REVIEW AND REIMBURSEMENT:

A SPECIAL CASE FOR BETTER CO-OPERATION

WORKSHOP
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WORKSHOP REPORT

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Section 1: Overview and Executive Summary

Background to the Workshop

The current dynamics of bringing new medicines to market are influenced by potential conflicts between the agendas of three important stakeholders: the pharmaceutical industry, regulators and payers. Regulators are under pressure to develop methods to speed the approval process through novel mechanisms such as conditional licensing, while maintaining an emphasis on safety, quality and efficacy. By contrast, there is an increasing pressure on payers to control spiralling healthcare costs via the assessment and practical application of clinical and cost-effectiveness. While, historically, the regulatory review and the consideration of products for listing and reimbursement by healthcare providers (health technology assessment – HTA) have been kept as separate exercises, the current approaches to drug development make a special case in which better cooperation and coordination of activities could be of significant benefit in making safe and effective new medicines available to patients in a timely and cost effective manner.

This Workshop was jointly developed by the Institute and the Office of Health Economics, UK to specifically address the related issues of overlap in activities between regulation and HTAs and the potential for mismatch of outcomes. It focused in particular on how consultation and cooperation has the potential to improve the process of bringing a new medicine to market for all three stakeholders.

Workshop highlights

Co-Chair, Professor Hubert Leufkens, *Utrecht Institute for Pharmaceutical Sciences, Netherlands,* introduced the first session by outlining specific questions to be addressed in the Workshop, including: How should we shape early and efficient regulatory dialogue between HTA and license authorities?

Professor Sir Michael Rawlins, *Chairman, National Institute for Health and Clinical Excellence, UK* explained that the clinical- and cost-effectiveness characterisation of new medicines is derived by posing four primary questions: Does it work? For whom does it work? At what cost? and How does it compare with the alternatives? Both HTA and regulatory agencies must accept that additional regulatory and HTA requirements increase development costs and may result in serious financial consequences to patients.

Because the maintenance of a firewall between industry, regulators and HTAs is no longer viable, **Dr Eric Abadie**, *General Directorate, Agençe France de Sécurité Sanitaire des Produits de Santé (AFSSAPS,); Chair, Committee for Medicinal Products for Human Use (CHMP), UK* stated that it should become the goal of all stakeholders to enable integrated drug development programmes that satisfy the requirements of both regulators and payers. The best way forward may lie in the issuance of joint scientific advice and the introduction of pragmatic assessments during randomised clinical trials.

The position of industry regulators, as detailed by **Dr Hilary Malone**, *Senior Vice President & Head, Global Regulatory Affairs, Wyeth, USA,* is that regulatory approval and determination of marketing access should remain separate but aligned functions. HTA assessors should recognise and accept the BR decisions of regulatory authorities and include a broad and societal perspective of value in their evaluation.

Andrew S. Mitchell, *Strategic Adviser, Evaluation, Australian Government Department of Health & Ageing; Chair, Health Technology Assessment International (HTAi) Working Group on Surrogate Outcomes, Canada* discussed the HTA perspective regarding the increasing trend in the evaluation of medicines to rely on surrogate endpoints. Because the evidence of incremental effectiveness is not consistently supported by changes in surrogate measures, the potential exists for new medicines to be judged as not cost-effective within acceptable levels of certainty. Therefore, Mr Mitchell proposed the use of an evidence base that combines surrogates with the assessment of target clinical outcomes.

Speaking on behalf of **Dr Leonie Hunt**, *Head, Office of Prescription Medicines, Therapeutic Goods Administration (TGA), Australia,* **Andrew S. Mitchell** provided the Regulatory Agency perspective regarding surrogate outcomes, saying that regulators will continue to use surrogate measures that offer a way of measuring response and harm when other ways

are not feasible in real time. The challenge is to use biomarkers and surrogate endpoints wisely, to make sure there is a valid scientific rationale, to monitor emerging information and to balance timely access with the desire for an ideal data set.

The Novartis pilot experience with bipartite and tripartite scientific advice from regulatory and HTA agencies was presented by **Dr Martin Backhouse**, *Head, Pricing & Market Access Operations, Novartis Pharma AG, Switzerland*. These pilots showed that HTA advice demonstrated far more similarities than differences across countries, and clinical evidence requirements of payers and regulators could probably be achieved in a well-designed phase 3 programme; meeting the different requirements identified would probably not significantly increase costs or development times.

Professor Robert Peterson, *Chairman, Canadian Expert Drug Advisory Committee (CEDAC); Clinical Professor, University of British Columbia, Canada* distilled the difference in perspectives between regulatory and HTA assessors of new medicines into requirements to demonstrate proof of concept (POC) versus requirements to demonstrate proof of value (POV). Limitations to POC studies are that they provide a dearth of information about a new medicine regarding its long- term use, full safety profile, potential drug interactions, effects in groups beyond the target population, comparisons to existing drugs, or variances associated with real clinical use – all of which are the data considered important evidence for POV assessment.

On 1 September 2009, the Swedish Dental and Pharmaceutical Benefits Agency (TLV) embarked on a pilot project of joint scientific advice with the Swedish Medical Products Agency (MPA). **Niklas Hedberg**, *Head, Department for Pharmaceutical Submissions, Dental and Pharmaceutical Benefits Agency (TLV), Sweden* provided the rationale and background for this programme. When complete, the pilot project will be evaluated and the agencies will decide how to continue to provide joint scientific advice and to proceed in other areas where interaction can facilitate effective medicine development.

Although EU Regulators have granted conditional approval for a small subset of medicines targeting high unmet need since 2005, **Clare McGrath**, *Senior Director, HTA Policy, Pfizer, UK* explained that time gained during regulatory approval is often lost during reimbursement negotiations. Ms McGrath suggested a programme of conditional reimbursement for those medicines promising significant clinical benefit especially where there is an unmet medical need that includes a periodic reassessment of price based on emerging real-world safety and effectiveness evidence.

Dr Franz Pichler, *Portfolio Manager, CMR International Institute for Regulatory Science, UK* presented the interim results of a 2009 survey of industry, regulatory bodies and HTA agencies on practices and attitudes surrounding health technology assessment. Although some regulatory respondents commented that joint advice could provide useful information to all parties, others felt that joint advice might result in a danger of increasing overall requirements and review time for pharmaceutical development. A full report of the survey results is being prepared.

Co-Chair, Professor Sir Alasdair Breckenridge, *Chairman, Medicines and Healthcare products Regulatory Agency (MHRA), UK* introduced the next session of Workshop presentations, entitled *Review and reimbursement: understanding the dynamics and how they are evolving*.

It is unlikely that HTA evidence requirements can be met at launch for products that receive conditional or accelerated regulatory approval. **Professor Adrian Towse**, *Director, Office of Health Economics, UK* explained, however, that early dialogue around a predetermined risk-sharing agreement can identify a pathway for evidence development in a global context for a product with an expected high health gain, with the price linked by formula to that evidence outcome.

To bridge the value gap between the short-term surrogate data that has previously been supplied at registration and the meaningful benefits and justifiable prices required by payers, GSK has begun thinking of the goal of medicine development as the creation of a "reimbursable file." **Dr Lawson Macartney**, *Senior Vice President, Global Product Strategy, GlaxoSmithKline, USA* discussed the importance of integrating input from internal and external payer advisors into the overall medicines development plan to ensure the creation of a reimbursable file.

Dr Ad Schuurman, *Head, Reimbursement Department Dutch Health Care Insurance Board (CVZ); President, Medicine Evaluation Committee (MEDEV), Netherlands*; detailed the progress of an alliance of networks including European Union Network for Health Technology Assessment (EUnetHTA), the Medicine Evaluation Committee

(MEDEV), and the Pricing and Reimbursement Network. These are working to identify, explore and exchange pricing and reimbursement practices and policies. By 2012 a EUnetHTA Working Group hopes to deliver an adjusted model for relative efficacy assessment of medicines that is consistent with the previously developed core HTA model.

In response to steadily rising healthcare costs and severe challenges to funding, stakeholders in the United States are working on a nationwide healthcare reform bill. **Dr Zeba M. Khan**, *Vice President, Pricing and Market Access, Celgene Corporation, USA* presented some of the elements of the new health care reform bill that will have a direct impact on the pharmaceutical industry and detailed industry's response to the changing business model.

Recommendations for action

1. Develop a modular approach to alignment: build a continuum from efficacy to effectiveness, relative effectiveness, and cost-effectiveness, addressing each in succession.
2. Create a framework for a common Health Technology Assessment (HTA) pathway in Europe.
3. Develop a common clinical development plan.
4. Develop a common regulatory/HTA dossier.*
5. Use the Institute Survey tool to identify areas for alignment between regulators and HTAs.
6. Optimise the quality of the HTA decisions by benchmarking the process.
7. Define the role and responsibilities of HTAs.
8. Examine the potential to align benefit-risk post-marketing assessments between HTAs and regulators.
9. Examine the potential to align transparency of process between HTA and regulatory agencies.
10. Agree on a common view on evidence by disease area.
11. Within the conditional approval setting: Evolve the discussion revolving around the alignment between regulatory agencies and HTAs to include Payer representation.
12. Within the conditional approval setting: Ensure that Sponsors coordinate their regional Market Access activities and include these with other development functions (i.e., regulatory, R&D, Clinical).
13. Within the conditional approval setting: Engage (HTAs, regulatory agencies and Industry) in early dialogue (internally and externally).
14. Within the conditional approval setting: Pilot a framework using the platform of a compound candidate for conditional approval.
15. Within the conditional approval setting: All stakeholders should collaborate to define and align on the consistent, acceptable use of methodologies/biomarkers/surrogate endpoints and their overall value to the evaluation of the dossier.
16. Conduct a survey of HTAs on their information needs.*
17. Follow pilots of joint scientific advice.
18. Develop a simple pilot registry.
19. Conduct survey of HTA strategic issues and trends.*
20. Perform quality analysis of HTA review and HTA submissions.*

**Syndicate recommendation for Institute action.*

Section 2: Syndicate and Panel Discussions

Workshop participants formed four syndicate groups to discuss the following topics:

Topics 1 and 2: Getting to the right evidence for regulatory and HTA authorities at the point of launch: An achievable endpoint? 1: Regulatory body perspective and 2: HTA agency perspective.

Topic 3: How can patients have rapid access to new medicines where there is an unmet medical need? Conditional approvals and conditional reimbursement.

Topic 4: Stakeholder partnerships - what mechanisms are required to bring the partners together?

The Chairpersons and Rapporteurs for the groups follow:

Syndicate 1	Chair:	**Professor Robert Peterson**, *Chairman, Canadian Expert Drug Advisory Committee (CEDAC); Clinical Professor, University of British Columbia, Canada*
	Rapporteur:	**Dr Pierre Sagnier**, *Vice President, GHEOR, BayerSchering, Germany*
Syndicate 2	Chair:	**Professor Ulf Persson**, *Professor of Health Economics, Lund University, CEO Swedish Institute for Health Economics, Sweden*
	Rapporteur:	**Dr David Williams**, *Section Director, HEOR, Clinical Development, AstraZeneca, UK*
Syndicate 3	Chair:	**Dr Brian O'Rourke**, *Vice President of the Common Drug Review & Acting President, Canadian Agency for Drugs and Technologies in Health (CADTH), Canada*
	Rapporteur:	**Dr Tracy Baskerville**, *Vice President, Head of Global Regulatory Affairs, Liaison, Cardio-Metabolic, Solvay, France*
Syndicate 4	Chair:	**Dr Franz Waibel**, *Senior Vice President, Global Market Access, Bayer Schering, Germany*
	Rapporteur:	**Dr Mel Walker**, *Director, Global Integrated Payer Strategy, GSK, UK*

Background

Syndicates 1 and 2 were asked whether having the right evidence for regulatory and HTA authorities at the point of launch is an achievable endpoint.

Underlying this question is the fact that HTA and regulatory bodies each ask sponsors for particular types of information to be generated during drug development (and also post-approval). While the nature of these data differs, there are overlaps for some of these requirements. Development efficiencies for companies and possibly a greater standardisation of evidence between authorities may be achieved if aspects of the drug development process are aligned or the HTA process harmonised and if greater information sharing between these agencies is enabled.

These syndicates were asked to discuss what aspects of the drug development process are practically amenable to alignment or harmonisation within and between regulatory bodies and HTA agencies and what aspects should remain independent. They also considered how such alignment should occur and what mechanisms would be required.

Syndicate 1 was requested to focus on the impact that such alignment would have on regulatory bodies, how current protocols could be adapted and what the costs and benefits would be to both Industry and the regulatory body. Syndicate 2 was requested to focus on the impact that such alignment would have on HTA agencies, how current protocols could be adapted and what the costs and benefits would be to both Industry and the HTA agencies.

Outcome of discussions

Syndicate 1

Critical issues

By definition, the outcomes of the discussions in Syndicates 1 and 2 demonstrated some overlap. The central issue of the topic as summarised by the Rapporteur for Syndicate 1 was the uncertainty and unpredictability surrounding the level of guidance that is received from HTAs. Other issues that complicate aligning the needs of regulators and HTAs include considering the needs of other relevant partners such as pricing bodies and regional and local decision makers, and the variation across EU countries in market access decision-making processes.

A 5-year vision

Syndicate 1 agreed on a 5-year vision which would encourage the alignment of regulatory and HTA guidelines. They discussed the role of HTAs as national decision makers for coverage, not pricing bodies, and not at sub-national levels. They agreed that it would not be possible to fully harmonise regulatory and HTA approaches in the short-term as regulatory agencies have a 20-year experience of building the regulatory framework and institutions whereas HTA purposes and methods are still nascent and require experience to mature. There are intense, ongoing exchanges between HTAs on harmonisation issues through such groups as the Medical Evaluation Committee (MEDEV), the European Union Network for Health Technology Assessment EUnetHTA, US Health Maintenance Organisations (HMOs) and Asia-Pacific agencies. There has been some pushback from EU Member States regarding the establishment of a central EU HTA body. However, regulatory-HTA alignment, that is, clear definition and coordination of the respective regulatory and HTA contributions to the market access process, can and should be be fostered.

SYNDICATE 1 RECOMMENDATIONS

1. Develop a modular approach to alignment: build a continuum from efficacy to effectiveness, relative effectiveness, and cost-effectiveness, addressing each in succession.
2. Create a framework for a common HTA pathway in Europe.
3. Develop a common clinical development plan.
4. Develop a common regulatory/HTA dossier.
5. Use the Institute Survey tool to identify areas for alignment between regulators and HTAs.
6. Optimise the quality of the HTA decisions by benchmarking the process.

Develop a modular approach to alignment: build a continuum from efficacy to effectiveness, relative effectiveness, and cost-effectiveness, addressing each in succession.

Methods

- Harmonise efficacy endpoints. Although achievable, this represents a significant challenge as there is a wide difference in expectations for randomised clinical trials (RCTs).
- Define effectiveness and relative effectiveness, assessing their dependence on real-world healthcare settings. To what extent could these parameters be estimated across countries?
- Address the apparent distrust of regulators regarding health-related quality of life (HR-QOL) by mapping methodological guidelines such as the FDA Guidelines on Patient-Reported Outcomes and documenting the extent to which disease-specific outcomes relate to the quality-adjusted life year (QALY) measures. Work on joint interpretation rules.
- Clarify differences and commonalities between multi-dimensional HR-QOL endpoints and "utility" QALY.
- Identify and collate the objectives and outcomes needs of HTAs and hold discussions whether those should be better aligned or harmonised across HTA agencies, between HTAs and regulators, and within or across therapeutic areas.

- Address some of the fundamental rules of RCTs that have been challenged with the emergence of HTAs. Should statistical, clinical or economic significance be considered? A too wide definition of non-inferiority margins can lead to unfair interpretations of efficacy data. Can an active comparator fit the HTA needs of several countries? A new paradigm is needed to address the need of trial sub-populations and of subsets of general population that do not easily access health care.

Create a framework for a common HTA pathway in Europe.

Methods

- Work on common issues/areas that lend themselves to harmonisation such as the interpretation and applicability of surrogate markers or non-inferiority rules.
- Address therapy area-specific aspects: oncology should be a top priority.
- Focus on early feedback to industry on development programmes.
- Do not use the International Conference for Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) model for RCTs as a prerequisite to regulatory-HTA alignment; rather consider the spectrum of value evidence such as adaptive design, confirmatory RCTs, observational research, enhanced design review and database methodology.

Develop a common clinical development plan.

Method

- Include endpoints, superiority versus non-inferiority margins, comparators and sub-group analyses issues in the plan.

Develop a common regulatory/HTA dossier.

Methods

- Start with clinical evidence and build on the data.
- Define applicability to other populations or sub-groups.
- Transform outcomes from surrogate to final and from clinical experience to practical utility.
- Create a tool kit that helps converting the information from the regulatory dossier to one for HTA application.

Use the Institute Survey tool to identify areas for alignment between regulators and HTAs.

Method

- Build on the Institute's 2009 survey to define areas amenable to standardisation.

Optimise the quality of the HTA decisions by benchmarking the process.

Methods

- The Institute should develop a scorecard or other approach to assess the quality of work, performance standards and transparency of the HTA review process.
- Build on earlier research[1] to benchmark key HTA agencies' work.

Reference

1. Drummond MF et al. Key principles for the improved conduct of health technology assessments for resource allocation decisions. *Int J Technol Assess Health Care*. 2008;24:244-258.

Syndicate 2

Critical issues

Syndicate 2 identified two critical issues for this topic: that there is a need for a common set of definitions for terms and techniques used by HTAs; and that HTAs are engaging in a growing number of stakeholder relationships that will have implications for streamlining decision making. Other issues that impact an HTA's approach to data analysis include the needs to:

- Improve the alignment of the sometimes conflicting agendas of a company's global development programme with the needs of national assessment and local implementation HTA agencies;
- Define the relative importance of evidence types and the use of appropriate comparators;
- Establish the timing of the initial reimbursement decision and a timeline for the re-evaluation of pricing;
- Facilitate the navigation of separate HTA/ Regulatory processes and requirements; and
- Ensure there remains flexibility within the established development process.

SYNDICATE 2 RECOMMENDATIONS

1. Define the role and responsibilities of HTAs.
2. Examine the potential to align benefit-risk post-marketing assessments between HTAs and regulators.
3. Explore the potential to align transparency of process between HTA and regulatory agencies.
4. Agree on a common view on evidence by disease area.

Define the role and responsibilities of HTAs.

Methods

- Revisit the definition of HTA by organisations, by task or groups of tasks.
- Deliver a clear map of tasks, how they are addressed and by whom.

Explore the potential to align benefit-risk post-marketing assessments between HTAs and regulators.

Method

- Discuss potential data sharing for ongoing assessment of the labelling and reimbursement.

Examine the potential to align transparency of process between HTA and regulatory agencies.

Methods

- Establish the regulator's and HTA's roles, responsibilities for interactions, timing and potential areas of overlapping review/ assessment.
- Consider methods to convey HTA findings to key stakeholders in a transparent manner.

Agree on a common view on evidence by disease area.

Methods

- Convene discussion groups with patients, industry, HTAs and regulators (facilitated by the Institute).
  - Establish key parameters to define data required by each stakeholder to assess new medicines for specific major disease profiles.
  - Define a common view of "value."

Syndicate 3

Background

Syndicate 3 was asked to frame their discussion with consideration of two recommendations issued during the 2008 Institute Workshop on this topic:

1. Conditional or progressive reimbursement should be introduced based on the premise that prices can go up as well as down when the value of the product to the healthcare system is assessed in a real-world setting.
2. Incentives: there should be specific advantages for the development of medicines for priority disease areas, such as early reimbursement and the possibility of extensions to exclusivity for products that are released early to restricted patient populations.

The resulting discussions centred on the potential mismatch of outcome that occurs when a regulatory body grants an accelerated approval for a new medicine for unmet medical need, and that approval is not compatible with current HTA requirements. This Syndicate was asked to identify and evaluate approaches that currently mitigate the risk of mismatched outcomes, as well as to suggest new approaches, and consider whether they could be applied more generally to noncritical medicines.

Critical Issues

The Syndicate began by recognising the lack of Payer representation in their deliberations, and recommending the inclusion of this group in future Workshops. The central issue that underpinned this Syndicate's discussions, however, was the existence of multiple philosophical and jurisdictional differences related to conditional approval of medicines. Despite these national and regional differences, regulatory agencies are moving towards harmonising their approaches to new dossier review. The differences among HTA groups, on the other hand, seem to be expanding. There is a lack of consistency of assessment approaches among these groups, with varying levels of tolerance for uncertainty and requirements for widely differing submission packages.

Little can be done to guarantee a match in outcomes for conditionally approved medicines since HTAs focus on cost-effectiveness in their review whilst regulators are driven by safety and efficacy issues (although this paradigm is changing in EU). Regulators and HTAs are often unclear as to one another's specific

data requirements. The threshold of evidence required by HTAs can be seen as higher than that required by regulatory agencies. If they were to require significant real-world data to formulate a decision, the practicality of a sponsor enrolling for example, tens of thousands of patients for a head-to-head comparative effectiveness study as part of a submission dossier may be problematic.

Although there is a need to align regulatory and HTA policies in clear areas of unmet need, evidence and pricing corridors are problematic where there is uncertain clinical or other value. Nevertheless, it may be possible to link processes through a common understanding of assessment procedures and expectations, while providing the opportunity for each body to make a unique decision.

The conditional review setting may be a good arena for a pilot experience, provided there can be an agreement of definition of acceptable evidence (eg, use of surrogates) and a consistency of methodologies. The Syndicate encouraged early regulatory agency-HTA negotiation to reach agreement prior to determining evaluation conditions and modelling specifications. The Syndicate recognised that the use of adaptive clinical design issues may in some cases hamper the ability for early alignment among stakeholders.

The cost of bringing drugs to market has grown exponentially and the reluctance to pay for long cycles of pharmaceutical development with uncertain outcomes has resulted in what is seen by many as an innovation drought. Uncertainty, however, can be managed through risk-sharing, scaled pricing and capped reimbursement, resulting in increased access to new medicines.

SYNDICATE 3 RECOMMENDATIONS WITHIN THE CONDITIONAL APPROVAL SETTING

1. Evolve the discussion revolving around the alignment between regulatory agencies and HTAs to include Payer representation.
2. Ensure that Sponsors coordinate their regional Market Access activities and include these with other development functions (i.e., regulatory, R&D, Clinical).
3. Engage (HTA, regulatory agencies and Industry) in early dialogue (internally and externally).
4. Pilot a framework using the platform of a compound candidate for conditional approval.
5. All stakeholders should collaborate to define and align on the consistent, acceptable use of methodologies/ biomarkers/surrogate endpoints and their overall value to the evaluation of the dossier.

Syndicate 4

Background

The starting premise of this Syndicate's discussion was that while both HTAs and regulatory bodies are asking sponsors for particular and differing types of information to be generated during drug development and post- approval, there may, in fact, be areas of overlap. Development efficiencies for companies and possibly a greater standardisation of evidence between authorities may be achieved if partnerships are developed between the stakeholders to align or harmonise aspects of the drug development process.

The focus of this Syndicate was to discuss whether such partnerships are desirable, would they be effective and whom would they benefit.

Critical Issues

The critical issues surrounding regulatory and HTA agency partnerships include the need for consistency and transparency of information requirements across stakeholders, a clear understanding of common objectives, ongoing dialogue and increased stakeholder engagement. Other fundamental requirements for this partnership include the convergence of

HTA principles and agendas across agencies and the establishment of more consistent timelines for HTA decisions.

Specific areas for collaboration

The Syndicate specified several areas in which HTAs and regulatory agencies could successfully collaborate, including the provision of more information on benefit-risk within the European Public Assessment Report (EPAR) for medicines. It was also envisioned that multiple HTAs could join to provide unified advice to industry. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR)/Health Technology Assessment International (HTAi) have developed positions regarding methodologies for clinical evaluation and QoL assessment. However, these initiatives have not involved all stakeholders and this presents an opportunity for the Institute to foster collaboration between the groups. Finally, registries and risk management plans designed for both regulatory and reimbursement purposes could greatly benefit by HTA and regulator cooperation.

SYNDICATE 4 RECOMMENDATIONS

1. Conduct a survey of HTAs on their information needs (the Institute).
2. Follow pilots of joint scientific advice.
3. Develop a simple pilot registry.
4. Conduct survey of HTA strategic issues and trends (the Institute).
5. Perform quality analysis of HTA review and HTA submissions (the Institute).

Conduct a survey of HTAs on their information needs (the Insitute).

Methods

- Assess what would be ideally communicated in an EPAR for use by an HTA.
- Discover if this is aligned with what EMEA is prepared to do or what Industry can provide.
- Determine areas of data commonality with regulator needs.
- Develop a standard HTA dossier template that could be used for any agency's assessment.

Follow pilots of joint scientific advice.

Methods

- Follow key pilots such as those taking place in Sweden and Canada.
- Share outputs with EMEA/CHMP and other interested parties.

Develop a simple pilot registry.

Method

- Involve all stakeholders, perhaps through various HTA consortia.

Conduct a survey of HTA issues and trends (the Institute).

Methods

- Could be HTA and company based to understand areas for partnership.
- Identify areas of mutual interest and establish best approaches to address each.

Perform quality analysis of HTA review and HTA submissions (the Institute).

Methods

- Use quality review to drive increasing transparency of HTA requirements.
- Use Institute's established Scorecard methodologies to rapidly implement this assessment.

Panel discussion

A panel discussion was held to delve deeper into the concepts discussed and recommendations raised by the Syndicates. The following briefly summarises the highlights of observations made by each panellist in response to the Syndicate presentations and questions from participants

Professor Claire Le Jeunne

Director General, Therapeutic Products Directorate, Canada

Professor Le Jeunne belongs to what could be called a true HTA, that is, one that provides scientific assessment and advice to payers but which takes no responsibility for the final economic evaluations. She explained that the Haute Autorité de Santé takes the point of view of the patient in the review of new medicines, asking if and to what extent that medicine will modify the patient's disease, based on the specific attributes of the new medicine.

Although the Autorité is not set up to offer advice concurrent with the regulator, it may be possible to provide guidance during early development phases. They have a special pathway for review of medicines for unmet medical need, but this expedited programme is used primarily for orphan drugs and only 5 drugs were reviewed using this pathway in 2008. Professor Le Jeunne felt that it is sensible for HTAs to begin assessing the dossier earlier than post-regulatory approval, as the content of the dossier is not altered significantly in the 3 or 4 months after regulatory review.

Conditional approvals may require harmonised assessment criteria, which could provide the context for a higher probability for similar outcomes between the regulator and HTA.

Dr Petra Dörr

Head, Management Services and Networking, Swissmedic, Switzerland

Dr Dörr focussed on the fact that HTAs and regulatory agencies are on a journey to partnership and alignment and that different jurisdictions are at varying stages in this journey. While Canada and Australia have already established partnerships, Switzerland is at the beginning of this new relationship.

Prerequisites for partnership are an established framework within which each group's responsibilities are clearly defined, transparency of communication and decision making, clarity regarding definition of terms and vocabulary, clearly established processes and responsibilities and defined technical aspects such as documentation structure. Regulatory agencies need to make their benefit-risk assessment review process transparent. Preparing a public assessment report, a mandate not currently in existence for Switzerland, is one possibility to improve transparency of each group's decision making.

Dr Supriya Sharma

Director General, Therapeutic Products Directorate, Canada

Dr Sharma explained that there has been some discomfort when regulatory agencies talk about harmonising with HTAs because of the expectation that they might harmonise to the lowest common denominator; thereby diluting each other's mandates.

Although there has been significant progress in terms of transparency of decision making, much remains to be achieved regarding transparency in the process for the management of uncertainty. While regulators may manage their level of uncertainty through labelling negotiations, from the HTA or payer perspective, uncertainty needs to be managed through pricing or payment, and the methods to do so are still in their infancy. Therefore, regulators continue to struggle with defining those criteria that tip the balance in their benefit-risk evaluation, whereas HTA evaluators can in theory and practice use pricing as a more flexible approach to managing risk.

Dr Sharma described the Canadian pilot joint HTA-regulatory review experience. Before this pilot, neither HTAs nor regulators had clearly understood the responsibilities and approaches that each side used. As with many other interactions, the success of this collaboration was personality driven, overcoming scepticism of each other's assessment procedures. After a year looking at an entire dossier of hundreds of volumes, however, it was recognised that difficult decisions had to be made by both sides using complex and often difficult-to-interpret data.

The pilot was initiated with a retrospective analysis of a product with no time or pressure constraints on either side. Next, a prospective

analysis took place, with a fairly intensive phase of information sharing. This level of communication, however, was found to slow down the regulatory process and eventually evolved into a process in which only the most strategic information was shared.

Because there was a fear that the joint review process might add additional requirements for marketing authorisation, it wasn't easy to recruit pharmaceutical companies for the pilot, but in fact, the process went quite smoothly, and the medicine reviewed in the pilot came to HTA decision before that of a competitor product that had been submitted earlier to Health Canada.

Dr Sharma concluded that a report of the process was published 1 July 2009, and Health Canada is now waiting for new applications for additional combined priority reviews to be made.

Dr Meindert Boysen

Director, Technology Appraisals Programme, NICE, UK

Similar to the situation reported by other agencies, Dr Boysen reported that there are enormous resource constraints at NICE. Although the organisation has a current need for 20 reviewers, they have been able to fill only 10 of those openings. NICE has engaged in several tactics to allow transparency in their functions as healthcare decision makers such as holding public committee meetings and presenting economic models on a web site.

Joint HTA-regulatory advice is not appropriate for every medicine, but should be focussed, as it now is at NICE, on therapies that are significantly innovative and where joint review could make a significant difference in rapid patient access. Although the requests for joint review should be industry driven, there are in fact, few such applications. This may be because companies are in a process of learning how to interact with HTAs concurrently with regulators. Future transparency in process, language, scope and selection will drive this collaborative process forward. There is an opportunity to work together on conditional licensing and HTA approval by ascertaining HTA assessment requirements, which might be based on real-world utilities.

General discussion

Patient involvement

Question: How do we involve our patients in support of some of our submissions? If we have a product whose claims are supported by a randomised clinical trial and we hear from our market research that patients want it; how do we address our patients' input into our evidence?

Response 1: Canada has added two public members to the HTA review committee, but there's been a lot of pressure from patient groups saying those public members do not completely represent patient views; Canada has tried to make it very clear that these members bring patient views not industry views, and help to ensure a broad support of the review documentation; they have a templated process where they'll answer very specific questions that address what the new drug does to address unmet need.

Response 2: Patients are struggling to find their voice in the regulatory/HTA process. Canada has had letter-writing campaigns when patients hear that there might be conditions on a license or when a product may receive second-line approval because of fears that the drug won't get funded. Certain groups are very savvy in process, but we have limited ways to bring them into the process prior to market authorisation because of competitive confidentiality. Canada does have an office of public involvement that consults with patients on broader issues.

Response 3: NICE has had great difficulty getting quantitative patient input with one exception: the Alzheimer's Society did an enormous questionnaire among their patients targeted to questions relative to HTAs and this provided guidance with respect to patient needs from new therapies.

Workshop Programme

Session 1: Early involvement of regulatory and reimbursement authorities in development: A recipe for success?	
Chairman's welcome and introduction	**Professor Hubert Leufkens**, *Utrecht Institute for Pharmaceutical Sciences, Netherlands*
Effective and efficient drug development: An HTA perspective	**Professor Sir Michael Rawlins**, *Chairman, National Institute for Health and Clinical Excellence (NICE), UK*
Where are HTAs and regulatory authorities going in the next 10 years? An EU regulator viewpoint	**Dr Eric Abadie**, *General Directorate, Agençe France de Sécurité Sanitaire des Produits de Santé (AFSSAPS,); Chair, Committee for Medicinal Products for Human Use (CHMP), UK*
Toward an effective access future	**Dr Hilary Malone**, *Senior Vice President and Head, Global Regulatory Affairs, Wyeth, USA*
Utilisation of biomarkers and surrogate endpoints in development of a new medicine: An HTA perspective	**Andrew S. Mitchell**, *Strategic Adviser, Evaluation, Australian Government Department of Health & Ageing; Chair, Health Technology Assessment International (HTAi) Working Group on Surrogate Outcomes, Canada*
The value of biomarkers and surrogate endpoints in decision making: A regulatory authority perspective	**Dr Leonie Hunt**, *Head, Office of Prescription Medicines, Therapeutic Goods Administration (TGA), Australia*
Experience of early dialogue with pricing and reimbursement agencies: scientific advice meetings	**Dr Martin Backhouse**, *Head, Pricing & Market Access Operations, Global Pricing & Reimbursement, Novartis, Switzerland*
Harmonising proof of concept with proof of value	**Professor Robert Peterson**, *Chairman, Canadian Expert Drug Advisory Committee (CEDAC); Clinical Professor, University of British Columbia, Canada*
The Swedish joint scientific advice pilot project	**Niklas Hedberg**, *Head, Department for Pharmaceutical Submissions, Dental and Pharmaceutical Benefits Agency (TLV), Sweden*
Conditional licensing and conditional reimbursement	**Clare McGrath**, *Senior Director HTA Policy, Pfizer, UK*
Review and reimbursement: the current environment and the implications for the future	**Dr Franz Pichler**, *Portfolio Manager, CMR International Institute for Regulatory Science, UK*

Session 2: Review and reimbursement understanding the dynamics and how they are evolving	
Chairman's introduction	**Professor Sir Alasdair Breckenridge**, *Chairman, Medicines and Healthcare products Regulatory Agency (MHRA), UK*
What is the role of risk sharing in ensuring access to patients for innovative medicines?	**Professor Adrian Towse**, *Director, Office of Health Economics, UK*
How are companies working with payers and how is this relating to development?	**Dr Lawson Macartney**, *Senior Vice President, Global Product Strategy, GlaxoSmithKline, USA*
HTA collaboration on scientific assessment for the purpose of reimbursement	**Dr Ad Schuurman**, *Head, Reimbursement Department Dutch Health Care Insurance Board (CVZ); President Medicine Evaluation Committee (MEDEV); Netherlands*
The USA paradigm: What are the options and how will this affect drug development?	**Dr Zeba Khan**, *Vice President, Pricing and Market Access, Celgene Corporation, USA*

Section 3: Workshop Presentations

Session 1: Early involvement of regulatory and reimbursement authorities in development: A recipe for success?

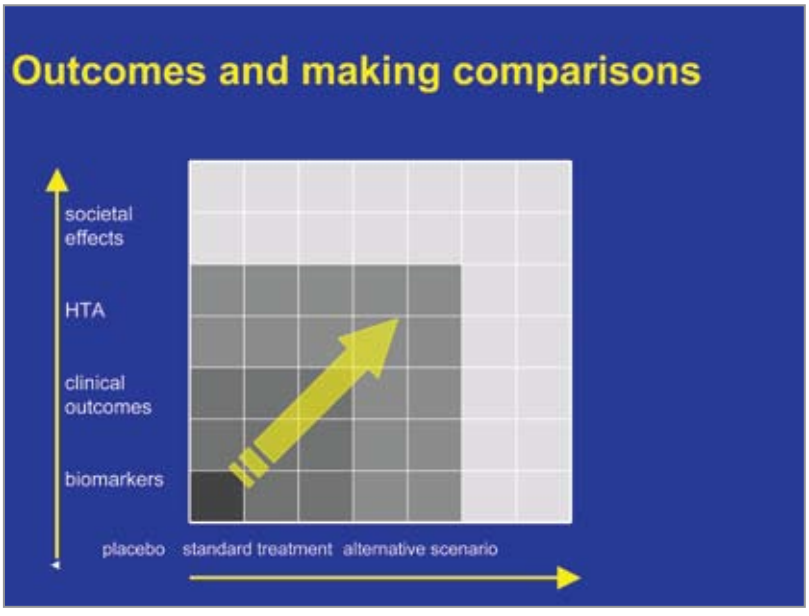
Chairman: Professor Hubert Leufkens

Utrecht Institute for Pharmaceutical Sciences, Netherlands

Review and reimbursement over the last decades

Professor Hubert Leufkens

Over the last several decades, various forces have made an impact on the timing of market authorisation and patient access to new medicines, with industry and patient groups pushing for shorter timelines for regulatory approval, and payers and the scientific community requiring longer timeframes for the accumulation of more comprehensive data. The question is at what time point should these two opposing needs converge?



Other forces have also had significant impact on marketing and payer authorisation. From 1999 to 2005, trials with active control comparisons were available before marketing authorisation for 48% of new medicines in the EU. Identification of cost- and clinically effective patient populations through advances in biology such as the use of biomarkers have also accelerated regulatory decision making.

Professor Leufkens introduced the first session by outlining some specific questions to be addressed in this portion of the Workshop:

- How should we shape early and efficient regulatory dialogue between HTA and license authorities?
- What is the most efficient and timely way to incorporate timely advances in science, biomarkers, and surrogate endpoints into regulatory decision making?
- If we acknowledge that the lifecycle of a medicinal product is an ongoing continuum, what is the correct point to make a regulatory decision?

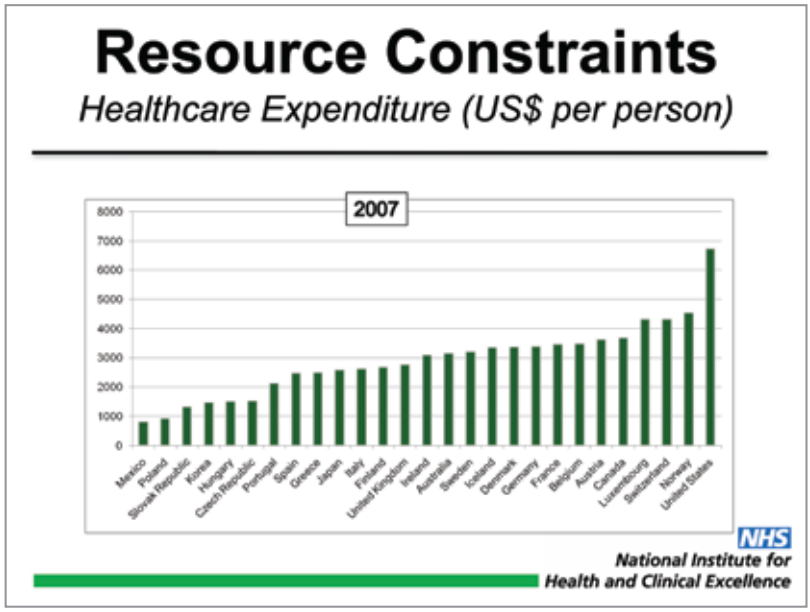
Effective and efficient drug development: An HTA perspective

Professor Sir Michael Rawlins

Chairman, National Institute for Health and Clinical Excellence (NICE), UK

How do Health Technology Assessment (HTA) agencies determine a new medicine's clinical and cost-effectiveness? Professor Sir Michael Rawlins said that these characteristics are derived by posing four primary questions:

- Does it work?
- For whom does it work?
- At what cost?
- How does it compare with the alternatives?



Except for outliers such as the United States, where healthcare spending greatly outstrips the gross domestic product (GDP) and Luxembourg, where the opposite is true, the amount of money that most countries spend on healthcare is directly proportional to its overall GDP. As a consequence, even among developed countries, healthcare expenditures vary widely, making cost-effectiveness comparisons of medicines among nations difficult, if not impossible. For example, medicines that are considered cost effective in the United States, where approximately $7,000 per person each year is spent on healthcare, could never be considered to be cost effective in Mexico, where the per capita healthcare expenditure is a little over a tenth of that amount. A similar situation in Europe can be found in the per- person healthcare spending in Austria, which is fourfold that of Poland, making a centralised European HTA evaluation of medicines problematic.

In addition, the current worldwide economic slow-down combined with the fact that the costs of new medicines have increased by as much as tenfold over the past two decades, make the funding of healthcare and medical innovation progressively more difficult.

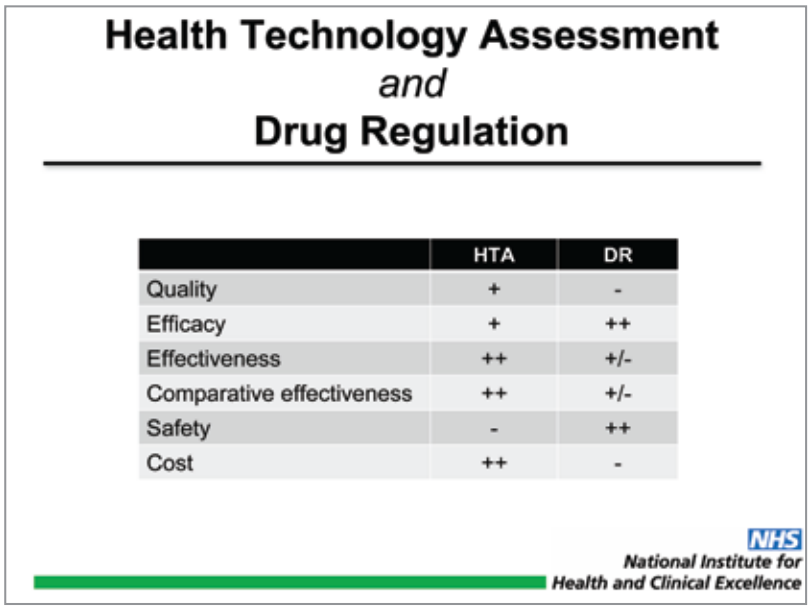
HTA authorities are responsible for judging a new medicine's clinical effectiveness. HTA decisions are guided by a medicine's effects on patients' quality of life and the duration of those effects compared with standard treatment. This judgement requires randomised clinical trials, observational studies, direct or indirect comparators and real outcomes or surrogates that have been validated.

In addition to clinical effectiveness, an HTA evaluation is also economic and three overarching principles direct economic evaluation of medicines at the UK's National Institute for Health and Clinical Excellence (NICE). The first principle is that of economic perspective, which at NICE unlike some other countries such as Sweden, is restricted by law to that of the UK National Health Services and Personal Social Services. The second principle is cost-effectiveness, which is neither a measurement of affordability nor of budgetary impact. Finally, a balance is sought between the two great approaches to distributive justices: efficiency (utilitarianism) and fairness (egalitarianism).

An important part of the HTA economic evaluation of new medicines is a cost-utility analysis, which seeks to measure the medicine's direct and indirect costs and savings against its benefits. These are often measured as incremental changes in utility measures such as

health-related quality of life. This analysis yields an incremental cost-effectiveness ratio or ICER which can be used in decision making.

There are acknowledged differences in the perspectives, roles and responsibilities of regulatory and HTA agencies. HTA authorities rely on their regulatory counterparts to evaluate the quality and efficacy of new medicines while they consider its effectiveness in a real-world setting in comparison with standard of care. Likewise, pharmaceutical safety is considered to be the domain of regulators, while a medicine's cost is of critical importance to HTA agencies.



There is, however, a commonality of principle between the two groups, and along with respect and appreciation of the differences in remit, better alignment of the two groups could expedite the time for medicines to reach the patient. Attitudes toward comparators, for example, are similar and recent publications have specified useful methodology for the use of indirect versus direct comparators.[1] Activities such as this Workshop represent first steps toward that alignment. Both groups must assist industry in the design of studies to support cost-efficient drug development. Harmonisation of HTA approaches, which differ widely among nations, would be extremely useful. In addition, both groups must accept that additional regulatory and HTA requirements can increase already staggering development costs and may have serious financial consequences to patients.

Reference

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Where are HTAs and regulatory authorities going in the next 10 years? An EU regulator viewpoint

Dr Eric Abadie

General Directorate, Agençe France de Sécurité Sanitaire des Produits de Santé (AFSSAPS); Chair, Committee for Medicinal Products for Human Use (CHMP), UK

Because maintaining a firewall between industry, regulators and HTAs is no longer a viable approach to efficient regulatory review and reimbursement assessment, Dr Abadie explained that it should become the goal of all stakeholders to design and enable integrated drug development programmes that satisfy the requirements of both regulators and payers.

Role of the regulators

In the European Union, regulators are working under clear rules: the European Commission (EC) Article 26 Directive states that marketing authorisation is to be denied if the benefit-risk (BR) balance of a medicine is not favourable, if its therapeutic efficacy is insufficiently substantiated, or if its qualitative and quantitative composition is not as declared. Marketing authorisation, therefore, is based on an assessment of the medicine's quality, safety and efficacy; there is no formal remit to evaluate need or to evaluate the medicine's BR profile in relation to existing products. The components of BR balance lie in a medicine's benefits as proven in clinical trials versus placebos and active controls and in its risks, derived from pharmaceutical quality and nonclinical and clinical records of safety.

Despite this being a requirement of the application,[1] only 50% of new drug applications in Europe cite the use of active-controlled trials.

Although rarely enforced, Annex 1 of the EC Directive 2001/83/EC states that in general, clinical trials should be controlled, randomised and conducted versus placebo and versus an established marketed product of proven therapeutic value; any other clinical trial design should be justified by the pharmaceutical sponsor.[1] In the end, however, BR evaluation remains a value judgement, and the simple question that must be answered by regulators is: does the medicine do more good than harm in a defined group of patients?

Role of the payers

Unlike regulators, payers need to make choices among particular therapeutic alternatives and balance expectations of universal access to top-level health care with limited resources, thereby maximising public health outcomes within a given budget. There is, however, an emerging interface between regulators and HTA bodies. Some HTA bodies and payers have become increasingly sophisticated in their assessment of drugs, having developed purpose-driven evidentiary and analytical standards. They are using modelling and observational studies to improve the external validity of the dossier data. They may challenge the relevance of the magnitude of a treatment difference versus placebo, or question the absence of health-related quality of life data in controlled studies.

Areas of difference between HTA and regulatory agencies

The Association of EU Payers has been quoted as being "wary of surrogate endpoints that may or may not reflect patient benefit." Examples of surrogate endpoints are the controversial measurements in oncology of overall survival versus progression-free survival versus overall response rate. However, Dr Abadie noted that regulators and HTA assessors are closer in their views of these and other outcome endpoints than is readily apparent.

The use of measurements of efficacy versus those of effectiveness represents an area of divergence between the two types of agencies. A common definition of a medicine's effectiveness is that it does more good than harm under real-life conditions, whereas a medicine's efficacy is considered to be that same attribute demonstrated under controlled conditions. However, the ever-shortening temporal proximity of regulatory and HTA review means that both groups are essentially reviewing the same data. Whilst both groups may find it necessary to accumulate more medical data, Dr Abadie felt that sponsors should not be required to undertake expensive "pragmatic" trials to convince reimbursement authorities of the real-world effectiveness of a medicine.

Although some HTA groups have specified that clinical trials of new medicines against established standards of care are preferable to those that use placebo controls, and despite this

being a requirement of the application,[1] only 50% of applications for new drugs in Europe use active-controlled trials. Some regulators are reluctant to ask for active controlled trials, questioning the pertinence of head- to-head randomised controlled trials versus indirect comparisons.

Future directions

The areas of possible interaction between HTA and regulatory agencies include BR evaluation, offering joint complementary scientific advice, and collaborating on drafting joint clinical guidelines and post-marketing activities including risk management plans. Indeed, the High-Level Political Forum (HLPF) in the European Union has issued a mandate to initiate dialogue between the two groups, exploring methods of incorporating and evaluating data contained within the European Public Assessment Report (EPAR) for the assessment of relative effectiveness. HTA and regulatory agencies should initiate dialogue on the scientific communication of BR, in line with HLPF recommendations.

There is a particular need for stakeholder collaboration for plans for post-marketing follow-up for conditional approvals, where the primary goal is the reduction of remaining BR uncertainty.

The first phase of ongoing efforts to improve the BR assessment section of the CHMP assessment report templates has been completed, incorporating a structured list of BR criteria and associated guidance. A structured and mainly qualitative approach is being used in which the importance of benefits and risks in the specific therapeutic context is made explicit and the sources of uncertainty and variability and their impact on the BR assessment are described. Such analyses can provide a basis for consistent communication between regulators and HTAs.

Post-launch activities are a crucial aspect of medicine development that can be improved by HTA and regulatory alignment. There is a particular need for stakeholder collaboration to develop comprehensive plans for post-marketing follow-up for conditional approvals, where the primary goal is to reduce uncertainty about the BR balance. The ongoing measurement of effectiveness along with measurements of safety will be required, and these can in part be based on the implementation of successful programmes in place designed for vaccine risk management.

Both regulators and HTA personnel should express their specific needs for evidence more clearly to medicine developers; efforts to improve the quality and use of information presented on EPARS need to continue. To bring down the firewalls between the two groups, the best way forward may lie in offering sponsors joint scientific advice and identifying ways to introduce some pragmatic measures of value into randomised clinical trials.

Reference

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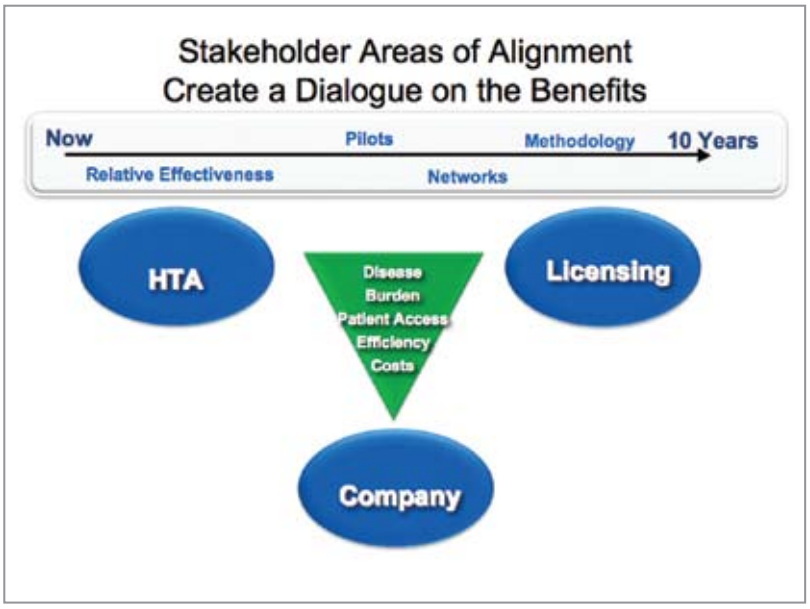
Toward an effective access future

Dr Hilary M. Malone

Senior Vice President & Head Global Regulatory Affairs, Wyeth, USA

The position of the Wyeth regulatory group, as detailed by Dr Hilary Malone, is that regulatory approval and determination of marketing access should be viewed as separate but complementary activities. Health technology assessment of new medicines is currently variable in form and function across the world and the related costs of these variables in terms of limited patient access, time delays, and financial investment are significant. Moving forward, HTA authorities must address the specific standards and cost realities within their own political remit while developing a clear common global paradigm that can be broadly applicable to a globally harmonised clinical development strategy. For example, HTA assessors should recognise and accept the BR decisions of regulatory authorities while including a broad societal perspective of the medicine's value. Wyeth believes in early and constructive alignment and dialogue with both HTA and regulatory agencies throughout the product life cycle: during development, at time of assessment for approval, and in the post-approval environment. To be successful in the current environment, however, multiple stakeholder demands must be addressed and the patient's views must also be represented.



Partnership opportunities

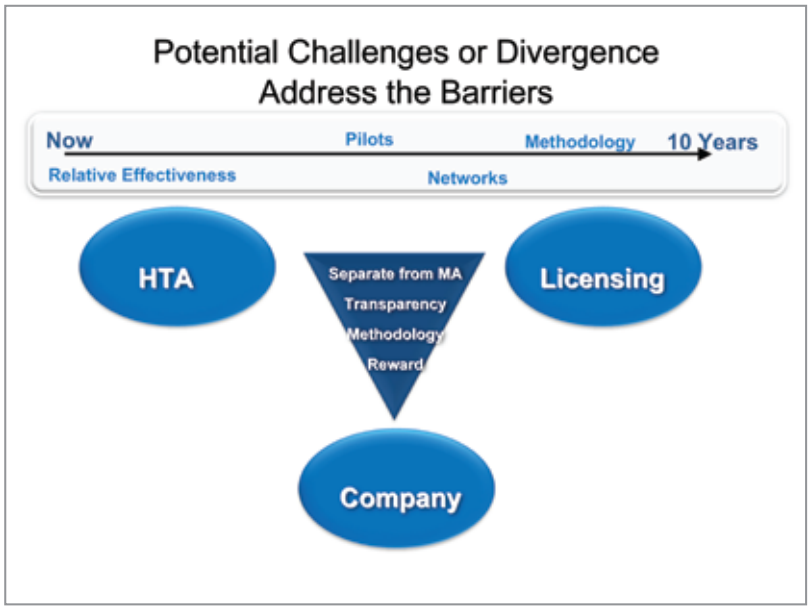
There is an undeniable partnership opportunity across stakeholder groups, particularly when defining and addressing unmet medical needs. All parties must be willing to engage and react to the dynamic and increasingly global environment focussed on expedited access to innovative medicines. Stakeholders must recognise the value of innovative medicines and improve the access to more patients.

Despite striving for a global standard, the assessment of economic value, including cost-effectiveness, must occur in the right context, for example, at the national level for European countries. There must be greater transparency and agreement on how to measure added therapeutic value (ATV) in order to determine if there are elements that should be assessed either nationally or regionally. In addition, the determination of ATV must include the needs of the patient.

Using the symptomatic treatment of Alzheimer's as an example of differing stakeholder points of view, an examination of those perspectives in determining the ATV of a new medicine reveals that regulators want a therapy that will improve cognition, payers want a therapy that will avoid long-term nursing costs, and patients and their families want to re-establish what has been lost in personality and behaviour. Addressing these divergent needs in an aligned development plan remains the challenge for improvement.

Barriers to alignment

There are significant barriers to achieving an effective access future. The use of competent EU authorities as well as in-country HTAs to provide advice promotes heterogeneity of process and function. Timing of HTA guidance also varies, with only some HTAs providing advice or input during development. Not all countries, however, even have a form of HTA. Among those that do, different countries currently assess the concept of ATV or innovation in different ways. Countries also differ in how they manage pricing, with varying levels of free pricing, pricing controls, control of access and control of re-imbursement. Only some HTAs have explored forming partnerships with companies to share some of the cost uncertainty when bringing an innovative treatment to patients.



The way forward

Wyeth believes that the marketing authorisation and determination of access to new medicines can remain separate functions, although these two activities could be variously defined and therefore may have important overlap. Ideally, the analysis by and decisions of the regulatory authorities on a medicine's benefit/risk should be fully recognised and accepted by HTAs without requirements for additional layers of assessment or the inefficient reanalysis of the original data.

The complexity of the regulatory process and political and budget constraints will impact the way we regulate, approve, and pay for new medicines. There are numerous challenges to aligning the needs of the key stakeholders, including the separation of regulatory remit from HTA decision-making, the transparency of information sharing between parties, a lack of methodology for harmonising value assessments, and the highly variable rewards for innovation across countries and even disease states. However, stakeholders could readily align key areas to foster dialogue about disease burden, requirements for patient access, and ways to improving efficiencies and ultimately reduce development costs.

WORKSHOP REPORT

Utilisation of biomarkers and surrogate endpoints in development of a new medicine: An HTA perspective

Andrew S. Mitchell

Strategic Adviser, Evaluation, Australian Government Department of Health & Ageing; Chair, Health Technology Assessment International (HTAi) Working Group on Surrogate Outcomes, Canada

HTA Assessors have a clear preference for direct measurement of patient-relevant and clinically important health outcomes. Whilst it is recognised that surrogates may be relied upon when there is no other alternative, they are associated with substantial uncertainty and increases the ratio of "assumption to evidence" as the basis for a decision. HTAs would prefer to base their decisions on direct evidence.

Terminology

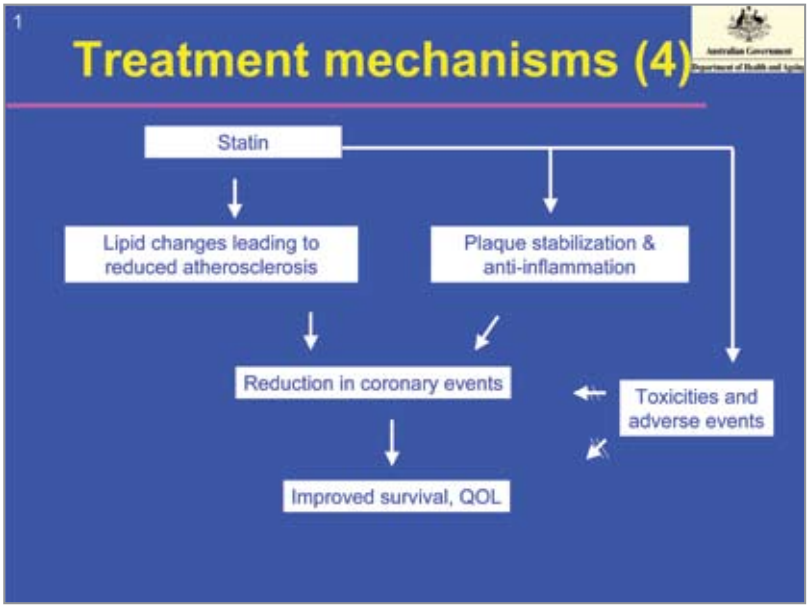
It is important to ascertain common definitions in the discussion of this topic. A surrogate outcome measure both substitutes for and predicts a subsequent clinical outcome, although neither substitution nor predictability are sufficient by themselves to indicate surrogacy.

Transformation is the means by which a target clinical outcome of a surrogate outcome with direct and immediate relevance to a patient is predicted and the extent and certainty of the impact is estimated. Surrogate markers can be characteristics used as prognostic factors for disease and development and progression; for example, levels of LDL cholesterol as predictive of risk of subsequently experiencing a heart attack. The core distinction for a surrogate outcome over a surrogate marker is that researchers seek to discover if, by changing the surrogate measure via a treatment effect of the new technology, the future patient-relevant outcome will also be changed. That is, will a technology to reduce LDL cholesterol reduce the risk of heart disease?

Surrogate evolution

The classic research and development pathway for new medicines follows a specified rationale in which measurable risk factors are identified, modifiable risk factors are focussed on and their biomolecular basis identified, the modification of that biological basis through a pharmacologic effect is sought and a proof-of-concept trial in humans is initiated. Increasingly, this research relies solely on the use of surrogate outcomes in randomised trials to predict the long-term effect of a new medicine. The advantages of using these outcomes lie in the reduction of trial duration and expense if an earlier conclusion can be reached with confidence.

In the late 1980s, when there was tremendous pressure to release AIDS drugs as early as possible to market, using surrogate outcomes in clinical trials seemed to be the obvious way to accelerate wider access to these drugs. However, the study of flecainide for treatment of arrhythmias cast substantial doubt on the use of surrogate outcomes. Despite the fact that the presence of arrhythmias after a myocardial infarction is a strong predictor of mortality and the fact that the drug flecainide had been shown to reduce arrhythmia, a trial of this therapy showed that it significantly increased rather than decreased mortality.[1] Nevertheless, reliance on surrogate outcomes remains. For example, over the past 5 years, of 143 initial submissions to the Australian Pharmaceutical Benefits Advisory Committee for new drugs or major new restrictions adopting a cost-effectiveness approach based on therapeutic superiority, 53 submissions or 37% relied on an inference that a surrogate outcome could be transformed to a future, more patient-relevant outcome.

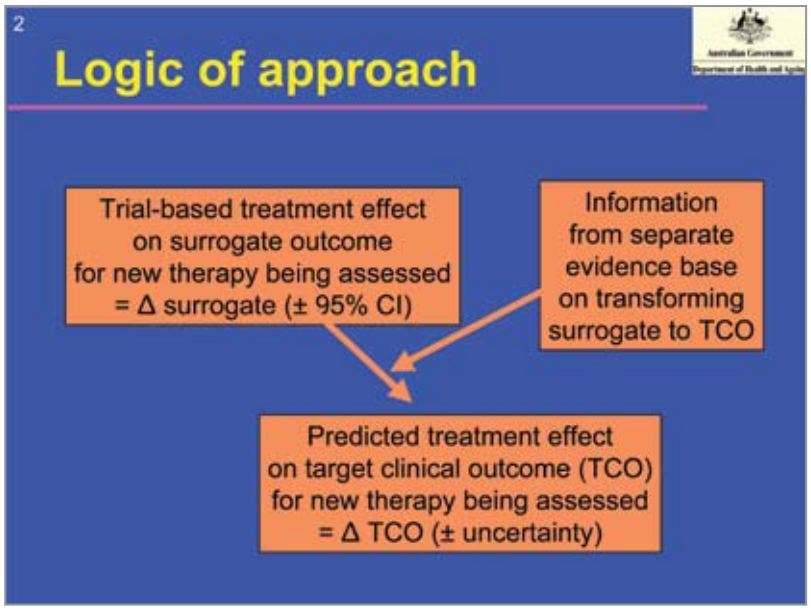


Much of the thinking and publishing in this area has been influenced by regulatory agencies, clinical trial investigators, clinical epidemiologists and biostatisticians, but recently, the involvement of health technology assessors (HTAs) has introduced a slightly different perspective. For example, although the classic definition of a surrogate has held that it is generally asymptomatic, health technology assessment recognises the need to transform surrogate outcomes irrespective of whether they are asymptomatic or can be perceived with direct meaning to patients. Also, while regulators require that surrogate outcomes simply validly predict a future treatment effect on a target clinical outcome, HTA assessors also require that the future treatment effect be quantified and the extent of confidence around in this quantification be estimated.

Surrogate rationale

The rationale assessing a new medicine typically requires a pathway by which it first improves the proposed surrogate, causing an improvement in the intended clinical outcome and thus an improvement in overall or net clinical benefit. However, the surrogate may inadequately predict the clinical outcome if the treatment has other beneficial effects and/or other adverse effects, which changes the extent of effect on the intended clinical outcome, and thus the net clinical benefit. The statin group of drugs provide an example of this multiplicity of potential mechanisms and treatment effects. The primary mechanism of action has long been thought to be mediated through lipid changes and improvements in atherosclerosis. Additional potential mechanisms, however, include plaque stabilisation and anti-inflammatory effects, and additional toxicities, such as rhabdomyolysis will have an impact on the overall health outcomes of therapy.

In the absence of direct evidence from trials of a comparative treatment effect on the clinical outcome of interest, the results for a proposed surrogate outcome need to be related to another body of information assessed separately in order to transform these results. The framework relies on building an assessment in two parallel streams. The first stream is the theory underlying the use of the proposed surrogate outcome by building biological rationale, from the underlying disease process,



to the mechanisms of actions of other therapies used to treat the disease, to the new therapy under consideration. The second stream is an assessment of the empirical evidence collected to support the biological rationale and to quantify the relationships. Typically this involves a review of population cohort studies and sometimes clinical cohorts from the placebo arms of randomised trials. The objectives are first to review the strength of the association and then assess the consistency of the association across studies. However, consensus is building that meta-analysis is the most convincing method to explore the relationship between the treatment effects on the surrogate outcome and on the target clinical outcome. Ideally this requires a meta-regression across multiple randomised trials, each of which has assessed the effects of other relevant treatments on both the surrogate outcome and the clinical outcome of interest.

For a modifiable risk factor to be a good surrogate outcome for a clinical outcome of interest, treatment-induced changes in the proposed surrogate outcome must be highly predictive of treatment-induced changes in future clinical outcomes. For example, although viral load was shown to be predictive of disease progression or death in untreated patients with HIV[2], a meta-regression analysis showed that treatment-induced reduction in viral load showed only a weak association with disease progression , which suggested that other mechanisms such as CD4 count were also influential predictors[3] In contrast, a recent meta-regression analysis of the relationship between rates of all-cause mortality and levels of LDL-cholesterol measurement showed a strong association.[4] Unfortunately, meta-regression analyses typically require multiple randomised trials usually followed up over an extended period for inclusion. These are not always available. For example, in hepatitis C, an indolent disease with a time horizon of over 30 years, use of interferon-alfa produced a sustained normalisation of serum amino alanine transaminase levels after 12 months of treatment. HTA models in the early 1990s assumed that this normalisation was equal to a cure of the disease, although it may in fact only signal a dormancy of the disease. Although there has been no strong evidence of recurring infection, which would suggest that the original models were over-optimistic, this cannot be determined conclusively without robust randomised trial evidence. There has also been recent controversy over economic modelling for ezetimibe, when it was observed that the incremental reductions in LDL-cholesterol were too small in comparison to those achieved by statin monotherapy over placebo to be considered sufficient to conclude an effect on major cardiovascular endpoints.

Conclusions

Although there is an increasing trend to rely on surrogates in the evaluation of new medicines, they often produce weak evidence of incremental effectiveness resulting in increased uncertainty for HTA decision-makers. This creates the potential for new expensive therapies to be judged erroneously as not cost-effective within acceptable levels of certainty. Therefore, the ideal regulatory and HTA decision making process may require direct randomised trial evidence of treatment effects on both surrogate outcomes and intended clinical outcomes.

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3. HIV Surrogate Marker Collaborative Group. Human immunodeficiency virus type 1 RNA level and CD4 count as prognostic markers and surrogate end points: a meta-analysis. *AIDS Res Hum Retroviruses*. 2000;16:1123-1133.
4. Johnson KR et al. LDL-cholesterol differences predicted survival benefit in statin trials by the surrogate threshold effect. *J Clin Epidemiol*. 2009;62:328-336.

Discussion

Question: Do you think different standards for surrogates can be applied at different times during a medicine's life, that is, higher standards for proof of efficacy and safety at time of marketing authorisation and somewhat lower standards for cost-effectiveness evaluation where you have the opportunity to validate over time?

Response: I'm uncomfortable with the implication that there are absolute standards; however, if we accept a surrogate with less than perfect evidentiary standards, the only way to later validate that surrogate would be with randomised clinical trials, at which time we would be ethically precluded from conducting. So this means that we would not be able to validate the medicine's reliance on a surrogate.

Question: Couldn't we use the evidence from other randomised clinical trials in other classes as models?

Response: That is what I have suggested through the use of meta-regression. However, existing examples of this model relate to placebo-controlled trials and, as has been discussed today, we're moving toward active comparisons involving smaller increments. Even meta-analyses of placebo-controlled trials do not produce a directly fit-for-purpose model to measure incremental outcomes in these circumstances.

Comment: Regulators as a whole have only accepted a limited number of surrogate measures to support marketing approval. I don't agree that we are using surrogates that haven't been translated into proven clinical benefit.

Response: Immediate clinical benefit does not always translate into further future clinical benefit and when surrogates are used to create a model to project some other effect, such as attempting to translate progression-free survival to future overall survival, HTA assessors have difficulty accepting that translation with confidence.

The value of biomarkers and surrogate endpoints in decision making: A regulatory authority perspective

Andrew S. Mitchell for

Dr Leonie Hunt

Head, Office of Prescription Medicines, Therapeutic Goods Administration (TGA), Australia

Mr Mitchell relayed apologies from Dr Leonie Hunt who was unable to attend the Workshop.

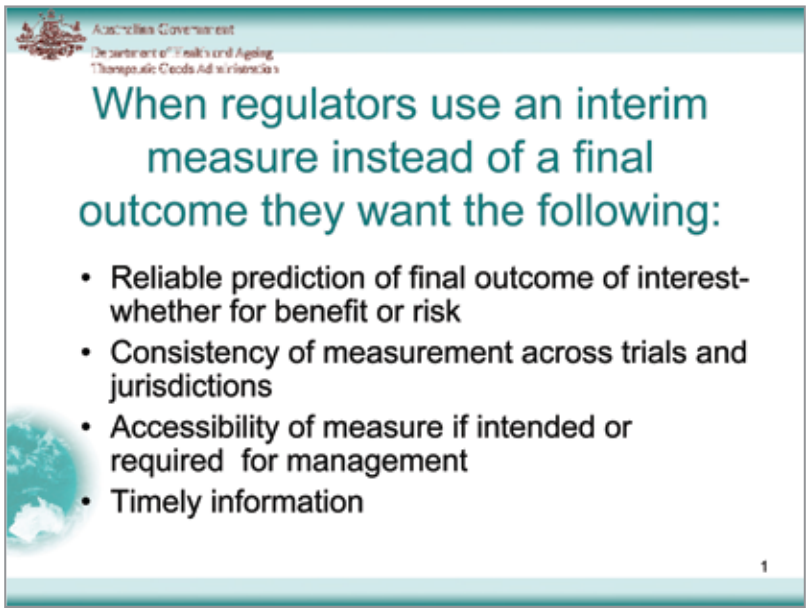
Generally, medicine regulators have the responsibility to grant market access for a medicine when it is established that there is adequate quality, safety and efficacy for the intended use of that medicine. The perspective of regulators is influenced by the history of the ways in which regulations on market access have evolved. In virtually all countries, regulatory systems were set up in response to issues around poor quality or counterfeit goods, safety issues, such as occurred with use of thalidomide for morning sickness in pregnant women, or efficacy concerns, for example the promotion of invalid cures for serious infectious diseases or malignancies. However, in parallel with the development of regulatory systems in the 20th century, there was also tremendous growth in the development and availability of new and emerging therapeutic options, vaccines, antibiotics, effective medicines and technologies that did make a tremendous difference to peoples' health.

By the late 20th century, most regulators had also been charged with an additional responsibility: not to act as a barrier to appropriate treatments that may assist people with serious illnesses and few or no alternatives. Obviously, these responsibilities are not always compatible. Promising treatments are not always safe and we may not know for certain that they will work in the way we hope and expect in the longer run, but regulators are meant to balance potential benefits and risks and to work to facilitate access to useful therapies while blocking access to inappropriate therapies. The problem is how do we reliably determine at the time of first approval what is useful and what is harmful.

To make this determination, regulators need information, and in an ideal world would have information that would tell them whether the treatment would work in both the short and long term, what harm it could cause, the likelihood of the harm occurring and the extent of the benefit. In other words, the information would tell them what could be done to help reduce the risk of harm and maximise the benefit for society and the individual patient.

Organising large-scale long-term trials to obtain this information is a slow process. Sometimes healthcare professionals treat acutely to measure immediately if that treatment is or is not working, but more often we treat disease conditions with the aim of alleviating short-term symptoms and preventing longer term morbidity and mortality. Hypertension, for example, is not treated to lower the blood pressure, but hopefully to reduce the risk of stroke, heart attack, renal disease and other complications of an elevated blood pressure that may appear many years after an increase is noted. If we required 20- to 30-year studies before approving a new therapy, then patients would go without treatment and in a changing world we would have multiple treatments being investigated on a rolling basis without us ever reaching a practical conclusion.

We may want good trials with hard data, but clearly we cannot always get these in a reasonable timeframe, and this is a shared problem. No consumer wants to take a product that could possibly harm them without knowing that there is a real benefit and what the likelihood of that benefit is. Doctors want to know how likely it is that a treatment will actually do good overall. Companies want to know if their products work and if they do harm because products that are safe and effective are good to develop and market. Payers have a duty to ensure they get good value for money and that what they pay for is likely to provide an overall benefit in terms of a real health outcome.



Regulators and other stakeholders therefore have compromised to allow the use of surrogate endpoints and biomarkers and measures that they believe reflect progress of the underlying condition and of the health and well-being of the patient and base decisions on these, sometimes with the addition of post-marketing requirements. When regulators use an interim measure instead of a final outcome however, they want reliable prediction of the final outcome of interest- whether for benefit or risk, consistency of measurement across trials and jurisdictions, and accessibility of measurement if intended or required for management and timely information. What is not acceptable is the use of a surrogate measure that does not link to or reflect underlying disease progress, even though it may appear to track in parallel for some time or with the predictive role of the measure in terms of the final outcome for the patient.

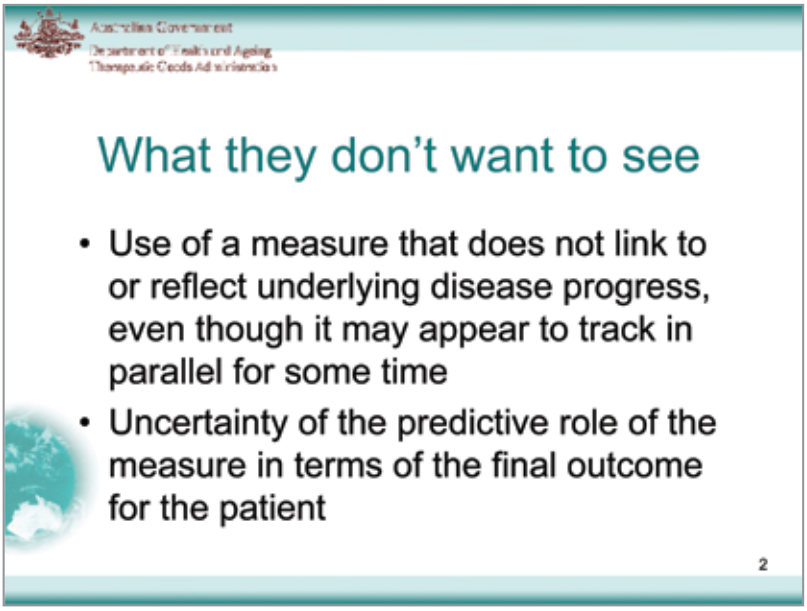
Despite these concerns there are surrogate measures that have been used and continue to be used, some more robust than others. Examples of traditionally accepted surrogate endpoints include the use of blood pressure and lipid measures for cardiovascular morbidity and mortality, measurement of HbA1c for prevention of morbidity and mortality from diabetic disease, and use of CD4 counts and viral loads for HIV treatment. In some cases there is still confidence in the surrogate measure. Few, for example, would advocate not treating sustained high blood pressure. For other surrogates we have seen results of research showing that previous understanding of disease processes was incorrect or incomplete and suggesting that either the surrogates may not reflect long-term outcomes or may be influenced by unidentified factors. We are also seeing the outcome of rapid growth in new technology-based, often highly targeted treatments, where we are increasingly asked to look at new surrogates, for which we have no experience.

Regulators will continue to use surrogate measures that offer a way of measuring response and harm when other ways are not feasible in real time. Many new surrogates such as

the measurement of HER2 receptors do offer potential value to the individual patient, but they require basic research to establish credibility of linkage and long-term measurement to confirm validity and we must be prepared to monitor and adjust as we all learn. A periodic reassessment of the value of older markers is also required to look for new evidence for a better marker or emerging evidence that a previously accepted intermediate measure does not reflect final outcome for the patient.

Regulators are increasingly recognising the need to be transparent about the basis for decisions, what has been measured and should clearly set out the limitations of knowledge both from use of measures and from inherent trial difficulties for all stakeholders to understand.

In summary, the challenge is to use biomarkers and surrogate endpoints wisely, to make sure there is a valid scientific rationale for their use, to monitor emerging information, and to balance timely access with a desire to base an approval decision on an ideal data set.



Discussion

Comment: It may be possible to design randomised clinical trials that use target clinical outcomes or surrogates that will satisfy all stakeholders using patient databases like General Practice Research Database (GPRD).

Response: Yes, randomised epidemiology trials would represent an excellent way of incorporating both clinical and surrogate outcomes with an opportunity for long-term follow-up. Although greater statistical power is needed for target clinical outcomes compared with surrogate endpoints, a prospective meta-analysis for target clinical outcomes can be projected from individual trials using surrogate outcomes.

Experience of early dialogue with pricing and reimbursement agencies: Scientific advice meetings

Dr Martin Backhouse*

Head, Global Pricing & Market Access Operations, Novartis Pharma AG, Switzerland

Having recognised that technology developers need to meet the evidentiary needs of HTA agencies as well as Regulatory Authorities, Novartis has recently participated in bipartite and tripartite scientific advice pilot initiatives with both groups.

Pricing and reimbursement (P&R) decisions typically focus significantly on clinical evidence and HTA challenges have often been directed at the strength and relevance of this evidence. Because of the need to address the clinical and economic value of a new product, ways to capture this evidence should be considered in constructing the clinical development plans particularly before beginning the phase 3 studies. However, because it has not previously been possible to interact directly with P&R / HTA agencies early in the product development cycle, a new strategy had to be crafted to try and incorporate directly the needs of P&R / HTA agencies earlier into Novartis' development programmes.

> Not all HTA agencies were prepared to give written advice or comment on meeting minutes, this variability is similar to that found in regulatory agencies.

What early dialogue means to Novartis

Traditionally, industry has had direct early interactions with patients, clinicians and regulatory authorities. Only recently have similar interactions with other important stakeholders been possible, including national and regional pricing and reimbursement agencies, HTA bodies and large private and public purchasers who determine the terms and conditions of market access following marketing approval.

Novartis has set the goal to interact directly with all customers, particularly in key markets early (phase II or before) in the development of a new product, to obtain scientific advice on product development and evidence plans. It is hoped that this will ensure that clinical evidence plans / phase III clinical trial designs provide data that are relevant for payers as well as regulators. In addition, early engagement with pricing and reimbursement agencies should, in principle, lead to faster patient access to good-value medicines.

Experience with early dialogue

Novartis first piloted the process of early HTA interactions with the UK National Institute for Health and Clinical Excellence (NICE) and has since repeated this approach with several other agencies across multiple continents. The process for these early engagement pilots has been similar across agencies, with comparable timings for advice and the scope and meeting format. As with scientific advice interactions with regulators, the advice given by P&R / HTA agencies is not binding on either party and it is not envisaged that these processes will become mandatory. The company found that, unlike NICE, not all P&R / HTA agencies were prepared to give written advice or comment on meeting minutes; this variability is also similar to that found in regulatory agencies.

Pilot projects were selected within one disease area (psoriasis) and a core briefing book was prepared. The outline of phase III trials as planned to achieve regulatory approval was presented, with the plans put in the context of local clinical practice and reimbursement considerations. Briefing book questions were structured around a number of possible positions in the psoriasis care pathway and most of the questions focussed on key clinical trial design characteristics required to generate data that could support alternative reimbursement positions. These characteristics included study population, comparator treatments, endpoints and the nature and duration of follow-up. Where relevant, economic evaluation design questions for value determinations, such as the development and use of existing models and specific data to be captured in clinical trials were also discussed.

Results

Although the results of these pilots relate to one disease area and may not be generalisable, Novartis was able to make comparisons amongst P&R / HTA agencies and with regulatory authority advice. The advice received showed far more similarities than differences across countries. In

this case, the clinical evidence required by payers and regulators could probably be obtained in one comprehensive phase III programme and meeting the specific requirements identified would not likely increase costs or development times significantly.

There was a strong interest and commitment from agencies and the Novartis teams to incorporate early P&R / HTA advice into the pivotal clinical programmes. Participation in advice meetings at a large number of P&R / HTA agencies is likely to be more challenging than reconciling the different perspectives from multiple sources. There are, however, significant challenges for P&R / HTA agencies that wish to offer advice routinely, including the manpower demands on agencies for these types of meetings and the constraints imposed by budgets and internal skills.

HTA advice showed far more similarities than differences across countries. Clinical evidence required by payers and regulators could probably be obtained in one comprehensive phase III programme and meeting the specific requirements identified would not likely increase costs or development times significantly.

Conclusions

Although the pharmaceutical industry is accustomed to balancing the evidentiary needs of regulators and payers, early direct dialogue with P&R / HTA agencies to address their specific needs is a new concept. Such early and direct engagement is preferable and provides feedback that is superior to that obtained from simulations, advisory boards, and collaborative expert judgement. We observed far more similarities than differences in advice, suggesting P&R / HTA agency collaboration on providing early scientific advice is possible. There are different models of early scientific advice involving pricing and reimbursement agencies. For example, a bipartite approach involves a technology sponsor meeting with an individual P&R / HTA agency or receiving joint advice from several P&R / HTA agencies in a coordinated process. In a tripartite approach, a sponsor participates in joint or parallel P&R / HTA and Regulatory Agency advice from one or more country representatives. It is recognised that P&R / HTA and Regulatory Agencies both have distinct (non-overlapping) areas of interest and responsibility so a tripartite process focuses on advice relating to the common areas of interest, in particular Phase III trial designs.

One approach for P&R / HTA agencies to overcome resource challenges in offering early dialogue is to offer collaborative advice to sponsors perhaps along the lines used by the EMEA. Elements of advice from one jurisdiction may be an adequate proxy for another. Furthermore, HTAs could issue scientific guidance documents for specific disease areas that can help guide a consistent approach to their needs.

Discussion

Question: Can you suggest criteria to select products that would most benefit from early P&R / HTA agency interaction?

Response: Products need to be in early developmental phases in order that the advice can be used effectively to inform development decisions and Phase III trial designs. Even though there was internal debate as to the need for more product-specific data before HTA engagement, it was thought that the process would yield scientific advice that would be generalisable to other compounds in the same disease area. Another criterion is the scale of evidence investment at stake. It was also important to select product teams willing to engage in the process.

Question: It seems as though there was a high likelihood of defining similar regulatory and HTA clinical requirements in the therapeutic area of psoriasis. Do you have insights on discussions in a disease area where there may be bigger gaps in requirements, for example, as in antihypertensives?

Response: There were some differences in requirements even with psoriasis treatment. Regulatory advisors in Europe were interested in the psoriasis area and severity index scores (PASI) and in the US the Investigator's Global Assessment (IGA). HTA assessors found those measures useful but also wanted to know the medicine's health benefit effect e.g. in quality-of-life terms. We have held meetings in other disease areas and still think there are more similarities than differences on the key trial design issues but more experience is required.

*The views expressed in this summary represent those of the speaker and do not necessarily represent the views or practices of Novartis Pharma AG.

Harmonising proof of concept with proof of value

Professor Robert Peterson

Chairman, Canadian Expert Drug Advisory Committee (CEDAC); Clinical Professor, University of British Columbia, Canada

Proof of concept (POC), the fundamental regulatory requirement for market authorisation of a new medicine, is confirmed through high-quality randomised clinical trials (RCTs) that are capable of providing a level of certainty and an absence of bias in observations. In fact, the needs of POC drive the design of phase II and III RCTs.

There are a number of limitations to RCTs, however, including their ability to answer only a few well-defined questions at a time. In addition, RCTs that are powered for efficacy outcomes yield limited safety data and RCTs powered for safety result in a narrow focus. Furthermore, the results may not be readily extrapolated to populations not specifically included in the RCT for subset analysis.

The different objectives of regulators and HTA assessors are reflected in their selection of RCT comparators. Active comparators are not often accepted for POC, and when they are used, non-inferiority margins may be too liberal for HTAs to use them in effectiveness assessments. The resulting limitations to POC studies are that they often provide limited information about a new medicine especially regarding its value during long-term use, full safety profile, potential drug interactions, applicability to a broad target population, comparison to existing drugs, or relevant place in therapy – all of which are the data considered important evidence for proof of value (POV) assessment.

Limitations to POC studies are that they provide limited information about a new medicine, especially regarding its value during long-term use, full safety profile, potential drug interactions, broad target population, comparison to existing drugs, or relevant place in therapy – all of which are the data considered important evidence for POV assessment.

Economic models

An additional element that is assessed in a POV analysis is a medicine's cost-effectiveness, and this requires the use of several pharmacoeconomic models. Economic models based upon direct comparison are preferred, and these vary based upon assumption of equal efficacy for cost minimisation or superior efficacy or safety measured through an incremental cost- effectiveness ratio. Models based upon indirect comparison are more common and require stricter rules than simple meta-analyses. Although it is possible to make these comparisons, agreeing upon appropriate assumptions underlying the evaluation can be problematic and analyses derived from these models are associated with a wide variability in sensitivity.[1]

Active comparators for POV may be preferred by HTA assessors based upon pharmacologic or therapeutic class or on economic factors such as frequency of prescription or likelihood of use outside of labelling that may have little to do with the regulator's approach to the scientific evaluation of medicines. These comparators are also highly subject to national and regional variation.

Non-inferiority margins

In order for a medicine to claim non-inferiority to another therapy, there must be both a statistical and clinical basis for the selection of a non-inferiority margin. This margin may be more generous for POC evaluations compared with POV assessments, as larger margins imply a willingness for payers to set aside benefits achieved by older medicines. A three-armed trial with test, reference and placebo allows within-trial validation of the choice of non-inferiority margin and should be used wherever possible.

It is not appropriate to use effect size as the sole justification for the choice of a non-inferiority margin. Although this statistic provides information on how difficult a difference would be to detect, it does not help justify the clinical relevance of the difference.

Although post hoc data analysis is used increasingly in economic models and is frequently the basis for requesting payment decisions as second- or third-line therapy, it is considered by many to be a perversion of RCT design strengths. Despite the fact that they can magnify bias through unblinding and that they remove concurrent evaluation of best practice, open-label extensions are often cited in clinical

practice guidelines as the basis for confirming real-world efficacy and safety. Unfortunately, outcome measures for open-label extensions are often relaxed, incompletely reported, or inconsistently assessed.

A three-armed trial with test, reference and placebo allows within-trial validation of the choice of non-inferiority margin and should be used wherever possible.

Conclusions

There is a basis for joint regulatory and HTA advice for new medicines regarding appropriate trial design. Furthermore, post-market safety and effectiveness monitoring and reporting is another potential area for cooperation. Sub-population trial analyses are suitable for the assessment needs of both stakeholders when pre-declared as part of the trial design, and open-label trial extensions with strong data analysis and comparison design can similarly inform the decisions of both stakeholder groups.

Discussion

Question: Have you considered the benefits in using adaptive studies in deriving HTA outcomes?

Response: Yes, although the use of adaptive design is fraught with many technical issues, we are confident in our ability to accept the reliability of the data in an adaptive RCT. We must look to Bayesian methodologies to provide a measure of probabilities rather than statistical differences.[2]

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The Swedish joint scientific advice pilot project

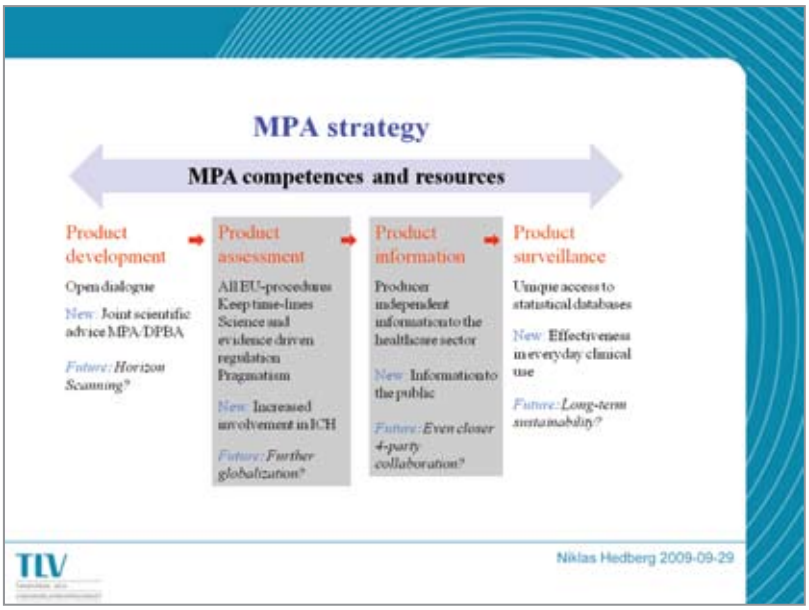
Niklas Hedberg

Head of Department, Department for Pharmaceutical Submissions, Dental and Pharmaceutical Benefits Agency (TLV)

The Swedish Dental and Pharmaceutical Benefits Agency (TLV) has been recently challenged to improve patients' access to medicine by developing strategies to increase the efficiency of new product reviews, developing advanced pricing models and strengthening collaboration with all stakeholders. In pursuit of these objectives, on 1 September 2009, the TLV embarked on a pilot project of joint scientific advice with the Swedish Medical Products Agency (MPA), which is scheduled to run until the end of December 2009.

> Whilst the SBU [HTA] asks pharmaceutical developers *Are you sure?*
>
> The TLV [Payer] asks *How sure can we afford to be?*

The aim of the programme is to improve the overall interaction between the regulatory and HTA agencies and to initiate cooperation with companies at an earlier phase in drug development. While there is a clear-cut difference in the missions for the two agencies, the scientific evaluation process is common.



It is hoped that joint advice will be given for four to six new products during the pilot project to a mixture of large pharmaceutical, medical technology and biotechnology companies. Applications for advice are administered by the MPA; it is not possible to request advice from the TLV alone. When complete, the pilot project will be evaluated and if the experience is judged to be positive, the agencies will decide how to continue to provide joint scientific advice and to proceed in other areas where interaction can facilitate effective medicine development.

The Swedish Council on Health Technology Assessment (SBU) is the HTA authority in Sweden. Although the TLV is a pricing and reimbursement agency, it works with HTA tools and brings a practical point of view to HTA assessment. That is, whilst the SBU asks pharmaceutical developers Are you sure? The TLV asks How sure can we afford to be? All stakeholders need to know the clearly identified and quantified gain from a new medical intervention and this joint scientific advice programme is one step toward this goal.

Discussion

Comment: To answer your question how unsure can we afford to be? One has to be able to communicate the costs and benefits of the alternative therapies.

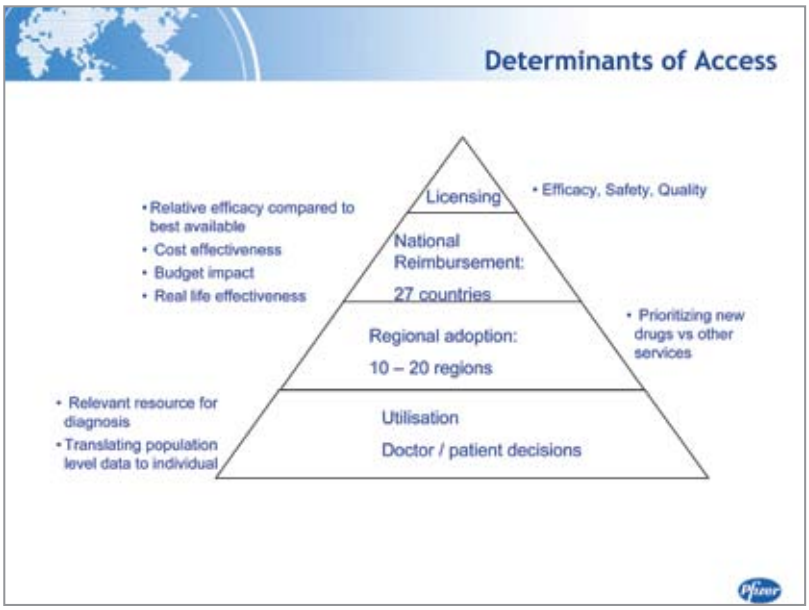
Response: Yes, there is a need for better transparency and clarity surrounding the tools used to communicate uncertainty. Health economists and clinical pharmacologists, for example, still haven't found a way to communicate their needs in expressing uncertainty to one another. If p-values are not appropriate measures of difference, new metrics will need to be employed.

Conditional licensing and conditional reimbursement

Clare McGrath

Senior Director, HTA Policy, Pfizer, UK

Since 2005, EU Regulators have granted conditional approval for a small subset of medicines targeting high unmet need that have the potential to yield significant clinical benefit, under the condition that sponsors continue to collect additional clinical data for eventual full approval. The time gained, however, through a shortened regulatory approval process is frequently lost during reimbursement negotiations. The question remains whether complementary conditional reimbursement is an answer to expedited access for these needed medicines.



Challenges to Conditional Reimbursement

Conditionally approved medicines are more likely to suffer from clinical and financial uncertainty at launch. Medical evidence that supports regulatory objectives is often criticised by payers as being inappropriate to support their decision needs. Clinical development programmes can demonstrate efficacy and sometimes relative efficacy, whereas payers demand proof of long-term patient benefit under real-world conditions (effectiveness). Furthermore, it is not always feasible to predict or to conduct the appropriate head-to-head comparisons in development that are relevant to the standard of care in every different health systems after launch. Consequently, the overall product use and resultant budgetary impact cannot be fully anticipated or sufficiently described prior to launch. Effectiveness in target sub-populations where value is maximised cannot always be studied and issues such as adherence/persistence, dosing and the impact on use of other medications and healthcare resources can only be considered once the medicine is in use in the health system.

Among European countries, differences in funding structure, size of health budgets, practice patterns and unit costs create the scope for differences in effectiveness and cost-effectiveness, whilst decision-making systems, social value judgements and health system priorities create the scope for differences in reimbursement decisions. In considering access, these variables need to be taken into account by the national and regional decision makers as well as in the patient-clinician interface.

A suggested programme of conditional reimbursement: periodic reassessment of price based on emerging evidence

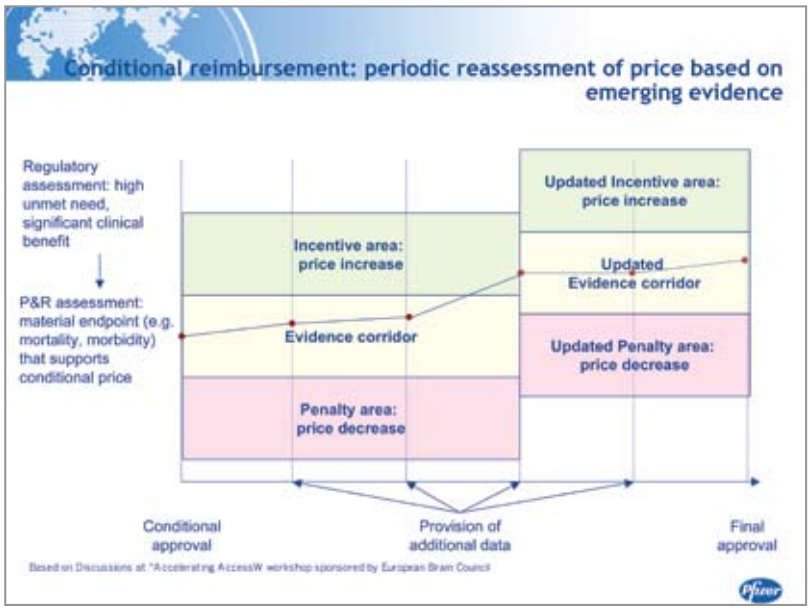
Conditional approval could be granted in areas of high unmet need on the basis of an indication of significant clinical benefit, which would be accepted by both regulators and payers. In this approach, significant clinical benefit could be translated through modelling into relevant endpoints for payers such as mortality or specific morbidity. Conditional pricing could then be set against the known clinical benefit through a pragmatic HTA assessment, which may require extrapolation from biomarkers to final outcomes.

An "evidence corridor" would need to be defined for clinical endpoints that have material impact on price assessment and for which additional data collection obligations have been agreed. Additional evidence falling into this corridor would support or undermine the initial price assumption. If the additional evidence accrued is less favourable than that originally assumed, a price reduction would be incurred, but if the evidence accrued is more favourable than originally assumed, an incentive such as a price increase or a relaxation of reimbursement restrictions would be triggered. Once all post-release obligations have been fulfilled and final approval is granted, the final price and reimbursement decision would then be imposed.

Key success factors for conditional reimbursement

The differences between the objectives of regulatory and payer decision making need to be made explicit. There are areas of overlap, however, and duplication of assessments of the same data should be avoided. It should be possible, for example, for HTAs to leverage the experience from regulatory processes in assessing outcomes that will meet reimbursement decision needs.

Better understanding and agreement must be obtained among the HTAs from different countries on the acceptable criteria and scientific standards for decision making, including an increased acceptance of the balance between observation and simulation for relative effectiveness assessment. It will also be necessary to develop mechanism(s) to agree on evidence and price corridors to balance affordability, return on investment and access for products that are subject to conditional approval. Programmes will be required to facilitate access to orphan drugs such those established for temporary access, for example, Autorisation Temporaire d'Utilisation (ATU) in France or for compassionate use in serious illness.



Conclusions

Provided stakeholders can agree on the level of acceptable uncertainty at the time of a product's release, conditional reimbursement provides part of the solution to expediting access to medicines for unmet needs. Getting the medicines to the right patients at the right time also depends on system factors such as resources and expertise devoted to diagnosis and translating population data to individuals. We should recognise that the conditions and decision will still be made in the local context and flexibility will be needed at this local level to balance return on investment for the developer, affordability for the payer and access by patients.

Discussion

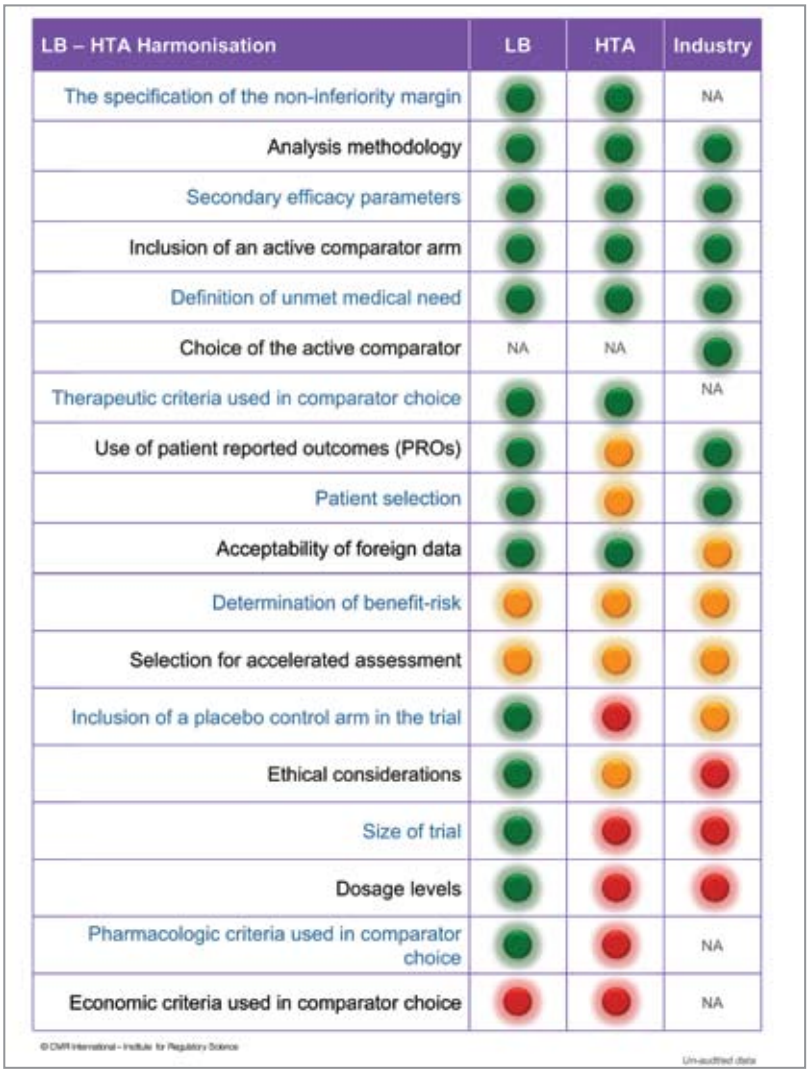
Question: What happens to the incentives for intellectual property rights during the period of conditional reimbursement?

Response: The patent rights would be retained by the patent holders during this time, and although the return on investment may be initially lower, it would certainly represent an improvement over a period of no distribution or reimbursement. Without conditional reimbursement for conditionally licensed products, there would be a loss of data exclusivity during the period where the conditional license is granted but there is no reimbursement. This is a disincentive to gain a conditional license without conditional reimbursement .

Review and reimbursement: The current environment and the implications for the future

Dr Franz Pichler

Portfolio Manager, CMR International Institute for Regulatory Science, UK



LB – HTA Harmonisation	LB	HTA	Industry
The specification of the non-inferiority margin			NA
Analysis methodology			
Secondary efficacy parameters			
Inclusion of an active comparator arm			
Definition of unmet medical need			
Choice of the active comparator	NA	NA	
Therapeutic criteria used in comparator choice			NA
Use of patient reported outcomes (PROs)			
Patient selection			
Acceptability of foreign data			
Determination of benefit-risk			
Selection for accelerated assessment			
Inclusion of a placebo control arm in the trial			
Ethical considerations			
Size of trial			
Dosage levels			
Pharmacologic criteria used in comparator choice			NA
Economic criteria used in comparator choice			NA

A **green light** indicates that the stakeholder in question thinks that harmonisation or alignment for that requirement is possible, yellow indicates that although the stakeholder does not think that harmonisation or alignment is possible, they do think that information sharing would be useful, and **red** indicates that they do not believe that either harmonisation, alignment or information sharing would be useful.

In 2008, the Institute presented the results of a survey of pharmaceutical companies at the Workshop entitled "Regulation and Reimbursement: Two Sides of the Same Coin." Participants at that Workshop recommended that the Institute hold a further meeting on this topic and that this be supported by the conduct of a similar study that also included the views and experience of licensing bodies (LBs) and HTA agencies (HTAs). Accordingly, in 2009, the Institute conducted two complementary surveys: one among industry where both Regulatory Affairs and Health Economics and Outcomes Research (HEOR) departments were asked to respond and the other among LBs and HTAs.

As of the current Workshop, 10 of the top 15 pharmaceutical companies (based on R&D spend), 7 LBs and 6 HTAs had responded. Key results are summarised here according to three themes: evidence and technical requirements; scientific advice; and reimbursement in an environment of conditional approval.

Evidence and technical requirements

Interim results of the survey indicated that harmonisation and information sharing between regulatory agencies and HTAs regarding evidence and technical requirements may be possible. Specific areas where information sharing could occur included specifications of the non-inferiority margin, determination of secondary efficacy parameters, and characterisation of an active comparator arm. There were in fact, few areas where information sharing was not considered feasible.

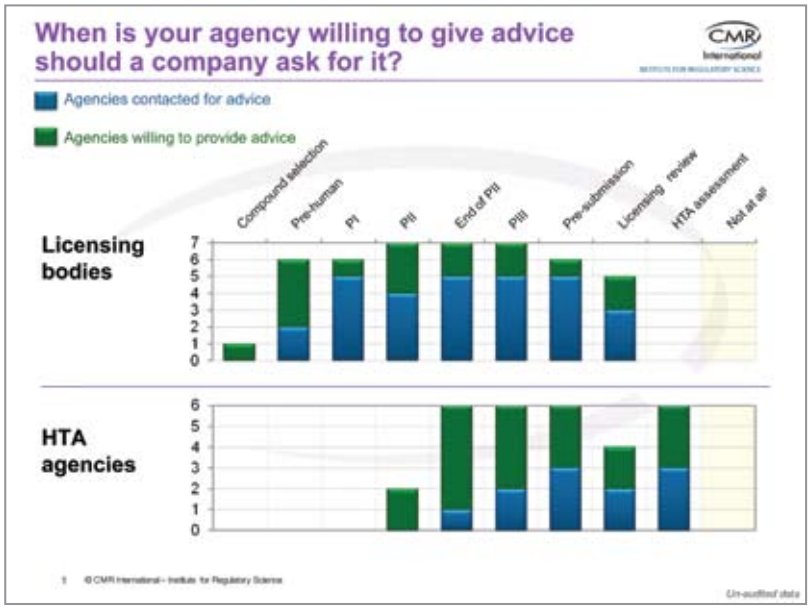
Agreement on the value of the use of biomarkers for patient selection and for the choice and use of surrogate endpoints was considered feasible although there was less consensus among LBs and HTAs regarding the validation of biomarkers or for stratification of patient populations by using biomarkers. The authorities' responses indicated that they were more conservative, in comparison to industry, in the types of surrogate endpoints that are considered acceptable for evaluation.

Scientific advice

Of the 28 pharmaceutical respondents, 24 were interested in receiving scientific advice from HTAs, with the majority indicating that the ideal timing for such advice ranged from the end of phase 2 through to the post-approval HTA evaluation period. The majority of HTAs polled either currently provide scientific advice or

think that it is possible to do so, and indicated a willingness to provide advice starting at the beginning of phase 2. When considering what type of scientific advice from HTA agencies would be of greatest benefit to the industry, there were seven areas of highest concordance among all respondents:

1. Use of patient reported outcomes (PROs)
2. Inclusion of an active comparator in the trial
3. Choice of the active comparator
4. Use of biomarkers for patient selection
5. Choice of and use of surrogate endpoints
6. Inclusion and choice of secondary efficacy parameters
7. Patient selection



Areas where HTA advice was not seen as beneficial included assessment of benefit- risk, calculating trial size, ethical considerations and dosage levels. In addition, concerns related to conflict potentially associated with HTA scientific advice were similar to those associated with regulatory agencies, that is:

- Could HTAs objectively review data for which they had provided advice?
- Was there a risk of bias if that advice was not followed?
- What is the confidentiality risk when HTAs advise different companies?

In four of nine jurisdictions in the survey, LBs and HTAs either offer joint advice in some form or plan to do so by 2015. Although some LB and HTA respondents commented that joint advice could provide useful information to all stakeholders and allow HTA agencies the opportunity for the articulation of their needs for assessment, others felt that joint advice might result in a danger of increasing the overall requirements for pharmaceutical development, and that there also was a potential for increase of review time prior to licensure. Furthermore, regulatory respondents were concerned that joint advice meetings were resource-intensive and efficiencies might only achieved by the pharmaceutical company.

Industry respondents indicated that joint advice should not be binding, that it should be optional - not mandatory, and that such advice should be limited to the content of the clinical package. Clarity on the endpoints that will be acceptable to both LBs and HTAs should be a goal of joint advice and advice should be structured to avoid agencies duplicating consultations. Industry survey results also specified that regulators and HTAs should agree on optimal timing for joint meetings and have a long-term goal of accepting one consolidated evidence package for their respective assessments.

Certain potential conflicts in joint advice were of concern to Industry, namely those relating to different mandates and requirements and to local versus global approaches. There was an overriding fear that compromises in advice could potentially compromise outcomes.

Conditional reimbursement in an environment of conditional licensing

Although most LBs can offer conditional licensing and most HTAs have mechanisms in place for conditional reimbursement, the two processes are not necessarily linked, reflecting a need for increased dialogue between stakeholders. Companies would like to see some form of risk-sharing among all stakeholders for these conditional approvals. One company commented that conditional licensing and reimbursement with further evidence being collected post-approval is an appropriate mechanism for expediting patient access to new medicines for unmet needs and should encourage expedited HTA decisions. It was also remarked that conditional reimbursement should be extended to standard approvals.

A full report of the survey results has been provided.

Session 2: Review and reimbursement understanding the dynamics and how they are evolving

Chairman: Professor Sir Alasdair Breckenridge

Chairman, Medicines and Healthcare products Regulatory Agency (MHRA), UK

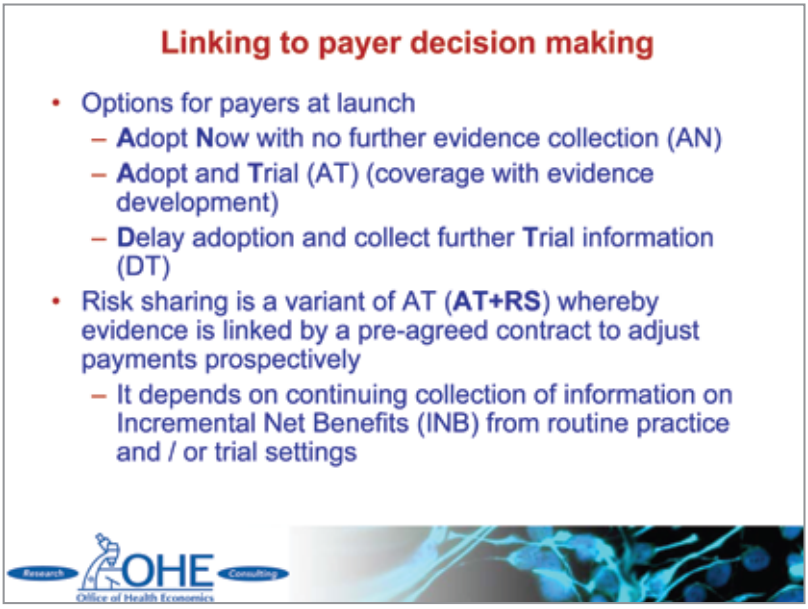
What is the role of risk sharing in ensuring access to patients for innovative medicines?

Professor Adrian Towse

Director of the Office of Health Economics, UK

Patient selection

Professor Towse began his presentation by defining a performance-based agreement as one between a payer and a pharmaceutical, device, or diagnostic manufacturer in which the price level or nature of reimbursement is related to the actual future performance of the product in either the research or "real world" environment rather than the expected future performance. This can also be called risk sharing (RS), pay for performance, or conditional reimbursement.



Key elements of these agreements include:

1. Consensus regarding a program of data collection to reduce uncertainty about expected cost-effectiveness
2. Prospective or retrospective linking of price or revenue by formula to the outcome of this program of data collection
3. A focus on health outcomes and cost-effectiveness rather than about budgets
4. A distribution of risk between the payer and the manufacturer that is different than "conventional" arrangements[1]

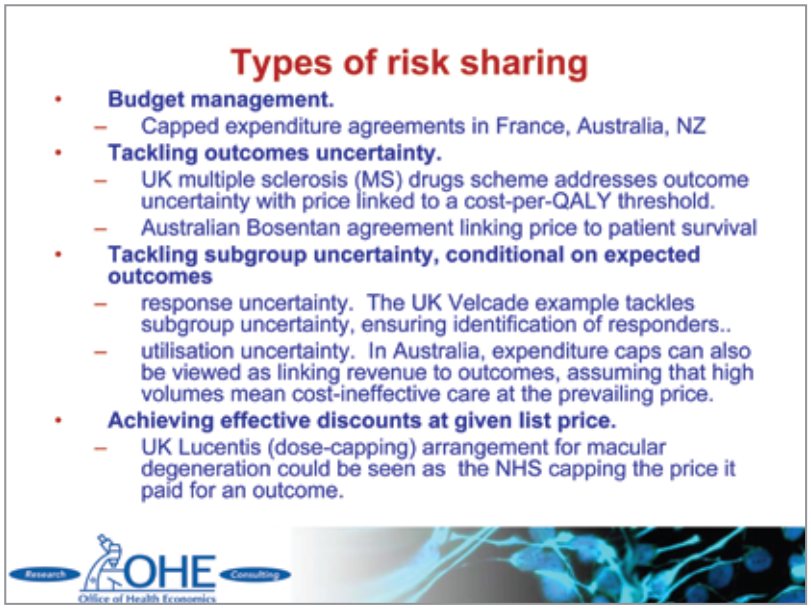
Performance-based agreements make sense in light of the problems that can arise in measuring a medicine's cost-effectiveness at launch when there is an overall asymmetry of information available to HTAs compared with regulatory agencies. Furthermore, HTA assessment requires data from experience rather than research and randomised clinical trials, and modelling may yield insufficient or inappropriate data for a comprehensive evaluation. These data may be from surrogate rather than clinical endpoints and be derived in clinical as opposed to real-world settings against what may be considered to be "irrelevant" comparators. Data may also be lacking for longer term outcomes or for effectiveness in relevant sub-groups.

There are three options for payers at launch for HTA assessment. First is the Adopt Now with no further evidence collected model (AN); second is the Adopt and Trial option (AT, initial coverage with ongoing evidence development); and third is the option for Delay of adoption and collect further trial information (DT).[2] Risk sharing is a variant of AT (AT+RS) whereby evidence is linked by a pre-agreed contract to adjust payments prospectively. It depends on the continuing collection of information on incremental net benefits (INB) observed in routine practice or real-world trial settings.

There are costs and benefits to each of these approaches. AN, which is based on an estimate of positive INB, brings benefits of rapid patient access to treatment and immediate return on a company's research and development investment without incurring costs of additional evidence collection. There is an inherent risk of error, however, in the use of insufficient data to make a long-term decision. DT presents the opposing set of benefits and risks: delays to access and costs of evidence collection but a reduced risk of erroneous decision making about

the utility and value of the product. AT avoids delays of DT, incurs evidence costs and may also lead to costs associated with reversing decisions. The value of each of these approaches can be quantified for the payer and manufacturer, facilitating a decision on whether further research reducing uncertainty produces overall positive benefits.

Risk sharing allows prospective price adjustments to maintain constant INB based on the latest available evidence. It also represents a type of reversal "insurance," and makes AT more attractive to payers. On the negative side, while risk sharing allows collection of information on INB from observational data, it faces the problem of adjusting for selection bias and local trials with adoption with universal coverage maybe infeasible. In addition, as a variant of AT, AT +RS needs to be regarded in a global context, that is, comprehensive data will be collected outside of the local jurisdiction.



Two typical medicine candidates for risk sharing are "type 1," for which there is a positive INB but weak efficacy evidence. AT is preferred for this type and a global trial can overcome local limitations; and "type 2," for which there is a positive INB and good efficacy evidence, but high uncertainty regarding long-term outcomes. AT is preferred for this type and a global trial for a longer period plus local observational data offer a superior outcome.

From a payer perspective, global trials offer feasible AT and robust risk sharing. There are clear advantages from reducing costs of delay in comparison with DT. AT+RS offers the ability to adjust price to reflect ongoing evidence and experience. In the absence of the flexibility offered by AT +RS, manufacturers may prefer the DT option in which there is a delay to collect better evidence and the subsequent opportunity to seek a higher price.

Types of risk sharing include budget management, which is a capped expenditure agreement such as those reached in France, Australia and New Zealand. Outcomes uncertainty is another type of risk sharing which is exemplified in the UK multiple sclerosis (MS) drugs scheme that addresses outcome uncertainty with price linked to a cost-per-QALY threshold and in the Australian bosentan agreement linking price to patient survival. There is also risk sharing that covers subgroup uncertainty such as response or utilisation uncertainty. Response uncertainty was addressed by NICE in the payment plan that was authorised for responders to bortezomib[3] (Velcade) and utilisation uncertainty links revenue to outcomes, assuming that high volumes mean cost-ineffective care at the prevailing price. Finally, achieving effectiveness and offering associated discounts at a given list price is another method of risk sharing. In the UK the dose-capping arrangement for Lucentis™ for macular degeneration could be seen as the cap set on the price paid for an outcome by the National Health Service.

Is risk sharing feasible?

The cost and practicality of ongoing evidence collection are critical factors in deciding whether to set up a performance-based risk-sharing agreement. Transaction costs, chiefly evidence collection costs, are key, and these costs should only be incurred if the uncertainties that can be resolved by the evidence are important, and if evidence collection can occur in a pre-agreed risk-sharing framework.

Another aspect tied to the feasibility of risk sharing is the need for prices to vary with INB. The withdrawal of discounts may be easier than a change in list price and there are other ways to change effective revenue, for example, the expansion of approved sub-groups for use. The UK Flexible Pricing and Patient Access Schemes may provide case studies for this.

Alternatives to risk sharing

If payers are to use the Adopt Now with no further evidence collection (AN) option for HTA evaluation, it becomes important to "get it right" the "first time." Dialogue with regulators and HTA bodies will help, but it will remain difficult to resolve all the uncertainties present at launch. If they choose to employ the Adopt and Trial (AT, coverage with evidence development) method, it will require renegotiation as additional information is obtained, but if there is no commitment to information collection or to how new evidence will be used in this model, problems may arise. Use of the Delay adoption and collect further Trial information (DT) model means a loss of the benefit of rapid access to the new medicine.

It is unlikely that HTA evidence requirements can be met at launch for products with conditional or accelerated approval. Early dialogue using the AT + RS approach can identify a pathway for evidence development in a global context for a product with an expected high health gain, with the price linked by formula to that evidence outcome.

References

1. de Pouvourville Risk-sharing agreements for innovative drugs: a new solution to old problems? *Eur J Health Econ*. 2006;7:155-157.
2. Eckermann S, Willan AR. Expected value of information and decision making in HTA. *Health Econ*. 2007;16:195-209.
3. Jack A. Drug pricing: No cure, no cost. *BMJ*. 2007;335:122-123.

Discussion

Question: Is there an opportunity to introduce patent term restoration during this period of uncertainty as an alternative to payment up front by payer?

Response: I think that stopping the clock on patent protection while additional data are being collected for HTA assessment will inevitably be raised as an issue. In the EU, pharmaceutical companies can get a supplementary patent but if that is not going to give them any additional access to the market because they don't have an agreement with the HTA bodies, there is no incentive to get a conditional license.

How are companies working with payers and how is this relating to development?

Dr Lawson Macartney

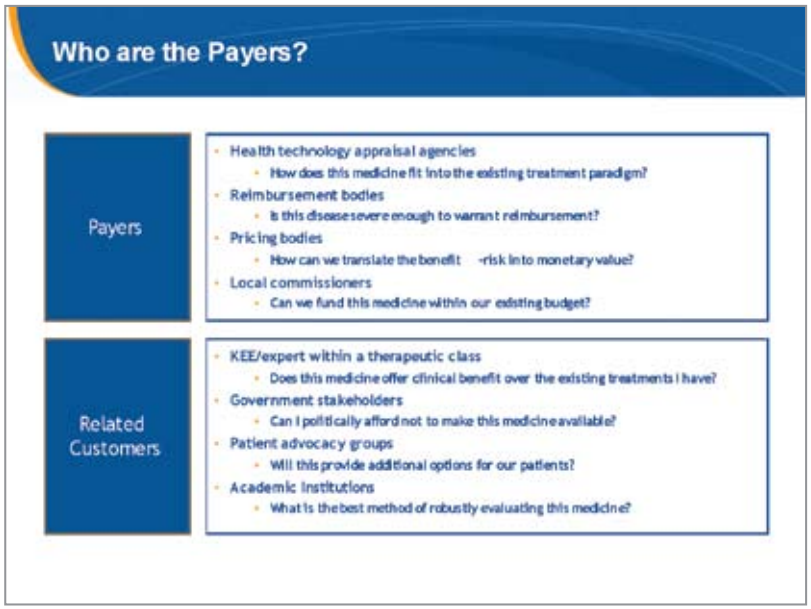
Senior Vice President, Global Product Strategy, GlaxoSmithKline, USA

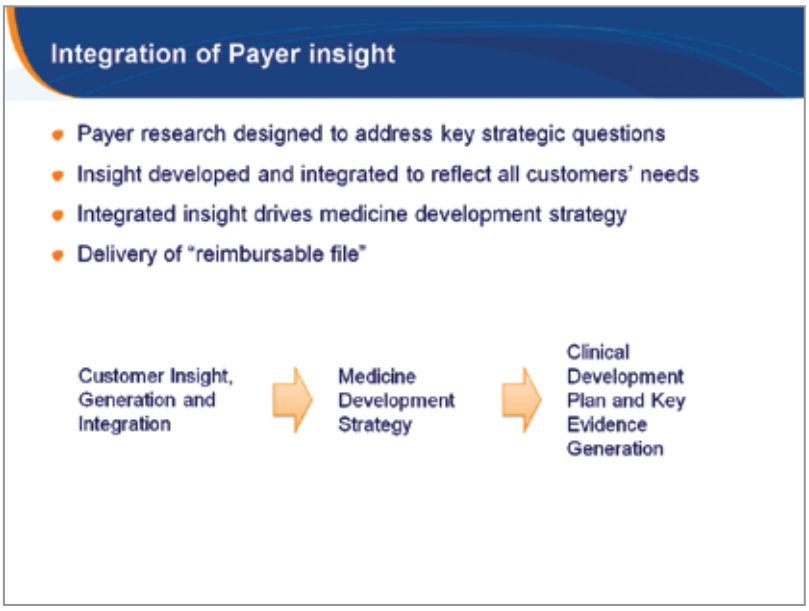
It's important to identify and understand the customers in medicine development, including patients, regulators, and clinicians, each with their own perspectives and needs. It has only been recently that industry has fully recognised payers as an important customer group, with that group comprising multiple stakeholders such as HTA agencies, reimbursement and pricing bodies and local health commissioners.

There is growing scepticism among payers, who have the view that many new medicines now reaching the market give little incremental gain in clinical effectiveness but are priced at a significant premium to the products they are intended to replace. Industry needs to consider alternative business models but given the cost of drug development and need to replace single blockbuster drugs with several targeted, patient-specific therapies, this is a significant challenge.

The challenge is to get scientists to think of evidence that will be required for a value analysis by multiple payer groups during development to ensure that the medicines we develop will be reimbursed. This evidence must be meaningful, relevant, and effective and take local reimbursement and treatment standards into account. There is an undeniable political aspect to payer requirements and increasingly, questions regarding a medicine's potential compliance profile are being raised. To bridge the value gap between the short-term surrogate data that has previously been supplied at registration and the meaningful benefits and justifiable prices required by payers, GlaxoSmithKline (GSK) has begun thinking of the goal of medicine development as the development of the "reimbursable file." This dossier provides the substantive data required for both registration and reimbursement decisions.

Payer requirements should be considered throughout a product lifecycle, and the





development of a broad ideal product profile in a therapeutic category is one point of potential payer involvement early in that lifecycle. At a minimum, however, industry must confirm the validity of its investment by receiving payer input at the end of phase II. At GSK, internal market access experts give frank and explicit advice to development teams while externally, formal and informal advice is sought from key experts. GSK is currently engaging in one such formal exercise for external payer advice with its participation in the Swedish pilot for joint regulatory and HTA advice on pazopanib. Payer insights are integrated to reflect all customers' needs and that integrated insight drives our medicine development strategy and results in the delivery of a reimbursable file.

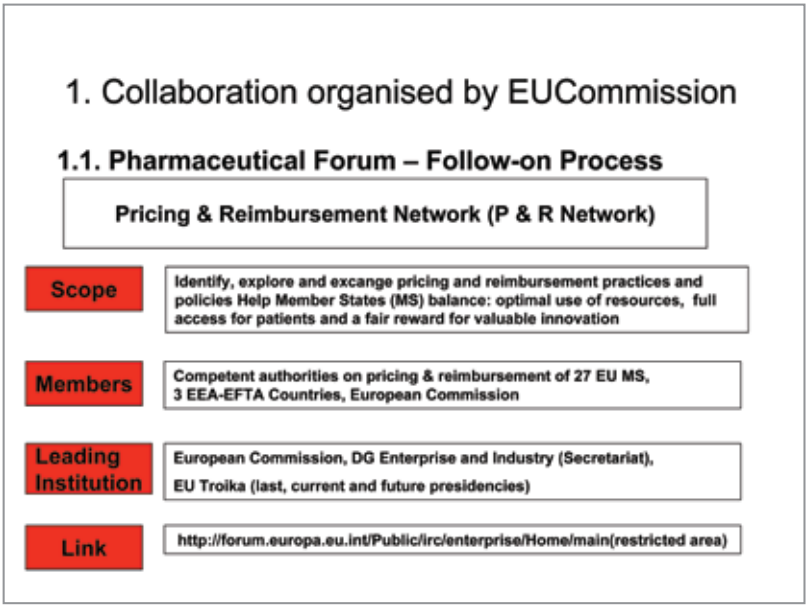
The key challenges in aligning HTA and regulatory reviews include endpoint selection, definition of the expected magnitude of clinical effect, selection of appropriate standard of care, determinations of relative efficacy and safety and relative effectiveness, definition of patient subgroups and the demonstration of a medicine's value to society. In addition to the new approaches that GSK has developed to ensure that their engagement with payers is more focussed on specific issues rather than on generic principles, there have also been external efforts such as engagement in the phase 3 advice process at NICE and the Swedish pilot for joint HTA/Regulatory advice. In addition there are other opportunities to consider such as 'The Innovation Pass' which is a model being piloted by NICE that permits selected new drugs to be reimbursed for three years prior to NICE approval.

HTA collaboration on scientific assessment for the purpose of reimbursement

Dr Ad Schuurman

Head, Reimbursement Department Dutch Health Care Insurance Board (CVZ); President, Medicine Evaluation Committee (MEDEV); Netherlands

The Pharmaceutical Forum is a working group set up by the European Commission to foster the development of HTA in the EU and its member states. In 2007, the Forum requested specific proposals to "support the aim of sharing data on relative effectiveness assessment at the European level and developing sustainable collaboration and networks between the competent authorities of the member states (MS) and other stakeholders."[1]



As a follow-on to this request, the Pricing & Reimbursement Network (P&R Network) identifies, explores, and exchanges pricing and reimbursement practices and policies, helping member states balance optimal use of resources, full access for patients and a fair reward for valuable innovation. Members consist of competent authorities on pricing and reimbursement representing 27 EU MS, European Economic Area (EEA) and European Free Trade Association-(EFTA) Countries, and the European Commission.

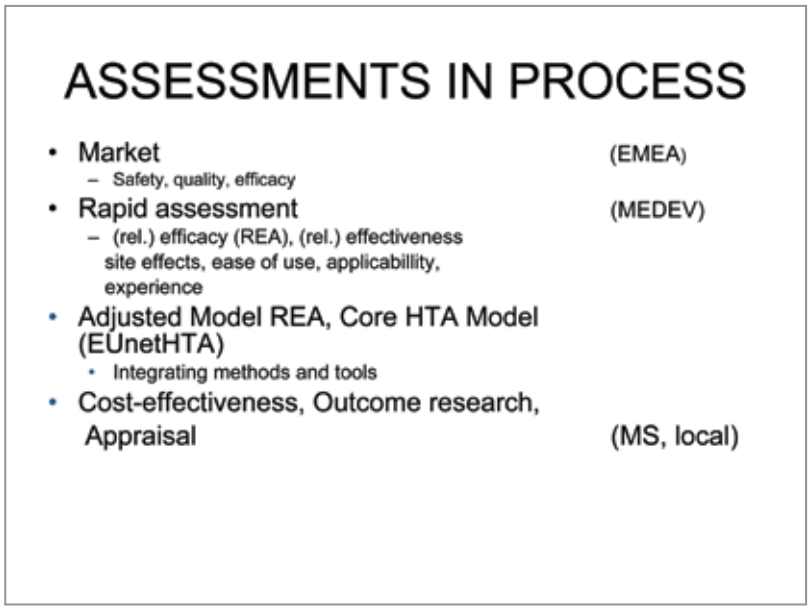
There is collaboration with other agencies including WHO Europe, Organisation for Economic Cooperation and Development, Association international de la Mutualité, the Vancouver Group, the Swedish pilot initiative and the EMEA working groups to make existing evidence available.

Patient rights in cross-border healthcare are managed by an alliance of networks such as European Union Network for Health Technology Assessment (EUnetHTA), Medicine Evaluation Committee (MEDEV), and the P&R Network. Each of these groups has a similar but often specific focussed mandate. Current assessments being undertaken by these collaborations include market assessments of product safety, quality and efficacy of new medicines by the EMEA, and the rapid assessment of the relative efficacy (REA), relative effectiveness, side effects, ease of use, applicability and experience for investigational new drugs by MEDEV. EUnetHTA meanwhile assesses core HTA models and adjusted REA, integrating methods and tools. Cost-effectiveness, outcomes research and specific medicines appraisals are carried out at the MS and local level.

MEDEV and EUnetHTA infrastructure for collaboration on EU HTA assessment

Currently 22 countries share HTA assessment information through MEDEV, using the evaluation criteria of relative efficacy, relative effectiveness, side effects, experience, applicability, ease of use for patient, and quality of life.

In EUnetHTA, 33 government-appointed organisations in 24 countries collaborate to work toward the strategic objectives of better coordination of HTA activities in its member states with less duplication, thereby increasing HTA output and input to decision-making in its MS and the EU. They also strive to strengthen the link between HTA and healthcare policy making and to support countries with limited experience with HTA. Between 2010 and 2012 a working group of 28 organisations in 20 countries will



examine the relative effectiveness of drugs. Their objectives include:

1. Final reporting of the exploratory phase, including review of available solutions (2010)
2. A proposal of relevant tools and methods (2010-2011)
3. Definition of framework for REA of pharmaceuticals (2011)
4. Pilot testing (end 2011)
5. Adjustment of the model on the basis of results of the pilots (2011-2012)

The final deliverable for the Working Group will be an adjusted model for REA, consistent with a core HTA model.

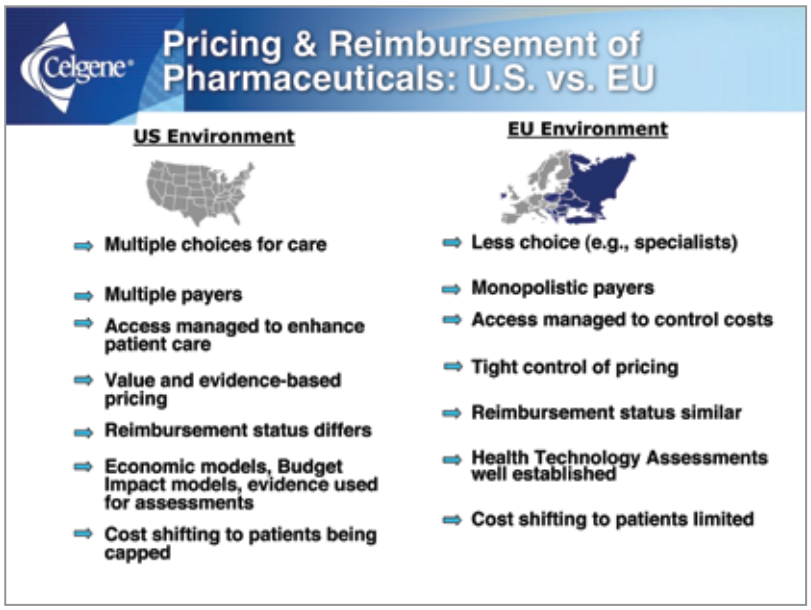
Reference

1. European Commission. Development of networking and collaboration. Available at http://ec.europa.eu/pharmaforum/docs/rea_networking_en.pdf. Accessed November 2009.

The USA paradigm: What are the options and how will this affect drug development?

Dr Zeba M. Khan

Vice President, Pricing and Market Access, Celgene Corporation, USA

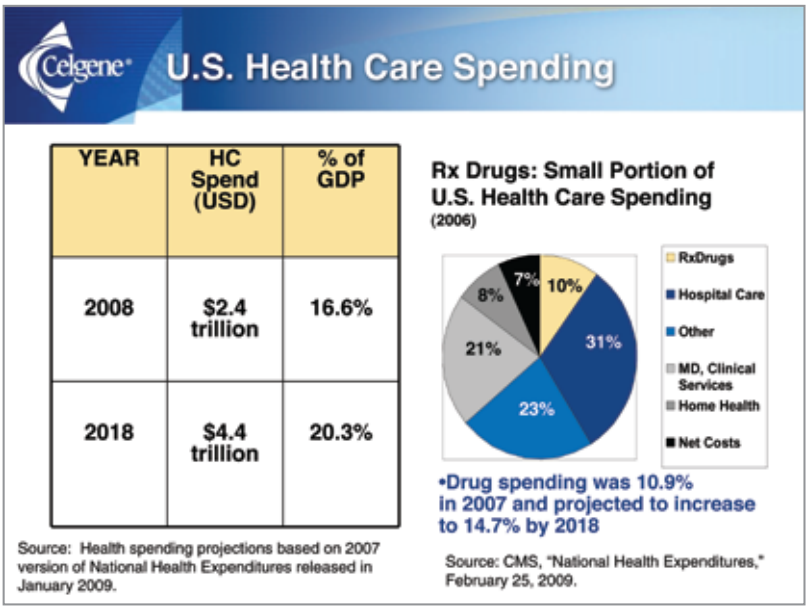


The US healthcare system provides Americans with multiple choices, offers broad access to very high-quality care, provides evidence-based / value-based therapies and integrated care services, promotes innovation, and utilises cutting edge technology. Funding for this system is achieved through public and private sources. Providers are paid via a combination of methods including fee-for-service, annual fees, salaries, and per admission, negotiated daily charges. A large percentage of the US population, however, is uninsured, reflecting the paradox of abundance and insufficiency within the system.

Healthcare spending reached $2.4 trillion in 2008, but only a small percentage (~10%-11%) of that represents prescription drug costs. The US Government is the largest payer of healthcare costs, including payments through Medicare, Medicaid, Veterans Affairs, Department of Defense (DoD), Indian Health Service (IHS), Federal prisons, and other programmes. Other payments come from commercial payers providing employee coverage, and private payments of cash from the uninsured. Approximately 35 to 46 million people are uninsured in the United States and 25 million are underinsured.

Efforts to control costs have been made and include wellness programmes, compliance /

persistence initiatives, and the use of preventive care strategies. Cost-control for pharmaceuticals has been initiated through efforts to encourage generic substitution, tiered co-payments, step therapy, prior authorisation of specific therapies, and the use of preferred drug lists and treatment guidelines. Furthermore, the government has also implemented cost-cutting procedures in its Managed Care, Medicare and Medicaid programmes.



There are external factors that are impacting healthcare costs globally, however. An aging population needs more and specific healthcare and their rising expenses are leading to budget dilemmas for government, payers, and society. Other external factors include increasing demand for an evidence-based value proposition for medicines and the emergence of price control and cost containment strategies. These factors add pressure to the industry's economic model as high research costs, increased safety expectations and requirements and stringent approval processes have contributed to the decline in approved new medicines.

In response to these steadily rising healthcare costs and challenges to funding, the Obama administration, Congress, and many other stakeholders have come together to address comprehensive health care reform. A combined bill by the Senate Finance and Senate Health, Education, Labor and Pensions Committees will be considered by the Senate. (Note: The US House of Representatives passed a healthcare reform bill, H.R. 3962, on 7 November 2009)

The elements of this bill include mandatory coverage for prescriptions, a decrease in prescription co-pays by 50% for low-and middle-income senior citizens, a cap on personal out of pocket expenses and a health reform fee on branded drugs sold to Government programmes. In addition, follow-on biologics will receive $8 billion, managed care organisations can negotiate directly for rebates above Medicaid price, and HHS Secretary will have authority to negotiate Medicare Part D prices. The Physician Payment Sunshine Act requires manufacturers and Group Purchasing Organisations to report on payments to physicians/physician-owned entities and if the aggregate annual amount paid to recipient exceeds $100, all payments are reportable.

In response to an established need for better information and information systems, more transparency, and more effective wellness incentives, the Institute of Medicine is pursuing a comprehensive assessment of Comparative Effectiveness Research (CER). The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care through the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care.

A changing market environment poses many challenges, and the pharmaceutical industry is adapting to a new business model that requires a demonstration of clear value to all stakeholders, from drug discovery all the way to patient care and its attending communications. Increasing interdependence of government, academia, industry, consumers, patients, and caregivers will accelerate cost-effective development of innovative, break-through therapies and build and establish a core competency of "evidence-based value" strategies throughout every product's life cycle. Industry will collaborate with payers to build dynamic value propositions with multiple levers and flexibility to influence payers.