



Regulation and Reimbursement

Two sides of the same coin?

16-17 January 2008
Cobham, Surrey, UK

Workshop Report

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Institute for Regulatory Science

CMR INTERNATIONAL INSTITUTE FOR REGULATORY SCIENCE

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CMR International, Institute for Regulatory Science,
Novellus Court, 61 South Street Epsom, Surrey KT18 7PX, UK

Tel: +44 (0) 1372 846100, Fax: +44 (0) 1372 846101

E-mail: institute@cmr.org

Website: www.cmr.org/institute

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16-17 January 2008

The Woodfield Park Hotel

Cobham, Surrey, UK

Workshop Organisation

Workshop organised by: Dr Neil McAuslane and Dr Kate Read, Institute for Regulatory Science

Report prepared by:

Margaret Cone, Director of Regulatory Science Publications, Institute for Regulatory Science

Dr Tracy Lisinski, Medical Writer, under contract from Thomson Pharmaceutical Consultancy and Writing Services

WORKSHOP ON REGULATION AND REIMBURSEMENT: Two sides of the same coin?

Section 1: Overview

Background to the Workshop

The topic for this Workshop, held in Surrey, UK, January 2008, was a departure from the subjects that the CMR International Institute for Regulatory Science has addressed in the past. Previous Workshops have focussed on regulatory requirements, strategies and best practices before, during and after the approval of new medicines but not on the all-important and question: *The medicine is approved but will anyone pay for it?*

Recommendations from earlier Workshops have, however, pointed to the need to address the R&D implications of the various types of post-authorisation evaluation upon which decisions are made on the reimbursement, pricing and availability of new medicines: The so-called 'fourth hurdle'. For the purpose of the Workshop (and this report) *Health Technology Assessment*: (HTA) is the term used for the assessments made by government and insurance reimbursement agencies, HMOs, hospital formulary committees and other bodies representing the 'payers' for health care and medicines.

In preparation for the Workshop, the Institute conducted a brief survey among its member companies to investigate current perceptions and future views on the ways in which reimbursement considerations are driving and shaping development decisions

Scope of the Workshop

The Workshop looked first at the changing environment for development and the extent to which reimbursement decisions are bringing about these changes. The Session was chaired by **Dr Elliott Sigal**, *Executive Vice President, Chief Scientific Officer and President, R & D, Bristol-Myers Squibb*, and the scene-setting keynote presentation was made by **Dr Garry Neil**, *Corporate Vice President, Corporate Office of Science and Technology, Johnson & Johnson*.

Dr Neil McAuslane, *Director, Institute for Regulatory Science*, reported on the outcome of the survey among companies and **Christopher Chinn**, *European Director of Health Outcomes, Eli Lilly* discussed the question 'Can we measure the value of new medicines before launch?'

Clare McGrath, *Senior Director, Evidence-Based Strategy, Pfizer* looked at the separation of the regulatory (licensing) assessment and HTA from the perspective of patient benefit and **Professor Hubert Leufkens**, *Utrecht Institute for Pharmaceutical Sciences, NL* looked, from a European perspective, at the extent to which

regulatory agencies are being drawn into the debate of 'efficacy versus cost'.

The second session, chaired by **Dr Garry Neil**, looked to the future and the way in which medicines might be assessed. The possibilities for greater harmonisation of HTA assessments was addressed from a company viewpoint by **Dr Jens Grueger**, *Global Head, Pricing & Health Economics, Novartis* and from an agency viewpoint by **Dr Andreas Laupacis**, *Director, Li Ka Shing Knowledge Institute St. Michael's Hospital, Toronto, Canada*.

Two speakers discussed 'conditionality'¹ as a way to translate research into health and economic benefits. **Professor Adrian Towse**, *Director, Office of Health Economics, UK*, looked at the way in which companies view 'conditional' licensing and reimbursement and would wish to see future progress. **Prof Hans-Georg Eichler**, *Senior medical officer, EMEA*, discussed examples of the conditional authorisation approach operated by EMEA and how this might be developed in the context of reimbursement.

In the two final presentations, **Professor John Hutton**, *Professor of Health Economics, York University of York*, discussed the way in which value-based pricing schemes might work. In practice, and **Dr Mick Kolassa**, *CEO and Managing Partner, Medical Marketing Economics, USA*, looked at the unique situation in the US arising from the existence of 'free pricing' and the mixture of private and government-funded healthcare.

The Workshops participants divided into Syndicates of industry, agency and HTA specialists to discuss *R&D, innovation and harmonisation* in the relationship between the 'safety, quality, efficacy' assessment of new medicines and the need to consider value and cost effectiveness. The Syndicates reported to the final Session which was chaired by **Professor Robert Peterson**, *University of British Columbia Faculty of Medicine, Canada*. A final presentation was given by **Professor Adrian Towse**, in which he gave his 'closing reflections' on the outcome of the Workshop. Professor Towse's contribution to the following summary is gratefully acknowledged.

¹ Note: 'Conditional' approval has a very specific regulatory meaning within the EU system but 'conditionality' in the context of this Workshop covered the continuum of 'progressive' licensing and reimbursement where decisions made at the time of initial approval can be re-visited and modified throughout the product lifecycle, for any product.

SYNOPSIS OF THE MAIN THEMES

The presentations and general discussion at the Workshop highlighted four main themes:

Organisation: Regulatory authorisation (Licensing) and reimbursement are operationally and conceptually distinct activities with different legal frameworks and operations. There is an obvious degree of overlap but the two activities are likely to remain separate for the foreseeable future. A structure is needed that recognises the potential for separate but related programmes of work.

Dialogue between regulatory agencies and industry during product development is well established but there is little or no history of pre-launch dialogue between HTA bodies and companies. Whilst it would be premature to look for tripartite pre-launch discussions on individual products, a mechanism or forum is needed to bring all stakeholders together to clarify some of the major issues and potential conflicts, in the interests of patient access to new therapies.

Conditionality: There is experience, in product authorisation, of the concept of 'conditional' licensing and there is a *continuum* within which licensing conditions can be revisited and changed. The type of 'conditional authorisation' that enables products to reach the market earlier will not, however, help patients if third party payers will not purchase or reimburse such products.

Inflexible pricing decisions, made prematurely, however, present an equal barrier to the innovator and the concept of 'conditionality' needs to be applied to reimbursement to allow pricing to be 'staged' after launch, with possibilities for funding to be withdrawn or for prices to rise as the true value of the product is recognised.

Harmonisation: There appears to be scope to bring about greater uniformity in the methodology and assessment criteria used by HTA bodies but it may be difficult, in the near future, to move towards a common approach to decisions and decision-making in view of the heterogeneous nature of health care and political systems.

SYNDICATE RECOMMENDATIONS

These themes and additional considerations were taken further by the Syndicate groups. The main conclusions and recommendations included the following:

Early consultation is the key to ensuring that the research and development of new medicines takes account of HTA considerations and procedures for dialogue between companies and HTA bodies need to be established.

It was recommended that this could be addressed in two ways:

■ **A pilot scheme** in which, for example, the Scientific Advice given by EMEA should be open to *observers* from HTA agencies.

■ **Panels of experts** convened from industry and HTA agencies which could work together (in a similar manner to ICH) and provide guidance on the principles and criteria needed to demonstrate the value to patients and health care systems of innovative medicines.

A common study protocol to meet the requirements of both the scientific regulatory and the health technology assessments was not felt to be a reality or the optimum development model in the majority of cases.

Biomarkers and surrogate endpoints are as inevitable and logical to the acceptance of new products for reimbursement as they are for authorisation by regulatory agents. Validation is equally important in both cases.

Conditional/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.

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 benefits of harmonisation and improved transparency among HTA bodies would be many, particularly in establishing a 'level playing field' for companies. More mutual understanding should lead to decreased tension between the pharma industry and HTA bodies and also between regulatory agencies and HTA bodies.

A forum should be established for taking forward the harmonisation of HTA methodology. The remit would include defining certain HTA best practices and recommending 'accepted' end points and comparators in selected disease areas for both licensing and reimbursement purposes.

Further involvement of the Institute

The CMR International Institute should keep the topic of 'Regulation and Reimbursement' on its Agenda and hold a further Workshop in this area. Consideration should be given to having separate meetings to address issues in North America and in Europe.

It was also recommended that the Institute should:

■ Repeat a similar study to that held among companies but include the views and experience of regulatory agencies and HTA bodies

■ Undertake a fact-finding study among HTA agencies to ascertain how reimbursement and access decisions are currently being made and look at the way in which different pieces of information are used and weighted.



WORKSHOP ON REGULATION AND REIMBURSEMENT: Two sides of the same coin?

Section 2: Outcome

Syndicate Discussions

Session 3 of the Workshop, during which the Syndicate discussions took place, was chaired by **Professor Robert Peterson**, *Professor of Paediatrics, University of British Columbia, Canada*.

The Workshop participants formed Syndicate groups to address three topics:

- **Research and development** – Integrating HTA considerations into R&D at an earlier stage
- **Innovation** – Incentives for innovative research
- **Harmonisation** – The Feasibility of a common approach to HTA methodology

The Chairpersons and Rapporteurs for the four groups were:

Syndicate 1	<i>Chair:</i> Prof Hans-Georg Eichler , <i>Senior Medical Officer, EMEA</i> <i>Rapporteur:</i> Robin Evers , <i>Assistant Vice President, Wyeth, UK</i>
Syndicate 2	<i>Chair:</i> Dr Leonie Hunt , <i>Director, Drug Safety and Evaluation Branch, Therapeutic Goods Administration, Australia</i> <i>Rapporteur:</i> Dr Linda Harpole , <i>VP, Global Health Outcomes GlaxoSmithKline, UK</i>
Syndicate 3	<i>Chair:</i> Prof John Hutton , <i>Professor of Health Economics, York Health Economics Consortium Ltd, University of York</i> <i>Rapporteur:</i> Anita Burrell , <i>Head, Health Economics & Reimbursement, Sanofi-Aventis, France</i>
Syndicate 4	<i>Chair:</i> Dr Andreas Laupacis , <i>Director, Li Ka Shing Knowledge Institute St. Michael's Hospital, Toronto, Canada</i> <i>Rapporteur:</i> Marlene Gylmark , <i>F Hoffmann-La Roche Ltd, Switzerland</i>

1. BACKGROUND

The CMR International Institute for Regulatory Science provides a forum for the discussion, among pharmaceutical companies and government regulatory authorities, of policies and issues that have an impact on the science of new drug development. Previous Workshops have discussed new technologies, such as pharmacogenomics, and the possibilities for identifying limited, targeted patient populations for whom new therapies should have maximum effect and/or minimum side effects. Other topics have included a 'new paradigm' for clinical research in which certain products are allowed on the market at an early stage with commitments to carry out further confirmatory studies in a 'real world' population. Both these scenarios have raised question 'but who will pay?' What is the incentive to produce 'personalised' medicines if they are not reimbursed at a level that gives a return on investment? What is the benefit of early release if payers will not reimburse medicines before the full clinical package is complete?

It was therefore agreed that the Institute should extend its scope of activities to address the so-called 'Fourth Hurdle' of having products accepted by those who pay for new medicines and their decision-making bodies. These, for the purpose of this report, are referred to as 'Health Technology Assessment' (HTA) bodies or agencies where HTA refers to the assessments made by government and insurance reimbursement agencies, HMOs, hospital formulary committees and other bodies representing the 'payers' of health care and medicines.

Institute survey

In preparation for this Workshop, the CMR International Institute for Regulatory Science carried out a brief survey among member companies with the objective of ascertaining companies' current perception of the way in which research and development of new medicines is being impacted by consideration of reimbursement decisions and HTA decision-making processes. Companies were also asked for their views on an 'ideal' future landscape for the reimbursement environment in relation to incentives for innovation.

Syndicate briefing notes

The outcome of the survey which was reported to the opening Session of the Workshop by Dr Neil McAuslane, Director of the Institute for Regulatory Science, provided material for the notes and 'discussion prompts' that were provided to the Syndicates to help focus their discussions. These included a series of 'propositions' that participants were invited to discuss, some of which are included in the following notes.

Consistency and predictability

One of the concerns to emerge from the Institute survey was encapsulated in the following statement that each of the Syndicates was asked to address:

Constant changes in the health care environment and in pricing and reimbursement regulations make long-term planning impossible. Lack of predictability in the post-approval HTA discussions result in increased costs and delays to marketing.

In response, Syndicate members felt that:

- Long term planning is not impossible but the uncertainty surrounding reimbursement makes it more difficult for companies to invest in high risk areas;
- Convergence of HTA systems (e.g., in the evidence that should be submitted) would be helpful in reducing the uncertainty and variability of outcomes;
- Lack of consistency in pricing between countries is not necessarily a major barrier to investment (given that companies can model different prices and import flows) but it is a complication;
- Increased transparency in the criteria for decision making could lead to more consistency in both regulatory and reimbursement situations and help companies in evaluating their portfolios

2. OUTCOME OF THE SYNDICATE DISCUSSIONS

2.1. Integrating HTA considerations into R&D at an earlier stage

Syndicate question: *How could companies, regulatory authorities and HTA groups interact during the development programme for new medicines such that the eventual outcomes of registration and reimbursement are better coordinated, more rapid and more predictable?*

Summary of Recommendations

Early consultation is the key to ensuring that the research and development of new medicines takes account of HTA considerations. Procedures for dialogue between companies and HTA bodies need to be established.

- **It was recommended** that there should be a pilot scheme in which, for example, the Scientific Advice given by EMEA should be open to *observers* from HTA agencies.
- **It was further recommended** that there should be panels of experts convened from industry and HTA agencies which could work together (in a similar manner to ICH) on the principles, criteria and guidance needed to demonstrate the value to patients and health care systems of innovative medicines.

A common study protocol to meet the requirements of both the scientific regulatory and the health technology assessments is not currently a reality or the optimum development model in the majority of cases.

Biomarkers and surrogate endpoints are as inevitable and logical to the acceptance of new products for reimbursement as they are to their authorisation by regulatory agents. Validation is equally important in both cases.

Points from the Discussion

Early dialogue

Proposition: *Dialogue with agencies/groups responsible for HTAs is critical to the success of a new product reaching the market.*

Discussion:

The proposition was agreed. The purpose of discussion with HTA bodies during the development of a new medicine is to try to establish a common viewpoint with respect to the disease, its treatment and the value of the new medicine. It was noted, however, that the procedures for obtaining scientific advice from regulatory agencies should be separated from new procedures for early dialogue with HTA bodies.

- Discussions must recognise that different HTA bodies have different mandates and are responsible for different levels of funding. Some agencies only assess medicines for reimbursement or purchase whereas others have a remit that covers devices and other treatments and may extend to overall healthcare considerations. Views may differ depending on the remit.
- Compared with regulatory agencies, the HTA agencies are relatively new and they have much less experience of interacting with companies at the pre-market stage. The Institute Survey indicated that less than 50% of companies have experience of early dialogue with HTA agencies.
- Early dialogue would help companies to understand the patient benefits that the agency would be seeking, the tools used for their assessments and better ways to communicate about the benefits. Such meetings would also provide an opportunity for the HTA agency to learn about the company's approach and research programme.

The recommendation for a pilot programme within the EMEA Scientific Advice procedure recognises that it would be premature to consider tripartite meetings (company, regulatory agency and HTA body) during product development but that there could be advantages in having HTA representatives as *observers* as a learning experience but also to contribute to discussions on, for example, the selection of a comparator for determining comparative efficacy.

Common studies for approval and access

Proposition: *It should be feasible to design a common study protocol that will meet the requirements of both the scientific regulatory assessment and the health technology assessment.*

Discussion:

On balance it was agreed that studies designed to meet the requirements of both regulatory agencies and HTA bodies would not provide added value for many development programmes.

- It was acknowledged that there could be advantages in terms of reduced costs and time and a smaller number of patients, particularly in products for chronic diseases where long term studies are required;
- Other potential benefits of common studies include:
 - Early transparency and understanding of the requirement of all parties;
 - The time saving in generating data in parallel rather than in sequence;

- The potential barriers include:
 - Lack of internal experience and communication within the company as well as the need to educate the HTA bodies on the nature of such trials;
 - The need for investment to ensure that HTA issues are considered early enough in the development process;
 - The danger that pivotal studies could become cumbersome if overburdened by additional secondary end points and the totality of data to be collected from patients;
 - Loss of the benefits of a controlled population in the clinical trials and the need to include the multiple subgroups that would be required for an access study.

Biomarkers and surrogate endpoints

Proposition: *Better evaluation tools such as biomarkers and economic models will, in the future, enable assessments at the time of launch to be more predictive of the long term value of new medicines.*

Discussion:

The proposition was agreed.

- Surrogate end points and biomarkers that are accepted as a validated, regulatory standard should also be acceptable to the HTAs;
- They can act as ‘enablers’ which identify the population (and sub-populations) where the cost/benefit of a medicine can be optimised;
- Prospective Large Scale Randomized Simplified trials carried out after marketing can help to evaluate critical outcomes related to value;
- The potential use of large scale databases of electronic information was recognised as a means of validating surrogates but it was also acknowledged that there are currently limitations in the robustness of the technology that limit their usefulness.

2.2 Incentives for innovative research

Syndicate question: *What are the key factors in an ‘ideal landscape’ for regulatory review and HTA that encourage the development of novel and improved medicines to meet unmet medical need?*

Summary of Recommendations

Definitions of innovation and value need to be addressed in a suitable forum that brings all the stakeholders to the table – payers, regulators, industry healthcare providers and patients.

Conditional/progressive reimbursement should be introduced as a means of ‘risk-sharing’ between those who develop and those who purchase innovative medicines. Conditionality must be 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.

Research priorities: There should be incentives for the development of medicines for specific disease areas including different standards for, and early reimbursement of, such medicines.

Extensions to exclusivity: Major incentives to innovative research could be built around allowing extensions to data protection and intellectual property for products that are allowed early, conditional market access with restricted patient populations.

‘Me too’ products can be a source of major step-wise product improvement and development. More balance is required in the way in which they are treated for reimbursement. They should not be penalised on price for not being the first to market.

Ideal landscape for regulation and reimbursement: It was recommended that the CMR International Institute should repeat its survey of perceptions of the current and future environment but include not only companies but also regulatory authorities and HTA bodies.

Points from the Discussion

Definitions of innovation and value

The term 'innovation' tends to be over-used in the context of new drug development but there are elements that can be identified that give new products added value.

It is these characteristics that need to be agreed by a suitable multi-disciplinary forum as a background to discussions on HTA. Attributes to be considered include:

- The novelty of the molecule
- The mechanism of action
- Whether it is a new therapeutic concept
- The delivery system
- Whether there is superior efficacy and/or improved safety
- The potential global and socioeconomic impact.

Conditional/progressive reimbursement

Proposition: *Conditional authorisation schemes have been developed and there should be a parallel concept of conditional reimbursement agreements with prices revised upwards or downwards depending on value to the healthcare system in a 'real world' setting.*

Discussion:

There was strong support for this proposition as a means of sharing the risks of new product development between those who invest in new medicines research and those who provide health care.

- Products that are authorised for early marketing should be reimbursed 'conditionally', with a price based on registration data, and then validate when additional post-launch data becomes available. The post-launch costs would not then be another obligation on the sponsor;
- The possibility that prices might increase as well as decrease would be ideal incentive for research as this would represent true risk sharing;
- Conditional reimbursement would require the initial cost effectiveness to be measured on the basis of surrogate measures (see 2.1 above). The responsibility for validation of surrogate measures should be shared between government bodies and sponsors.

Research incentives

Priority diseases

It was agreed that there should be incentives for addressing particular disease areas. Prioritisation of disease areas could be established in the same way as for orphan medicines and different standards could then be put in place for the assessment of reimbursement.

- Rare diseases may need earlier consideration of conditional reimbursement since it takes longer to collect evidence in the post-launch period;
- Price should be based on the marginal cost of developing more personalised therapies but this requires sharing of the fixed costs of building an evidence base for the use of these therapies

Data exclusivity

A major incentive for innovative research and incremental development would be the possibility to extend the period of data protection (exclusivity) for products that are authorised and reimbursed on a limited and conditional basis. This would be similar to the extensions allowed for major line extensions, new indications etc, under the current systems.

Price, value and 'Me Too' products

Proposition: *The current emphasis on the price of medicines rather than their value in the healthcare environment is a disincentive to innovative research.*

Discussion:

This was agreed but also discussed in the context of the 'incremental' advances that are made in areas where generics exist. Small improvements to products are often important and a small percentage increase in the price, if any, is unlikely to provide a return on investment or an incentive to make such changes.

Similarly, the development of "me-too" products is often discouraged by significant reductions in price compared with the first-in-class. This is a disincentive to 'fast followers' and to the development of potentially improved alternatives

Policy and innovation

Proposition: *Initiatives such as the US Critical Path and the EMEA Road Map should also address the impact of reimbursement schemes and HTA on the incentives for innovative research.*

Discussion

This was not agreed. The impact of reimbursement and HTA considerations on new product development should be recognised within these initiatives but this is outside their direct remit.

Within Europe, disincentives to innovation such as price, reimbursement and limited access should be addressed at a higher level, such as the European Commission. Conditionality will require more interaction between the regulatory and reimbursement agencies that also needs to be managed at a policy level.

The ideal landscape

The CMR International Institute study, reported to the Workshop by Dr Neil McAuslane, gave an insight into the future environment for regulation and reimbursement, from a company perspective. This study should be repeated to include the views of regulatory authorities and HTA bodies.

It was recommended that the Institute organise further Workshops on the Regulation and Reimbursement, within its work programme, and possibly organise different meeting to address the topics from a North American and a European perspective.

A preliminary listing of factors to be considered in identifying and 'ideal' environment for the development, review and reimbursement of new medicines is set out in the table below.

Key factors for an 'ideal' landscape	
Regulatory Review	Health Technology Assessment
Continuation of critical path initiatives The ability to continue frequent discussions for scientific advice Fast-track systems for urgently needed products Consistency and predictability of procedures Transparency and openness Procedures for priority review Rating for the degree of 'innovation' with a possible differential fee-structure Continuation of special procedures for conditional approval and for orphan medicines A better framework for benefit-risk assessment Innovative ratings Better agreement on endpoints - surrogates, bio-markers and on the use of patient-centric results (Patient Reported Outcomes- PROs) Greater intra/inter agency harmonisation Communications with HTAs	Early discussion and agreement linking regulatory and HTA viewpoints, especially in relation to the target product profile (TPP) Timeframe for the HTA review: - sequential to the regulatory assessment, in parallel or overlapping Transparency of the HTA process Better access to the actual Payers Harmonisation of HTA methodologies Targeting profiles and agreement on endpoints Conditional reimbursement with prices going up and down An explicit understanding of the weightings of various components of a reimbursement 'package' Timeframes- of benefit, of review Post-funding reviews - continuous evaluation of 'economics and value' A greater role for Patient Advocacy

2.3. Harmonisation: The feasibility of developing a common approach to HTAs

Syndicate question: *How can progress be made towards defining a more harmonised basis for HTAs in order to improve planning and decision-making in the development process and to establish an equitable basis for the availability of medicines to patients through reimbursement systems?*

Summary of Recommendations

Harmonisation: Whilst harmonisation of HTA methodology is feasible to a certain extent, it is premature to consider harmonisation of the decision process, at this stage and the mutual acceptance of reimbursement decisions is not currently feasible.

The starting point, however, is to aim at the lower level of agreeing on a common language and on the level of information that is required.

The benefits of harmonisation and improved transparency among HTA bodies would be many, particularly in establishing a 'level playing field' for companies. More mutual understanding should also lead to decreased tension between the pharma industry and HTA bodies and also between regulatory agencies and HTA bodies.

Harmonisation Forum: It was recommended that a forum should be established for taking forward the harmonisation of HTA methodology. The remit would include defining certain HTA best practices recommending 'accepted' end points and comparators in selected disease areas for both licensing and reimbursement purposes. It would also have a role in educating stakeholders.

Study of HTA methodology: It was also recommended that a further study should be undertaken by the CMR International Institute among HTA bodies to collect information on how reimbursement and access decisions are being made and the way in which different pieces of information are used and weighted.

Points from the Discussion

As background to the discussions on harmonisation, two contrasting standpoints were set out (using the EU as an example):

- Firstly, that every drug that is approved under the EU system should be available to all patients, and funding should be made available to make this possible.
 - Following this philosophy, the question of harmonisation of reimbursement systems would not arise
- Alternatively, as financial resources are limited, one has to prioritise: Medicines with a less favourable benefit-cost ratio should not be reimbursed as this would restrict the supply of more cost effective treatments for large patient groups.
 - The need for selective reimbursement and 'rationing' is obviously the realistic scenario in the absence of unlimited healthcare funding.

Scope of harmonisation

Premise: *International harmonisation of the differing processes and methods for health technology assessments would be a major step forward for the ICH Regions.*

Discussion

Whilst this is a desirable goal, in theory, the practicalities are that HTA methods can be harmonised to some extent but not decision processes or the reimbursement decisions themselves.

- Rather than discussing total harmonisation, degrees of harmonisation should be considered starting with a lower level e.g.:
 - Collecting similar types of information;
 - Agreeing a common language.

Benefits of harmonisation

Premise: *Communication and transparency are key to a better understanding of HTA systems and to establishing an even-handed approach to establishing the value of new medicines within different health care systems.*

Discussion

The many benefits of greater harmonisation between HTA agencies include:

- The creation of 'a level playing field' for all pharmaceutical companies and creating an environment where there is a better understanding of the criteria that are applied and provide relevant evidence;
- A better understanding of the process might also lead to decreased tension between companies and HTA agencies;
- A clarification of the different methods used by regulatory agencies and HTA bodies could also help to 'defuse' any tension that might exist between the two types of agency;
- Increased transparency by the HTA agencies would provide insight into the way in which they make decisions and the criteria used:
 - Countries with less developed systems for medicines control could also benefit from a greater understanding of HTA in other countries.

Harmonisation Forum

A forum should be established to review existing techniques and define best practices for HTA methodology. As well as the immediate stakeholders (industry, regulatory agencies and HTA bodies) this forum should include academics and representatives of ISPOR and ISPE¹. The role of the forum would be to:

- Provide insight and give advice on the main issues;
- Educate stakeholders
- Help define and make recommendations on 'accepted' end points and comparators in selected disease areas for both licensing and reimbursement purposes

The CMR International Institute could have a role in establishing, or encouraging the establishment of such a forum. It was recognised that the group could only be advisory and not have the authority to bring about change but participation should be representative of the major players, in order to increase its influence.

Any guidelines from the forum would need to encourage flexibility in a rapidly changing research environment where it is important not to stifle innovation.

Study of HTA methodology

The CMR International Institute for Regulatory Science should undertake a study among HTA bodies aimed at investigating:

- How decisions on reimbursement and consequent access to patients are being made
- How different pieces of evidence are being used and the way in which different criteria are weighed against one another.

One objective would be to give companies a greater insight into the type of information that should be generated and submitted to support assessments for reimbursement.

¹ International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society of Pharmacoepidemiology (ISPE)

Summary

Following the reports from the Syndicate groups, **Professor Adrian Towse**, *Director of the Office of Health Economics, UK*, gave his 'closing reflections' on the outcome of the Workshop. These are reported in the Overview (Section 1 of this report) and his summary of the outcome is given below.

There are many factors in the complex interaction between companies, HTA bodies and regulatory agencies that need to be taken forward in suitable fora and/or through surveys and studies. Topics include:

- The need for HTA, regulator, company dialogue;
- The potential for common studies or the sequencing of studies to meet HTA and regulatory requirements;
- The validation of biomarkers and surrogate measures;
- Definitions of value;
- Post launch data collection issues;
- The nature of 'conditionality' in licensing and reimbursement
- Harmonisation of HTA processes based on a better understanding of what happens.

There was consensus the CMR International Institute for Regulatory Science should keep the topic of 'Regulation and Reimbursement' on its work programme and convene a further Workshop in 2009.

Last Word

The plenary discussions referred to the 'inevitability' that the supply of healthcare and medicines will be rationed but **Dr Garry Neil**, *Corporate Vice President, Johnson & Johnson*, suggested that this was too pessimistic a view. The premise that the purpose of health technology assessment should be 'rationing' needs to be revisited in the light of history which has shown many examples of the way in which technology increases to a point where it lowers costs. Amazing progress has been made over the last fifty years from the end of the 'iron lung' and cures for peptic ulcers to recent developments in percutaneous delivery and novel methods of diagnosis.

While it is important to demonstrate value, the challenge is to introduce more cost-effective medicines and to find better and safer ways to do so.

'Health, in a population, is a source of productivity and wealth and an industry that drives real health innovation and enables different ways of treating disease will also be recognised as source of such wealth'.

WORKSHOP PROGRAM

SESSION 1: REIMBURSEMENT DECISIONS – A CHANGING ENVIRONMENT FOR DEVELOPMENT?	
Chairman's introduction	Dr Elliott Sigal , <i>Executive Vice President, Chief Scientific Officer & President, Research & Development, Bristol-Myers Squibb, USA</i>
Future vision for a new reimbursement model	Dr Garry Neil , <i>Corporate Vice President, Corporate Office of Science and Technology, Johnson & Johnson, USA</i>
How are companies currently building HTA requirements into the development process and what are the issues?	Dr Neil McAuslane , <i>Director, Institute for Regulatory Science, CMR International</i>
Can we measure the value of new medicines before launch?	Christopher Chinn , <i>Director European Outcomes Research, Eli Lilly</i>
Patient Benefit: What separates Regulatory (licensing) from HTA Assessments	Clare McGrath , <i>Senior Director, Evidence-Based Strategy, Pfizer</i>
Efficacy versus Cost: Are Regulatory Agencies being drawn into the debate?	Professor Hubert Leufkens , <i>Utrecht Institute for Pharmaceutical Sciences, The Netherlands</i>
SESSION 2: HOW SHOULD NEW MEDICINES BE ASSESSED IN THE FUTURE?	
Chairman's introduction	Dr Garry Neil , <i>Corporate Vice President, Corporate Office of Science and Technology, Johnson & Johnson, USA</i>
HTA and patient access to new medicines: Would Harmonisation of assessments be of value?	
Company viewpoint	Dr Jens Grueger , <i>Global Head, Pricing & Health Economics, Novartis</i>
Agency viewpoint	Dr Andreas Laupacis , <i>Director, Li Ka Shing Knowledge Institute St. Michael's Hospital, Toronto, Canada</i>
Future of regulation and reimbursement: Is conditionality the best route to translate research into health and economic benefits?	
Companies' viewpoint	Prof Adrian Towse , <i>Director, Office of Health Economics, UK</i>
Regulatory viewpoint	Prof Hans-Georg Eichler , <i>Senior Medical Officer, EMEA</i>
Value-based pricing schemes: How will it work in Practice?	Prof John Hutton , <i>Professor of Health Economics, York Health Economics Consortium Ltd, University of York</i>
The US market – scenarios for the future and the role of reimbursement	Dr Mick Kolassa , <i>CEO and Managing Partner, Medical Marketing Economics, USA</i>
SESSION 3: SYNDICATE DISCUSSIONS	
Chairman	Prof Robert Peterson , <i>Clinical Professor of Paediatrics, University of British Columbia Faculty of Medicine, Canada</i>
Feedback from the Syndicates	<i>See Section 2</i>
An economist viewpoint and reflections	Prof Adrian Towse , <i>Director, Office of Health Economics, UK</i>

**WORKSHOP ON REGULATION AND REIMBURSEMENT:
Two sides of the same coin?**

Section 3: Summary of Presentations

Note: These brief summaries are intended to be used in an electronic, web-based version of the report that will give access to all the slides presented at the Workshop

**SESSION 1: REIMBURSEMENT DECISIONS –
A CHANGING ENVIRONMENT FOR DEVELOPMENT?**

Chairman's Introduction

Dr. Elliott Sigal

*Executive Vice President, Chief Scientific Officer & President, Research & Development,
Bristol-Myers Squibb, USA*

Opening the Workshop, Dr Sigal made two observations about the changing environment for drug development:

- The value of medicines — like that of beauty, value is in the eye of beholder. The value appears differently if you are an individual wanting that medicine, or if you are the individual in a position that affects the lives of many. Value changes according to disease state, climates of safety or cost, geography, payer systems, assessment tools, trial settings, and the life cycle of the product. In all these settings, assessments of value can change.
- Approval is only one step in the development of a drug. Not all aspects of value can be known at drug approval. Many questions exist: What needs to be known before and after approval? Does this knowledge affect development? Should cost change over time?

The presentations in the first Session took these themes further. Several speakers spoke of the tension of innovation versus reimbursement but acknowledged the need for both. The results of the CMR International institute survey were presented and other topics included viewpoints on pre-market assessment, important methodology to assess clinical benefit, and the convergence of regulatory assessments and health economics.

Future vision for a new reimbursement model

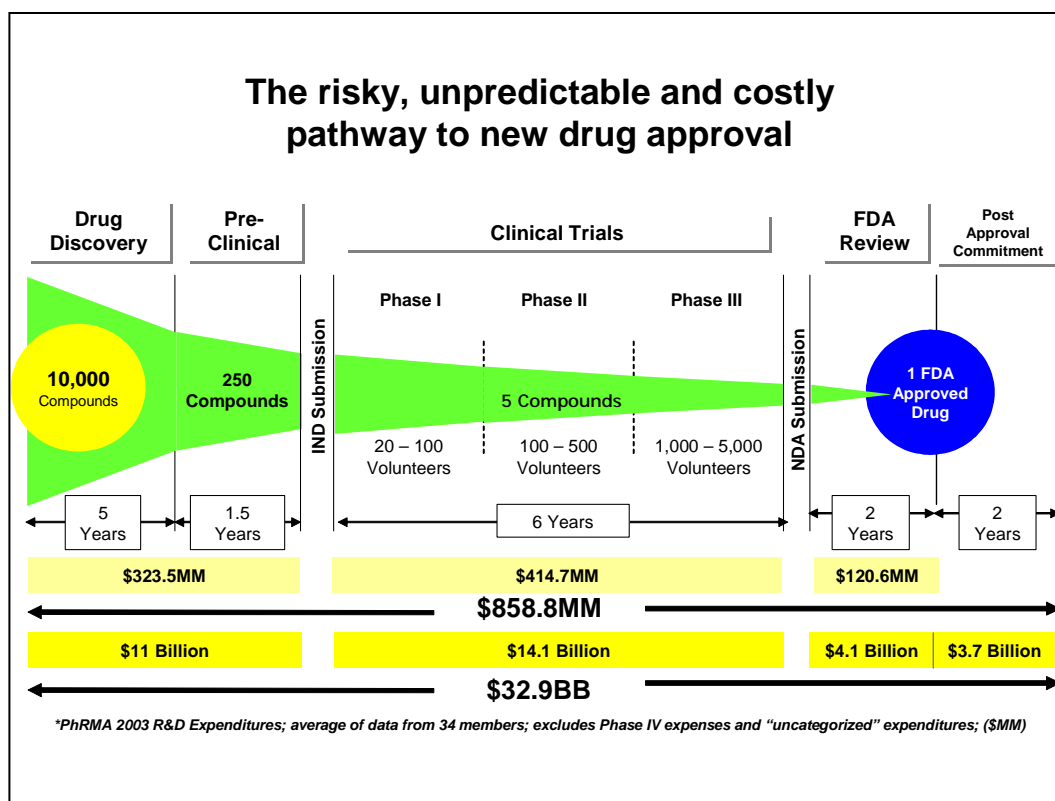
Dr. Garry Neil

*Corporate Vice President, Corporate Office of Science and Technology,
Johnson & Johnson, USA*

The industry is facing a crisis in healthcare. The process of drug development has become more risky and costly. New molecular entity (NME) approvals have decreased, while generic drug approvals have increased. The FDA is more vigilant about safety; black box warnings have increased since 2003. Healthcare costs are rising in the US and globally. The aging population will consume more healthcare costs.

Cost control does not necessarily improve outcomes. Currently, providers are not paid for outcomes, but for procedures. Consumers do not experience the true cost of healthcare. In the pay-for-performance model, standard definitions of quality are lacking, consequences of paying for quality on cost and innovation are not known, and questions remain about measurement, patient compliance, and non-responders in this system.

For health technology assessments, there is a need for a fair, predictable, and consistent process; consolation during development; and evaluation of total value generated, rather than emphasis solely on cost control.



Discussion:

- The value of medicines can only be determined after a couple years on the market, but companies are trying to determine this earlier in the drug development process.
- Definition of response and acceptable surrogate endpoints require dialogue between companies and agencies.
- Value and cost effectiveness are critical items. Volume pricing and emerging markets may affect future pricing. In the future, companies may look to other markets that are volume markets; however, much uncertainty surrounds this topic. There is growth and demand for the drugs in emerging markets that are usually marketed in developed countries (e.g., drugs to treat diabetes).

CMR International Institute Survey

How are companies currently building HTA requirements into the development process and what are the issues?

Dr. Neil McAuslane

Director, Institute for Regulatory Science, CMR International

Pharmaceutical companies are investing 70% of their budgets on R&D while new molecular entities (NME) output has decreased by 30% when compared with 10 years ago. The current way of developing drugs is unsustainable.

The objectives of the CMR survey were to investigate companies' current perception and future views of how the ultimate reimbursement decisions are driving development decisions, and to identify the regulatory and reimbursement landscape with regard to innovation and how companies would like to see/predict changes in the future landscape. The survey explored the current HTA and reimbursement environment, reimbursement, development decisions and incentives, and the future landscape of regulation, and reimbursement. Of the 32 companies that were sent the survey, 19 responded.

The major findings of this survey are:

- Changes in the HTA environment have increased the cost and time taken to bring a new medicine to its first market over the last 3 years.
- Reimbursement factors influence “go/no go” decisions mainly at entry into late-stage development and submission. A few companies have terminated development because of reimbursement as the main factor.
- Price controls within a country have a direct effect on the timing of marketing in that country.
- During drug development, consideration of HTA is occurring at the early stages of development, but not all companies are meeting with HTA.
- Companies are seeking earlier involvement of HTA in development, but are not looking for joint reviews.
- The needs and requirements of HTA groups around the world are not harmonised, and companies have or are developing their own models for assessing cost and clinical effectiveness.
- HTA requirements are transparent in Australia and Canada, but less so in other countries and variable across the EU.
- The USA is perceived as providing good incentives for companies to develop innovative medicines from both a regulatory and reimbursement perspective.
- Outside the USA, the regulatory systems seem better at providing incentive for development than the reimbursements systems in place.

Possible solutions	Possible solutions - 2
<ul style="list-style-type: none"> • Clear agreement between industry and authorities on terms of reimbursement, review and criteria for success/failure <ul style="list-style-type: none"> – support from reimbursement authorities, agreement on study design, comparators, sub groups and endpoints. • Industry needs to foster a health public policy debate of the appropriate resource allocation by markets and the price mechanism in health care • Flexible budget allocation and consistent re-assessment of older health technologies <ul style="list-style-type: none"> – Higher willingness to pay for innovative approaches in difficult to treat disease areas • HTA methods should / can be harmonised across countries so that methodological standards and type of data required are consistent 	<ul style="list-style-type: none"> • Partnership and agreement with payers early in drug development about what constitutes innovation <ul style="list-style-type: none"> – Education/engagement with key stakeholders around developing new approaches – Create 'think tanks' of cross party representatives to tackle the issues and formulate solution; – Use existing and ongoing research on topics like “HTA principles” to inform better policy reform that is actually evidence based and focused on the high level objectives, not driven by trying to maintain the status quo • Move R&D organizations away from thinking only about registration needs and commercial organizations away from overly optimistic appreciation of opportunity and value • Sponsor's being realistic about pricing and access for true innovation

Discussion:

- A question is whether companies should have conditional approval linked to pricing regimes.
- Getting product out early in the marketplace would be better (e.g., in Phase 2 instead of Phase 3).
- A small proportion of company participants expect that in 2015 regulatory agencies will look at cost effectiveness data.
- The survey did not include HTAs themselves, but sending future surveys to HTAs would be of value.
- In future surveys, a different population of survey takers should be included (e.g., commercial people may have different outlook from outcomes people).

Can we measure the value of new medicines before launch?

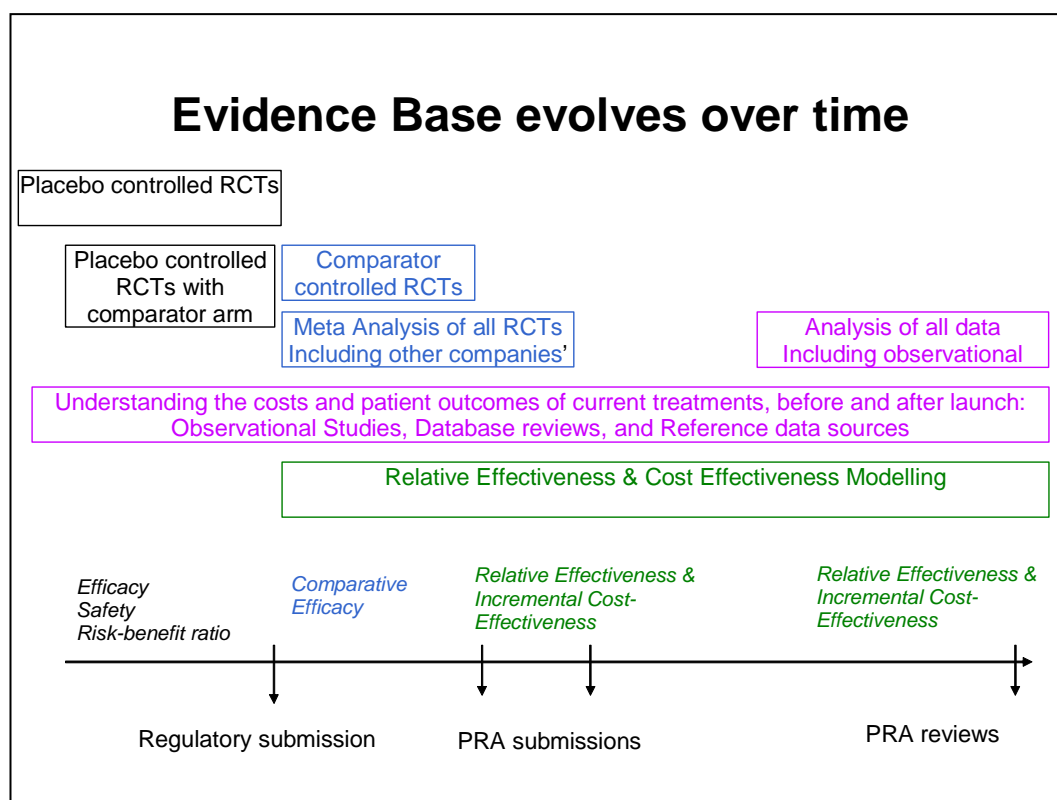
Christopher Chinn

Director, European Outcomes Research, Eli Lilly

Value is assessed differently by regulatory and reimbursement agencies. The former are addressing the question “should this medicine be sold?” while the latter are assessing “should we buy this medicine at this price”. For reimbursement, valuable medicines may be defined as those which, when used, are sufficiently “better” than existing alternatives to justify their price. In this context, “better” could refer to patient survival, quality of life, provider efficiency, safety, risk reduction, likelihood of delivering promised efficacy, or some other measurement.

The decision to “invest” in a new drug is made considering expected future value in the context of a particular healthcare system’s structure, priorities and affordability, and balances risk, reward, and uncertainty. Regulatory assessment should be much less dependent on context. Future value cannot be measured before launch, but can be estimated using all available pre-launch data.

Pricing, reimbursement, access, and HTA bodies require some or all of the following types of data to assess value: epidemiology, public health/socio-economic burden, trial data, relative effectiveness, quality of life and patient-reported outcomes, economic modelling showing effect on patient direct/indirect costs and cost-effectiveness, overall budget impact, safety data, and (if a post-launch review) observational data.



Comparators recommended by the EMEA do not always meet the needs of reimbursement agency requirements in each country. Comparators for assessments include the Standard of Care (SOC) defined as the most recently launched drug and/or the most prescribed drug. However, SOC is defined differently in each country, and it is a challenge to predict SOC at launch when selecting molecules.

In early development, products can be assessed against the values of patients, payers, and prescribers to create a more inclusive value proposition, and an objective assessment of the value of new products can be made by using rigorous health technology assessment, comparing the evolving profile of new products with alternative treatments.

Discussion:

- Value cannot be measured before launch but can be estimated.
- Safety issues are unresolved until a larger population is available.
- A question is what the incentives are to create products for unmet medical need.
- A separation in regulatory agencies between cost decisions and efficacy/safety decisions may be desirable; economics should not be a part of the regulatory agency's decision.
- Conditional regulation and conditional reimbursement are linked: the reimbursement agency can negate conditional licensing by denying access.
- EMEA likes comparators, but the choice of, and even the need for, a comparator is sensitive. Companies should consult the agency involved.
- A challenge to companies today is how to blend what the HTA and regulatory agencies want in the same study.
- Biomarkers are useful for targets, efficacy, setting patient populations, and setting value if they can be linked to the final endpoint. Further discussion is needed to bridge the gap in assessing the value of biomarkers.
- In models of trial designs, real-world data are useful to regulatory agencies for safety and for reimbursement agencies for cost and outcomes. Companies should have parallel tracks for these.
- Approval is always conditional, because drugs can be withdrawn at any time.

Patient-Benefit:

What separates Regulatory (licensing) from HTA Assessments?

Clare McGrath

Senior Director, Evidence-Based Strategy, Pfizer

In addressing this question, we need to consider the definition of patient benefit, the decision context for regulatory approval and HTA assessment, the decision criteria and scientific standards applied in each case as well as the implications for drug development.

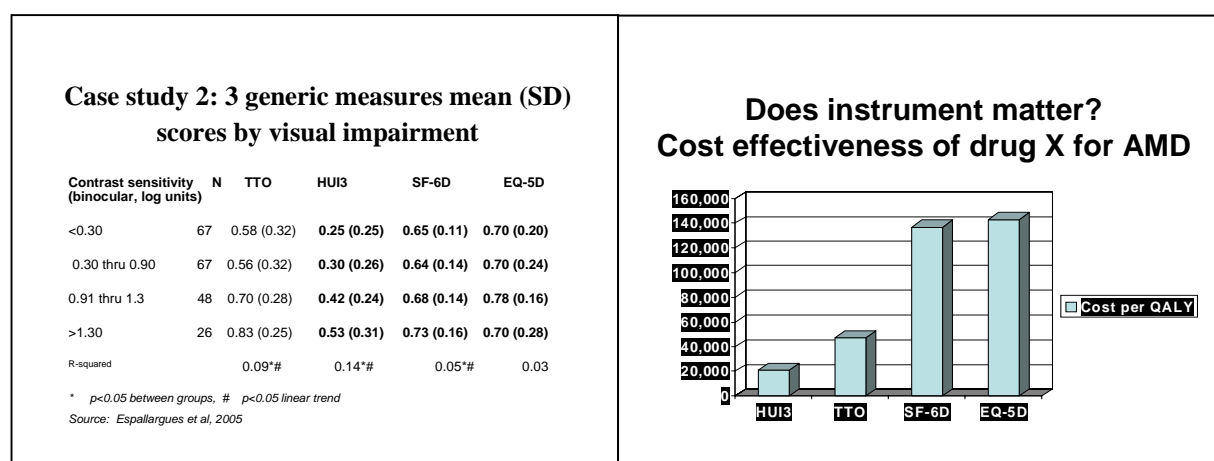
Patient benefit (as distinct from clinical outcomes) has been described as a continuum of parameters ranging from those "proximal to the individual" such as symptoms. Symptoms may then have an impact on the individual that is specific to the disease or patient group such as measure by "symptom bother" and impact on daily life, functioning and well-being such as assessed by specific Quality of Life measures. Additional impact of disease may affect areas of life that are also common to other diseases and can be assessed using "generic" Health Related Quality of life measures (some of which also allow one to assess the relative importance or weight of different health states). More peripherally still is the impact on dependency, use of health and social services, concepts that are more influenced by external factors and less easy to measure. All of this may drive more distal factors such as dependency and service use as well as productivity and all of these contribute to the economic impact of disease and interventions. Patient Reported Outcomes (PROs) as defined by the FDA comprise all of these other concepts, symptoms, QOL and economic as long as they are assessed by the patient directly.

In an ideal world with no constraints, we would be able to study the interrelationships between symptoms, health, how each is valued and contributes to service use and other health outcomes. However this is rarely the case with drug development where we are working against the clock and competing for resources across the portfolio of development opportunities.

The decision context for patient benefit assessments depends on whether the decision is being made for a label claim or reimbursement. Regulatory agencies are interested in

patient reported benefit to be used in decisions at the doctor–patient level. Some reimbursement authorities wish to compare patient benefit across diseases so as to decide on what is cost effective for a population or group of patients (using cost per QALY thresholds). These differences in use drive differences in accepted scientific standards and measurement properties of the patient reports. Regulatory agencies require a rigorous approach that ensures the content and measurement properties of the instrument reflect what patients say is important to them and can measure a minimally important difference due to treatment. Cost utility analysis uses a cost per QALY threshold that requires consistency in assessment across diseases and may trade off a loss of information or precision to achieve this consistency. Utility measures do not meet the FDA scientific criteria for patient reported outcome often because they are not derived directly from patients and not validated to ensure the abovementioned content and measurement properties are relevant to the disease in question. The preferred utility measure may also be driven by a jurisdictional preference such as the NICE’s stated preference for the ICH EQ5D guideline.

Many measurement systems exist with varying levels of dimensions, severity, and sensitivity. No single measurement covers all patient groups. The choice of instrument can however have significant impact on the results of the cost per QALY values obtained. Too little relevant content in an instrument can result in a cost per QALY estimate 4 times higher than that produced by an instrument that contains the relevant information for the research question.



Abbreviations refer to three preference-based measures (the Health Utilities Index Mark III [HUI-3], the EuroQoL Health Questionnaire [EQ-5D], and the Short Form 6D Health Status Questionnaire [SF-6D]) and the time trade-off (TTO).

The FDA label determines what can be used in promotion. This is relevant in the US market that uses a high level of direct to consumer advertising to ensure that information about patient benefits is robust. The FDA guidelines mandate more up-front investment in hypothesis development, instrument selection, and validation. This does present challenges in meeting these requirements during the development programme. Despite the high level of research spending in this field, there appears to be a shortage of robust instruments to meet the FDA requirements especially for disease areas of high unmet need where the up front research investment in instrument development may not have been made. This is being addressed through both FDA and IMI sponsored initiatives but may not yield instruments for several years to come.

In Europe however, the importance given to patient benefit assessments in regulatory decision-making varies by country. Payers have barriers to the use of quality of life (QoL) which is supposed to be more scientifically rigorous than QALYs. However, QALYs are systematically used in 3 to 5 countries (such as UK, Sweden, Netherlands). Many uncertainties around the use of QALYs as a single decision criterion exist, so QALYs should be used judiciously in decision making with full knowledge of the limitations of the method for each disease and treatment situation.

Clinical Development needs to meet both licensing and multiple-payer requirements in the same programme. This presents challenges in the design of Phase 2 and 3 clinical development programmes within competitive time frames and with affordable resources.

Discussion:

- In picking the best measure, dialogue is necessary. There is uncertainty in each method, and all parties need to be aware of the uncertainty associated with the measurements.
- Regulatory and reimbursement agencies are looking at different aspects. It is too early to say if they are moving together. Currently, they are separate.
- It is difficult to explain the QoL registration component to patients.
- Affordability is an issue.
- Patient-reported outcomes and patient assessments are important even in Phase 2 studies.
- The definition of patient benefit depends on who is answering the question.
- Regulatory agencies differ in rigor. The FDA is more prescriptive and more rigorous, and has a more documented process. If a company follows the FDA then it will meet EMEA requirements. The FDA requires more documented validation of measurements. Companies will have to make more investment in new measures.
- QoL is interesting but secondary to endpoint. Endpoints are relevant in clinical studies.

Efficacy versus Cost:

Are Regulatory Agencies being drawn into the debate?

Professor Hubert Leufkens

Utrecht Institute for Pharmaceutical Sciences, The Netherlands

European countries vary in pharmaceutical policies on cost containment, and this European variance represents a challenge. Comparing “like with like” in justifying price and reimbursement remains a challenge.

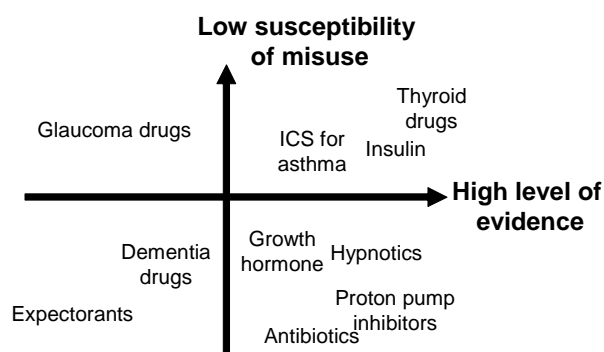
However, there has been progress. It is important to note the “effect difference” in comparison with “cost difference.” The dosages of new drugs may be too high.

There is an increasing tension between randomised, controlled trial (RCT)-based clinical evidence (efficacy) and mechanistic/ pharmacological thinking. RCTs (and meta-analyses) become more dominant important drivers and sources for evidence and for risk assessment.

In regulating marketing approval, a certain pathway of the new drug in the reimbursement trajectory is prepared involving indication dynamics (e.g., close to the evidence, but will it be close to practice), risk management plans, susceptibility of misuse, and class labelling.

Many safety issues essentially result in efficacy/effectiveness evaluations (e.g., glitazones).

Ranking ‘evidence’ and ‘susceptibility of misuse’



Bégaud B, Bergman U, Eichler H-G, Leufkens HG, Meier PJ. Br J Clin Pharmacol 2002; 54: 528-34.

Discussion:

- There are no incentives for companies to include an active comparator in studies. When companies include active comparators, there is no change in the resulting outcomes of reimbursement.
- Size and number of trials are more important than having an active-comparator- or placebo-controlled trial.
- Cost-effectiveness data do not play a role in decisions by regulatory agencies (so far).

SESSION 2: HOW SHOULD NEW MEDICINES BE ASSESSED IN THE FUTURE?

Session Chair: Dr Gary Neil, *Corporate Vice President, Corporate Office of Science and Technology, Johnson & Johnson, USA*

HTA and patient access to new medicines:

Would Harmonisation of assessments be of value?

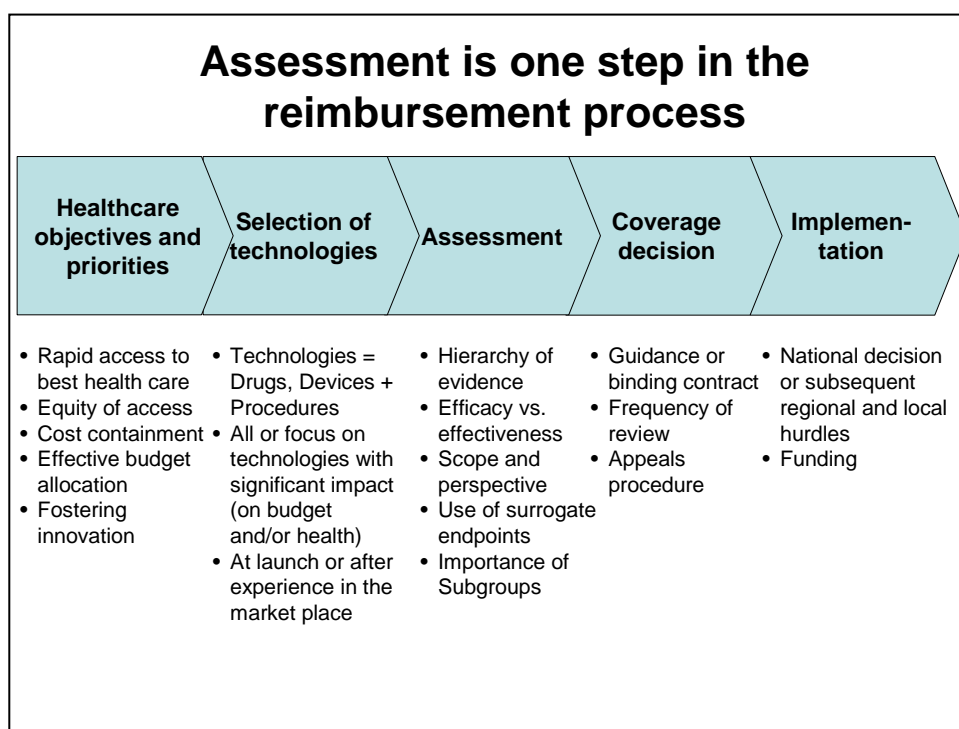
Company viewpoint

Dr. Jens Grueger

Global Head, Pricing & Health Economics, Novartis

Key areas of concern include the political and financial context of the assessment, effectiveness versus efficacy, price versus coverage, and the benefits of methodological harmonisation.

Assessment is a tool and one step in the reimbursement process, not an end in of itself. There is limited value of a harmonised tool, if the objectives are diverging. HTA, whether harmonised or not, may not be the suitable tool because objectives like “fostering innovation” and “equity of access” have not been achieved through HTA.



Within one country, assessments should be driven nationally. HTA is further decentralised within countries with several local HTA/reimbursement assessments (e.g., UK, Spain, Sweden). Further dilution of scarce HTA resources will not benefit assessments.

It is easier to harmonise assessment of efficacy than of effectiveness.

Regulatory approval is based on efficacy, safety, and quality, and can be assessed on the basis of RCTs (often against placebo) on the basis of statistical hypotheses testing. In contrast, HTA examines relative effectiveness, and RCTs are not necessarily the best model to assess effectiveness.

Methods will benefit from harmonisation. Industry agrees that the benefits of harmonisation include avoiding duplication in assessment of clinical evidence, improving competence and confidence in evaluation of epidemiologic and economic models, and sharing best practices in including benefits for patients, families, and societies. However, there are also concerns. Methods are still underdeveloped, and strict guidelines will reduce flexibility and curtail further methodological innovation.

Discussion:

- There is a lack of evidence of effectiveness of HTA. Pharmacy budgets for some therapies (e.g., cancer) have benefited from a positive assessment, and others have not.
- One issue in Europe is medical tourism because of the differences in health services across countries. It is disappointing that more countries do not follow the Dutch model of a solid package of healthcare services with additional services to be paid by the individual. This is happening in Switzerland with a competition between services. In these systems, patients are more responsible for the healthcare services they receive.
- Agencies should meet and try to harmonise their processes.

Agency viewpoint

Dr. Andreas Laupacis

Director, Li Ka Shing Knowledge Institute St. Michael's Hospital, Toronto, Canada

Harmonisation of HTAs would be of value to pharmaceutical companies, but not necessarily for payers. Drugs that are not more effective than a comparator cannot be cost-effective unless they are less expensive. Costly drugs that are extremely effective are likely to be cost-effective. Payers are buying health outcomes, not drugs. Payers are comparison shopping. Much of the reimbursement discussion is "on the margin" (drugs are marginally more effective or cause slightly less harm than a comparator, but are considerably more expensive).

Before reimbursement, agencies consider cost-effectiveness, comparative effectiveness, real-world harm, and budget impact matters; they want to see clinically important outcomes (and clinically important effects on those outcomes), active comparators, complete evaluation and reporting of harms, representative patients and clinicians, and adequate follow-up.

Summary

- Harmonization of HTA less attractive to reimbursement agencies than to pharma
- Possible to harmonize some aspects of effectiveness trials
- Even with harmonization, jurisdictions' different health care priorities, practice patterns, economic and political realities will likely lead to different reimbursement decisions or require different prices

However, reimbursement agencies usually receive surrogate markers, uncertainty about clinical importance, placebo-controlled studies, highly selected patients and clinicians, incomplete reporting of harms, and short follow-up.

Potential solutions to this problem include: agreement on valid surrogate markers/quality of life/functional status measurements; agreement about minimal clinically important differences; trials with active controls early in development; and administrative data or registries to assess some harms.

Although the underlying model may be similar across countries, harmonisation of cost-effectiveness and budget impact analyses will be difficult because of variations in practice patterns, resource use, and unit costs.

Discussion:

- EU problems seem similar to those in provinces in Canada. A problem among the provinces is that when one province says 'yes,' other provinces feel pressure to agree.
- Observational technology is useful for rare and unusual events. One can look at a population database. For example, hormone replacement therapy (HRT) RCT showed harm, but observational data were different.
- For HTA and economic models, there will be no one harmonised system for all countries. Harmonisation of methods is possible. An economic model is needed that depends on clinical and price information. If a company has a new drug and prices it the same as a comparator, then for reimbursement, in theory, the company does not need a head-to-head study, since company is not going for a price premium. Companies do not need to use models if they have actual data. Models do not have as big a role in these decisions.
- International cooperation about outcomes and comparators to keep drug development costs down will require funding to bring decision-making groups together.

Future of regulation and reimbursement:

Is conditionality the best route to translate research into health and economic benefits?

Companies' viewpoint

Professor Adrian Towse

Director, Office of Health Economics, UK

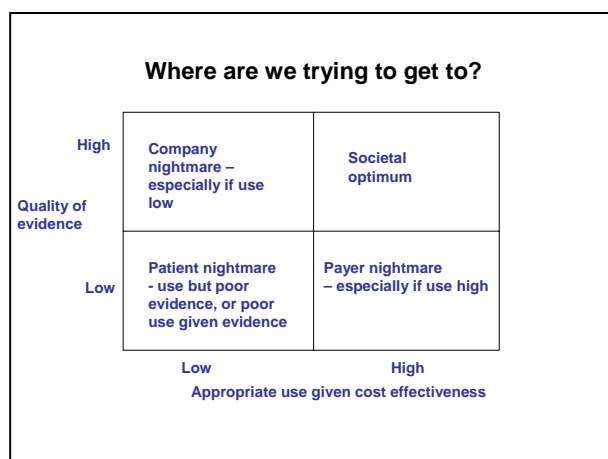
There is context for considering conditional licensing and conditional reimbursement, with the Cooksey report and the Office of Fair Trading (OFT) report. Conditional licensing is a continuum and is already present today. Companies and licensing bodies enter into dialogues for licensing that is dependent upon future evidence to be supplied.

Issues for companies include keeping licensing and reimbursement decisions separate, determining whether conditional licensing is adding to uncertainty and to development cost, and whether conditional licensing approval leads to quicker access to the market.

Conditional reimbursement means that price and/or volume is provisional, and is dependent upon additional information being collected. However, there may not be clarity about when and if a review will take place, the outcome and subsequent price/use, and agreement on data collection and costs sharing.

Payers want patients to have cost-effective treatment, but there is much uncertainty about effect linked to price. Differences of opinion exist between payers and suppliers on likely cost-effectiveness. A concern for companies is that more pre-launch requirements means a potential delay for a drug to come to market.

Conditional licensing and conditional reimbursement provide incentives for the company to collect and pay for more evidence, and allow for an ability to start using the product, which could benefit the patients.



Discussion:

- The progressive license idea means there is more work to be done. A drug can enter the market after Phase 2 but needs more work. As work continues, a more progressive reimbursement strategy could be in place. Risk sharing in the earlier part of development might be possible.
- Companies could accept a lower price.
- Companies and payers have to deal with uncertainty at launch. If a drug works but not that well, then it will be stuck at that price. It is difficult to stop use of product once on the market. One way to handle uncertainty is to have a low price. However, the company can get stuck at a low price. A framework is needed to deal with such uncertainty. If the evidence shows effectiveness, then the price will go up.
- Conditional reimbursement should be seen as an exception for a high unmet medical need.

Future of regulation and reimbursement:

Is conditionality the best route to translate research into health and economic benefits?

Regulatory agency viewpoint

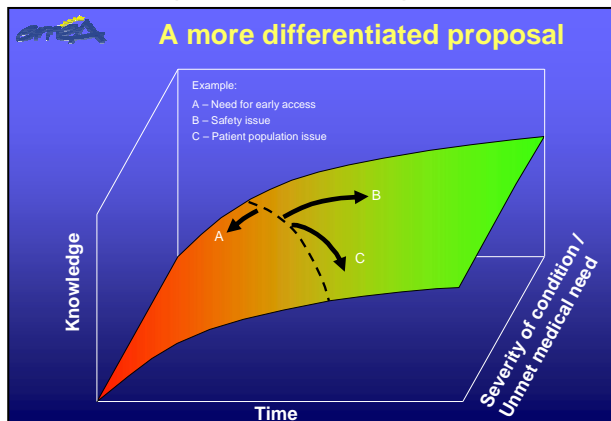
Dr. Hans-Georg Eichler

Senior Medical Office, EMEA

Conditionality is defined as authorisation granted on the condition that additional data will be provided after approval when benefit of immediate availability to public health outweighs the risk that additional data are still required.

One example is Sunitinib, a tyrosine kinase inhibitor (Sutent®), used in the treatment of metastatic renal cell carcinoma (MRCC). MRCC has a poor prognosis despite current treatment options. The magnitude of the observed biological effect in terms of overall response rate (ORR) provided sufficient confidence to gain a favourable safety profile and obtain conditional marketing authorisation (CMA) granted. Subsequently, prolonged progression-free survival (PFS) was shown in an RCT, and approval was switched to normal marketing authorisation.

Another example is the glitazones in the treatment of diabetes. Glitazones were approved on the basis of improved glycaemic control, which is a surrogate endpoint. Meta-analysis data showed an increased risk of myocardial infarction and potential cardiovascular mortality associated with use of glitazones. Several issues exist in diabetes treatment, including the safety and validity of surrogates. There are about 70 compounds in the pipeline for the treatment of diabetes. Regulatory agencies have several options: to maintain business as usual, to request clinical endpoint studies, or to grant license on the basis of glycaemic control on the condition of subsequent clinical endpoint studies. Another question is whether this information meets the needs of the reimbursers.



The wider use of the “conditionality” approach may not address the regulators’ dilemmas of early access versus comprehensive data. However, the different information needs of regulators and reimbursers (e.g., comparative information, effectiveness) may ultimately lead to a “lifecycle” approach.

Discussion:

- There is precedent around safety issues and conditional approval. However, with regard to reimbursement, more transparent guidelines are needed.
- If a company does not perform the promised studies, an agency theoretically could revoke a license if it is a conditional approval. (However, dying patients and their families would soon be outside the agency's door!)
- A question is the extent to which reimbursement bodies will be willing to predict boundaries of potential rewards to improve standard of care over current options.
- Reimbursement thresholds may be needed for companies to decide to continue development of a drug.
- Conditional approval is tricky. If a company obtains conditional approval, but subsequent data show negative results, it could be difficult to withdraw the drug.

Value-based pricing schemes:

How will it work in Practice?

Professor John Hutton

Health Economics, York Health Economics Consortium Ltd, University of York, UK

Estimating the value of a medicine involves examining the methods, data needs, and policy issues. Various methods can be used which involve assessment of the effectiveness and costs of a medicine, relative to alternative treatments, in an economic evaluation framework. Comparative effectiveness can be assessed using a generic measure of health benefit (eg, QALY), with results expressed as a ratio of Cost/QALY. The value of a medicine is sufficient to justify reimbursement if the cost/QALY ratio falls below an agreed threshold e.g £20,000-30,000 in England. Alternatively the results can be expressed in purely monetary terms by applying a social valuation to the QALY. Effectiveness and resource use data by patient group are necessary to target the applications of greatest value. Several issues influence the accuracy and relevance of estimates of value (eg, timing and speed of appraisal, maturity of data, allowance for uncertainty, and perspective of analysis).

The organisation of the Office of Fair Trading (OFT) value-based pricing (VBP) model involves ex ante fast-track appraisal of all new drugs, ex post review of all drugs on a 5-year cycle or at patent expiry, risk-sharing if cost-effectiveness is unclear, a rebate system for multiple indications, and generic entry triggering of price reductions.

Some implications of the OFT model are the need for increased precision in cost-effectiveness analysis (CEA), and an increased HTA burden on industry and decision-makers. An agreed cost-effectiveness threshold value is central to the approach (reflects social value of health benefits); price negotiators must understand technical details of the VBP approach, and decisions must be transparent.

Discussion

- How does this differ from the current UK situation?
- How dependent is the proposed system on external factors e.g. success of clinical guidelines; competitiveness of the generics market?
- Is all the ex post appraisal necessary?
- Can VBP work in one country in isolation?

Discussion:

- In the definition of price, the sensitivity of the VBP is proportional to the benefit.
- Some assumptions are not necessary. For example, if there is new drug for rheumatoid arthritis (RA), then the company needs to price it similar to one on market using the last used cost-effectiveness data in that area.
- The National Institute for Health and Clinical Excellence (NICE) already has some useful models.
- VBP has some useful attributes, but some areas have not been completely thought out.
- It is hard in the UK to determine which drugs are being prescribed for which indications.
- All drugs are theoretically reimbursable if patients are identified for whom they will be cost effective. NICE rejects drugs that do not meet the threshold. Justification of data is still necessary for positive and negative decisions.
- There is no consensus in the health economics field on how health should be valued. In the UK, health is valued from a collective social viewpoint, and not from an individual perspective. However, NICE does not apply its threshold unthinkingly, and tends to relax its criteria for some treatments e.g. some cancer drugs.

The US market:

Scenarios for the future and the role of reimbursement

Dr. Mick Kolassa

CEO and Managing Partner, Medical Marketing Economics, USA

Commonalities and differences are the context for global pharmaceutical pricing. Different national and supranational regulations make health systems different; however, the payers' approaches to controlling drug budgets are becoming increasingly similar.

In the US, total medical costs increased 8.4% in 2006. The American government is the single largest payer through various programs (e.g., Medicaid, Medicare), and commercial payers cover the bulk of the population with insurance purchased through employers. Drug manufacturers can freely set prices for new medicines, and pricing decisions are based on a number of items (e.g., value of therapy, reimbursement expectations, corporate goals).

Major trends in the US include: increasing patient cost sharing, better tracking of actual product costs for reimbursement, continued convergence of public and private systems, and continued lack of insurance for a significant proportion of the population.

Major Trends

- ▶ Patient Cost Sharing is Increasing
 - Higher co-pays and more tiers
 - Co-insurance for specialty items
- ▶ Better (?) tracking of actual product costs for reimbursement
- ▶ Continued convergence of public and private systems
 - Reimbursement basis
 - More government contracting with private insurers
- ▶ Continued lack of insurance for a significant proportion of the population

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Scenarios for the future of the US market:

- New ways to continue the same thing — The pattern has been to implement only minor changes. The market adapts to changes by absorbing them into current behaviours (i.e., "system resilience"). The likelihood of this scenario occurring is greater than 50%.
- Movement toward a single-payer system — This is the dream of the liberal wing of the Democratic Party. Americans in general resist the idea of the government as the single payer. The likelihood of this scenario occurring is less than 10%.

- Market transformation — “Pay for performance” for providers and medicines is enabled by the greater use of information technologies. These concepts are being built into many systems now and will impose pharmacoeconomics requirements on the industry. The likelihood of this scenario is less than 50% within 5 years, but greater than 75% in 10 years.

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