agencies, however, comparisons are not only possible but advisable in order to compare performance against accepted measures, implement a process of continuous improvement and to support national and international efforts at harmonisation already taking place through agencies such as the International Network of Agencies for Health Technology Assessment (INAHTA), the European Network for Health Technology Assessment (EUnetHTA) and CIRS.

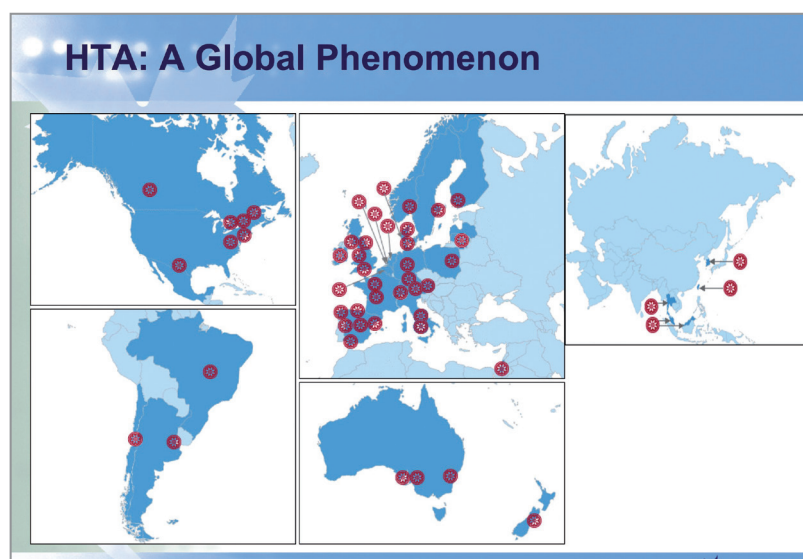
Representatives from the Canadian pharmaceutical industry have indicated that they encourage efforts that would see CADTH work toward international benchmarks in all of its processes and practices. They also support the principles of good HTA practices espoused by international HTA leaders and organisations including inclusion and meaningful involvement of all stakeholders, transparency and rigour of HTA process and decision-making criteria and the incorporation of broad-based considerations of societal and patient value.

What should be benchmarked?

Having established that the benchmarking of HTA agencies is worthwhile, it must be decided what is to be measured (Figure 4). It may be that benchmarking should centre on the three main aspects of HTA:

1. Planning and prioritisation must be practiced at HTA agencies with limited budgets and personnel who cannot hope to evaluate all new drugs and devices submitted for approval. CADTH, for example, reviews only new molecules and new indications for existing molecules – approximately 30 to 35 products each year.

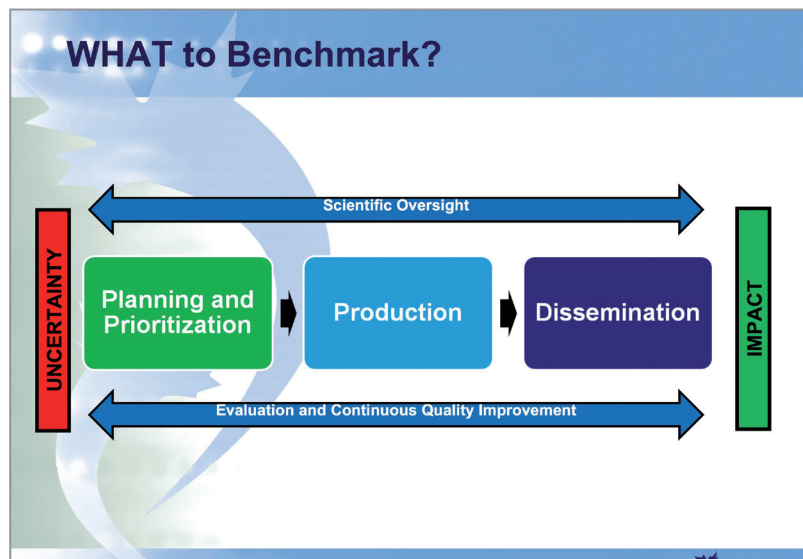
Figure 3. Some international HTA agency locations.



2. Production, or the actual conduct of the review may be led by internal staff or expert committees.
3. Dissemination of the decision and rationale for the decision

Another system of benchmarking could be based on the 15 Principles for the evaluation of HTA developed by the International Working Group for HTA Advancement, as discussed by Professor Bengt Jönsson, Professor of Health

Figure 4. Benchmarking HTA might centre on its three key aspects: planning and prioritisation, production, and dissemination of results.



... regardless of who conducts the evaluations [of HTA agencies], simplicity of process and transparency of the results to all stakeholders are essential.

Economics, Stockholm School of Economics, Sweden (see page 25). Most stakeholders agree, however, that initially, benchmarking HTA agencies should centre on their processes and methods.

Who should benchmark?

Several groups have taken the initiative in evaluating HTA agencies, including CIRS, INAHTA, EUnetHTA, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Drug Information Association (DIA), each with a slightly different approach. Coordination of efforts among these groups is required to avoid duplicative efforts, and regardless of who conducts the evaluations, simplicity of process and transparency of the results to all stakeholders are essential.

References

1. *The Rx&D International Report on Access to Medicine*, 2010. Available at www.patientscomefirst.ca. Accessed December 2011.
2. O'Donnell JC, Pham SV, Pashos CL et al. Health Technology Assessment: Lessons Learned from Around the World—An Overview. *Value Health*, 2009;12: S1–S5.

WORKSHOP REPORT

Why innovators want greater HTA clarity and predictability

Greg Rossi

Vice President, R&D Payer Evidence, AstraZeneca, UK

Issues faced by both industry and payers are remarkably similar: steadily increasing stakeholder expectations in the face of escalating costs and decreasing revenue. In fact, median returns are below the cost of capital for the entire pharmaceutical industry, creating a lack of confidence in the profitability of future research and development among investors. Thus, transparency and predictability in the methods, assessments and pricing of health technology assessment (HTA) and coverage bodies has become essential for the future of innovation in medicine.

HTA Methods

Little if any harmonisation in evidence standards and expectations is emerging from the many international health technology assessment agencies. For example, randomised, control trials are the gold standard of evidence for the German Institute for Quality and Efficiency in Healthcare (IQWiG), and observational research and effectiveness trials assume a much lower position in the hierarchy of data validity. Other HTA agencies, however, have indicated an interest in the results of observational studies that might reveal the actual costs and outcomes of healthcare in real-world settings.

Harmonisation in methodologic rigour would be particularly valuable for the evaluation of emerging technologies. Today's pharmaceutical industry is heavily invested in personalised medicine and many therapeutics are currently being developed with companion diagnostics that will identify the patients who will most

benefit from these medicines. Iressa, (gefitinib), a chemotherapy for which ideal patients are those who have tested positive for an epidermal growth factor receptor mutation (EGFR+) is one such medication. Having a clear understanding of the expectations of HTA for the nature of the supportive data that will help make an informed decision about the value of these approaches will encourage investment and innovation in this arena. However, requests for evidence development should be based on logical yet practical approaches.

Despite evidence published in 2009 that demonstrated significantly improved outcomes with gefitinib for pulmonary adenocarcinoma for EGFR+ patients¹, the draft guidance document for companion diagnostics developed by the Pharmaceutical Benefits Advisory Committee of Australia calls for clinical trials that produce “Level 1 evidence” for medicines with companion diagnostics. In this case, this would mean clinical trial patients would be randomised for EGFR testing and then six treatment arms would need to be developed consisting of patients who were not tested being treated with gefitinib or the comparator, and patients who were tested divided into EGFR+ patients being treated with gefitinib or the comparator and patients who are EGFR- being treated with gefitinib or the comparator (Figure 5). The complexity and cost of such a trial would represent a significant barrier to development.

HTA Assessments

HTA and regulatory bodies have different mandates and criteria for assessment, sometimes leading to different conclusions. For example, between 2006 and 2009, less than one third of therapies approved by the European

Medicines Agency (EMA) were recommended for reimbursement by the National Institute for Health and Clinical Excellence (NICE) for the entire approved treatment population. In fact, the patient populations for these therapies have been reduced by NICE recommendations to less than half of the population specified in the product labels.

Citing the upcoming HTA review of the AstraZeneca platelet inhibitor ticagrelor in Germany as an example, Mr Rossi pointed out that mandates and criteria for assessment also vary among HTA bodies. Ticagrelor was recommended for reimbursement by NICE as cost-effective therapy to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome. In Germany, however, the 2011 German Act on the Reform of the Market for Medicinal Products (AMNOG) specifies that new pharmaceuticals should be subjected to a benefit assessment through a dossier containing proof of the added benefit in comparison to the “appropriate comparator” specified by the Federal Joint Committee (G-BA). Because the comparator used in the registration trials for ticagrelor was not the reimbursed standard of care in Germany the results of the assessment in that country may not be positive.

[Note: Following this Workshop, IQWiG issued a statement regarding the AMNOG decision on ticagrelor²:

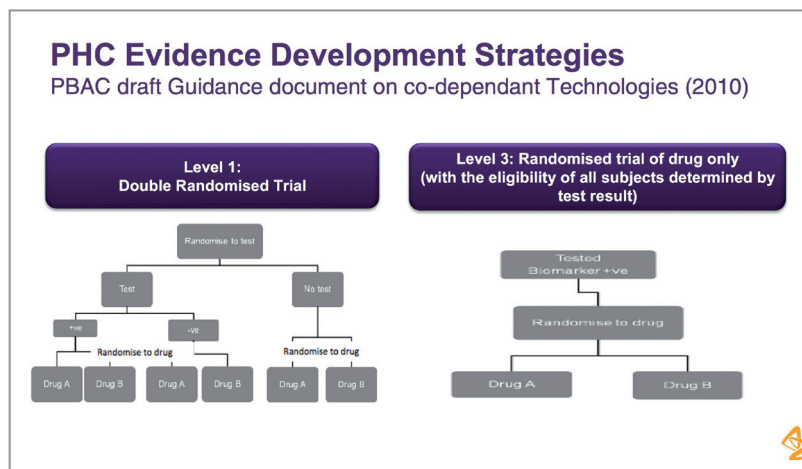
The Institute has come to the conclusion that ticagrelor provides considerable added benefit to patients with “mild” myocardial infarction without the typical changes in the ECG (NSTEMI), as well as to patients with unstable angina pectoris, by reducing the risk of death and myocardial infarction. However. . .The dossier failed to provide proof that ticagrelor is of added benefit for patients with STEMI. . . One reason for this was that AstraZeneca deviated from the appropriate comparator which the G-BA specified for the therapeutic indication “STEMI”.

IQWiG called the AMNOG process “practicable and transparent.”]

Transparency and pricing

Research by Russo and colleagues of the time to patient access for oncology therapies in Italy showed that medicines that were authorised with a risk sharing agreement were associated with a more rapid time to access that those that were authorised without this type of agreement.³ Mr Rossi attributed this earlier approval to a negotiated reimbursement process that

Figure 5. Complex and costly level 1 evidence may be required for companion diagnostics.



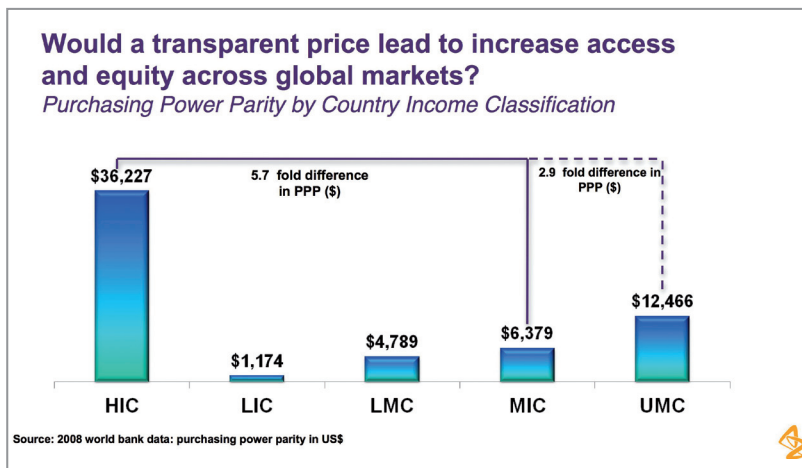


Figure 6. There is a lack of purchasing power parity in geographically connected regions.

provided payer confidence secured through risk sharing.

Because of extreme variations in purchasing parity, however, transparency in prices may not lead to more rapid access, even in regions such as Europe that are linked in terms of movement of free goods, price and transparency legislation, parallel trade and reference pricing (Figure 6).

Moreover, some economists have claimed that drug price transparency would prove more beneficial to wealthier countries than to poor ones.⁴

Conclusions

Mr Rossi concluded by remarking that innovators look for consistent, predictable features in

Because of extreme variations in purchasing parity, however, transparency in prices may not lead to more rapid access

health technology assessments. Value, which reflects the needs of relevant parties, should be rewarded with appropriately valued funding by the healthcare system. HTA recommendations should be science-based and objective, consider all relevant data and be conducted in an open transparent dialogue with all appropriate stakeholders. It should be based on a common set of clear, prospectively defined and scientifically appropriate methodologies and decisions should reflect the needs and values of the population, made explicit and reconsidered only when new evidence becomes available.

References

1. Mok TS, Wu YL, Thongprasert S et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med.* 2009;361:947-957.
2. Institute for Quality and Efficiency in Health Care. *Ticagrelor: Considerable added benefit for specific patients.* Found at <https://www.iqwig.de/index.1366.en.html?random=b9a2aa>. Accessed December 2011.
3. Russo P, Mennini FS, Siviero PD, Rasi G. Time to market and patient access to new oncology products in Italy: a multistep pathway from European context to regional health care providers. *Ann Oncol.* 2010;21:2081-2087.
4. Kyle MK, Ridley DB. Would greater transparency and uniformity of health care prices benefit poor patients? *Health Affairs* 2007;26:1384-1391.

Benchmarking performance: Enhancing the quality and efficiency of healthcare

Dr Marc L. Berger

Executive Vice President & Senior Scientist - OptumInsight Life Sciences

OptumInsight, a health technology research and consulting company is part of United Health Group, an organisation that also encompasses United HealthCare (UHC), one of the largest managed care commercial payers in the United States. At UHC, the quality of healthcare decisions is benchmarked through the availability of patient information, access to evidence-based science and benefit information and the ability to track outcomes over time.

Benchmarking healthcare

As Dr Marc Berger explained, healthcare quality and efficiency are the direct result of patient and clinician decisions, and payers, who are endeavouring to obtain the optimal health outcomes for the lowest cost, must consider the factors implicit in those decisions in the evaluation of a new medicine. Among those factors, the clinical judgement and technical skills of healthcare professionals are recognised to be highly variable from community to community across America, with a resulting disparity in health outcomes.

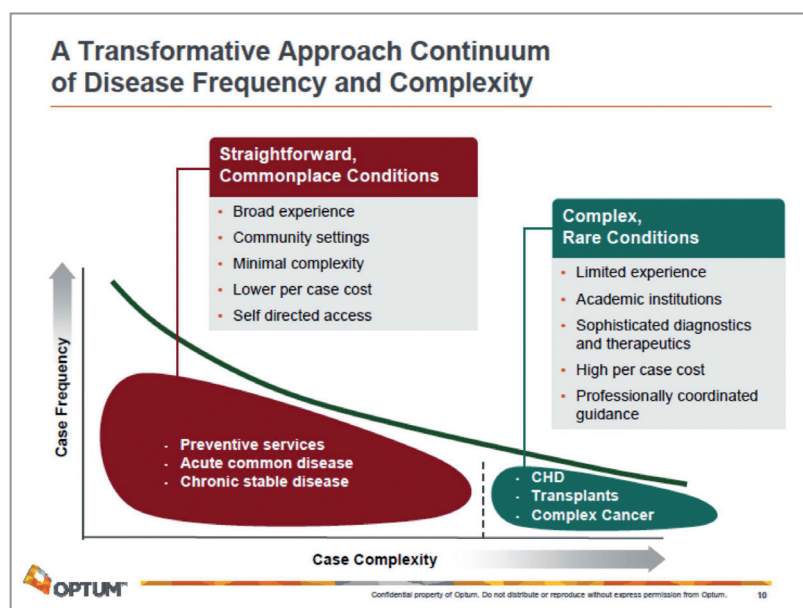
In an analysis of the quality of healthcare delivery in the United States, McGlynn and colleagues demonstrated that 11% of patients received care that was not recommended by professional treatment guidelines or that was ultimately

harmful. For example, 35% of patients with hypertension were not diagnosed or correctly treated; and 55% of patients with diabetes were not adequately monitored for glucose control.¹ Lack of patients' support of their treatment plans also produces a negative effect on health outcomes, with nearly one in five prescriptions never being filled and less than half of patients adherent to long-term medication therapy 6 months after starting the prescription.²

One of the United States' largest integrated networks of physicians and hospitals allows UHC to benchmark its therapeutic approaches within the organisation and against other commercial payer organisations, thereby improving the quality of overall care over time. More than 75% of physicians and 85% of hospitals in the United States are part of the United Healthcare network, resulting in 600 million portal transactions a day and multiple terabytes of claims, laboratory and medical records data. All of these data are used for the purpose of driving quality and efficiency enhancement.

UHC optimises the impact of care management along the continuum of disease frequency and complexity, using two coordinated approaches (Figure 7). For the majority of patients who experience straightforward, more commonly occurring conditions involving self-directed access to lower cost treatment in community settings, UHC incentivises changes in clinical and patient behaviour that close gaps in patient care by encouraging preventative treatments and adherence to therapy.

Figure 7. UHC utilises a two-pronged approach to optimise disease management.



For patients who experience more complex and rare conditions . . . UHC endeavours to direct treatment to “Centres of Excellence” that have demonstrated the best and most cost-efficient health outcomes.

For patients who experience more complex and rare conditions for which there is limited experience and which involve professionally guided access to sophisticated diagnostics and therapeutics at academic institutions at a high cost per patient, UHC endeavours to direct treatment to “Centres of Excellence” that have demonstrated the best and most cost-efficient health outcomes. In this way UHC rewards and inspires continuous improvements in the delivery of exceptional clinical performance.

Dr Berger cited several examples of how UHC manages complex illnesses: in one programme that enrolled high-risk patients after myocardial infarction, treatment compliance was actively encouraged; patients incurred significantly lower treatment costs and rehospitalisation rates compared with those who were not enlisted in the programme. In another example of care and cost management optimisation, after developing a list of Centres of Excellence in heart transplantation that was based on both high volume of patients and superior survival rates, UHC contracted with those centres with a guarantee to direct future patients in exchange for volume-based price reductions. Subsequent decreases in incidence and length of hospital stay and follow-up charges in addition to this incremental discount resulted in an overall 59% savings, as well as a significant improvement in health outcomes. In fact, Centres of Excellence in heart, kidney, liver and allogenic bone marrow transplantation have achieved incremental improvements in survival as high as 97% (Figure 8).

Using episodes of care provided by an integrated team of specialists as a metric, UHC examines variances in outcome and cost of treatments among clinicians, urging patients toward treatment by healthcare professionals of the highest quality. In the Premium Designation Programme, primary care physicians and specialists are evaluated for the quality of care delivered and the average cost of treatment. Physicians are provided with the results of these evaluations to enable treatment or practice modifications. This transparent treatment information, available on the UHC website, does affect the therapeutic decisions of

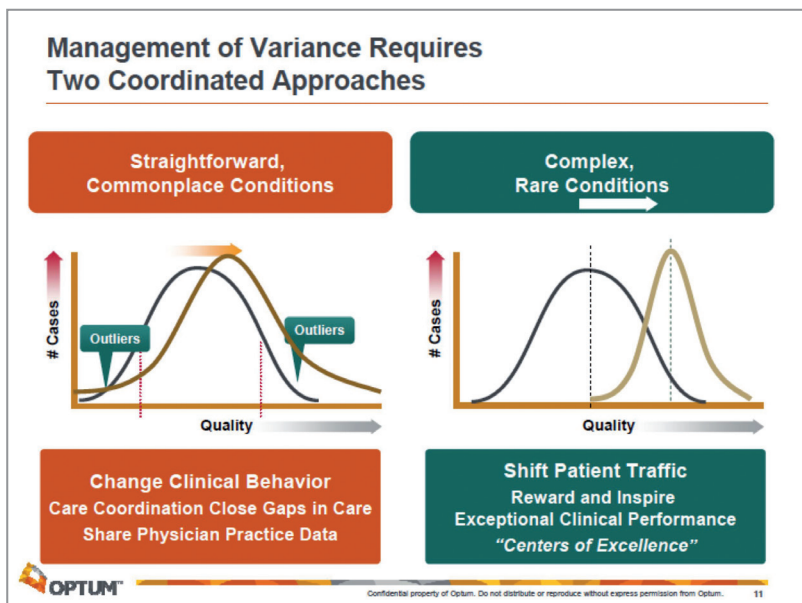


Figure 8. Sharing of clinician practice data and shifting patient traffic have resulted in enhancements of health outcomes and costs.

patients. Data have shown that 13% of patients experiencing a wide variety of health conditions who are provided with this type of information choose a treatment different from that initially recommended to them and choose clinicians who recommend this different treatment. In addition to significant improvements in health outcomes such as 25% fewer complications achieved by Premium Designation cardiologists, UHC has achieved a 15% average saving per treatment episode for all designated specialties.

At UHC premium cardiac, surgical spine and total joint replacement specialty centres, standards are incorporated to and aligned with national quality improvement efforts by specialty societies and by the Center for Medicare and Medicaid Services. For example, designated cardiac facilities are required to report their outcomes for percutaneous coronary intervention procedures to the American College of Cardiology – National Cardiovascular Data Registry®, and coronary artery bypass graft (CABG) surgery outcomes to the Society of Thoracic Surgeons National database, non-ST-segment elevation myocardial infarction data to one of three registries and morbidity and mortality for all interventional cardiac procedures and CABG.

Benchmarking UHC performance

In the American Medical Association National Health Insurer Report Card, which provides physicians and the general public a reliable and defensible source of critical metrics concerning the timeliness, transparency, and accuracy of claims processing by health

insurance companies, UHC was rated first among commercial payers in claim payment accuracy.

Approximately 15 years ago, the National Committee for Quality Assurance (NCQA) developed the Healthcare Effectiveness Data Information Set (HEDIS), the primary means for assessing competitive standing amongst managed care organisations on clinical quality performance. Over 90% of America’s health plans submit HEDIS data to NCQA, and that wealth of data as well as its specifically defined measurements allows the comparison of the performance of health plans on an “apples-to-apples” basis. The Quality Compass, produced annually by NCQA, provides detailed HEDIS results for individual plans across the country as well as national percentiles and means for plans to benchmark performance. Using tools like Quality Compass and other internally developed analytics, UHC is able to monitor trend and competitive performance across the country at the national, regional and market levels.

Sample results of use of the Quality Compass demonstrate UHC provider performance in haemoglobin A1C testing, monitoring of kidney function and LDL screening in patients with diabetes falls approximately within the 75th percentile. Although these measurements show that performance quality is trending upward amongst UHC providers, they also demonstrate the need for continued improvement and partially reflect the measured pace of quality enhancement in such a large and diverse group of clinicians.

Summary

Using its significant data warehouse derived from actual patient and clinician activities, UHC is able to benchmark performance, analyse practice variation and identify higher quality, higher efficiency providers to provide practical information to patients, targeting appropriate patients for care management, and providing referrals to centres of excellence. The use of standardised benchmarking measures provides a tool for monitoring and encouraging cost-effective medical care

References

1. McGlynn E, Asch, SM, Adams J et al. The quality of healthcare delivered to adults in the United States. *N Engl J Med* 2003;348:2635-2645.
2. Vermeire E, Hearnshaw H, Van Royen P, et al. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther.* 2001;26:331-342.

Improving regulatory agency performance: measuring time, performance and quality

Dr Petra Dörr

Head of Management Services and Networking, Swissmedic, Swiss Agency for Therapeutic Products

Swissmedic is the central agency for the regulation of medicinal products and medical devices in Switzerland. A small to mid-sized agency with 325 full time equivalents (400 employees), Swissmedic authorises approximately 40 new chemical entities per year. It operates on a budget primarily generated by user fees, with less than 20% of costs funded by the Swiss government.

Internal and external benchmarking

After an external analysis conducted in 2006 revealed the need for improvements in processes and procedures, Swissmedic embarked on a programme to increase efficiency, consistency and transparency within the agency. Facing a backlog of 3,500 applications in 2008, Swissmedic assembled a task force to ensure that target timelines were met and that delays were eliminated by 2010. The goal in 2011 is to further enhance operations, and to optimise activities by benchmarking performance against larger regulatory agencies such as the European Medicines Agency (EMA) and the US Food

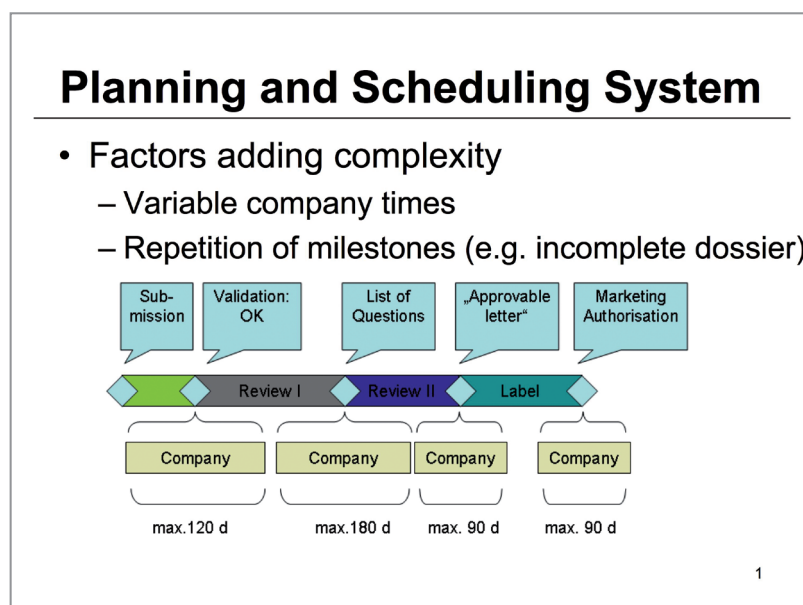
and Drug Administration (FDA). However, it is recognised that greater resources, funded by higher user fees will be required to meet these goals.

In addition to benefiting from comparisons to external performance management initiatives through benchmarking against other agencies, increased stakeholder expectations for high-quality performance within target time have led to a growing role for internal performance management at Swissmedic. The agency has therefore instituted a system of performance indicators comprising five elements:

- **input:** the number of applications, adverse event reports and requests for information received;
- **output:** the number of application reviews completed, enforcement measures taken and manufacturing licenses granted;
- **quality:** the number of complaints received or deviations noted from internal audits;
- **efficiency:** the number of hours spent on activities or processes; and
- **performance:** the number of application reviews completed and requests answered within target time.

Swissmedic also participates in the Regulatory Benchmarking Programme of the Centre for Innovation in Regulatory Science (CIRS). Dr Dörr remarked that Swissmedic regards this programme as an independent and unbiased “apples to apples” comparison of performance related to marketing authorisation procedures. The agency uses the resulting data to identify best practices, assess the position of Swissmedic relative to other agencies, document the long-term development and influence of performance improvement initiatives, verify the results of other benchmarking studies and to measure the impact of process and structural changes. Dr Dörr suggested enhancements to the CIRS programme that included timely updates, the use of an online data entry and reporting interface, and an expansion of the programmes scope to include additional types of products and agencies.

Figure 9. Approximately 12,000 applications are received by Swissmedic each year, involving differing levels of complexity.

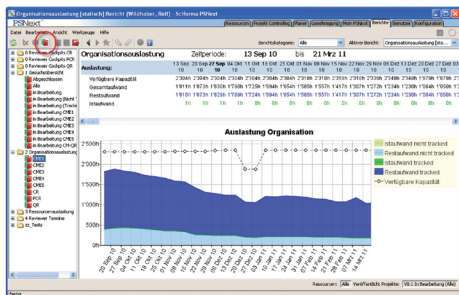


Advanced planning and scheduling system

Swissmedic receives approximately 12,000 applications per year, each of which requires multiple interactions and exchange of administrative and scientific information. There had been little transparency regarding the

Planning and Scheduling System

- Examples of views of the system
Capacity utilisation per organisation unit



2

Figure 10. Reports that can be generated by the Swissmedic planning and scheduling system include the utilisation of capacity per organisational unit.

status of the review of these applications, each of which involves differing levels of complexity and timelines affected by many diverse factors (eg, incomplete dossiers, which necessitate the repetition of milestones) (Figure 9). To effectively meet these and other challenges, the agency has introduced an advance planning and scheduling system. The goal of this system is to improve adherence to target timing through the ability

to flexibly and quickly react to personnel and project changes, thereby optimising the use of resources. Appropriate planning efforts will also be facilitated by this system, with a resulting improvement to efficiencies.

Reports that can be generated from this tool can provide updates on project status, employee performance, resource utilisation per case and capacity utilisation per organisation unit (Figure 10). Expected benefits include transparency regarding case status and resource utilisation, a strengthening of the role of case management, the provision of automated reports to managers and enhanced information regarding the actual time required for specific activities.

Conclusions

The current focus on quality and performance enhancement at regulatory agencies has required a culture change, and even smaller agencies must have sufficient staff and suitable technologic tools to achieve and maintain optimal performance. Objective benchmarking data can facilitate stakeholder discussions, and the timely availability of comparative data on performance and process enables timely actions such as the identification and broader use of best practices and the orderly implementation of planning and change practices.

WORKSHOP REPORT

Activity indicators for the Pharmaceutical Benefits Scheme

Emeritus Professor Lloyd Sansom

Special Advisor, Commonwealth of Australia

The need for performance indicators

In Australia, as in other economies, the goal of pharmaceutical payers is the equitable, affordable and timely access to new technologies that improve health outcomes. The comparison of performance by these agencies against that goal, however, is complicated by the lack of a common framework and terminology. For example, because the Pharmaceutical Benefits Advisory Committee (PBAC) has a legislated timeframe for decision making of 17 weeks from the time of submission, comparing the timing of reimbursement evaluations in Australia with most other countries is not useful.

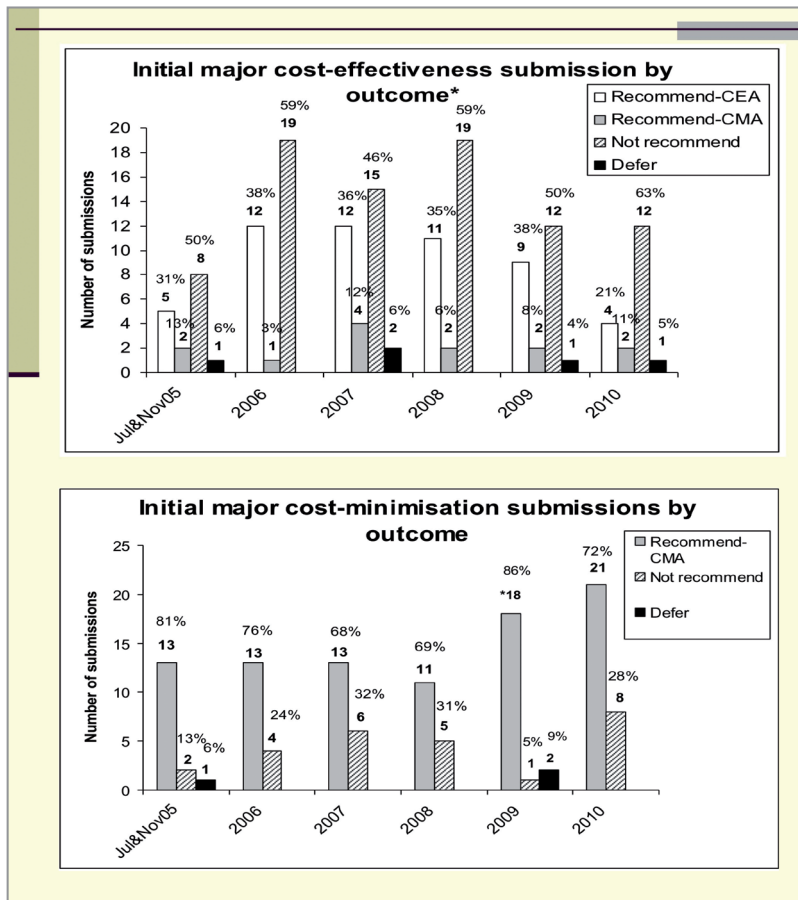
In recognition of the complexity of international benchmarking and in response to industry

association requests for a set of values that would measure the agency's performance with respect to pharmaceutical payment decision making, the PBAC created a system of activity indicators to identify trends in the process of adding items to the Pharmaceutical Benefits Scheme (PBS) and the National Immunization Programme (NIP). In the development of this system, it was determined that these indicator data should be publicly available and independently verifiable. In Australia, where the unrestricted access to full pharmaceutical submissions and evaluations is not permitted, publicly available documentation for verification primarily consists of Australian Public Assessment Reports (AusPARs), and Public Summary Documents (PSDs).

AusPARs are comprehensive reports of the evaluation of a new medicine by the regulator and of the recommendations and rationale for the recommendations. They are available no more than one month after the drug has been listed on the Australian Register of Therapeutic Goods, and AusPARs for drugs that have been rejected by the regulator cannot be published until a 90-day appeals period is complete. PSDs, which are based on the minutes of the consideration of submissions, follow a template structure and provide information to the public pertaining to PBAC recommendations and their rationale. In addition to these documents, the outcomes of PBAC decisions are posted approximately 6 weeks after a decision has been reached.

In addition to publicly available and independently verifiable data, consistency in terminology was determined to be critical in the construction and use of PBAC performance indicators. Accordingly, the outcomes of submissions to the PBAC from 2005 to 2010 were evaluated according to strictly defined submission categories, including whether they were considered major or minor. A *major submission* was defined as that of a new drug or for a substantial change in an existing drug with the requirement for economic analysis. Submissions classified as *minor* were those generally not evaluated prior to PBAC consideration, covering, for example, a change in quantities or clarification of a use restriction. If, however, the PBAC accepted the clinical and economic analysis of a major submission but required a price reduction to attain an acceptable incremental cost-effectiveness ratio, the application might be resubmitted as a minor submission. The PBAC evaluates approximately 60 major submissions each year.

Figure 11. Outcomes of PBAC submissions on the basis of cost effectiveness versus cost minimisation.



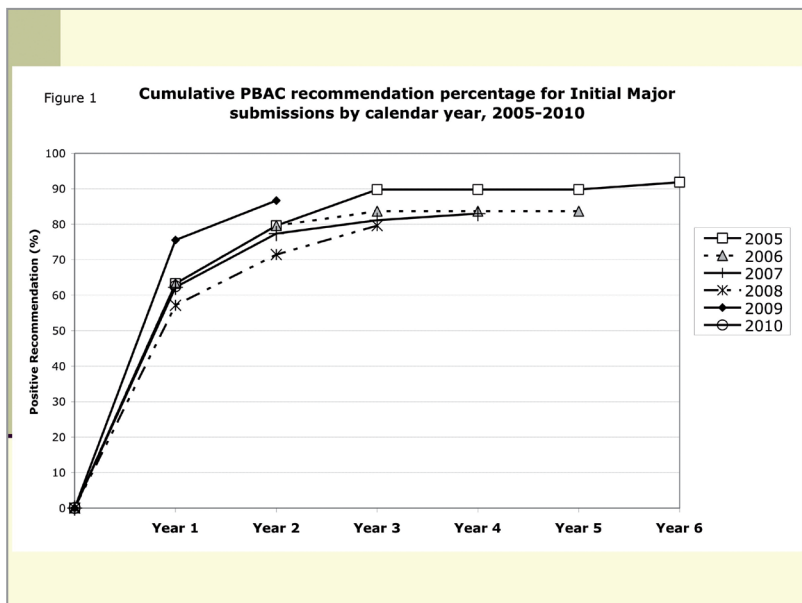


Figure 12. Analysis of PBAC performance indicators shows that most medicines are recommended for reimbursement within 5 years of initial submission.

Performance indicator analysis

Evaluations of performance indicators from 2005 to 2010 revealed that more minor submissions were recommended than major submissions. Furthermore, and perhaps reflecting the submission of data that were more appropriate for regulatory than reimbursement approval, more drugs submitted (or resubmitted) on the basis of cost minimisation were recommended for coverage than those submitted on the basis of cost-effectiveness (Figure 11).

Multiple resubmissions are permissible in Australia, and in fact an analysis of performance indicators shows that by year 5, approximately 90 percent of all major submissions are finally funded (Figure 12).

The high cumulative rate of approval for new medicines in Australia may indicate the potential for a reduction in the number of required resubmissions and reduced time to recommendation with improved and earlier dialogue between industry and regulatory and reimbursement evaluators.

The high cumulative rate of approval for new medicines in Australia may indicate the potential for a reduction in the number of required resubmissions and reduced time to recommendation with improved and earlier dialogue between industry and regulatory and reimbursement evaluators. A programme of parallel submissions to regulatory and reimbursement authorities has recently been initiated to further expedite patients’ access to new medicines.

The analysis of these indicators will be used in a review of the fees for submissions to the PBAC. A similar approach is currently being employed for devices, prostheses and medical services and a new category for co-dependent technologies is being established.

Professor Sansom concluded by remarking that the PBAC is committed to enhancing international dialogue and cooperation with all stakeholders to optimise the efficiency and effectiveness of the health technology assessment process.

Recommendations in technology appraisal guidance 1–232

Recommendation	1 March 2000 to 31 July 2011			1 January to 31 July 2011
	STA	MTA	Total	
Yes	45 (55%)	228 (65%)	273 (63%)	16 (57%)
Optimised	15 (18%)	68 (19%)	83 (19%)	5 (18%)
Only in research	2 (3%)	22 (6%)	24 (6%)	-
No	20 (24%)	34 (10%)	54 (12%)	7 (25%)
TOTAL	82 (100%)	352 (100%)	434 (100%)	28 (100%)

STA, single technology appraisal; MTA, multiple technology appraisal

¹Six recommendations were subsequently withdrawn after publication; on 3 occasions after the EMEA revoked marketing authorisation due to safety concerns, on 1 occasion where the product was no longer produced by the manufacturer and on 2 occasions when a nationally funded program for a technology rendered the guidance obsolete.

²Ten recommendations could not be made in the absence of a submission from the manufacturer ('non-submission').



NICE...intends to remain at the heart of new health policies that aim to improve access and innovation.

be assigned to a new drug's benefits, with higher price thresholds set for medicines that treat diseases of high unmet need or severity, that demonstrate greater therapeutic improvement and innovation or that can demonstrate wider societal benefits. Categories and weights will be determined by the Secretary of State on the basis of expert advice and using a predetermined framework.

This move to value-based pricing reflects the need to make scientific and social value judgements the basis for the appraisal of the value of new health technologies. Ms Pinwill concluded her presentation by explaining that NICE recognises the need to adapt to the new environment and significant changes to the NHS. Over the past decade NICE has shown itself to be responsive to the needs of a broad set of stakeholders by adjusting its processes and methods to meet expectations and intends to remain at the heart of new health policies that aim to improve access and innovation.

WORKSHOP REPORT

Figure 14. NICE recommendations from 1 March 2001 to 31 July 2011.

In this programme, the government will set out a range of thresholds or maximum prices, reflecting different values that medicines offer, using basic cost-effectiveness thresholds and quality-adjusted life years (QALYs). Weighting will

Identification of good practice when using HTA for resource allocation decisions

Professor Bengt Jönsson

Professor of Health Economics, Stockholm School of Economics, Sweden

The International Working Group for HTA Advancement was established in July 2007 with unrestricted funding from the Schering Plough Corporation. The mission of the Working Group is to provide scientifically based leadership to facilitate significant continuous improvement in the development and implementation of practical, rigorous methods into formal health technology assessment systems and processes. By facilitating the development and adoption of high-quality, scientifically driven, objective, and trusted health technology assessments, the group hopes to improve patient outcomes, the health of the public and overall healthcare

quality and efficiency.

In 2008, the Group published *Key Principles for Improved Conduct of Health Technology*.¹ The fifteen principles outlined in this publication were organised into four components of health technology assessment: structure, methods, processes and use in decision making.

The Structure of HTA

According to the Key Principles, the goal and scope of health technology assessment should be explicit and relevant to its use. A detailed scoping document should be developed before initiation of the HTA process, with broad, multidisciplinary, stakeholder involvement. The document should focus on defining the questions to be addressed by the HTA, plus the link between the HTA and any decisions about the use of the technology should be specified.

HTA should be an unbiased and transparent exercise. Given the inherently complicated and controversial nature of HTA-based decisions and their importance to multiple decision makers and stakeholders, the HTA process is

best conducted independently of the body that ultimately will be responsible for adopting, paying and implementing the HTA decisions. Furthermore, the HTA process and the detailed basis on which recommendations and decisions are made must be transparent.

All relevant technologies that compete for allocation of resources should be included in health technology assessment. That is, to avoid inequalities in the investment in and use of resources, all health technologies should be considered potential candidates for HTA. However, because not all technologies will be assessed owing to limitations in personnel and budget, a clear system for setting priorities is required.

Methods of HTA

HTA should incorporate appropriate methods for assessing costs and benefits. The development and consistent implementation of rigorous, analytical methods is required to engender stakeholder and public trust in the process and its findings. This requires clarity of HTA process and methods, as well as access to experts with appropriate clinical and multidisciplinary methodological training.

Assessment of new technologies should consider a wide range of evidence and outcomes. HTAs require use of data from experimental, quasi-experimental, observational, and qualitative studies, integration of both endpoint and validated surrogate data, and assessment of the incremental impact of and trade-offs among multiple clinical, economic and social outcomes in clinically relevant populations.

A full societal perspective should be considered when undertaking HTA assessments. HTAs should adopt a broad societal perspective to optimise the efficient use of limited healthcare resources and the resulting societal benefit and to avoid and identify potentially distorted clinical decisions and health policies resulting from adoption of narrower perspectives used by various healthcare system stakeholders.

HTAs should explicitly characterise uncertainty surrounding estimates. Data can be imperfect

point estimates of underlying distributions that may incorporate a variety of errors, and analytical methods are subject to biases and limitations. Thus, extensive sensitivity analyses are required to determine the robustness of HTA findings and conclusions, and the limitations of an analysis should always be acknowledged.

Issues of generalisability and transferability should be addressed in health technology assessments. Examination of the generalisability and transferability of HTA findings across clinical populations and policy relevant perspectives is required, given the inherent variability of disease, intervention responses, and outcomes across patients, populations, providers, healthcare delivery sites and healthcare systems.

Process for conduct of HTA

HTA programmes should actively engage all key stakeholders in all stages of the HTA process, as this is likely to result in technology assessments of higher quality that are more widely accepted and that stand a greater chance of being implemented. Moreover, such an open process will enhance transparency and trust in the process, as stakeholders develop a greater understanding of the criteria and standards used.

Those undertaking HTAs should actively seek all available data. In situations in which confidential data are used, confidentiality should be defined, and efforts should be made to make the data publicly available as soon as possible in the interests of maintaining transparency and engendering understanding of and trust in decisions.

The implementation of HTA findings needs to be monitored, both to ensure that the original investment in conducting HTAs is valuable and to ensure that findings are being implemented in a fair and even-handed manner.

Use of HTA in decision making

HTA assessments should be timely, that is, conducted when they can inform key decisions in the payment for and use of health technologies, and assessments should be constantly updated. To accomplish this goal requires timely conduct of studies by manufacturers and other advocates and, in selected circumstances, requires limited reimbursement, conditional upon further study to inform safety, effectiveness, and cost-effectiveness.

HTA findings must be communicated appropriately to different decision makers. Given

By facilitating the development and adoption of high-quality, scientifically driven, objective, and trusted health technology assessments, the group hopes to improve patient outcomes, the health of the public and overall healthcare quality and efficiency.

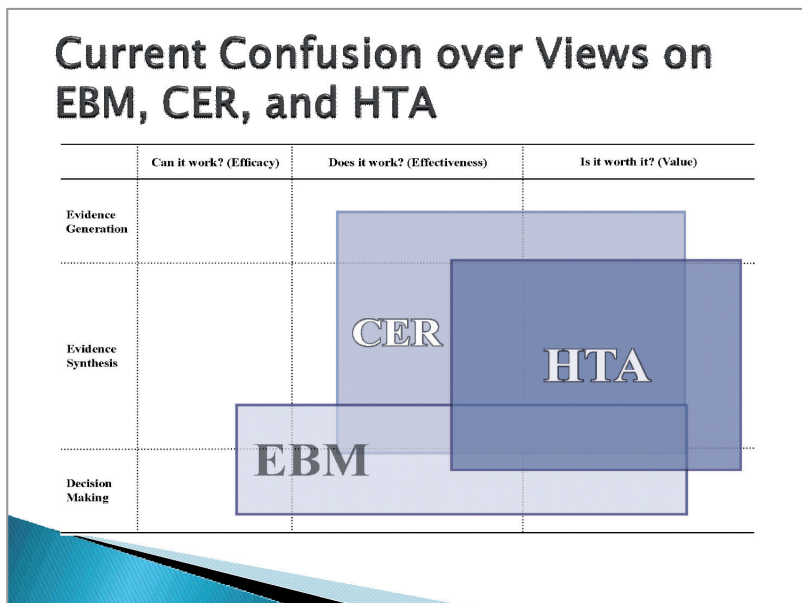


Figure 15. The overlapping functions and positions of evidence-based medicine, comparative effectiveness research and health technology assessment.

the multiple audiences for HTA findings, effective communication strategies need to be developed to meet the disparate needs of different users. The link between HTA findings and decision-making processes needs to be transparent and clearly defined. A clear distinction must be made between the HTA assessment process itself and the resulting decisions. The link between the assessment and the decision will be different in various settings, but in all cases it should be transparent.

Additional publications

In 2010, the Group published a report that elucidated the relationship between evidence-based medicine, comparative effectiveness research and health technology assessment² (Figure 15). A subsequent manuscript published that year reported its investigation of how the Key Principles were implemented and supported at 14 international HTA agencies.³ Results of this research indicated that no organisation supported and implemented all principles, although more principles were supported by European HTA agencies. It was agreed that more work is needed on methods for benchmarking exercises.

Two additional publications are planned. *Can we reliably benchmark HTA organisations?* will discuss issues in benchmarking HTA using audit criteria developed from the Key Principles. *Principles for comparative effectiveness research (CER)* is being developed in collaboration with the National Pharmaceutical Council of the United States.

References

1. Drummond MF, Schwartz J, Jönsson B. Key principles for the improved conduct of health technology assessment for resource allocation decisions. *Int J Technol Assess Health Care*. 2008;24:244-258.
2. Luce BR, Drummond M, Jönsson B. EBM, HTA, and CER: Clearing the confusion. *Millbank Quarterly*. 2010;88:256-276.
3. Neumann PJ, Drummond MF, Jönsson B. Are key principles for the improved conduct of health technology assessment supported and used by Health Technology Assessment organizations? *Int J Technol Assessment Health Care*. 26: 71-78.

Benchmarking pilot study of HTA impact on industry

Dr Franz Pichler

Manager, HTA Programme, Centre for Innovation in Regulatory Science

Background

In 2009, CIRS (the Centre for Innovation in Regulatory Science) conducted a survey among industry, regulators and health technology assessment (HTA) agencies on a variety of issues surrounding the review and reimbursement of medicines. In this survey, 94% of industry participants felt that regulatory requirements for the review of a new medicine were clear

and transparent, whilst only 13% of those participants indicated that the requirements for health technology assessment were similarly apparent.

As a result of this survey as well as of recommendations from CIRS Workshops and requests from member companies of the CIRS HTA Programme, CIRS proposed to undertake a research study to determine the impact of HTA requirements and advice on the development of new products and their rollout. It was envisioned that the study would provide data to inform a range of internal company functions and act as an aid to internal decision making.

The pilot

With the assistance of an industry task force, the pilot proposal was developed in early 2011 with two components. The first part of the

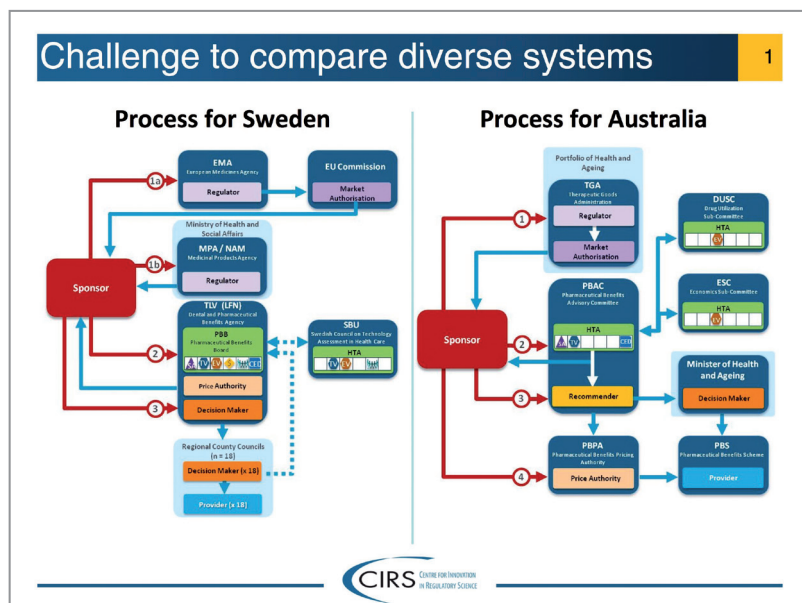


Figure 16. The methodologic variety among HTA agencies adds complexity to comparisons.

study examined drug development, focussing on the role of HTA requirements and scientific advice, and the second part analysed the rollout of a new product to different jurisdictions in terms of timelines, additional local advice or requirements, outcomes and other outstanding issues.

Programme participants agreed to provide CIRS with data for two new active substances or major line extensions that had been rolled out to at least of 50% of jurisdictions in the study. Additionally, to better reflect more recent practices, it was also requested that data be included for one further product that had been recently submitted for its first regulatory review. Vaccines, label changes and generics were excluded. Three basic research questions were employed:

1. How do HTA requirements influence development plans?
2. What has an impact on successful outcomes with HTAs?
3. Are review times for HTA and coverage bodies predictable?

Pilot results

Participants chose six national-level HTA

jurisdictions and two private payers within the United States as the initial focus for this study. Five companies provided data on twelve products. This response was sufficient to enable CIRS to both test the methodology and to provide indications of what a benchmarking programme could potentially deliver.

For these products, the pilot collected data for the timing of the key milestones in development typically used by companies for benchmarking, such as the date of the first patient dose, first pivotal dose, and first regulatory submission. Through the accumulation of data regarding timing for these developmental milestones, it is believed that this study will help demonstrate the impact on timing and outcome from the inclusion of HTA requirements. Whilst examining these milestones within an individual jurisdiction was relatively straightforward, the challenge is in the comparison of milestones across jurisdictions.

In addition to this development data, the timing for the review processes for the products were mapped for individual countries and the HTA and payer agencies. It is anticipated that as the dataset grows, it will be possible to develop confidence levels and a measure of predictability regarding timing for review functions within agencies. Again, the challenge is the identification of comparable processes and milestones across agencies with diverse review methodology and procedures (Figure 16).

The preliminary data, however, do permit activities to be examined in the context of individual agency processes; for example, whether those processes are sequential rather than parallel. The data also allow questions to be posed relative to timing gaps for which industry is responsible such as whether delays in submission to secondary jurisdictions are the result of company strategy or the need for dossier revisions.

Companies also provided data relative to a specific list of HTA requirements that were included in development of the analysed products such as patient-related outcomes, quality-of-life measures, comparators, cost-effectiveness, and HTA-related safety. Also included were data regarding additional issues of concern cited by HTA agencies in their review of some the products such as generalisability of the data, analysis methodology, and insufficient safety evidence. Dr Pichler noted that these preliminary data seem to indicate that companies were more likely to achieve

...preliminary data seem to indicate that companies were more likely to achieve an expected result (not necessarily positive) from the review by HTA jurisdictions that specified the need for additional clinical requirements

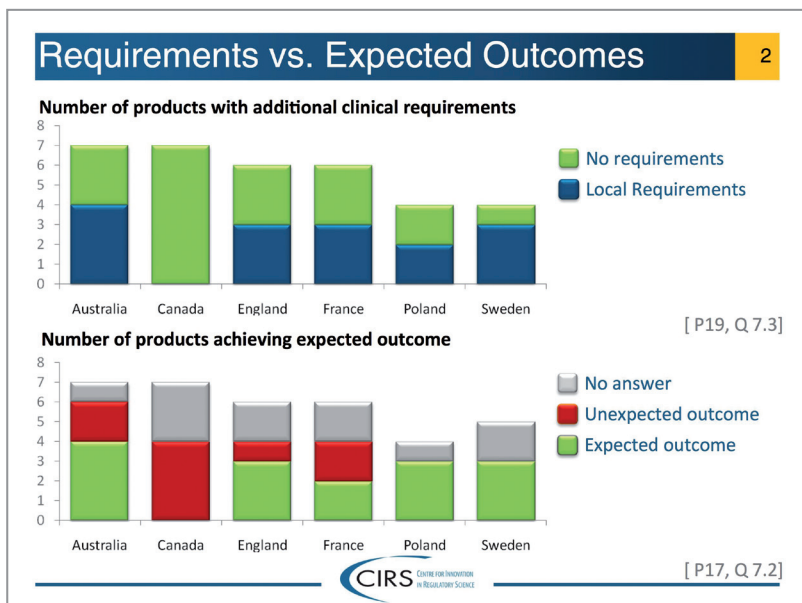


Figure 17. The effect of additional HTA requirements on industry-expected outcomes.

their expected result from the review by HTA jurisdictions that specified the need for additional clinical information (Figure 17). These data could also be examined for their effect on the HTA limitations to the reimbursed populations in comparison to populations included in the regulatory approved product labelling.

Conclusions

These early results demonstrated the feasibility of the survey tool and process while identifying areas for refinement. It was clear that obtaining historical information from a dynamic pharmaceutical industry represented a challenge for this retrospective analysis, but data received to date nevertheless provided an indication of potential insights, identified new areas to investigate and highlighted the need to contextualize individual findings. It is expected that the second phase of the study will be launched early in 2012.

Development and implementation of good practice principles for assessing relative effectiveness based on the EUnetHTA HTA Core Model

Professor Finn Børlum Kristensen

Director, European Network for Health Technology Assessment (EUnetHTA)

In addition to therapeutic and economic values, health technology assessment (HTA) should incorporate consideration of the organisational, personal and societal worth of an intervention. Seeking to implement that broad scope across Europe, the European network for HTA (EUnetHTA) comprises 35 government-appointed organisations from 24 EU member states, Norway and Croatia and a large number of regional agencies and not-for-profit organisations that produce or contribute to HTA.

The EUnetHTA Joint Action between the European Commission and EU Member States

was developed to facilitate the efficient use of resources available for HTA, create a sustainable system of HTA knowledge sharing, and promote good practice in HTA methods and processes. Progress toward the ultimate goal of a permanent and sustainable European HTA network is being made through the activities of five work streams, and a stakeholder forum is linked to the governance of the work streams, with advisory groups providing input for each of the activities. Professor Kristensen reported on the progress of two of those work streams, the development of a Core HTA model and the Relative Effectiveness Assessment of Pharmaceuticals.

The HTA core model

The core model of health technology assessment being developed as part of the EUnetHTA Joint Action seeks to identify the questions that the HTA process should pose and provide guidance as to how those questions should be answered and the results presented to stakeholders. To permit a consistent presentation of information, the model requires that information be categorised into nine domains:

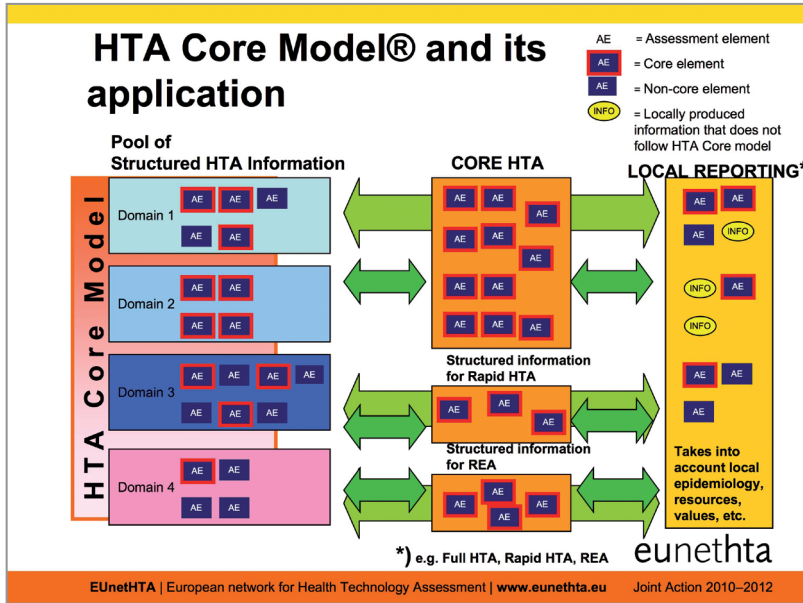
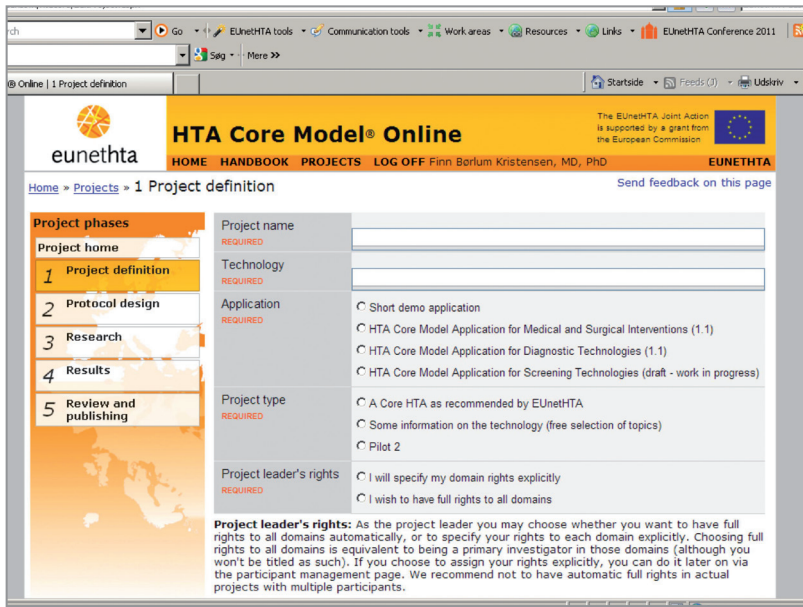


Figure 18. The EUnetHTA HTA Core Model allows the combination of generalised HTA information about a product to be combined with context-specific information from local jurisdictions.

1. Health problem and current use of the technology
2. Description and technical characteristics
3. Safety
4. Clinical effectiveness
5. Costs and economic evaluation
6. Ethical analysis
7. Organisational aspects
8. Social aspects
9. Legal aspects

Figure 19. The EUnetHTA core model is currently being piloted online.



Next, information within those domains is further categorised according to topics. For example, topics within the clinical effectiveness domain include mortality, morbidity, function, health-related quality of life, and patient satisfaction. Finally, topics are themselves divided into issues, or appropriate questions for the assessment to address. Issues within the mortality topic may produce questions such as what is the effect of the intervention on overall mortality or on the mortality caused by the target disease or on the mortality due to other causes than the target disease?

Using this organisational system in the evaluation of specific technologies will result in an increasing pool of structured HTA information that is resistant to contextual differences and is thus shareable among assessment bodies. Shareable information, for example, data on efficacy can then be combined with context-specific information derived from local reporting such as epidemiology (Figure 18) for use in specific regions.

The core model is currently being piloted online (Figure 19).

Relative effectiveness of pharmaceuticals

The objective of Work Package Five of the EUnetHTA Joint Action is to develop principals and methodological guidelines to improve the relative effectiveness assessment (REA) of pharmaceuticals. As the first step in achieving that objective, an overview was developed of the processes, scope and scientific methods used for the REA of pharmaceuticals in Europe, the United States, Canada, Australia and New Zealand.¹ This document indicates that most countries carry out some form of REA to support national reimbursement decisions of pharmaceuticals. There are more similarities than dissimilarities in the scope and the methods used across jurisdictions. The differences between countries, as well as the reasons behind them, need to be considered in the development of a common European methodology for REA. The development of guidelines for REA is ongoing and will address issues including the use of composite and surrogate endpoints, indirect comparators, health-related quality of life and internal and external validity. The draft of these guidelines will be subject to public consultation and stakeholder advisory group review.

Professor Kristensen concluded by summarising the recent successful EUnetHTA collaboration with the European Medicines Agency (EMA) on the adaptation of the revised template for

The differences between countries, as well as the reasons behind them, need to be considered in the development of a common European methodology for REA.

European Public Assessment Reports (EPARs) which can more easily be used as a source of information for HTA decision making. This work as well as the progress on the HTA Core Model, the Relative Effectiveness Assessment and other

work packages of the EUnetHTA Joint Action Project will be highlighted at the upcoming EUnetHTA conference in Gdansk, Poland in December 2011.

Reference

1. Kleijnen S, Goettsch W, d'Andon A, et al. *EUnetHTA JA WP5: Relative Effectiveness Assessment (REA) of Pharmaceuticals Background review*. Available at http://www.eunethta.eu/Public/Work_Packages/EUnetHTA-Joint-Action-2010-12/EUnetHTA-JA-Public-Consultations/REA-Background-Review-public-consultation. Accessed December 2011.

Will transparency and comparison of systems benefit HTA-regulator interaction?

Professor Hans-Georg Eichler

Senior Medical Officer, European Medicines Agency, (EMA), UK

Transparency and comparison

Although regulatory agencies are striving for openness and transparency in their processes and output, a public perception of secrecy continues to surround many of these organisations. Health technology assessment (HTA) agencies are also being drawn into the transparency debate, as industry, payers and patients expect increasing openness regarding the assessment models used to make reimbursement decisions. Changing this perception may require that regulators and HTA

assessors function outside of their comfort zones in the ways that they present and provide access to factors that underlie their decision-making processes to other healthcare stakeholders.

In addition to a perceived lack of transparency from regulatory and HTA agencies, comparisons between procedures, timing and decisions by different regulatory agencies are now being made by third parties in the public space, and listings of national and international differences in reimbursement for individual products are being published by groups such as the European Organisation for Rare Diseases (EURODIS) and others, resulting in reputational risks to unfavourably compared agencies.

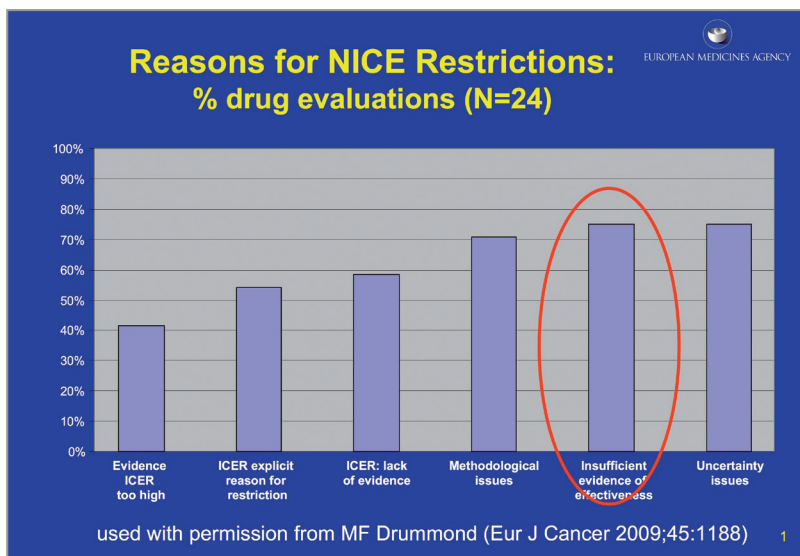
Relevance to regulator and HTA/payer interaction

These issues in transparency and interagency comparison can have a direct impact on interactions among regulators and HTA/payer assessors. In their research published in the *European Journal of Cancer*, Mason and Drummond compiled the reasons supplied by the National Institute for Health and Clinical Excellence (NICE) for advising either to not reimburse or to impose restrictions on the reimbursement for 24 oncology drugs. In over 70% of these decisions, "insufficient evidence of effectiveness" was cited as the decision rationale.¹ This reasoning seem contradictory to the previous approval of these medicines by regulatory agencies charged with ensuring that only technologies with sufficient evidence of effectiveness are approved for use (Figure 20).

Although some might rationalise this apparent contradiction by explaining that regulators examine a medicine's efficacy in clinical trials, whereas health technology assessors evaluate its real-world effectiveness, Professor Eichler sees the efficacy and effectiveness of a medicine

WORKSHOP REPORT

Figure 20. For over 70% of 24 oncology drugs not recommended for reimbursement or recommended with restrictions by NICE, insufficient evidence of effectiveness was cited.



How to mitigate reputational risk?

- Harmonise methodology/ evidence standards
- Explain divergent decisions on the basis of credible differences in healthcare environments
- Anticipate and manage (high-profile) divergent decisions

2

Figure 21. Three methods for diminishing the effects of contradictory agency decisions.

as a continuum rather than as a binary option; therefore, an interplay between these agencies could facilitate a structured discussion about the most effective use of data contained in market authorisation dossiers. Whilst it is understood that treatments may produce effects in randomised controlled settings that differ from those seen in real life, the difference in effects should not be so great as to render the clinical trial results meaningless.

Diminishing the effects of contradictory decisions

Professor Eichler suggested three methods of mitigating the confusion caused by divergent agency assessment outcomes: harmonising regulatory and HTA methodologies and evidence standards, explaining divergent decisions on the basis of credible differences in local healthcare environments, and anticipating and managing instances of high-profile diversion (Figure 21).

Harmonising regulatory and HTA methodologies and evidence standards:

Although some stakeholders have indicated that premature efforts to align regulatory

and HTA standards and processes may result in harmonisation to the wrong paradigms, Professor Eichler stated that instruments such as EQ5D, a tool for measurement of health outcomes have been established and have been in wide use for over two decades, represent appropriate standards approaches to begin evidence alignment.

Explaining divergent decisions on the basis of credible differences in healthcare environments:

Research has demonstrated that variations in healthcare settings and the influence of local medical practice may result in differences in a medicine's effectiveness. In their investigation of the efficacy and safety of dabigatran compared with warfarin, Wallentin and associates concluded that the quality of warfarin administration varied widely across international treatment centres, with the result that the efficacy of dabigatran, which had a simpler dosing regimen than warfarin, was found to be greatest at centres with poor control over warfarin administration.²

Anticipating and managing instances of high-profile diversion:

In the conclusion of his presentation, Professor Eichler cited the US FDA and EMA press conferences to discuss the results of the evaluation of Avandia (rosiglitazone) as an example of the effective management of a high-profile difference in regulatory decisions. In this example, having anticipated opposing results to their evaluation of the drug, the two agencies planned and conducted simultaneous media announcements at which spokespersons stated that although both agencies had examined the same evidence applying the same scientific standards, regional differences in legal and healthcare environments had resulted in differences in regulatory decisions. This strategy was well received and resulted in valid and useful public debates that centred on healthcare environments rather than on unproductive criticisms of either agency.

References

1. Mason AR, Drummond MF. Public funding of new cancer drugs: Is NICE getting nastier? *Eur J Cancer*. 2009;45:1188-1192.
2. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet*. 2010;376:975-983.

Whilst it is understood that treatments may produce effects in randomised controlled settings that differ from those seen in real life, the difference in effects should not be so great as to render the clinical trial results meaningless.

What Industry would like to see from HTA

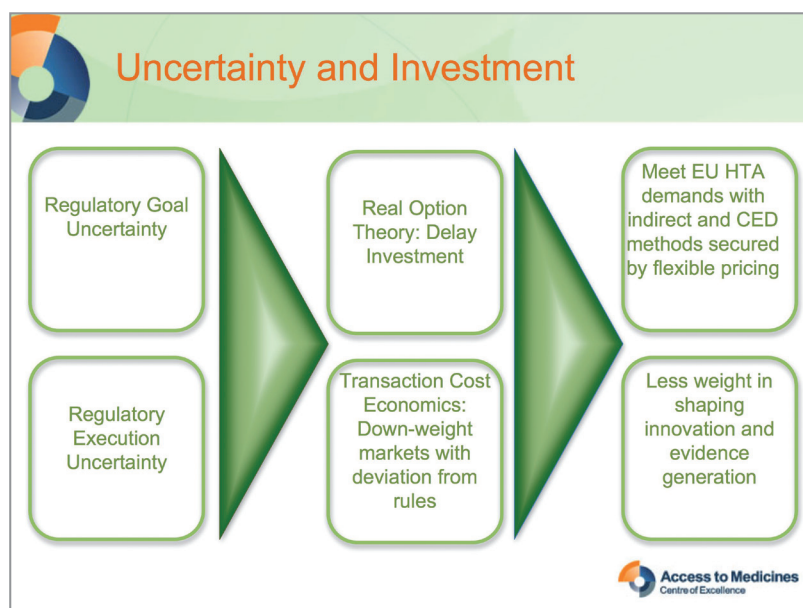
Ed Godber

Vice President, Access to Medicines Centre of Excellence, GlaxoSmithKline, UK

In 2010, the Joint Report on Health Systems from the European Commission and the Economic Policy Committee stated that the current economic upheaval “provides a window of opportunity to reflect on the role and performance of health systems.”¹ Mr Godber discussed the probable consequences of that reflection and the dramatic changes that healthcare systems are likely to undergo within the next decade, as the level of accountability for use of healthcare resources continues to escalate.

Regulatory agencies are attempting to address these new demands with greater involvement in the “continuum” of effectiveness and efficacy discussed by Professor Eichler in his presentation. To maintain relevance in this new environment, health technology assessment (HTA) agencies will need to similarly broaden their mandate from making simple reimbursement recommendations at product launch to a full participation in the development of treatment pathway efficiencies as detailed in Dr Berger’s talk.

Figure 22. Uncertainty in HTA goals and execution may affect investment.



... shared decision making in which healthcare professionals and patients work together will herald the “Century of the Patient.”

Foundations for an innovation process

Mr Godber outlined four methods for the development of innovative processes that would facilitate this necessary evolution of health technology assessment to develop an enhancement of predictability, transparency, quality and timeliness.

Predictability in health technology assessment will come from an alignment with improved healthcare system efficiency. Uncertainty, or lack of predictability in health technology assessment, however, can have serious financial consequences. Uncertainty regarding the goals of HTA evaluations results in a minimum of early industry investment. In this model, once HTA requirements are finally elucidated, last-minute investments are made for evidence generation, with the higher cost of this inefficient process currently being borne by flexible global pricing. However, the impact of this uncertainty is likely to increase in the future, when it is anticipated that widespread reference pricing will remove the ability to underwrite late-stage HTA requirements afforded by flexible pricing.

Uncertainty in the HTA processes of individual jurisdictions results in a down-weighting of industry investment in those jurisdictions, with the consequence that HTA agencies with unpredictable execution exercise less influence in evidence-generation decisions (Figure 22).

As a first step in aligning HTA advice with the goals of improved healthcare systems, links between assessments of individual treatment pathways and clinical guidelines should be improved. In addition, health technology assessment considerations must be broadened to incorporate both the increasing concerns of payers with the multiple disease pathways associated with the elderly and the concerns of health ministers regarding the value of new technologies to society as a whole. Finally, the focus must shift from clinical trials demonstrating the burden of illness to those that generate evidence regarding the value of therapy (Figure 23).

Transparency in health technology assessment will result from a commitment to review HTA performance using a pre-committed set of

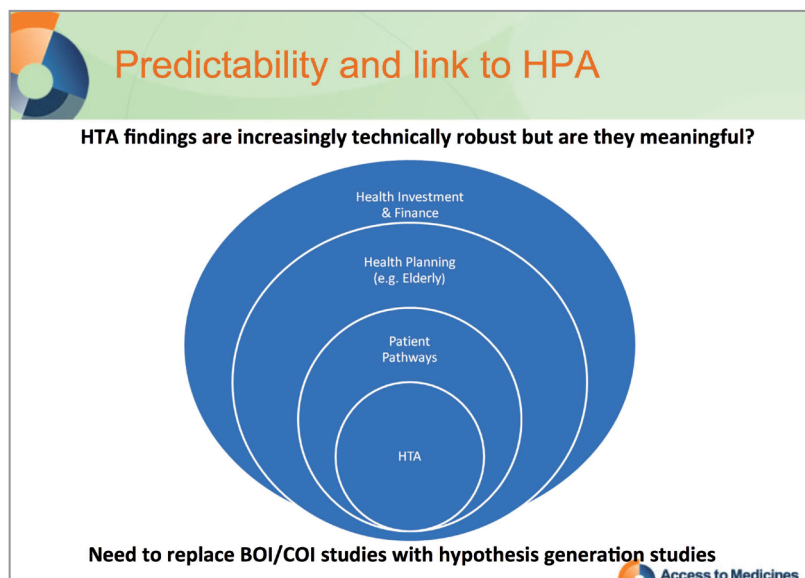


Figure 23. HTA considerations must be broadened to consider multiple disease pathways and the value of new technologies to society as a whole.

performance metrics and with the goal of continuous improvement. Confidential inquiries into past decisions involving multiple HTA bodies will result in a clearer understanding of decision-making processes and consequently an enhancement of HTA reputation and increased confidence in the HTA system.

Quality in health technology assessment can be achieved through the value mapping of new

medicines with a focus on improvements in methodology. Supported by a pan-European research consortium, the development in the precompetitive space of a joint agenda of key research questions and the methodology to be used for HTA evaluation, would guide the precision to address the scientific evidence needed to support a medicine throughout its life cycle, particularly in its post-approval, real-world use, as its long-term impact on public health is decided.

Timeliness in health technology assessment can be facilitated through alignment of systems that are already in place. HTA scientific engagement planning can be enhanced by understanding the alignment of a new medicine throughout its lifecycle with broad public health plans and individual patient treatment pathways. Assessors should anticipate where in development pathways the misalignment will be greatest, determine the most efficient form of precompetitive and pre-jurisdictional dialogue across industry portfolios and establish shared evaluation frameworks where they are most needed.

Reference

1. The European Commission and the Economic Policy Committee. *Joint report on Health Systems*. Available at http://europa.eu/epc/pdf/joint_healthcare_report_en.pdf Accessed November 2011.

Appendix: Workshop Attendees

Regulatory and Government Agencies		
Irina Cleemput	Senior Health Economist	Belgian Health Care Knowledge Centre (KCE)
Dr Petra Dörr	Head of Management Services and Networking	Swissmedic
Prof Hans-Georg Eichler	Senior Medical Officer	European Medicines Agency
Prof Bruno Flamion	Chairman	Belgian Committee for Reimbursement of Medicines, Belgium
Katrine Frønsdal	Senior Researcher	Norwegian Knowledge Centre for Health Services
Niklas Hedberg	Head of Department	Dental and Pharmaceutical Benefits Agency (TLV) , Sweden
François Meyer	Advisor to the President, Assessment Division	Haute Autorité de Santé, (HAS), France
Fredrik Nilsson	Health Economist	Dental and Pharmaceutical Benefits Agency (TLV) , Sweden
Dr Brian O'Rourke	President and CEO	Canadian Agency for Drugs and Technologies in Health (CADTH)
Professor Robert Peterson	Executive Director	Drug Safety and Effective Network, Canadian Institutes of Health Research
Nina Pinwill	Associate Director	Centre for Health Technology Evaluation, National Institute for Health and Clinical Excellence (NICE), UK
Barbara Sabourin	Senior Executive Director, Therapeutic Products Directorate	Health Canada
Chander Sehgal	Director of Formulary Reviews and Rapid Response	Canadian Agency for Drugs and Technologies in Health (CADTH)
Professor Zbigniew Szawarski	Member of the Consultative Council	Agency for Health Technology Assessment, Poland
Professor Adrian Towse	Director	Office of Health Economics, UK
Industry		
Fredrik Andersson	Associated Professor, Director	Novo Nordisk A/S, Denmark
Dr Stephane Andre	Head of EU/ROW Regulatory Affairs	F. Hoffmann-La Roche AG, Switzerland
David Budd	Director, Global Health Economics and Outcomes Research	Bristol-Myers Squibb
Dr Graham Burton	Senior Vice President, Regulatory Affairs, and Corporate Compliance	Celgene Corporation, USA
Frank DeFelice	EU Policy Office	Merck, Sharp & Dohme, Belgium
Ed Godber	Vice President, Access to Medicines Centre of Excellence	GlaxoSmithKline
Angus Grant	Vice President, Business Development and Global Strategic Alliances	Celgene Corporation, USA
Dr Jens Greuger	Vice President, Head of Global Market Access	Pfizer Ltd, UK
Dr Sanjay Gupta	Head/Executive Director, HEOR	Daiichi-Sankyo Inc, USA
Dr David Jefferys	Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety	Eisai Europe Ltd, UK
Alan Martin	Health Outcomes Director	GlaxoSmithKline
Clare McGrath	Senior Director, HTS Policy	Pfizer Ltd, UK

Trevor Mills		Biogen Idec
Dr Brigitta Monz	Head, Global HE & OR	Boehringer-Ingelheim GmbH, Germany
Dr Isaac Odeyemi	Senior Director and Head of HEOR	Astellas Pharma Europe Ltd, UK
Greg Rossi	Vice President, R&D Payer Evidence	AstraZeneca, UK
Pierre Sagnier	Vice President, Development Projects, Global Market Access	Bayer Health Care Pharma, Germany
Louise Timlin	Director, HTA for Australia, Canada, Europe and Japan	Eli Lilly and Company, UK
Martin Zagari	Vice President, Global Health Economics	Amgen, USA
Academic institutions, networks and consultancies		
Prof Bengt Jönsson	Professor Emeritus	Stockholm School of Economics, Sweden
Prof Finn Børlum Kristensen	Chairman, Executive Committee	European Network of Health Technology Assessment (EUnetHTA)
Dr Thomas Lönngren	Director	Pharma Executive Consulting
Prof Lloyd Sansom	Emeritus Professor, Division of Health Sciences	University of South Australia, Australia
Payer Organisations		
Dr Marc Berger	Executive Vice President and Senior Scientist	OptumInsight, UnitedHealth Group, USA
Centre for Innovation in Regulatory Science		
Nicola Allen	PhD Student	Cardiff University
Patricia Connelly	Manager, Communications	Centre for Innovation in Regulatory Science
Lawrence Liberti	Executive Director	Centre for Innovation in Regulatory Science
Dr Iga Lipska	Senior Research Fellow	Centre for Innovation in Regulatory Science
Professor Stuart Walker	Founder	Centre for Innovation in Regulatory Science
Tina Wang	Research Analyst	Centre for Innovation in Regulatory Science