REVIEW AND REIMBURSEMENT:

ALIGNING THE NEEDS AND REQUIREMENTS IN CLINICAL DEVELOPMENT

WORKSHOP
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WORKSHOP REPORT

CMR International
INSTITUTE FOR REGULATORY SCIENCE

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Section 1: Overview and Executive Summary

Background to the Workshop

The current dynamics of bringing new medicines to market are being influenced by conflicts between the agendas of regulators and payers. Regulators are under pressure to develop methods to speed the approval process, including mechanisms such as accelerated approvals, 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 of clinical and cost-effectiveness. The two processes of licensing and reimbursement, continue to add uncertainty to drug development decisions as market approval does not necessarily mean that the product will be reimbursed. While, historically the regulatory review and the consideration of products for formulary listing and reimbursement by healthcare providers (health technology assessment – HTA) have been entirely separate, the current dialogue around comparative effectiveness research (CER) may lead to a closer alignment among the two approaches.

This Workshop has been developed to specifically address the related issues of overlap and/or differences in requirements between licensing, HTA, formulary listing and reimbursement, and the potential for mismatch of outcomes, in the multi-payer healthcare system of the USA. The current Workshop follows the Institute's September 2009 Workshop: *Review and Reimbursement: a special case for better cooperation* that focussed on the single-payer systems of Australia, Canada, Europe and Switzerland. At the September Workshop, the implications of the current experiments into information sharing, alignment of technical requirements and even joint scientific advice being offered by regulatory authorities and HTA agencies was explored.

This Workshop examined

1. How these experiments in improving dialogue and efficiency may or may not be applied in the US context, given the different mandates and requirements of federal and private technology assessors and payers
2. How the changing requirements of regulatory authorities in other nations as a result of dialogue with HTA / Payers may impact the nature of scientific advice given by the FDA
3. Ways to address the needs of regulators and HTAs during drug development programmes
4. Mechanisms by which the potential mismatch of evidence requirements by the FDA and HTA/reimbursement authorities might be mitigated

Objectives

- Improve efficiency of global development: by identifying areas of overlap between the evidence requirements of HTAs and the regulatory authorities in drug assessment and by discussing mechanisms by which dialogue and information sharing may minimise duplication or divergent requirements
- Improve the predictability of outcomes: by identifying mechanisms to mitigate the risk of mismatch of outcomes that can occur when a regulatory authority grants an approval that is not compatible with current HTA requirements
- Develop a white paper: the recommendations of the two Workshops and the supporting survey will be used to create a white paper that addresses the global implications of changes to the current model of separate regulatory and HTA reviews by aligning the evidence needs and requirements for licensure with those of the HTA evaluator in order to achieve greater efficiency of process and predictability of outcome

Workshop Attendees		
Regulatory agencies		
Prof Sir Alasdair Breckenridge	Chairman	Medicines and Healthcare products Regulatory Agency, UK
Dr Petra Doerr	Head of Management Services and Networking	Swissmedic
Prof Hans-Georg Eichler	Senior Medical Officer	European Medicines Agency
Dr Rohan Hammett	National Manager	Therapeutic Goods Administration, Australia
Dr John Jenkins	Director, Office of New Drugs, Center for Drug Evaluation and Research	Food and Drug Administration, USA
Dr Murray Lumpkin	Deputy Commissioner for International Programs	Food and Drug Administration, USA
Prof Tomas Salmonson	Vice Chair, Committee for Medicinal Products for Human Use, European Medicines Agency	Medical Products Agency, Sweden
Dr Supriya Sharma	Director General, Therapeutic Products Directorate	Health Canada
Dr Robert Temple	Deputy Center Director for Clinical Science	Food and Drug Administration, USA
Dr Janet Woodcock	Director, Center for Drug Evaluation and Research	Food and Drug Administration, USA
Industry		
Tracy Baskerville	Vice President, Head of Global Regulatory Affairs, Liaison, Cardio-metabolic	Solvay Pharmaceuticals – A business unit of Abbott Laboratories, France
Dr Marc Berger	Vice President, Global Health Outcomes	Eli Lilly and Company, USA
Dr Steve Caffe	Vice President, Global Regulatory Affairs and Pharmacovigilance	Baxter Healthcare Corporation, USA
Juliet Cronin	Director, Oncology Marketing	EMD Serono Inc, USA
Peter DiRoma	Vice President, Global Regulatory AIID and ET	EMD Serono Inc, USA
Michael Doherty	Global Head – Pharma Regulatory Affairs	Roche/Genentech, USA
Véronique Frechin	R&D Strategic Planning Director	Institut de Recherches Internationales SERVIER, France
Dr Tim Garnett	Senior Vice President and Chief Medical Officer	Eli Lilly and Company, USA
Dr David Guez	Director of Strategic Planning R&D	Institut de Recherches Internationales SERVIER, France
Dr Sanjay Gupta	Head, Health Economics and Outcomes Research	Daiichi-Sankyo, USA
Dr Linda Harpole	Vice President, Global Health Outcomes	GlaxoSmithKline, USA
Dr Ansgar Hebborn	Head - Global Payer & HTA Program Policy and Global Pricing &Payer Strategy CNS & Metabolism	F. Hoffmann-La Roche AG, Switzerland
Dr Paul Huckle	Senior Vice President, Global Regulatory Affairs	GlaxoSmithKline, USA
Jijo James	Senior Director, Chief of Staff	Pfizer Medical, USA
Dr Zeba Khan	Vice President, Pricing and Market Access	Celgene Corporation, USA
Dr Simon Larkin	Executive Director, Inflammation and Immunology	Celgene, Switzerland
Alison Lawton	Senior Vice President, Global Market Access	Genzyme Corporation, USA
Dr Freda Lewis-Hall	Senior Vice President, Chief Medical Officer	Pfizer Inc, USA

Dr Hilary Malone	Senior Vice President and Head, Worldwide Regulatory Strategy	Pfizer Inc, USA
Dr Clare McGrath	Senior Director, HTA Policy	Pfizer Ltd, UK
Dr Robert Meyer	Vice President, Global Regulatory Strategy, Policy and Safety	Merck & Co, USA
Dr Steven Miller	Vice President, Global Regulatory Affairs	Johnson & Johnson, USA
Dr Garry Neil	Corporate Vice President	Johnson & Johnson, USA
Mary Jo Pritza	Director, Regulatory Affairs	Astellas Pharma Global Development, Inc, USA
Dr Victor Raczkowski	Senior Vice President, US Regulatory Affairs	Solvay Pharmaceuticals – A business unit of Abbott Laboratories, France
Dr Pierre Sagnier	Vice President, Global Health Economics, Outcomes & Reimbursement	Bayer Schering Pharma AG , Germany
Dr Joseph Scheeren	Head of Global Regulatory Affairs	Bayer Healthcare Pharmaceuticals Inc, USA
Gerhard Schlueter	Head of Regulatory Affairs, Speciality Medicine	Bayer Healthcare Pharmaceuticals, USA
Dr Brian Seal	Senior Director Evidence Based Medicine	Sanofi-Aventis, USA
Dr Mel Walker	Director, Integrated Payer Strategy	GlaxoSmithKline, UK
Dr Richard Wolgemuth	Senior Vice President of Global Regulatory Sciences, Pharmacovigilance and Epidemiology	Bristol-Myers Squibb, USA
Health technology assessment, payer or managed care agencies		
Dr Naomi Aronson	Executive Director	Blue Cross/Blue Shield Association, USA
Prof Finn Børlum Kristensen	Director, Chairman of Executive Committee	EUnetHTA Secretariat, National Board of Health, Denmark
Dr Sharon Levine	Associate Executive Director	The Permanente Medical Group, Kaiser Permanente, USA
Andrew Mitchell	Strategic Adviser, Evaluation	Department of Health and Ageing, Australia
Dr Brian O'Rourke	Acting President and CEO	Canadian Agency for Drugs and Technologies in Canada
Dr Murray Ross	Vice President, Director	Kaiser Foundation Health Plan, Kaiser Permanente Institute for Health Policy, USA
Jean Slutsky	Director, Center for Outcomes and Evidence	Agency for Healthcare Research and Quality, USA
Other		
Dr Peter Doukas	Dean and Professor	Temple University School of Pharmacy, USA
Prof Lou Garrison	Professor and Associate Director, Pharmaceutical Outcomes Research and Policy Program	University of Washington, USA
Dr Clifford Goodman	Vice President	The Lewin Group, USA
Dr Steve Phurrough	Chief Operating Officer/Senior Clinical Director	Center for Medical Technology Policy, USA
Prof Adrian Towse	Director	Office of Health Economics, UK
CMR International Institute for Regulatory Science		
Patricia Connelly	Manager, Communications	CMR International Institute for Regulatory Science
Lawrence Liberti	Executive Director	CMR International Institute for Regulatory Science
Dr Neil McAuslane	Director	CMR International Institute for Regulatory Science
Prisha Patel	Portfolio, Manager, Emerging Market Programme	CMR International Institute for Regulatory Science
Dr Franz Pichler	Manager, HTA Programmes	CMR International Institute for Regulatory Science
Prof Stuart Walker	Founder	CMR International Institute for Regulatory Science

Workshop Highlights

Despite representing only a small fraction of healthcare expenditure, and contributing significant value and cost reduction, pharmaceuticals have been a favourite – and easy target – for cost cutting among national health authorities and private payers. In this atmosphere there have been calls for better regulatory science and tools, and the question asked by Session Chairperson **Dr Gary Neil**, *Corporate Vice President, Science and Technology, Johnson & Johnson*, was: Now that the US Healthcare Reform bill has become law, where do we go from here?

Dr Janet Woodcock, *Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), USA*, pointed to two potential sources of major impact on drug development that have emerged with the passage of the US Healthcare Reform Bill: the Institute for Patient-Centred Outcomes Research Institute (PCORI) and the increased government role in paying for healthcare. However, comparative effectiveness efforts per se are unlikely to impact drug development in US over the medium-term horizon due to legislative limits on the use of government funded CER results together with societal disagreements over the role of government in this area.

The US healthcare context was provided by **Dr Murray N. Ross**, *Vice President, Kaiser Foundation Health Plan and Director, Kaiser Permanente Institute for Health Policy*, who described unsustainable cost trends, dubious quality and a general distrust of institutions and science among the public. Cost pressures will continue to dominate the environment, with or without reform, but reform efforts will provide new funding for health information technology, comparative clinical effectiveness research, coverage expansion and new insurance rules.

Rather than trying to predict what the future will look like, **Dr Freda Lewis-Hall**, *Chief Medical Officer & Senior Vice President, Pfizer*, explained that stakeholders now have an opportunity to decide where they want to be, with a clear, aggressive, specific vision, one that incorporates goals such as achieving 80% global alignment or subtracting 100 days from standard approval times.

In her second Workshop presentation, **Dr Woodcock** discussed the 10-year horizon for CER in the United States. Although it is not wholly clear how or by whom new US evidentiary standards will be implemented, it is clear that expectations for evidence will continue to evolve. For efficient and effective drug development, a worldwide clinical research infrastructure must be created, science used to decrease empiricism in the clinical development and use of medicine, and research enabled with data standards and informatics.

Dr Clifford Goodman, *Vice President, The Lewin Group* outlined the implications for the US pharmaceutical industry arising from CER, saying that expanded support of US CER and HTA will increase global capacity and rigor for assessing technologies. Pharmaceutical developers are advised to track where and how HTAs will evolve their technology. CER, HTA and related trends suggest the need to change processes for innovation, validation and commercialisation to meet these evolving needs.

In an examination of ways to make the case for the reimbursement of a new drug in the United States, **Dr Robert J. Temple**, *Deputy Center Director for CDER,FDA, USA*, pointed to a decrease in the number of drugs being developed even within popular therapy classes, presumably reflecting difficulties in achieving substantial use of a new member of a class (without a clear advantage) once some members of the class are generic. He expressed the hope that these more stringent conditions will lead to more rigorous study of differences in adverse event profiles, non-responders and intolerants, and genetic predictors of response.

In good clinical studies, as in good accounting and financial practices, deviation from standards leads to unreliable results and misinformed decisions. In considering the quality of the clinical evidence for therapies, **Dr Naomi Aronson**, *Executive Director, Technology Evaluation Center, Blue Cross and Blue Shield Association*, said these deviations may introduce significant obstacles to assessing outcomes. Among the difficulties faced in assessing supportive information, scales may not be validated nor reflect consensus outcomes, there may be a lack of robust evidence of effects and comparative effects, and a gap can exist between the efficacy shown in clinical trials and the effectiveness observed in a real-world setting.

Dr Tim Garnett, *Chief Medical Officer, Eli Lilly and Company*, portrayed the need of regulators for controlled experimental study results, preferably compared with placebo as being in contrast to the need of HTA groups for cost-

effectiveness information evaluated against all possible comparators. This divergence can create friction between the two entities in helping to define a sponsor's clinical development programme, in particular, in setting the criteria for the comparisons required and thereby influencing access to medicine and the state of public health. Aligning the requirements of regulators and HTAs during the development cycle by building early partnerships with these stakeholders will support a sustainable business model that will generate an increasing number of valued treatments, based on a more efficient development paradigm.

Professor Hans-Georg Eichler, *Senior Medical Officer, European Medicines Agency* explained that whilst current EU regulations call for "controlled clinical trials if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value" stating that trials that employ "any other design shall be justified", the reality is that only a small percentage of medicines are approved based on active comparator trials. Therefore, establishing a clinical programme whose design can meet the needs of both regulators and HTAs, may be challenging.

Agencies, health ministries, and research groups from 24 countries in Europe united to form the European network for Health Technology Assessment (EUnetHTA), an organisational framework to develop standardised tools for global health technology assessment. **Professor Finn Børlum Kristensen**, *Chairman, EUnetHTA Executive Committee; Director, EUnetHTA Secretariat, National Board of Health, Denmark* told Workshop participants that a variety of joint actions are planned by EUnetHTA within the 2010-2012 timeframe including identifying ways to facilitate the generation of informative evidence and collaboration on pre-coverage assessments of new technologies, developing a business model for the sustainability of the organisation, and establishing information management systems and other methods of communication and evaluation.

Dr Garry Neil, *Corporate Vice President, Science and Technology, Johnson & Johnson* detailed the ways in which the process of drug development must continue to evolve. Over the near-term horizon, within the next five years, we must restore public trust and confidence, increase transparency and open scientific debate, invest heavily in regulatory science modernisation and continue our experiments in new drug development paradigms. Within the next ten years we should adopt the new development models and tools, implement new risk assessment and communication technology, emphasise personalised medicine, and develop products where there is an unmet medical need.

Citing escalating research costs and drug prices with an exponential impact on incremental cost-effectiveness ratios and diminishing marginal returns on health outcomes, **Andrew Mitchell**, *Strategic Adviser, Evaluation, Australian Government Department of Health & Ageing* and *Chair of the HTAi's Working Group on Surrogate Outcomes* offered one potential solution. Using comparative cost-effectiveness, some payers have already developed an outcomes-based reward system in which a greater net health benefit for a therapy can result in a correspondingly higher market price. There is the potential to modify this system by rewarding pharmaceutical researchers who develop more convincing clinical evidence for a new therapy during the development process with a higher price for that therapy at launch.

Coverage with evidence development (CED) is a type of comparative effectiveness research that can be defined as temporary reimbursement for a new, non-covered service, which is contingent on participation in an organised research study, and which reconciles tension between establishing strict evidence standards and the need for rapid medical innovation. **Dr Steve Phurrough**, *Chief Operating Officer/Senior Clinical Director, Center for Medical Technology Policy*, said that there is also growing interest among private payers in the CED approach, and although significant issues remain for CED, coordinated multi-payer CED could contribute significantly to of the knowledge base of comparative effectiveness research.

Alison Lawton, *Senior Vice President, Global Market Access, Genzyme* provided the industry perspective on pay for performance and risk sharing, saying that early, proactive involvement and engagement, fairness and transparency are aspects of the risk-sharing process. All stakeholders (mainly payers and manufacturers, but also regulatory authorities, legislators, healthcare providers and patients) must collaborate towards patient-centric, value models and a climate of mutual trust and respect is essential to accomplish this end. Reimbursement systems should be structured on the basis of the overall approach to treatment of the disease rather than in terms of the cost-

value assessment of the use of a certain number of pharmaceutical units.

Commenting on the fact that risk-sharing has not typically been found in the United States, **Professor Lou Garrison**, *Associate Director, Pharmaceutical Outcomes Research and Policy Program, University of Washington*, said that in the future, the role of CER in the US may become increasingly important in influencing pricing strategies and increasing interest in risk-sharing approaches, in particular if CER is publicly subsidised. It is not clear, however, whether private payers will fund the research needed to underpin outcome guarantees without public subsidisation and the development of the necessary infrastructure to collect, monitor, interpret and apply the results of CER to their risk-sharing payment paradigms

Section 2: Syndicate and Panel Discussions

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

Aligning the needs and requirements in clinical development

Getting to the right evidence for registration and reimbursement: An achievable endpoint?

How can patients have rapid access to new medicines where there is an unmet medical need?

How can you use HTAs and Regulation to enable innovation?

The Chairpersons and Rapporteurs for the groups follow:

Syndicate 1	Chair	**Dr Peter Doukas**, *Dean and Professor, Temple University School of Pharmacy, USA*
	Rapporteur	**Dr Linda Harpole**, *Vice President, Global Health Outcomes, GlaxoSmithKline, USA*
Syndicate 2	Chair	**Dr Brian O'Rourke**, *Acting President and CEO, Canadian Agency for Drugs and Technologies in Health (CADTH)*
	Rapporteur	**Dr Zeba Khan**, *Vice President, Pricing and Market Access, Celgene, USA*
Syndicate 3	Chair	**Prof Hans-Georg Eichler**, *Senior Medical Officer, European Medicines Agency*
	Rapporteur	**Dr Marc Berger**, *Vice President, Global Health Outcomes, Eli Lilly & Company, USA*
Syndicate 4	Chair	**Prof Tomas Salmonson**, *Vice Chair, Committee for Medicinal Products for Human Use, European Medicines Agency*
	Rapporteur	**Dr Brian Seal**, *Senior Director, Evidence-Based Medicine, Sanofi Aventis, USA*

Syndicate 1: Aligning the needs and requirements in clinical development

The Syndicate was asked to identify recommendations regarding how the increasing CER requirements in the US may impact on global development and what needs to be aligned between regulatory agencies and HTAs.

Points for consideration

- The American Recovery and Reinvestment Act 2009 provided a stimulus supporting increased CER, in part to help reduce increasing healthcare expenditure. How will CER impact on the choices of which drugs to take forward in development programmes?
- Will CER promote greater risk taking by moving development towards more innovative medicines or, alternatively, will this change the post-authorisation marketing strategies of sponsors via risk-sharing or the targeting of high-responder sub-populations?
- Who should decide upon how to align HTA and regulatory requirements and what is the appropriate process for this decision making?
- Will CER implications increase or decrease the amount of niche or orphan drug development?
- What might the global implications be once CER becomes implemented in the US?

Outcome of discussion

Critical issues

Although some may question what the short-term impact of CER will be in the United States, there is increasing global pressure to deliver new medicines with measurable value to patients. However, there is still not a global consensus on what evidence will be required to be generated during drug development in order to provide sufficient information for assessment

of the value of the new medicine and whether that evidence should be generated through randomised clinical trials, meta-analyses, or observational studies. Likewise, appropriate CER endpoints must be determined, that is, will surrogates be as valid as clinical results; what will be the roles of biomarkers or patient-reported outcomes? Infrastructures will need to be created to implement CER at both the pre- and post-approval stages of development, including establishing the health information technology necessary for electronic medical records as well as actual bricks-and-mortar clinical research facilities focused on CER. Incentives for incremental evidence generation should be developed using novel development and approval paradigms such as conditional registration, risk sharing or another methodology acceptable to all stakeholders. The future of CER is further complicated by the fact that HTA decisions are local with tremendous regional variation, and it may be necessary to develop core versus customised evidentiary standards to address the needs of global research programmes yet tailored to regional CER requirements. Finally, although it has the potential to generate a major impact on the development and approval of new medicines, how CER will be paid for remains to be resolved.

Strategies

Companies are advised to consider the areas in which CER is going to be most relevant and start early in clinical development to plan accordingly. These areas are likely to include the establishment of the prevalence and burden exerted by disease and the most efficient approaches to establish comparisons of multiple therapies. The clinical development plan needs to be informed with input and insights from all relevant stakeholders, including payers or HTA groups, regulators, patients, and providers. These stakeholder contributions can be elicited through the creation of collaborative venues for dialogue such as forums and roundtables.

Policy issues such as the role of consortia and research infrastructures must be confronted and core dossier requirements should be established to meet common evidentiary standards applicable to HTAs across many diverse regions. Changes in market exclusivity or patent extensions may result in changes to regulatory requirements especially to support HTA evidentiary needs. Support must continue for the evolution of methodologies for evidence evaluation and improvements to scientific approaches to personalised medicine.

Recommendations

- Encourage mechanisms for dialogue between regulatory and HTA agencies regarding early advice to sponsors for CER study design/ expectations
- Establish "core dossier" parameters and format to meet common evidentiary standards applicable to the key HTAs
- Require transparency in decision making by regulatory and HTA authorities that is clearly communicated over the product life-cycle
    - Pre-competitive information to be made more widely available
- Develop a common policy forum to determine what should be considered as an adequate evidence base for specific therapeutic classes, or for medicines with common mechanisms of action
- Explore approaches to improve CER infrastructure and the use of research consortia
- Align regulatory and CER evidentiary standards; CER should address the areas of greatest residual uncertainty after regulatory approval
- Recognise that CER will be a public good, and that this is a strong basis for significant public funding

Syndicate 2: Getting to the right evidence for registration and reimbursement: An achievable endpoint?

The Syndicate was asked to identify recommendations regarding the role HTAs, regulators and companies can take in order to have the appropriate evidence for both registration and reimbursement by the end of the clinical development phase.

Points for consideration

- What would be required for agreement prior to the drug development process on the health priorities for new medicines in order to meet registration and HTA criteria for approval and reimbursement?
- Which technical requirements within a drug development plan can be aligned to suit both

sets of requirements; would these be suitable within the US context and what mechanisms could be used to align them?

- What is the active role that companies, regulators and HTAs have in this process?
- How can regulators and CER/HTA bodies reach consensus on biomarker choice, surrogate endpoints, and the development of comparator arms of trials? If so, what is the best way to achieve such a consensus and what would be the implications for drug development programmes?

Outcome of discussion

Critical issues

Regulators, whose priorities lie in the establishment of the absolute efficacy and safety of a medicine for registration and the collection of long-term evidence post-approval, typically are not charged with including HTA requirements in their evaluations. HTA stakeholders on the other hand are interested in the comparative assessment of new medicines in relation to other treatments for a disease and wish to determine the incremental value improvement of the new therapy. Because the evidentiary needs of these groups differ, the scope and cost of supportive research is a real and material limitation to research. For their part, industry has to consider the viability of the product development process, including implications for costs, resources and organisational and investor expectations. They must judge what size of clinical effect is necessary to translate into an economically viable value proposition, taking into consideration clinical practice pattern variations and unmet medical needs. There is the potential that innovation may be more likely to occur when industry is given the opportunity to conduct open discussions with HTA groups and regulators to plan the evidentiary requirements during the early stages of medicines development.

Strategies

Industry, payers and regulators need to move the CER agenda forward. It must be decided who will drive and who will act as stewards of this process and what the incentives will be for taking on those roles. Consensus needs to be reached considering the unique needs of all stakeholders and how each will be represented in this new collaborative environment.

Alignment, rather than integration within and across groups will be required, and true harmonisation would be implemented only on a case-by-case basis; for example, in addressing the stakeholders' approaches to the analysis methodology. Stakeholders must first analyse the feasibility of aligning their respective needs, and establishing as the goal a reduction in clinical development plan variability rather than a guarantee for coverage. It will be necessary to reach a broader agreement on methodological approaches and to agree on guiding principles for alignment.

Recommendations

- Establish a mechanism for discussions to take place among HTA groups, regulators and industry on modernising and evolving the needs for alignment; patients and providers could be included as next steps
- Discover what HTA groups and payers want to know; these groups need to clearly articulate research questions and their specific evidence needs
- Determine consensus on biomarkers: definitions, methods of assessment, application and acceptance
- Streamline data collection and innovate study design by ascertaining the type of endpoints to use, that is, surrogate versus clinical endpoints and how these endpoints will be measured; discuss the development of comparator-arms of trials and the use of non-inferiority versus head-to-head comparisons early in development
- Determine the technical requirements amenable to alignment or information sharing

Syndicate 3: How can patients have rapid access to new medicines where there is an unmet medical need?

The Syndicate was asked to identify recommendations for the role regulators and payers can play to enable the development of innovative medicines for unmet medical needs through the use of real world evidence development experience.

Points for consideration

- Can we avoid a mismatch of outcomes between marketing approval based on surrogate endpoints and a payer refusing to pay for the same product due to lack of real-world outcomes evidence?

- What is the best way to decide upon the required endpoints and information to enable accelerated licensing acceptable to private or public payers? Would this require a list of acceptable and/or unacceptable endpoints or biomarkers to be agreed upon by all parties? Who would decide?
- What conditions are payers looking for that would enable coverage with evidence development? How does this link in with the post-marketing conditions of the regulator?
- Can the models currently used for early release of critical care compounds such as anti-cancer treatments be extrapolated to the early release of a wider set of medicines? How would payers react to this?

Outcome of discussion

Critical issues

Both HTA groups and regulators have discrete information needs. Currently regulatory information needs have largely focused on efficacy and safety, while payers have focused on assessing effectiveness and cost-effectiveness. In order to expedite time and manage development costs, it is desirable that the designs of studies to meet these separate needs be informed by each other, and we should find a way for a single development programme to meet the assessment needs of both groups. However, alignment may not mean that all data needs will be combined into one study, and caution must be taken to ensure that the harmonised information requirements do not entail a development programme so large and costly that it inhibits innovation. This is of particular importance for products for unmet needs, where the number of patients is relatively small, and the development time and costs need to be managed expeditiously.

Harmonisation of HTA guidance across HTA bodies that is similar to the harmonisation being achieved across regulatory bodies through International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) may be one approach. Joint guidance will be needed at the jurisdictional level between HTA and regulatory bodies on how to develop pre- and post-market data requirements for new disease treatments. Both regulators and payers have specific information needs and these should be aligned to the extent possible.

Although conditional access schemes have been used effectively to accelerate patient access to critical care medicines, there are significant barriers to these schemes. Industry fulfilment of phase IV commitments has not been reliable, in some cases undermining trust in potential conditional access plans. However, this unreliability in some cases has been due to practical difficulties in implementing the post-approval studies, and it is not clear that these difficulties would be encountered if clearer study commitments were part of an aligned conditional access agreement.

Recommendations

- Align the data requirements to enable earlier decisions for marketing authorisation and access, and implement single development programmes that meet these needs where feasible and affordable
- Harmonise guidance to industry across HTA bodies
- Develop joint guidance at the jurisdictional level between HTA and regulatory bodies on clinical development plans for specific conditions, focusing on data requirements
- Harmonise HTA and regulatory post-marketing requirements, where possible
- Allow payers to calibrate penalties for failure to meet post-marketing commitments through decreasing levels of reimbursement; this would encourage rapid, early access while providing incentives for adherence to stringent post-marketing surveillance

Syndicate 4: How can you use HTAs and regulation to enable innovation?

The Syndicate was asked to identify recommendations for the role regulators and payers should play in enabling the development of innovative medicines.

Points for consideration

- What are the incentives that regulators can provide to stimulate innovation?
- What are the incentives HTAs provide can use to stimulate innovation?
- Is early dialogue the only answer, or is it possible to set criteria for innovative change in particular therapy areas?
- Will harmonisation or alignment of the scientific and technical requirements for

phase III clinical development or for post-marketing studies help achieve this goal or is more needed?

Are new approaches to drug development such as adaptive designs and early (end of phase II) release needed to stimulate innovation and if so, then how would the different stakeholders view such changes?

- Should authorities be incentivising incremental innovation as well as milestone step-change innovation?
- What are the steps authorities would implement for companies to actively engage in the incentive programmes?

Outcome of discussion

Critical issues

It is important to understand that innovation may be defined differently by all stakeholders. The regulatory definition would centre on improvements in efficacy and safety, whilst HTA might prioritise cost per quality-adjusted life years and impact on budget as the key elements of an innovative therapy. The societal point of view would be as diverse as its members: patients, payors, employers, clinicians, health economists and actuaries and might define innovation by focussing on quality of life, work hours saved, or rates of survival.

Strategies

Incentives for innovation can include regulatory strategies such as accelerated and priority review schemes, or through extending the exclusivity period for innovative products. HTAs can encourage innovation through the acceptance of surrogate endpoints as predictors of patient improvement, rather than relying solely on real-world effectiveness experience. An ever improving clinical infrastructure can also advance innovation through the acceptance of adaptive trial designs, the support of trials using expert physicians and through the development of combination products and a focus on personalised medicine.

Recommendations

- Partner with academic, patient advocacy groups, and government agencies to create clinical trial infrastructures that provide high-quality data in a patient friendly environment
- Meet early and often with regulatory and HTA groups and include the viewpoints of patients, payers, providers, patient advocacy groups, and employers in study designs and development programmes
- Understand during drug development the endpoints and supportive data that define the value of the product
- Have the Institute organise a Workshop to create the environment to foster guidelines that define and align the current and future needs of regulators and HTAs
- Create incentives from both HTA and regulatory agencies to foster innovation while requiring transparency and building consensus

Panel presentations

Regulator-HTA interactions that drive innovation

Jean Slutsky, *Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, USA*

Since 2005, the Agency for Healthcare Research and Quality (AHRQ) has been the sole agency with a comparative effectiveness research (CER) programme authorised by the US Congress. The agency has experienced explosive growth in the past 5 years, going from a budget $15 million to $350 million, and puts much of its emphasis on training the next generation of the research community.

In the United States, CER, which compares health interventions, can be perceived as being broader than health technology assessment (HTA), which assesses one technology at a time. For example, a CER study can be designed that looks at the broad spectrum of treatments for a particular condition from drugs to surgery to behavioural intervention. This type of evaluation can add several additional degrees of complexity when compared with HTA, and methods for a simple HTA may not be sufficient for complex CER study, which may be a systematic review or a large adaptive trial.

One way that the AHRQ has dealt with this complexity is to employ horizon scanning, trying to anticipate the needs of decision makers some years in advance. The AHRQ also uses systematic reviews of the medical literature to identify knowledge gaps in ways that can inform researchers and funders of research. In addition the AHRQ commissions and funds new research and works at getting the findings implemented into the fabric of clinical practice and clinical decision making.

When considering the future role of CER in the US, it is important to identify the stakeholders in the research and the context in which it may be used. Whereas there has historically been an issue of substantial distrust between patients and payers, there recently seems to be more of an alignment of goals between the two groups. Another aspect of CER that has seen recent improvement is the evaluators' access to proprietary clinical trial evidence, which in the past has been spotty.

Whether CER seeks to identify treatments that are equivalent or better than current treatment is an important issue with serious potential impact on implementation. Other issues such as monitoring cohorts outside a registry, using distributed research networks to collect real-world data, and governance issues must all be dealt with transparently. CER can speed innovation by helping to identify populations for which the benefit of the treatment is greater than for the population as a whole. CER methods should be regarded as an innovation in themselves, however, and the evolution of methods over time should be examined so that CER is designed to be as rigorous and transparent as possible. A discussion of methods of research across a distributed system is critical especially as regarding registries, which may be the only venue to study certain conditions.

There has been much discussion about the CER infrastructure in the US, and a little over half of the $350 million spent thus far has been dedicated to the creation of that infrastructure and methods based on it. It is important to remember that as a public good, CER is not solely the responsibility of industry and will benefit from a true public-private partnership.

Dr Sharon Levine, *Associate Executive Director, The Permanente Medical Group, Kaiser Permanente, USA*

Kaiser Permanente is a large healthcare delivery system representing the integration of a health plan, a set of hospitals and eight fully dedicated multispecialty group practices in eight geographic regions. It operates much like a small national health system, caring for 8.5 million beneficiaries. The Group operates with a global budget and the decisions about allocation of resources are made jointly by the health plan, the hospital organisation and the leadership of physicians groups in partnership. Like many tax-funded health systems, it has to make tradeoffs in deciding among multiple goods, which is not necessarily typical of the US environment.

HTA, and to a much smaller extent, CER goes on everywhere in the United States, from the organised and systematic investments that the AHRQ makes, to physicians deciding between two new drugs based on the information dossiers from competing drug companies. Additionally, there are 100 million payers who make decisions about value every day when they decide to fill a prescription or follow through their physicians' advice. Over the last ten years, the CER model has moved away from a coverage-versus-non-coverage model and now makes decisions based on clinical quality and

efficacy and the economic model, managing access through the tiering of pharmaceuticals. This allows payers to remove themselves from the position of restricting access to potentially beneficial or potentially lifesaving therapies but allows a customised approach to address specific patient needs in a cost-effective manner.

Payers want one dollar of health value for every dollar spent, but imperfect information is often used to make value assessments and this ratio may therefore be hard to attain. In considering reward for innovation, many stakeholders believe the market has very amply awarded innovation. But the definition of innovation has not been clear and the ability of a payer or patient to distinguish "new" from "improved" or actually producing incremental health value is very difficult given the diversity of health information sources in the US on which such decisions must be based.

The US political environment is contradictory: there is the simultaneous belief that we should only pay for what works and yet we have specific prohibitions from using the product of government-funded CER for coverage decisions. There has been much discussion in the United States about new pharmaceutical business models and evidence-based pricing strategies, in which the evidence would dictate market price as it accrues, versus the notion of risk sharing, which is not a strategy that is likely to work in the United States in the short run.

With the possible exception of Medicare, the ability of a private payer in the United States to drive reimbursement is limited. This is particularly true for an innovative or sole-sourced innovative product, which is very difficult to exclude from coverage. There is almost no negotiation of price for pharmaceuticals based on the level of evidence. Pricing opportunities can only be obtained through the opportunity for refusal in a crowded or competitive field or by committing to a percentage of prescription use. In the United States, 70% of medical care is delivered through practices of three physicians or less, and these physicians are reluctant to abide by prescription use commitments made without their input. This lack of unity remains as a huge challenge in the United States and is one of the reasons that there has been so much difficulty in organising the prescriber market to force manufacturers to compete for value.

The Kaiser Permanente drug information services organisation is able to begin to track new medicines while they are still in the pipeline, supporting our 15,000 physicians with an independent, credible source of information about the relative risks, benefits and costs of medications as they are brought to market. This information is not available, however, to the largest part of the market in the United State and the combination of its absence along with heavy direct-to-consumer marketing and physician detailing may further explain the inability to organise prescribers to make independent fact-based decisions about the value of new medicines.

Dr Supriya Sharma, *Director General, Therapeutic Products Directorate, Health Canada*

All stakeholders across the spectrum of medicine development will need to adjust to the challenges posed by the increased availability of orphan drugs and combination products and from the growing influence of the personalised medicine approach to therapy. Medicines are now being evaluated for efficacy, comparative efficacy, effectiveness, relative effectiveness and comparative effectiveness. Although different types of studies may be required to support those evaluations, there are many studies that can be designed to answer multiple questions.

Early and frequent scientific consultation with both regulators and HTA agencies is often cited as a particular need, but in reality, it does not seem to occur. There currently is a programme in Canada designed for the sharing of information among these stakeholders prior to authorisation. In the nine months since this programme has been available, however, not one pharmaceutical company has come forth to take part.

It may be that companies are reluctant to ask questions unless that they are fairly certain of the answers they will receive. In fact both regulators and companies are uncomfortable with uncertainty, but somewhere the cycle needs to be broken to help build certainty into the process. The situation is similar to that faced by regulators prior to ICH 20 years ago, when the discussions also centred on harmonisation of heterogeneous systems. The question of what value lies in this current push for harmonisation has not yet been fully answered, however, and harmonisation only where it makes sense may be the best place to start. For example, in the regulatory arena, although the common technical document (CTD) and the Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety

and Performance of Medical Devices (STED) document, relate primarily to the organisational structure of the information presented in a dossier, they are extremely helpful and a similar single structured assessment format may be valuable in the HTA environment.

From a reviewer perspective, it is inefficient and frustrating to work on a priority review of a new medicine in a shortened time frame only to have the medicine ultimately not go to market for lack of data to enable a pricing or reimbursement decision. In Canada, both regulators and HTA stakeholders have each already learned a great deal about the realities faced by the other group. Regulators may not yet have a tremendous amount of comfort in the area of comparative effectiveness research, but that is expected to improve with time. Every gate keeper in the system, whether regulatory, reimbursement, payer or comparative effectiveness assessor, is now looking at which levers to use most effectively to ultimately improve access to innovative medicines.

Dr John Jenkins, Director, *Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, USA*

Because the United States has much more of a free-market economy with many payers compared with single-payer jurisdictions, the US FDA is unlikely to be the driver linking the needs of regulators and payers. The FDA diligently adheres to its remit not to include a consideration of costs in its evaluation of medicines, and the consideration of whether a new therapy adds value to the system as part of the decision-making process is rare. Furthermore, as has been previously stated, this country's position regarding CER can be seen as paradoxical: spending millions of dollars to implement research, and then severely restricting the use the resulting information.

Payers almost always deal at the patient level, making value-added risk-benefit decisions for individuals, whereas regulators need to make societal decisions based on whether a drug has been shown to be effective and safe, given its benefits and instructions for use. Accordingly, a drug may be approved by regulators on a population basis, even if it is associated with a very rare risk of a serious adverse event, which may represent an unacceptable risk for an individual. It is, therefore, the HTA/payer's role to assess the patient-level risk associated with this therapy.

Emerging science can bring HTA/payers and regulators closer together, however, by better defining individuals that would receive the greatest benefit from new therapies as well as those at risk for adverse events. For example, clinical trial results may show a 10%, statistically significant improvement in symptom scores, meaning a product meets the requirements for efficacy, but we now may be able to identify the 10% of patients who drive that improvement as well as those who show no improvement. As a result, payers can have better data concerning whether an individual has, for example, the enzyme systems or genetic markers of someone who would benefit from a drug, enabling them to pay for therapies of optimal value to individuals.

There have been some interactions between FDA and the Centers for Medicare and Medicaid Services (CMS), and this may be the most logical US payer-regulator collaboration at this time. However, despite the fact that both groups operate from the same government department, there are tremendous legal hurdles to overcome for the FDA to share information received from sponsors across both groups. Likewise, strict conflict of interest rules governing FDA employees and their families may not apply to CMS personnel. Despite these challenges, the two groups have begun to interact and the FDA has recently shared information and observations with CMS relevant to its upcoming advisory committee meeting on exclusive sourcing agreements (ESAs). Such activities may lay the groundwork for innovative approaches to expediting patient access to medicines.

Workshop Programme

Session 1: Review and reimbursement: Understanding the dynamics and how they are evolving	
Chairman's welcome and introduction: The changing face of healthcare in the USA	**Dr Garry Neil**, *Corporate Vice President, Corporate Office of Science and Technology, Johnson & Johnson*
US healthcare reform and global drug development	**Dr Janet Woodcock**, *Director, US Food and Drug Administration Center for Drug Evaluation and Research*
Healthcare reform in the US: Implications for the development of new medicines?	**Dr Murray Ross**, *Vice President, Kaiser Foundation Health Plan; Director Kaiser Permanente Institute for Health Policy*
Where are licensing authorities, HTA agencies and decision makers going in the next 10 years and what is the pathway to the future?	**Dr Freda Lewis-Hall**, *Chief Medical Officer & Senior Vice President, Pfizer*
Drug development in the era of comparative effectiveness: 10-year horizon	**Dr Janet Woodcock**, *Director, US Food and Drug Administration Center for Drug Evaluation and Research*
HTA/Decision-maker perspective	**Dr Clifford Goodman**, *Vice President, The Lewin Group*
Registration (Approval) vs payment	**Dr Robert Temple**, *Director, Office of Medical Policy, US Food and Drug Administration*
HTA: View from the Technology Evaluation Center	**Dr Naomi Aronson**, *Executive Director, Technology Evaluation Center, Blue Cross/Blue Shield Association*
Review and reimbursement: Aligning the needs and requirements in clinical development	**Dr Timothy Garnett**, *Chief Medical Officer & Senior Vice President, Global Medical Regulatory and Safety, Eli Lilly*
Session 2: Global implications of an increasing emphasis on HTA requirements in drug development	
Chairman's introduction	**Dr Paul Huckle**, *Senior Vice President, Global Regulatory Affairs, GlaxoSmithKline, USA*
(How) is the EMA adapting to include the needs of HTAs and payers?	**Prof Hans-Georg Eichler**, *Senior Medical Officer, European Medicines Agency*
European network for HTA joint action between European Commission and EU member states	**Prof Finn Børlum Kristensen**, *Director, EUnetHTA Secretariat; Chair, EUnetHTA Executive Committee*
What is the pathway to the future of sustainable drug development?	**Dr Garry Neil**, *Corporate Vice President, Corporate Office of Science and Technology, Johnson & Johnson*
Session 3: Focus session : Getting to the right evidence at launch and post-launch	
Chairman's Introduction	**Prof Adrian Towse**, *Director, Office of Health Economics*
The challenge of the lack of evidence for HTA at launch: Some solutions create more problems than they solve	**Andrew Mitchell**, *Strategic Advisor, Department of Health and Ageing, Australia; Chair, HTAi Working Group on Surrogate Outcomes*
Coverage with evidence development	**Dr Steve Phurrough**, *Chief Operating Officer & Senior Clinical Director, Center for Medical Technology Policy*
Pay for performance and risk sharing: An industry perspective	**Alison Lawton**, *Senior Vice President, Global Market Access, Genzyme*
Why is risk sharing largely a non-US phenomena?	**Prof Lou Garrison**, *Professor and Associate Director, Pharmaceutical Outcomes Research and Policy Program, University of Washington*

Section 3: Workshop Presentations

Session 1: Review and reimbursement: Understanding the dynamics and how they are evolving

Chairman's Welcome and Introduction: The changing face of healthcare in the USA

Dr Garry Neil

Corporate Vice President, Science and Technology, Johnson & Johnson

It's been apparent for many years that healthcare costs are rising around the world. Of course much of the increased healthcare cost is a result of increasing demand, rather than being technology driven. Older individuals consume more healthcare and the entire developed, and increasingly the developing world, is aging. Despite representing only a small fraction of healthcare expenditure, and contributing significant value and cost reduction, pharmaceuticals have been a favourite – and easy target – for cost cutting. Citing low success rates and their associated high development costs that translate into product costs that are difficult for some payers to justify, some have argued that pharmaceutical costs are the main cause for healthcare inflation. The decline in pharmaceutical productivity, however, was not for a lack of effort. US companies invest an average of 20% of their annual sales into research and development, about four times the average of all other industries and almost twice as much as the computer industry. Aggregate R&D spending has almost quadrupled every ten years, from less than $1 billion in 1970 to over $91 billion in 2008. The predictability of the value of investments, however, is less certain than for other industries and risk assessment is top of mind for investors. To address these and related issues, there has been a call for the application of improved regulatory science and tools. The question now that the US Healthcare Reform bill has become law is where do we go from here?

US healthcare reform and global drug development

Dr Janet Woodcock

Director, Center for Drug Evaluation and Research, US Food and Drug Administration

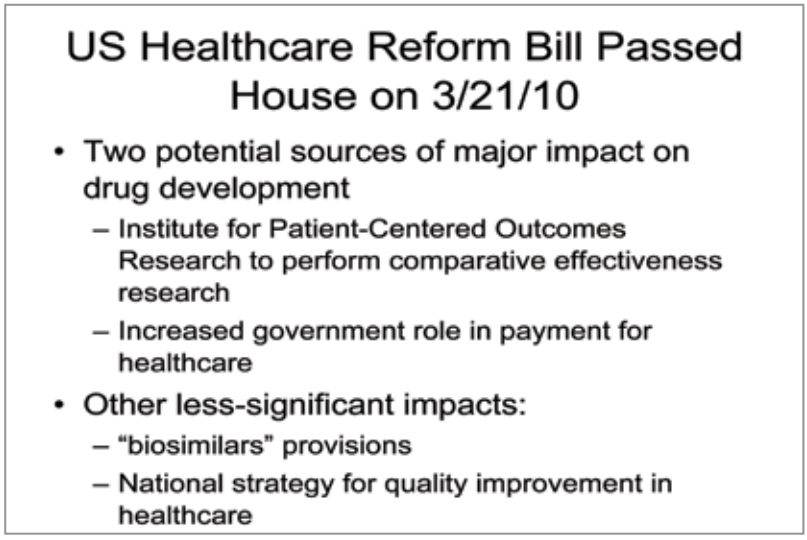
As the US Healthcare Reform Bill, the Patient Protections and Affordable Care Act (PPACA), passed into law on 21 March 2010, just two days prior to this Workshop, two potential sources of major impact on drug development have emerged: the Patient-Centered Outcomes Research Institute and the increased government role in payment for healthcare.

Patient-Centered Outcomes Research Institute (PCORI)

PCORI is a non-governmental, non-profit corporation with a mandate to work on comparative clinical outcomes research, set a research agenda and carry out that research.

It is further expected that PCORI will develop methodologic standards for CER within 18 months using a board appointed by the comptroller general of the United States. Ultimately it is charged with publishing its findings.

Dr Woodcock explained that according to the healthcare reform bill, the purpose of PCORI is to "assist patients, clinicians, purchaser and policy-makers in making informed health decisions by advancing the quality and relevance of evidence concerning the manner in which diseases, disorders and other health conditions can effectively be managed…through research and evidence synthesis, and the dissemination of research findings." The healthcare bill goes on to define comparative clinical effectiveness research as "research evaluating and comparing health outcomes and clinical effectiveness, risks, and benefits of two or more medical treatments, services, and items. Healthcare interventions, protocols for treatment, care management and



delivery procedures, medical devices, diagnostic tools, pharmaceuticals, integrative health practices and other strategies…."

Despite this broad remit, limitations for PCORI have also been outlined: "research findings should not be construed as mandates for practice guidelines, coverage recommendations, payment, or policy recommendations." Neither shall the comparative healthcare statute be construed "to permit the Institute to mandate coverage, reimbursement or other policies for any public or private payer." There are other limitations on certain uses of CER data contained within the reform bill: "the Secretary may only use CER data to make coverage decisions through an interactive process that includes public comment. The Secretary is not authorised to deny coverage of items or services under Title XVIII solely on the basis of CER, nor use CER in a manner that treats extending the life of an elderly, disabled or terminally ill individual as of lower value. Furthermore, the Institute shall not develop or employ a dollars-for-quality adjusted life year or similar measure as a threshold to establish what type of healthcare is cost effective or is recommended." Finally, the bill contains language to terminate the "Federal Coordinating Council for Comparative Effectiveness Research." Therefore, the practical limitations imposed on the use of the data collected through the Institute cast uncertainty on how the findings can most effectively be interpreted by clinicians and be implemented by public and private payers.

Increased role of government in healthcare, including pharmaceuticals

It is expected that as the Federal government's involvement in healthcare increases lawmakers will pay more attention to the underlying sources of rising cost. Because PCORI is initially not likely to play a significant role in evidence generation about comparative effectiveness of drugs, it can be postulated that pressure will instead be exerted through FDA regulatory pre- and post-market requirements.

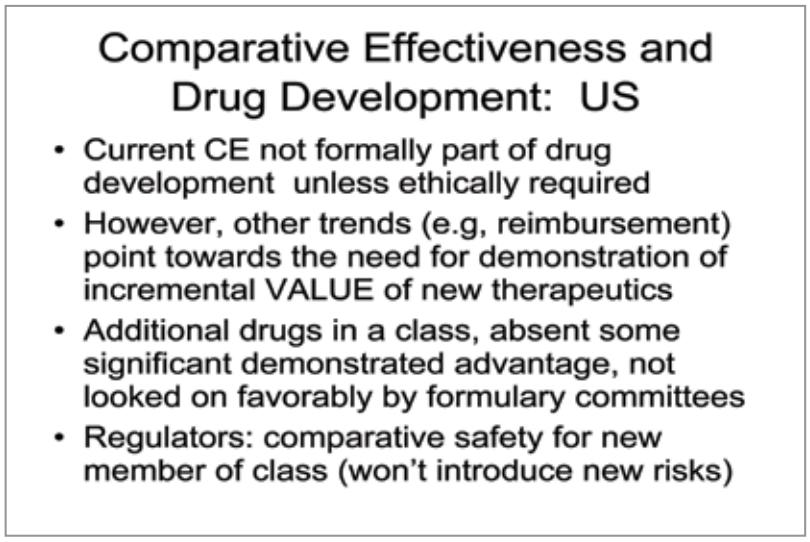
Comparative effectiveness (CE) and drug development

Currently, drug development is in crisis with costs, particularly those for pivotal clinical trials, rising without concomitant rises in their efficiency. At the same time, regulatory expectations appear to have increased in their stringency. Drug regulators are often therefore caught between conflicting societal expectations and demands.[1] Patients expect access to innovative drugs yet want extensive premarket evaluation to reduce uncertainty about the product's safety and efficacy profiles. Eichler and colleagues point out that eventually, at least in the UK, technology assessors, such as the National Institute for Health and Clinical Excellence (NICE), will contribute to the design of phase 3 development programmes so that the evidence they need will be available in a timely manner. For its part, NICE plans to offer scientific advice at the pre-phase 3 stage. The likely focus of technology assessors on comparative data will also impact the design of pivotal trials.

In the US, CE is not formally part of a drug development programme unless ethically required; however, trends surrounding reimbursement point towards the need for demonstrating incremental value advantages for new therapeutics. Absent some significant demonstrated advantage, new drugs in a class may not be looked on favourably by formulary committees. Regulators likewise will be reticent to introduce new sources of risks for an established class. US drug regulators, with their 40 years of experience in efficacy trial evaluation, do not share the same conceptual paradigms as technology assessors. The methodology of CE evaluations has not had the same level of scientific, legal, political, and economic scrutiny that more traditional placebo-controlled regulatory assessment had undergone, and extensive evolution in these techniques should be expected.

Policy Issues for drug development

Current FDA requirements to prove safety and efficacy can at times be at conceptual odds with real-world information needs. The limited duration of trials do not usually provide long-



term outcomes and restricted entry criteria leave out many subgroups that will be exposed in practice. There is generally a lack of comparison of regimens, combinations of therapies and non-medical product interventions, and trials do not mimic how products will actually be used in the uncontrolled healthcare arena. Therefore, although regulatory requirements have historically driven evidence generation, that evidence has had its limitations and often does not address important broader clinical questions. There has been pressure to increase the comprehensiveness of regulatory assessments, but the balance between the cost of development, the need for the availability of therapies and the level of required evidence needed to make a regulatory decision will be challenging to maintain. There are many evolving questions related to mechanisms to effectively generate solid decision-making evidence. These questions include:

- WHO is responsible for generating this additional evidence?
- WHAT evidentiary standards will be applied? (since "comparative effectiveness" or "outcomes" are at present rolling targets)?
- HOW will the requirement be implemented?
- WHEN in the drug development process should this evidence be generated?

Summary

Federally sponsored comparative effectiveness efforts per se are unlikely to directly impact drug development in US over the medium-term horizon due in part due to societal disagreements over the role of government in this area. The more lasting impact on drug development will be to respond to the increasing costs of healthcare, as payers, including the US government, will seek ways to control costs. Pressures on the development process will be exerted through FDA regulatory pre- and post-market requirements. Unfortunately, the questions surrounding the alignment of regulator-HTA policy issues for pharmaceutical development will probably be pioneered outside the US by regions with single-payer systems.

Reference

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Healthcare reform in the US: Implications for the development of new medicines?

Dr Murray Ross

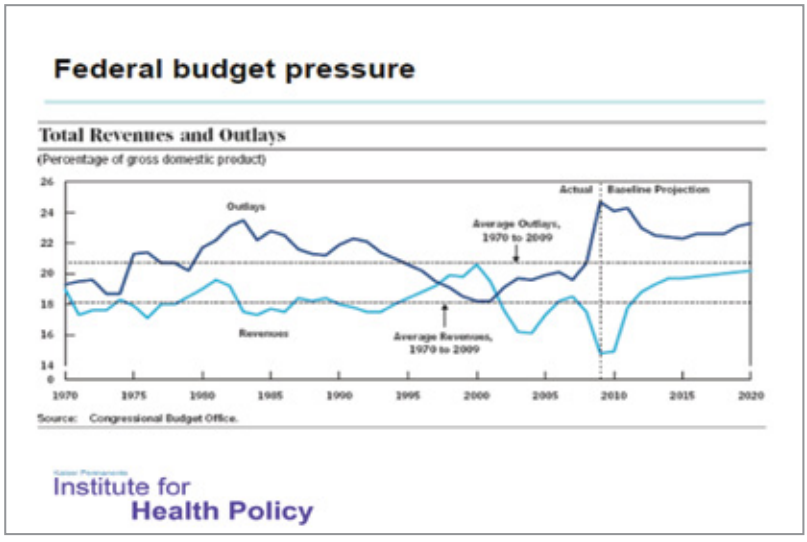
Vice President, Kaiser Foundation Health Plan; Director, Kaiser Permanente Institute for Health Policy

Snapshot of the US health system

Of the 301 million people in the United States, 160 million receive employer-based health insurance coverage, 45 million receive Medicare and 55 million are covered by Medicaid or the Children's Health Insurance Program (CHIP). Coverage, cost-sharing, and provider payments all vary widely. In addition, the system has few consistent rules across payers, a problem with nonpayers and unaligned incentives. In 2010, healthcare spending reached $2.6 trillion or 17.3% of the gross domestic product, with public and private payments accounting for almost equal shares. However, despite the fact that the US is the seventh largest economy in the world, by various objective metrics, the overall quality of the healthcare that its citizens receive is not commensurate with these spending levels.

Where is the public?

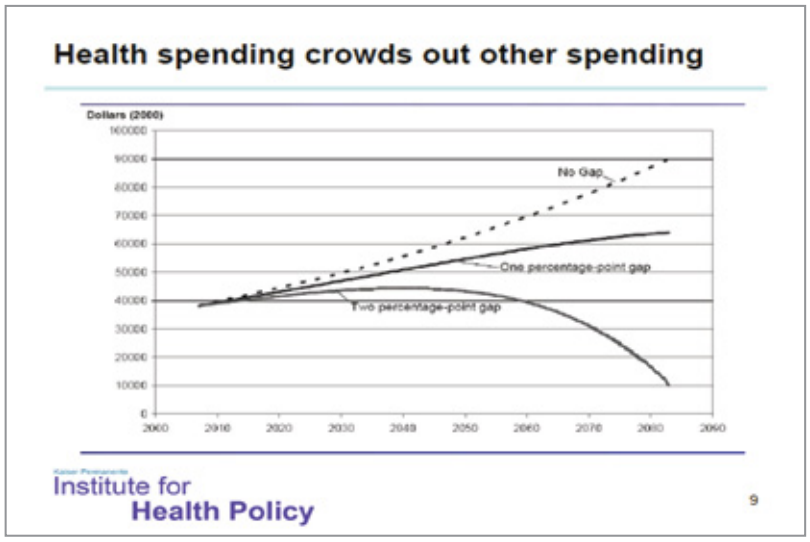
Americans as a whole do not want to see the rationing of healthcare, and the so-called "managed care" revolution was short lived in the US. Despite the observation that approximately one third of Americans receive some form of government-sponsored healthcare benefit, speaking broadly, there is a general distrust of government-run programmes, exacerbated by frequently repeated horror stories of government-rationed healthcare outside the US. Furthermore, because "quality" is a service concept, not a clinical one, American patients have a different perspective on, and expectation for, healthcare compared with regulators, providers and payers. Patients' cost worries centre on their share of premiums and out-of-pocket expenses, and they see industry profits, fraud and abuse as the major cost drivers for healthcare. To some degree, the pharmaceutical industry has benefited from public scepticism of government; the separation of regulatory approval from payment decisions has resulted in explicit non-consideration of costs in coverage decisions. Additionally, there has been political and media pushback on insurers who deny coverage. The changes in healthcare reform are now focussing attention on the interactions of clinical and cost-effectiveness benefits as part of the therapeutic decision-making process.



Health reform: the stimulus bill

US healthcare reform is expected to bring 30 million people into the paid healthcare market and to improve coverage for others. The new bill expands Medicaid to cover 15 million new people and enhances Medicare prescription drug coverage. Private insurance is to be revamped, with new restrictions in place for insurer pricing/underwriting and it is expected that the mandate for coverage for employers and individuals will extend coverage to additional 15 million people.

The bill ensures permanent CER initiatives with joint federal and private funding of $500 million per year initially, but as Dr Woodcock stated, there are limits on the applicability of that research. Funding is also provided to the Center for Medicare and Medicaid (CMS) Innovation Center to pilot delivery system reform. The first round of coverage expansion in the US healthcare reform bill additionally calls for $20 billion for providers who make "meaningful use" of health information technology and $1 billion for clinical CER. These programmes will be funded through new taxes levied on insurers, manufacturers and the wealthy. In addition Medicare payments to health plans and hospitals will be reduced.



Implications

Cost pressures on the US healthcare system will accelerate, with or without government-sponsored reform. Pharmaceuticals are a small piece of overall costs, but a highly visible one. Private payer clients are demanding cost containment because their out-of-pocket expenses rise dramatically each year, whilst public payers are concerned with overall fiscal solvency. We can expect that the feedback loop from payers and consumers to the industry will be faster and more vocal than in the past and pharmaceutical development costs and value for cost will be closely examined. There will be expanded use of registries and health information technology as part of a growing commitment to generate valid and broadly applicable CER data. The question is whether or how the new information will be acted upon. Who will have the incentives to use that information? Will the public support science?

Where are licensing authorities, HTA agencies and decision makers going in the next 10 years and what is the pathway to the future? An industry perspective

Dr Freda Lewis Hall

Chief Medical Officer & Senior Vice President, Pfizer

There is a vast amount of important ongoing research in the pharmaceutical industry, and rather than trying to predict what the future will look like, stakeholders now have an opportunity to decide where they want to be, with a clear, aggressive, specific vision. Fifty years ago, President Kennedy inspired the nation when he said that the United States would be the first to reach the moon within a decade. A similarly clear goal must be articulated for the development of medicines. Our vision should incorporate some specific goals for the next ten years and ways to measure success such as achieving 80% global alignment or subtracting 100 days from standard approval times.

Continued harmonisation and global development must be high on the list of goals; silos and barriers dissipate creative scientific energy. An array of promising compounds are being developed that do not require a common pathway, but a clear pathway, with links and ways to leverage similarities while exploiting unique properties.

Industry has the opportunity to broaden partnerships with regulators, payers, patients and caregivers rather than to institutionalise those relationships. The continuum between the discoverers and the users of medicine is full of hurdles, but asking the right questions will advance our thinking and allow us to convert the possible to the typical. Now and in the future, development strategies should always attempt to arrive at the best outcome to the most patients.

Drug development in the era of comparative effectiveness: 10-year horizon

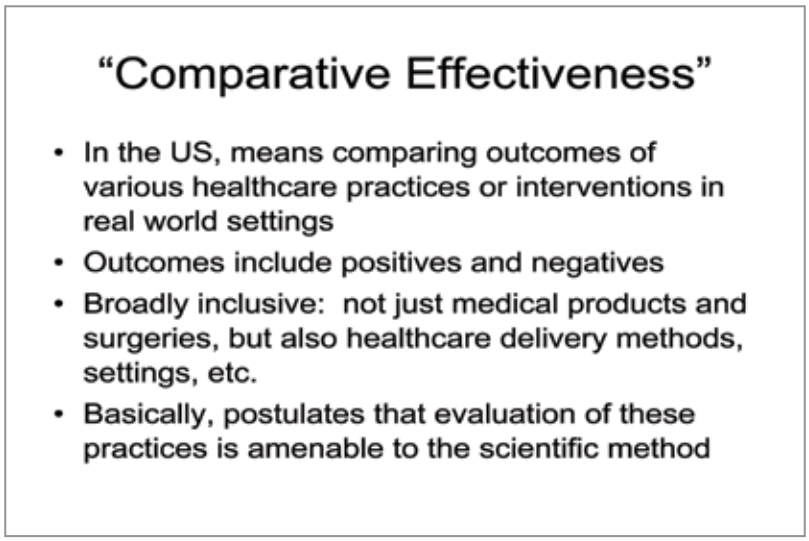
Dr Janet Woodcock

Director, Center for Drug Evaluation and Research, US Food and Drug Administration

Comparative effectiveness and drug development

Dr Woodcock began by explaining that in the United States, the term comparative effectiveness encompasses comparing positive and negative outcomes of various healthcare practices or interventions in real-world settings. The concept is broadly inclusive and in addition to medical products and surgeries also has included assessing the roles of healthcare delivery methods and settings.

Intervention in or prevention of a disease process requires an evidence base that is informative about the outcomes, and when selecting among multiple interventions, comparative data are needed to inform the choice of therapeutic option. The idea of comparative effectiveness as another milestone in the progress of medicine from an art to a science and drug regulation evolves in concert with this progress. While this approach is scientifically and ethically sound, it is tempered by political, social and economic ramifications. The degree of pressure to evaluate outcomes will be proportional to the level of government involvement in payment for healthcare. In response to this stimulus, leaders in technology assessment now appear to be emerging in the first instance from outside the United States.



Evolution of regulatory requirements in the United States

In 1962, amendments to the Food Drug and Cosmetic Act established a requirement for demonstration of a medicine's efficacy prior to marketing, a requirement that was hard won and opposed by many. The next 20 years were spent establishing methodologic approaches and evidentiary requirements necessary to demonstrate efficacy in preapproval clinical studies. Safety assessments were more observational so the focus of efficacy assessment was on a rigorous demonstration that the medicine worked in a defined population.

In the 1990s, the concept of effectiveness (the activity observed in the general population following market release of a drug) as opposed to efficacy (that which was observed during controlled clinical trials) emerged. There was an increasing sophistication in the designation of endpoints and in the overall design of registration trials, with a focus on evaluation in subgroups such as paediatric and geriatric patients. Active-comparator trials became more common, including non-inferiority designs, randomised withdrawals and entry criteria to allow for a fair comparison.

The evaluation of safety evolved as well, although clinical trials still focussed mainly on demonstrating efficacy. The ICH safety database guidance became rapidly outdated. There were efforts to characterise drug metabolism, the role of organ dysfunction and special problems such as cardiac QT segment elongation. Although there were some combined safety and efficacy endpoints in cardiology and a few other therapeutic areas, there were few trials that focussed solely on safety. There has been a significant expansion in the size of clinical programs, however, with many more patients studied for longer durations and a concomitant significant increase in the cost of development programmes.

The historical trajectory of medicine development is clear: there has been a move toward developing greater certainty about drug effects as a basis for approval based on increasing amounts of real-life scientific evidence. Prior to 2007, there was an almost exclusive focus on premarket evidence generation. The US Food and Drug

Administration Amendments Act (FDAAA) puts increasing emphasis on the post-approval monitoring of medicines to more completely characterise each therapy's safety profile.

Enabling efficient and effective drug development: Ideas for the future

In the 1970s, basic biomedical bench research in the United States was extensively supported by the government, while clinical research was the province of the private sector. Consequently, the United States lacks a consistent, robust clinical research infrastructure, which would include standard accredited clinical research personnel and research sites. This lack of cohesive infrastructure underlies several problems in the US: conducting a clinical trial is extremely costly, company-conducted trials can be clouded by suspicion because of a perceived lack of independence, and the majority of clinical investigators quit after a single study experience. Commercial clinical research organisations attempt to fill the gaps, but issues with data incompleteness and integrity, a lack of standardisation of basic procedures and difficulties in accomplishing patient follow-up surround the industry.

Faced with this milieu, how will CER be accomplished in the US? It is unlikely that study designs, will exclusively be observational, non-randomised in nature, but rather may encompass novel approaches such as randomisation by site. However, an integrated US clinical research infrastructure is needed to enable CER and the development of an evidence base for US healthcare practices. Such an infrastructure would enable the cost-efficient conduct of investigational trials in the US, providing access to trained investigators and study personnel, standardised procedures and access to patients for whom data capture and follow-up will be less problematic. Enabling clinical studies to be carried out in the community would allow participation by patients who want to be treated by their own doctors and facilitate the acceptance of the trial results into community care.

New science: Personalised medicine and drug development

In the current difficult economic climate, an increasing scrutiny of the value of new chemical entities is inevitable. Comparisons with alternatives in the armamentarium are also inevitable, and this assessment is now being performed by payers as it is not within the mandate of the regulators. The use of new biomarkers to identify more likely responders and to help differentiate therapies is a promising approach to improving both the size of a treatment effect and its safety. The question facing the healthcare community now is not just "what is the best medicine?" but "what is the best medicine and for whom?"

One way to increase the value of new therapeutics is to use novel markers of treatment response to restrict a treatment population and thereby improve treatment effect. Pharmacogenetic profiling can also improve dosing selection and therefore the safety profile in the target treatment populations. Comparative evaluations will become more common prior to marketing, even if they are not required by the regulators, and drugs that represent a true therapeutic advance will have a significant advantage. Therapeutic advances, however, may pertain to smaller, biomarker-defined subpopulations for whom the drug presents a unique advantage, either in superior safety or efficacy. This is good medicine, not just a good business approach.

Patient advocates are concerned that CER may translate into a cost-minimisation exercise. Some are concerned that the knowledge gained from basic research into the molecular basis of physiology and disease processes will not be incorporated into the overall cost-benefit analysis; therefore, they are advocating for the incorporation of cutting-edge technology applications and scientific rigor in the CER decision-making process.

The application of new science

Better surveillance and intervention is now possible through the use of electronic healthcare records. A stronger post-marketing safety net can help improve value of drug therapy if the resulting knowledge is translated into practice.

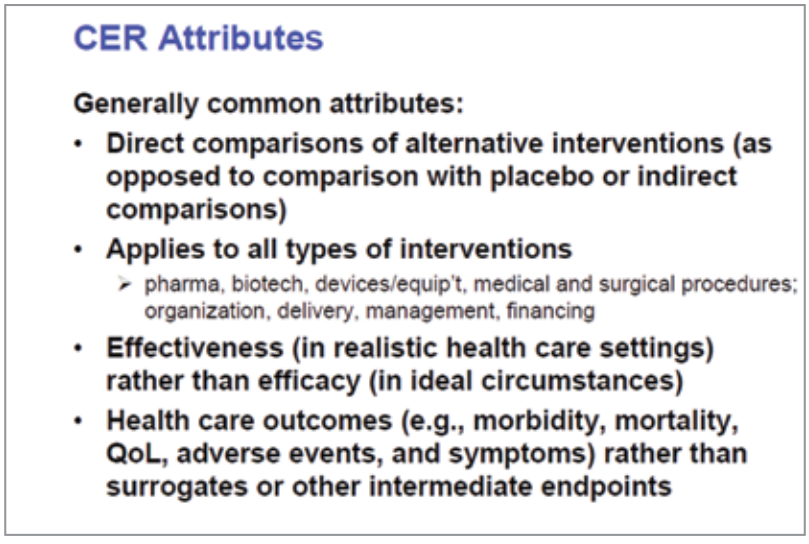
Although it is not wholly clear how or by whom new CER evidentiary standards will be implemented in the US, it is clear that expectations for comparative evidence will continue to evolve. For efficient and effective drug development, a worldwide clinical research infrastructure must be created, science used to increase empiricism in the clinical development and use of medicine, and research enabled with data standards and informatics.

The HTA/decision-maker perspective

Dr Clifford Goodman

Vice President, The Lewin Group

Although health technology assessment has has been the foundation for the practical applications of new interventions for thirty years (Figure1), there are multiple reasons why CER brings a new dimension to therapy assessment. CER has become of increasing importance as evidence has emerged of inappropriate use of healthcare technologies, including over-use, under-use, and improper use, as well as evidence of large variations in their application in clinical practice. Moreover, there is inconsistent or insufficiently rigorous evidence to justify the safe and cost-effective use of some technologies not regulated by FDA, such as many medical and surgical procedures, and CER can provide the justification for the rational use of these therapies. A lack of head-to-head comparisons of alternative interventions for particular health problems is paired with a lack of evidence in real-world practice. The data used to support market approval by a regulator are often not sufficient to support broader clinical and policy decisions. Finally, the continued and rapid increases in healthcare costs have made CER essential. All of these factors make CER a critical decision-making tool for the HTA evaluator.



CER attributes and methodology

The generally common attributes of CER include direct comparisons of alternative interventions (as opposed to comparison with placebo or indirect comparisons); its applicability to diverse types of interventions such as pharmaceuticals, biotechnology, devices and medical and surgical procedures as well as in healthcare organisation, delivery, management and financing. In addition CER measures effectiveness in realistic healthcare settings, rather than efficacy in ideal circumstances, together with clinically relevant healthcare outcomes such as morbidity, mortality, quality of life, adverse events, and symptoms rather than surrogates or other intermediate endpoints.

The methods of CE are evolving and include all types of clinical trials: randomised, nonrandomised, controlled, practical (pragmatic); adaptive; regression; discontinuity; combined; and single-subject trials. Observational studies for CER, whether prospective or retrospective can be population-based longitudinal cohort studies; patient registries; claims databases; clinical data networks; electronic health record data analyses or active or passive post-marketing surveillance. Syntheses of existing evidence can also be performed for CER, including systematic reviews (comparative effectiveness reviews),

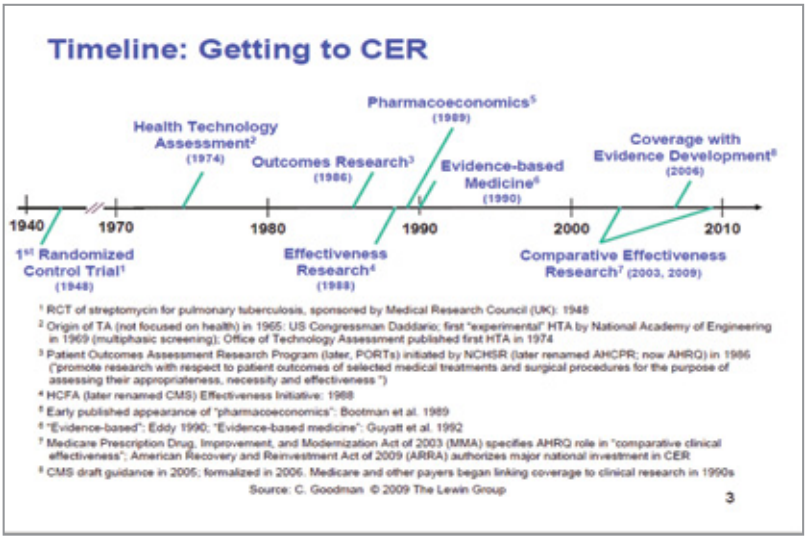
meta-analyses or modelling.

The value of CER is apparent in making coverage determinations. For example, the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC), examines available evidence pertaining to current or potential national coverage determinations made by the Center for Medicare and Medicaid Services (CMS). MEDCAC uses strategies that help identify the critical aspects of new therapies and their place in the treatment continuum.

Incorporating personalised medicine into CER

It is clear that the block-buster approach to new drug development is now being supplanted by the use of technologies that identify the right therapy for the right patient, underpinning the personalised medicine approach. For CER to contribute to personalised medicine, it will have to emphasise characteristics and study designs that account for individuals' genetic, behavioural, environmental, and other personal traits that mediate the impact of screening, diagnostic, therapeutic, and other interventions on patient outcomes. To date, only a small percentage of published comparative effectiveness studies have focussed on treatment effectiveness in patient subgroups.

The extent to which population-based evidence can be used to inform healthcare decisions for specific individuals depends not only on how well the study population represents those individuals, but also on whether the study designs and analytical methods used are capable of detecting important treatment effects and adverse outcomes for the patient subgroups representing those individuals. Contributing to the appropriate study design and analytical methodologies will be one of the main challenges for HTA decision-makers.



Essential role of HIT for CER in personalized medicine

Health Information Technology (HIT) can help align CER and personalised medicine in at least two main ways. First, through the capture of genetic and other personal health information from clinical trials and clinical practice in electronic health records, HIT can support CER to augment the evidence base to identify best therapies as part of a personalised medicine approach. Second, clinical-decision support systems and other forms of HIT can ensure that evidence pertaining to personalised medicine is present and actionable at the point of decision making by patients and clinicians. Despite these advantages, adoption of HIT has been slow but may now be stimulated by the new US Healthcare Reform Bill.

The assessment of safety and efficacy that is required for marketing authorisation should not to be confused with assessments of relative or comparative effectiveness that are used for non-regulatory decisions. To this end, the EU Working Group on Relative Effectiveness has been formed with the stated goal that it "aims to support Member States by the application of relative effectiveness systems in order to allow containment of pharmaceutical costs as well as a fair reward for innovation. Relative effectiveness assessment systems are comparatively new for many Member States and rather complex. Nevertheless, the outcome of relative effectiveness assessments is promising as they will help identify the most valuable medicines, both in terms of clinical efficiency and cost-effectiveness, and will help set a fair price for these medicines. The Working Group will bring experiences of different Member States and of industry together in order to further develop this promising field."[1]

The EMA statement on relative effectiveness concludes "The notion of the assessment of benefit-risk of a new product being informed by an active comparator is considered part of the assessment of efficacy and safety and fundamentally different from the concepts of placing the product in the therapeutic strategy or relative effectiveness which implies two components: the added therapeutic value and cost effectiveness. These two components go beyond the standards of marketing authorisation (quality, safety, efficacy)."[2]

Compared with the European approach to relative effectiveness, the US approach does not yet have a formal "home" or centralised driver and has only indirect, non-explicit ties to policies and decision making. CER findings have been designated as nonapplicable for government reimbursement or practice guidelines. US CER has the potential to play a major role, on reimbursement, however, with its emphasis on personalised medicine, which derives from subgroup analyses.

Implications for Life Sciences Industry

It is not clear how CER evidence requirements will inform regulatory, payment or other HTA decisions. In any case, the evidence standards will remain high because it is particularly difficult to demonstrate superiority versus an effective standard of care, or the impact of screening and diagnostics (including pharmacogenomics) on health outcomes, or statistically significant treatment effects in subgroups. CER and HTA redefine the concept of "value" and can shift the direction of innovation, thereby resulting in both opportunities and shakeouts. Industry should anticipate the need to integrate the collection of specific types of evidence requirements throughout the technology lifecycle, considering who will want what evidence and when. Strategies for developing products for broad, population-based indications versus subgroup or personalised medicine will become the focus of intense debate.

Expanded support of US-based CER and HTA will increase global capacity and rigor for assessing technologies. Pharmaceutical developers are advised to track the evolving priorities of CER and its use by HTA. CER, HTA and related trends may suggest a need to change decision processes for innovation, validation and commercialisation.

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Registration (approval) vs payment

Dr Robert Temple

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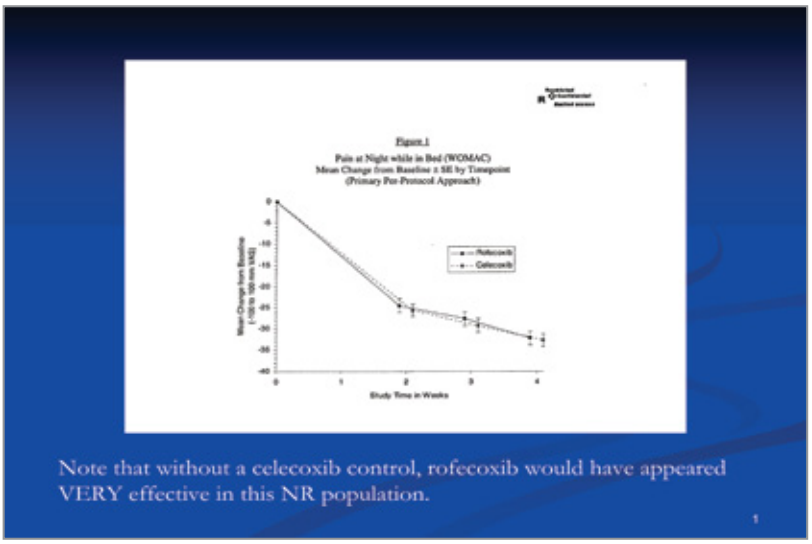
Regulatory status

Except where the possibility of a new drug being less effective than a standard can result in a clinically dangerous situation, the FDA does not have a clear ability to insist that a sponsor submit comparative effectiveness data as part of a new drug dossier. Where the use of a placebo would be unethical and only an active comparative study can be done, there are sometimes studies showing an advantage of the new drug over the control, but more often these studies are designed as "non-inferiority" studies. These were once called "equivalence studies" but in fact, showing true equivalence, that is, ruling out any possibility of inferiority, is only possible by demonstrating superiority, and proving even a reasonable degree of similarity (within an 80% to 125% confidence interval) is statistically demanding when the endpoints are clinical rather than pharmacokinetic. Furthermore, merely showing non-inferiority (or equivalence if you could do it) to the older, more established therapy would not make a very strong case for using a new medicine. So how can the case for reimbursement for a new drug be made?

Why a new drug?

Case 1: Different pharmacologic class – Easier

In general, clinicians and patients like to have pharmacologic choices, because they expect therapies with different pharmacologic actions to demonstrate differences in response or safety (whether favourable or unfavourable), even if those differences have not been confirmed in direct comparisons. Moreover, there may be additive effects with another pharmacologic therapy, which is often an important benefit, although the order in which to use the drugs may not be clear from available data. Disagreements persist, for example, as to whether patients requiring antihypertensives



should be treated first with chlorthalidone, which is extremely low in cost or should start with a more expensive class of drug. But on average, a drug of a new pharmacologic class will be included in most formularies and will be used widely, even if the older, more cost-effective agents are generally tried first. Typically, the way to move a therapy to a position of first use is to show a safety or effectiveness advantage through direct comparison, showing effects not achieved with other therapies or showing that an adverse effect of the older drug is avoided. For example, statin outcome trials showed a clear effect on survival not generally observed with other classes of cholesterol - lowering drugs. Similarly, angiotensin II receptor blockers, for example, do not cause cough as their predecessor antihypertensives, angiotensin-converting enzyme inhibitors did.

CATIE

1493 schizophrenics randomized to olanzapine, perphenazine, quetiapine, or risperidone (later ziprasidone).

Endpoint was "discontinuation" of treatment for any cause.

Outcome	Olanz 330	Quet 329	Risp 333	Perph 257	P-value
All DC (%)	64	82	74	75	< 0.002
Lack of E (%)	15	28	27	25	< 0.001
Intolerability (%)	18	15	10	15	

Case 2: Same pharmacologic class – Harder

There is an expectation that drugs in the same pharmacologic class will generally have similar effects, but in some therapy areas, the expectation (proved or not) is that there are likely to be different responses in different patients, and in particular, that non-responders to one drug may respond to another. This expectation can be rigorously tested in appropriately designed studies in non-responders to the earlier class member, by randomising patients to the failed and to the new drug. This was done with clozepine, for example, showing a clear advantage over the failed therapy and allowing approval of a relatively toxic drug (1.5% agranulocytosis) for use in people whom had failed previous treatment. This does not always prove true, as shown in a study of patients with osteoarthritis who had failed celecoxib. These patients were then randomised to celecoxib (the failed drug) or rofecoxib. Despite the reasonable expectation that rofecoxib would be more effective in these patients, that was not seen: the two drugs had identical effects (see figure)

Although it is not easy to show an actual clinical advantage for a new therapy within a pharmacologic class, there have been successes. New therapies could alternatively show some other advantage that is at least a potential gain, such as lack of a particular drug-drug interaction or sensitivity to genetically mediate, reduce or enhance drug metabolism.

Comparative effectiveness studies are challenging and often need to be quite large to detect what are almost always small differences. The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) study, for example, despite 40,000 patients, did not show clear difference between chlorthalidone, lisinopril and amolodipine in treating hypertension. The Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE), in contrast, did report differences. CATIE compared four atypical (olanzapine, risperidone, quetiapine, ziprasidone) and one typical (perphenazine) anti-psychotics used in schizophrenia. Data showed that olanzapine was most effective, being associated with the fewest discontinuations for lack of effectiveness, but it was also the least well tolerated, being associated with the most discontinuations for intolerance. CATIE was considered an effective trial because it did reveal head-to-head comparative differences among the therapies.[1]

In summary there are ways to carve out a

niche for new pharmaceuticals by comparing their profiles to alternative therapies. As noted, demonstrated or not, there is a broad belief that individuals will respond differently to different drugs within a pharmacologic class but solid evidence is needed to justify these actual differences. There has been a decrease in the number of drugs within even popular classes being developed, presumably reflecting difficulties in getting substantial use of a new member of a class (without a clear advantage) especially once some members of the class are available as generics. Hopefully these challenging regulatory and economic conditions will lead to more rigorous study of differences in adverse event profile, non-responders and intolerants, and genetic predictors of response.

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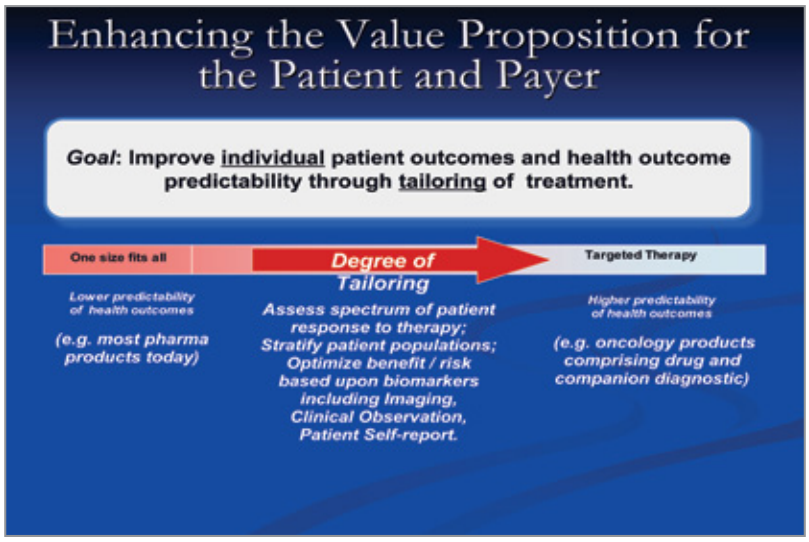
Review and reimbursement: Aligning the needs and requirements in clinical development

Dr Tim Garnett

Chief Medical Officer, Eli Lilly and Company

History of Pharmaceutical Development

In the late 19th century, what came to be called "modern medicine" emerged after a struggle with other forms of medicine, such as homeopathy. This new medicine was grounded in antiseptic surgery, the germ theory of infectious disease, and the scientific method, including reliance on evidence-based medicine and clinical trial results. As early as 1904 the American Medical Association, through its Council on Medical Education (CME), recognised the importance of structured science in medicine by defining a medical education as consisting of two years training in human anatomy and physiology followed by two years of clinical work in a teaching hospital.



The Food, Drug and Cosmetic (FDC) Act of 1938, which imposed a requirement to demonstrate that medicines were safe, was the federal response to the sulfanilimide crisis in which ethylene glycol was substituted for propylene glycol, causing severe toxicity issues. The Kefauver-Harris Amendments to the FDC Act in 1962 created the efficacy hurdle for new medicines and mandated the premarketing testing for efficacy.

While the healthcare professions and regulators have worked to standardise the practice of quality medicine, for more than 20 years, the Dartmouth Atlas Project has documented glaring variations in how medical resources are distributed and used in the United States. The project uses Medicare data to provide comprehensive information and analysis about national, regional, and local markets, as well as individual hospitals and their affiliated physicians. These reports, used by policymakers, the media, healthcare analysts and others, have radically changed our understanding of the efficiency and effectiveness of our healthcare system. These valuable data form the foundation for many of the ongoing efforts to improve health and health systems across America.

The 21st century

Mitigating the continued rise of healthcare costs is now a public priority and the pharmaceutical industry is being asked to be part of the solution in US healthcare reform. Meanwhile, payers and providers are managing access to new and expensive technologies through

a variety of methods that will increase the downward pressure on industry's return on investment. More than 40 countries have pharmacoeconomic guidelines, and health technology assessment is being widely adopted to inform payers in Europe and Asia. In the United States, The Academy of Managed Care Pharmacy (AMCP) Format for Formulary Submissions, a template for health plan formulary submission, has been used extensively since 2000 to inform payer assessments of new medicines. Tiered formularies and benefits, coverage with evidence development and risk-sharing contracts are all new methods of healthcare cost management that are evolving from the use of health technology assessments.

Regulation and HTA assessment

A medicine's efficacy is generally well characterised at launch while its real-world effectiveness can only be estimated. The assessment of a medicine's benefits and risks is the charge of the regulators, whereas assessing or predicating the cost effectiveness of that therapy is the responsibility of the HTA groups. Regulators require valid experimental data to evaluate a new drug while health technology assessors need indicators that will help them assess how the intervention will work in the intended clinical population. Understanding the heterogeneity of that population helps predict the potential variability of real-world response. Regulatory submissions are large, detailed compilations evaluating in details the quality, safety and efficacy of a drug, whereas HTA submissions are comparatively shorter (usually less than 200 pages) and summarise the drug's clinical aspects. HTA submissions also including meta-analyses of the comparators, cost-effectiveness modelling (usually by applying a decision-analytic framework) and scenarios of the impact of the drug's effects based on its use in subpopulations and different placement in the clinical treatment paradigm. The need of regulators for controlled experimental study results, preferably compared to placebo, is in contrast to the need of HTA groups for cost-effectiveness information evaluated against all possible comparators. This divergence can create friction between the two entities in helping to define a sponsor's clinical development programme, in particular, in setting the criteria for the comparisons required and thereby influencing access to medicine and the state of public health.

On the basis of 2005 mortality rate data, nearly 2,400 Americans die of cardiovascular disease each day[1] and approximately 1 in 2 men and 1 in 3 women will develop cancer during their lifetimes.[2] To address this challenging environment we need a unifying principle that links the environmental changes to stakeholders' needs. Some companies will develop new strategies for research and development, commercialisation and industry policy initiatives. Eli Lilly has sharpened that focus even further by uniting under the need to deliver "improved outcomes for individual patients."

Strategy for drug discovery

As the years have passed in drug development, the pharmaceutical industry has had to expand from an inward-based perspective to a more generalised, outward-facing point of view. In addition to the industry's need to develop increased expertise and creative approaches to drug development it also needs to develop research expertise in epidemiology and the broad field of health economics as well as validated predictive patient outcome measures. Efforts to decrease cycle time and make better decisions early in drug development to avoid phase 3 failures must be enhanced by identifying scientific opportunities such as the application of biomarkers and genomics and fulfilling those opportunities by providing the necessary evidence of their value to regulators and payers.

Today, the industry's one-size-fits-all approach to many therapies means that, in many cases, some patients will do better and some won't do as well as expected, in effect providing an overall average outcome for the patient cohort.

At Eli Lilly, the tailored therapeutics programme aims to improve individual patient outcomes and the overall predictability of health outcomes through various types of tailoring – including drug design and dosing. Ultimately, the goal of tailoring is to identify therapies that will benefit specific groups of patients, which will improve their health outcome predictability. The shift to tailored therapeutics will occur at different rates across therapeutic areas due to several factors such as how well we understand the underlying disease biology and pathophysiology, how biomarkers can be used to characterise the illness, and how diagnostic tools can be used to identify patients most likely to respond with limited side effects.

New opportunities

Consultation with scientific and payer thought-leaders during a product's development cycle can identify opportunities to enhance the value of the new product at its launch. By defining the relevant differences of the new product, sponsors will be able to justify the cost value of their new therapies. The supportive information will provide payers with the information they need to make reimbursement decisions and to formulate rational polices for patient access to the new products. Understanding the unique therapeutic value across sub-populations opens the door to novel contracting and pricing strategies. Aligning the requirements of regulators and HTAs during the development cycle by building early partnerships with these stakeholders will support a sustainable business model that will generate an increasing number of valued treatments, based on a more efficient development paradigm.

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Session 2: Global implications of an increasing emphasis on hta requirements in drug development

Chairman: Dr Paul Huckle

Senior VP, Global Regulatory Affairs, GlaxoSmithKline, USA

(How) is the EMA adapting to include the needs of HTAs and payers?

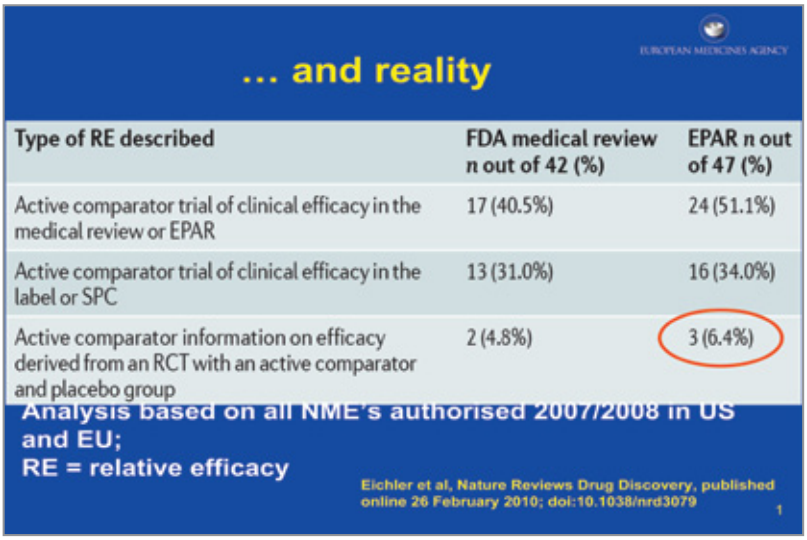
Professor Hans-Georg Eichler

Senior Medical Officer, European Medicines Agency

Interaction between regulators and HTA agencies or payers in the EU – an update

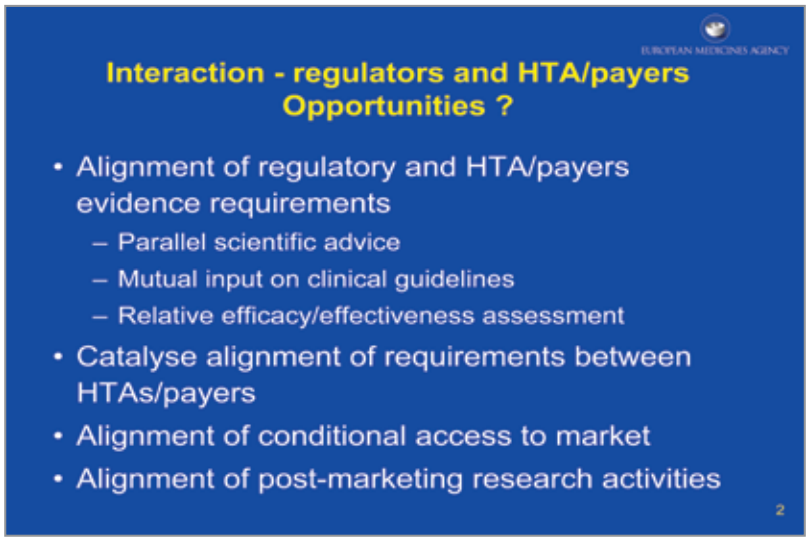
The regional divide within the European Union presents a dilemma. There is one standard for drug approval, one application, one assessment and one decision valid in 27 EU and three European Free Trade countries, but there are more than 30 different health technology assessment (HTA) methodologies and interpretations and more than 30 independent decisions about whether a medicine will be reimbursed.

This regional divide is coupled with the legal and physical separation between regulators and HTAs or payers as well as a separation of mission and responsibilities. Indeed, there was no interaction between the groups until an informal visit by National Institute for Health and Clinical Excellence (NICE) representatives to the EMA as well as various personal interactions in 2007-2008. In October 2008, the High Level Pharmaceutical Forum (HLPF) issued a report saying that "…Member States, with the involvement of the European Medicines Agency (EMA), should continue their efforts to consider how European Public Assessment Reports (EPARs) can further contribute to relative effectiveness assessments.." The report also recommended "continued momentum" on pricing and reimbursement in the EU stating that "Further cooperation and exchange of experiences at EU level is needed." The Commission, in cooperation with Member States, is called upon to build on and bridge the work of the Pricing and Reimbursement Working Group and the Relative Effectiveness Working Group in order to evaluate the direct outcomes and follow up of the Pharmaceutical Forum.[1] February 2010 marked the first meeting between the EMA and the European Network for Health Technology Assessment Joint Action (EUnetHTA JA).



In a letter to the EMA, a group of payers indicated that regulators can further improve the EPARs to facilitate interaction between the two groups by including fewer deviations from the standard template and by the presentation of both medians and means for clinical outcome parameters within the reports. The letter also recommended that a description of pivotal trials in the Clinical Efficacy section of the EPAR should always contain a patient or study flow chart and tables containing relevant data on patient demographics. They made further suggestions regarding the content of the EPARs, and expressed concern regarding the increasing reliance on surrogate endpoints such as progression-free survival and composite endpoints to guide regulatory approval decisions.

Whilst the EMA acknowledges that it is possible to improve EPARs through modifications in data presentation, it is questionable whether harmonisation of evidentiary standards for marketing authorisation and reimbursement is possible. Each group considers different levels of uncertainty to be acceptable and each maintains differing standards for validation. Moreover, regulators and payers hold varying perceptions of clinical relevance and can be at odds regarding methodologic issues such as the validity of quality of life instruments, composite



endpoints, surrogate outcomes and the practical application of Bayesian statistics.

Whilst current EU regulations call for "controlled clinical trials if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value" stating that trials that employ "any other design shall be justified"[2], the reality is that only a small percentage of medicines are approved based on active comparator trials.[3] Therefore, establishing a clinical programme whose design can meet the needs of both regulators and HTAs, may be challenging.

Threat or opportunity?

Harmonisation of the evidence requirements of regulators and payers may be both a threat and an opportunity. A threat if harmonisation would require developers to fulfil the highest possible evidence standards: For example, if regulators require placebo-control trials with objective primary endpoints and HTAs or payers require active-control trials with quality-of-life primary endpoints, then a three-armed study with co-primary endpoints would probably serve all needs. However this might raise the entry barrier to unrealistic levels.

Alignment of regulatory and HTA or payers evidence requirements presents opportunities for parallel scientific advice, mutual input on clinical guidelines, and the design of studies to assess relative efficacy and effectiveness. In addition, these discussions may also enable alignment of conditional access to markets and the design of consistent post-marketing research activities. Considering that the EU has universal, public healthcare systems for which improvement of public health is a societal goal, regulators and HTA-payers are under pressure to make value-added drugs available to their constituents.

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WORKSHOP REPORT

European network for HTA joint action between European Commission and EU Member States

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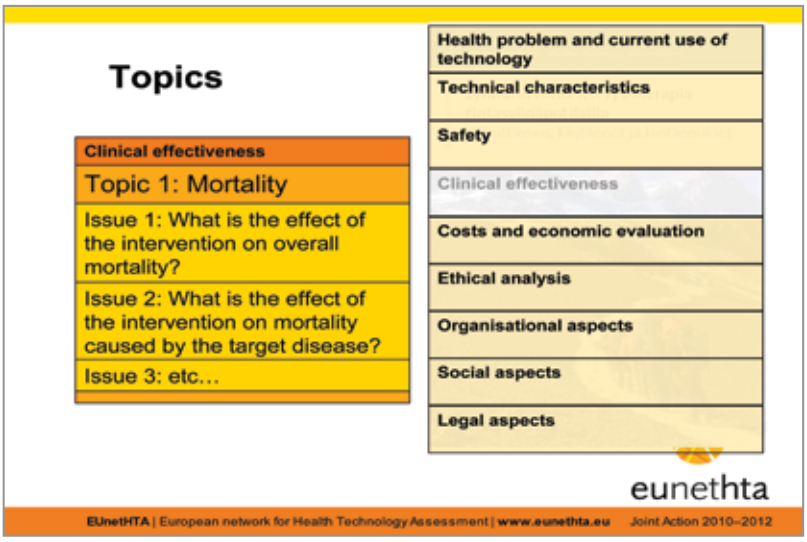
The European network for Health Technology Assessment (EUnetHTA)

Agencies, health ministries, and research groups from 24 countries in Europe united to form the European network for Health Technology Assessment (EUnetHTA), an organisational framework to develop standardised tools for global health technology assessment. HTA itself can be defined as a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. The aim of HTA is to inform the formulation of safe and effective health policies that are patient focused and seek to achieve best value in the use of therapies. HTA must always be firmly rooted in research and the scientific method.

All activities of the EUnetHTA collaboration arise from the premise that its tools and outputs



will be used to inform, but not mandate, the content of national, regional and institutional HTA reports. In the EUnetHTA project, which took place from 2006-2008, the focus was on methodology, but also on developing practical tools for collaboration and good management among partners from European countries and international partner organisations. The final technical report to the European Commission is available online[1] and fourteen related scientific articles were published in the *International Journal of Technology Assessment in Healthcare*.[2]

A variety of joint actions are planned by EUnetHTA within the 2010-2012 timeframe including identifying ways to facilitate the generation of informative evidence and collaboration on pre-coverage assessments of new technologies, developing a business model for the sustainability of the network, and establishing information management systems and other methods of communication and evaluation. The domains of HTA that will be covered in this 3-year cycle will promote the multidisciplinary nature of HTA and have been identified in previous EU projects, particularly the European Commission supported collaboration to harmonise HTA methodology known as EUR-ASSESS and the European Collaboration for the Assessment of Health Interventions and Technologies (ECHTA/ECAHI).

Relative effectiveness assessment of pharmaceuticals

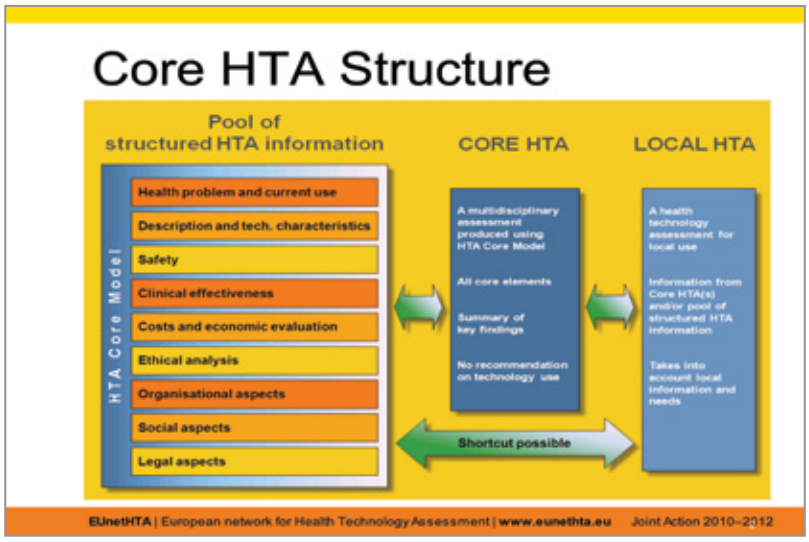
Although decisions on reimbursement for pharmaceuticals can best be made on a national level, relative effectiveness assessment (REA) may be more easily accomplished by integrating experiences from multinational networks. Relevant issues in the REA of pharmaceuticals include the presence or absence of guidelines that inform methodology such as the choice of comparators or the use of clinical endpoints versus surrogate markers. In 2008, the High-Level Pharmaceutical Forum of the European Commission recommended that Member States should exchange REA information, implement agreed good practice principles for REA, and with the involvement of EMA to consider how EPARs can further contribute to REA.

The integration of the REA of pharmaceuticals into the scope of EUnetHTA Joint Action in 2010- 2012 is also envisioned, based on the definitions of the Pharmaceutical Forum's Relative Effectiveness Working Group: "Relative effectiveness can be defined as the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of healthcare practice."[3] A stepwise approach for the integration of REA in the 2010-2012 timeframe is planned, with a background review in 2010 and a proposal of relevant tools and methods for REA consistent with the EUnetHTA "HTA Core Model" through 2011. A framework for the applicability and pilot testing of REA tools and methods are also intended for 2011 with a resulting modification of the model or toolbox and the identification of improvements needed to the available methods, tools and potential gaps. The deliverable planned for these projects is an adjusted model toolbox for REA that is consistent with the HTA Core Model.

Tools for collaboration

There are a steadily increasing number of new health technologies, and decisions regarding their access are often made under conditions of uncertainty regarding their safe and effective use. Policy mechanisms are therefore required that will focus on these promising new technologies, identify evidence gaps and generate additional data to reduce uncertainty while expediting access to their use.

Collaboration on new health technologies is supported and duplication of work reduced by exchanging information and developing common tools to facilitate evidence generation and assessments. Furthermore, pooling expertise and experience aids the timely collection of a critical mass of data. The EUnetHTA Interface to Facilitate Furthering of Evidence Level (EIFFEL) is a web-based toolkit for information sharing



that is helping HTA agencies to exchange and share information on evidence generation. It includes structured and standardised forms for requesting or posting information on promising technologies, an online database, and easy, user-friendly, and quick access to exchanged information.

The EUnetHTA Toolkit for information sharing on new technologies provides information on the level of diffusion of the technology in different healthcare systems, the status of technology assessment and of monitoring actions, measures for evidence generation, protocols and results of clinical studies or registries describing the effective use of the new evidence.

The application of these new approaches should facilitate standardised shared assessment elements where appropriate of new therapies across regions, while still leaving the full assessment to each country which will make its own decision based on a common, robust data collection combined with their own data and analysis process.

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What is the pathway to the future of sustainable drug development?

Dr Garry Neil

Corporate Vice President, Science and Technology, Johnson & Johnson

The process of drug discovery has become riskier and more expensive in recent years in part because we are attempting to modify the process of chronic diseases, where target outcomes have not been well validated and incompletely defined surrogate endpoints add uncertainty to predicting the long-term value of a new medicine. Expectations for safety have never been higher and the proven efficacy and safety of existing drugs must be bested if one is to succeed in the market. The end result has been a steady increase in the complexity, duration, and ultimately the cost of discovery and development, unfortunately coupled with progressively decreasing discovery and approval success rates.

Under the pressure of decreased earnings and eroded public trust, new pharmaceutical development models have emerged such as the "quick win, fast fail" concept in which molecules must demonstrate clear advantages in earlier, less expensive phase II trials. Reliance on external innovations in which revenue is generated through divestiture, product licensing and industry partnership is also growing in prominence. While these new approaches provide a pathway to improved development paradigms, it should be recognised that the perception of an adversarial relationship between industry and regulatory agencies serves no one well. Public trust in the pharmaceutical industry and regulatory bodies must be restored through free scientific exchange between all key stakeholders; patients and caregivers, physicians, and regulatory and industry scientists; in order to craft a sustainable new drug development paradigm.

There are numerous other requirements to build a model for a sustainable future for medicine development, including a consistent, predictable approach to health technology assessment. We

must invest in regulatory science to promote drug safety and in a clinical trials infrastructure to address the critical questions of science.

Patients and their needs must be a primary goal of drug developers, regulators and access controllers and the flexibility of decision making should be controlled by the physician and patient rather than by the legislators. New technology and processes will allow real-time communication of up-to-date benefit and risk information to healthcare professionals and patients, which will improve the correct use of tailored therapies. Ultimately, improved access to medicine can occur as a result of reducing the cost of new product development.

There is a need for consistency and clarity of expectation throughout the product life cycle. Uncertainty repels investment in needed therapies, highlighting the need for better methods of benefit-risk assessment and communications in which the gap is bridged between quantitative analysis and emotional reaction to rare events. Genomics, proteomics, metabolomics have begun to revolutionise biomedical science and medicine. They have also captivated the popular press and greatly raised expectations, and as shown in Gartner's "hype cycle," the true utility of new technologies can only emerge over time.[1] For example, we have discovered more than 1 million single-nucleotide polymorphisms (SNPs) and a number of web-based companies are now offering SNP analyses. However, we have scant data linking phenotype with genotype, as well as a poor understanding of many risk factors, and it's not at all clear how these results can improve therapy selection.

The process of drug development must, therefore, continue to evolve. Over the near-term horizon, within the next five years, we must restore public trust and confidence, increase transparency and open scientific debate, invest heavily in regulatory science modernisation and continue our experiments in new drug development paradigms. Within the next ten years we should adopt the new development paradigms and tools, implement new risk assessment and communication technology, emphasise personalised medicine, and develop products where there is an unmet medical need.

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Session 3: Focus session : Getting to the right evidence at launch and post-launch

Chairman: Professor Adrian Towse

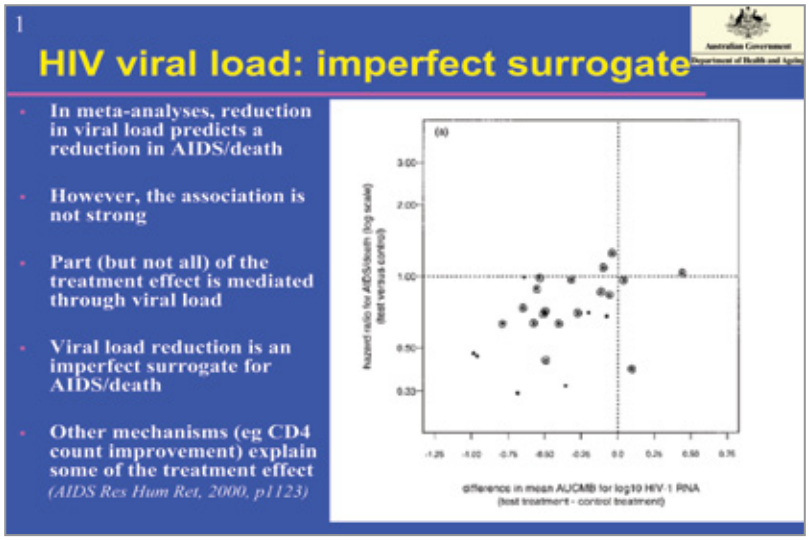
Director, Office of Health Economics

The challenge of the lack of evidence for HTA at launch: some solutions create more problems than they solve

Andrew Mitchell

Strategic Adviser, Evaluation, Australian Government Department of Health & Ageing; Chair, HTAi's Working Group on Surrogate Outcomes

The developers, regulators and payers of new medicines are broadening the questions for research, moving from hypothesis testing to point estimation. They are seeking ways to measure sometimes disparate dimensions such as quality and quantity of life and harm and benefit through a single metric. This process, moreover, is moving developers and payers to the use of an even more all-encompassing comparative framework that includes a consideration of costs. The evidence required by regulators and payers using health technology assessment (HTA) can overlap, but often there is also a disconnect between their requirements, which hinders timely, parallel HTA decision making.



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 largely 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. However, the difficulty ensues in applying the results of the surrogates to predict effects on outcomes which are more meaningful to patients, prescribers and payers. For example, the use of viral load reduction, which was initially believed to be a valid surrogate for improvement in subsequent HIV disease, was later found not to be a strong predictor of the effect of therapy.[1] Imperfect surrogate data available at launch complicate the predictability of treatment and reimbursement decisions.

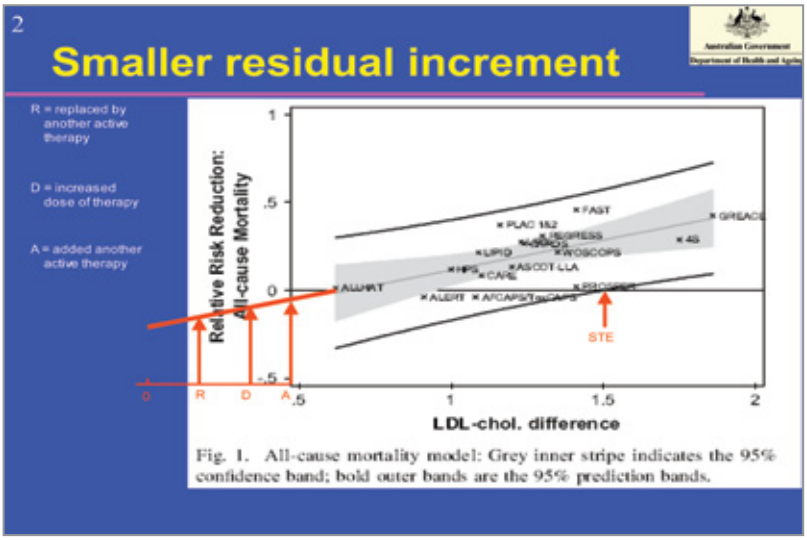
Having a high degree of confidence that a target outcome can be achieved, however, is extremely important. For example, the Pharmaceutical Benefits Advisory Committee (PBAC) of Australia was willing to pay an additional AUD$25,000 in the context of a resubmission for a product where it was confident in the clinical significance of the treatment effect. Given that the mean incremental cost per quality-adjusted life year was $46,400, this represented a substantial marginal willingness to pay for greater confidence in the clinical significance of the effect and similar to the increase for treatments in patients whose illness is life threatening.[2] In a review of 143 submissions to the Australian PBAC for new drugs adopting a cost-effectiveness approach based on therapeutic superiority over the past 5 years, fifty-three submissions (37%) relied on an inference that a surrogate 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 and methodologists – clinical epidemiologists and biostatisticians. In more recent times, payers and HTA agencies have become involved and are raising a slightly different set of issues to help frame the question of how surrogate evidence can be

used to support cost-effectiveness decisions. For example, although the classic definition of a surrogate has held that it is generally an asymptomatic metric, HTA recognises the need to assess surrogate outcomes irrespective of whether they are asymptomatic or have effects that are discernable by patients. Also, while regulators require that surrogate outcomes validly predict a future comparative treatment effect on a target clinical outcome, HTA assessors also require that this future treatment effect be quantified and the full extent of confidence around this quantification be estimated.

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.

Meta-analysis is emerging as 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 that have assessed the effects of other relevant treatments on both the surrogate and the clinical outcomes. This generates a predictive relationship, which needs to be assessed like any other association. For example, in contrast to the strong epidemiologic evidence of a prognostic value for HIV viral load on future AIDS progression, the treatment-induced reduction in viral load shows only a weak predictive association for treatment-induced reduction in AIDS-defining events and death as evidenced by the wide dispersion in the meta-regression. See slide *HIV viral load* and reference 1. This suggests that other mechanisms are influential in predicting treatment effects on future AIDS progression.



Another issue is emerging in exploring this relationship is that available meta-regressions are mostly based on placebo-controlled randomised trials which have relatively large comparative treatment effects. However, the context of many HTA considerations are in the context of smaller comparative treatment effects on the surrogate outcome such as substituting one active treatment for another, or increasing the dose of a therapy of adding another active therapy. As the slide *Smaller residual increment* shows, these effects fall outside the range of those used to generate the published meta-regression,[3] which hinders interpretation of their predictive value.

Conclusions

There is an increasing trend to rely on surrogates despite the often weak evidence these provide for predicting incremental effectiveness on unambiguously important patient outcomes. Assessing randomised trials through the application of a meta-regression, can provide some basis to validate a surrogate with another new therapy, although it may be difficult to justify a requirement for multiple placebo-controlled randomised trials for this purpose. In addition, there may be a limited ability for the resulting data to answer relevant research questions because of a smaller residual increment. Without randomised trials to generate a meta-regression there is no robust basis to assess the validity of a new surrogate with a new therapy; and without strong evidence to validate a surrogate in a new therapeutic area, assessors of new medicines must rely primarily on biological rationale and epidemiologic evidence. There is, therefore, a high potential for new expensive therapies to not be acceptably cost-effective within tolerable levels of certainty to HTA assessors at time of their regulatory approval.

Research costs and drug prices are escalating, with an exponential impact on incremental cost-effectiveness ratios and diminishing marginal returns on health outcomes. Using comparative cost-effectiveness, some payers have already developed an outcomes-based reward system in which a greater net health benefit for a therapy can result in a correspondingly higher market price. There is the potential to modify this system by rewarding pharmaceutical researchers who develop more convincing clinical evidence for a new therapy during the development process

with a higher price for that therapy at launch. Other methods for moving the assessment of medicine into a more comparative framework include:

- Validate surrogates using large, simple randomised trials
- Conduct multiple randomised trials of an intervention with participant data captured within administrative databases
  - Prospectively designed meta-regression analyses of these trials can be powered to directly address clinical questions beyond the time horizon of the initial surrogate outcome
- Encourage discussion forums like this Institute Workshop to enable more informed engagement across the different perspectives of drug developers, regulators and payers.

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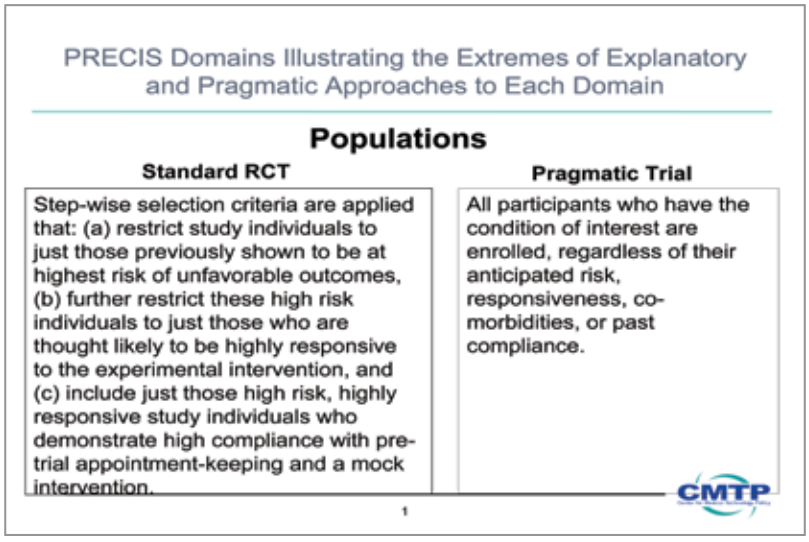
Coverage with evidence development

Dr Steve Phurrough

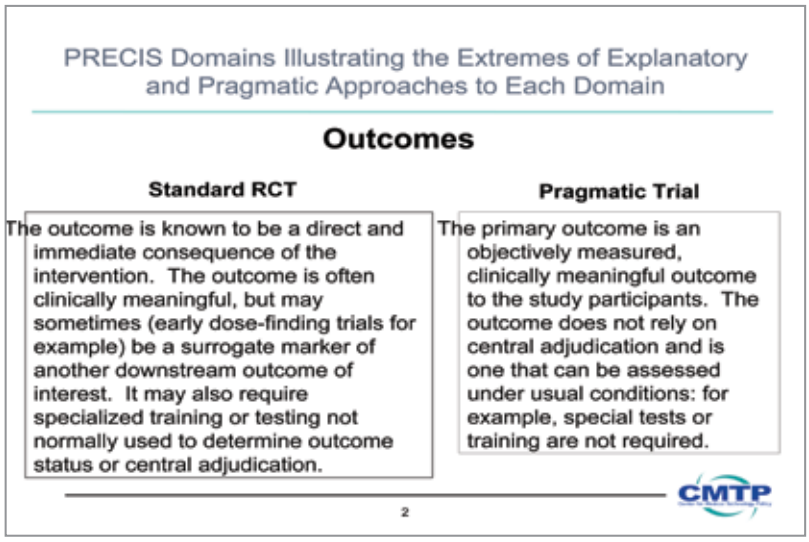
Chief Operating Officer/Senior Clinical Director, Center for Medical Technology Policy

The Center for Medical Technology Policy (CMTP) is a private, non-profit organisation that provides a neutral forum in which patients, clinicians, payers, manufacturers and researchers can work together to design and implement prospective, real-world studies to inform healthcare decisions. The primary goal of CMTP is to improve the process for generating reliable and credible information about the real-world risks, benefits, and costs of promising new medical technologies. These services are extremely relevant to today's pharmaceutical industry, which is currently faced with critical knowledge gaps. Although 18,000 randomised clinical trials are published each year, much of the available evidence is of limited or poor quality. Furthermore, patients, settings, comparators, outcomes and timing for the trials are often not aligned with the needs of decision makers such as patients, clinicians, payers and policy makers. Two options are available to positively impact this situation: a requirement for more effectiveness data in addition to efficacy data or a slowing of the introduction of new technology until effectiveness data are available.



Coverage for Evidence Development and Comparative Effectiveness Research

Comparative Effectiveness Research (CER) is the direct comparison of existing healthcare interventions to determine which work best for the most appropriate patients and which pose the greatest benefits or harms using real-world evidence. Coverage with Evidence Development (CED) is a type of CER that can be defined as temporary reimbursement for a new, non-covered service, which is contingent on participation in an organised research study, and which reconciles tension between establishing strict evidence standards and the need for rapid medical innovation. CED is one tool to improve the relevance and quality of evidence for the best use of emerging medical technologies, and many believe that the use of some version of CED is likely inevitable.



Historical CED efforts in the US

In one highly cited example, thousands of patients were treated off-protocol with high-dose chemotherapy (HDC) with autologous bone marrow transplantation (ABMT) for breast cancer, while 1,000 were enrolled in randomised clinical trials, which after 8 years led to conclusions of "no benefit" and costs of approximately $2 billion. This was considered a classic example of uncoordinated research and premature dissemination of research results and this combination treatment is now rarely used or covered by insurance. CED, however, can result in clinically and financially appropriate treatment with the right balance of access and evaluation, as was the case with combining HDC with ABMT for multiple myeloma. Initial trials showed promise, but more evidence was required, and randomised clinical trials led to coverage for appropriate patients.

Dr Phurrough described other examples of the practical application of CED. The National Emphysema Treatment Trial (NETT) was cosponsored by The Centers for Medicare and Medicaid Services (CMS) and conducted to identify the benefits and risks of lung volume reduction surgery (LVRS) in severe emphysema. CMS covered treatment for participants receiving Medicare during the trial and is re-evaluating general coverage in light of the trial results, which showed that LVRS was associated with improvements in quality of life, particularly in a defined group of patients. Other instances of Medicare CED include the off-label use of drugs for colorectal cancer, use of fluorodeoxyglucose-positron emission tomography (FDG-PET) for oncology treatment, use of an artificial heart and genetic testing for warfarin sensitivity.

There is, however, a lack of a clear statutory foundation for CED and questions regarding its statutory foundation impede development of a precise policy approach. Furthermore, because of a lack of a clearly defined framework, all CED projects are created de novo, which is a labour intensive unpredictable process. The lack of process to support thoughtful clinical and scientific discussion of study design highlights the need for a priority-setting mechanism. Furthermore, there is a need to actively seek out potential CED candidates and to shift the dialogue to an analysis of evidence, rather than of coverage.

The best choice for a CED strategy depends on the technology being evaluated and the needs of the decision makers. Importantly, the design and oversight of CED studies is influenced by the entity that provides funding. In the private payer CED arena, there are operational, ethical and anti-trust issues, multiple coverage model options, the need to align with other regulatory requirements and the identification of providers and patients who will participate, which all influence the approach to CED. Other issues that might influence the implementation and use of CED include administration of the benefits, payment of patient care and research costs and institutional review board approvals.

There are several design options for CED including practically designed clinical trials and the use of prospective or retrospective registries. Clinical trials typically take the form of traditional randomised or explanatory trials, but there has been a movement toward so-called pragmatic trials, which optimise design to better inform post-FDA decision makers, clarify patient, clinician, and payer evidence needs and identify critical regulatory, methodologic, financial, and operational barriers.

Conclusions

Medicare's experience with CED to date has fallen short of the original policy objectives. CED shortcomings, however, are not intrinsic to the concept and experience has highlighted potential strategies to improve its implementation. There is also growing interest among private payers in the CED approach, and it is likely that those private payers will follow the decisions made by CMS based on solid CED results. Significant issues remain for CMS and private payers, but coordinated multi-payer CED could contribute significantly to of the knowledge base of CER.

Pay-for-performance and risk sharing: An industry perspective

Alison Lawton

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According to health economist Gerard de Pouvourville, *a risk-sharing agreement, otherwise known as an innovative pricing and reimbursement scheme*, is "a contract between two parties who agree to engage in a transaction in which there are uncertainties concerning its final value. Nevertheless, one party, the company, has sufficient confidence in its claims of either effectiveness or efficacy that it is ready to accept a reward or penalty depending on observed performance."[1] In reality, however, industry regards these agreements less as options to enhance treatment outcomes and value and more as related to payers seeking ways to control their budgets.

Risk-sharing and pay-for-performance plans can be non-outcome based, existing to manage funding budgets and as such are disguised product discounts. Examples of non-outcome based plans are population-level product utilisation caps and patient-level price caps. Outcome-based pay-for-performance plans, by comparison, are a true form of conditional coverage, based on the concepts of coverage with evidence development (CED). Population-level evidence collected in these latter plans can result in price change accommodations, while the patient-level data could provide evidence to support an outcome based adjustment, such as rebates for non-responders. Innovative risk-sharing agreements can reduce the uncertainties that surround the development of medicines by clearly establishing the value and cost associated with the management of a specific indication. Price adjustments based on "real world" therapeutic effectiveness, enables the mitigation of risks associated with patient variability and the widespread use of the product in the 'wrong" indication or patient population.

Challenges

Most innovative risk sharing schemes have been reactively designed as a response to specific market access issues and many practical challenges remain in designing more equitable and proactive plans. The product's effectiveness must be objectively and promptly assessable, with agreed and accepted endpoints or outcomes. Transparent use by the target population must guarantee that fixed-cost supplies are not redistributed to other patients for whom the product is not intended. Selecting which patients will receive the product must be done in a fair and medically reasonable manner. Logistics and transaction costs to monitor drug distribution and patient access will provide additional challenges. It must be decided if randomised clinical trials are required for evidence development or if data from registries or observational studies will suffice. Whether the data are collected by a company sponsor or by a healthcare system or payer, the method in which it is collected and whether the collection is global or local are other logistic issues that must be resolved. Other challenges lie in the analysis of data and the evaluation of performance. Patients and physicians must be willing to accept the special provisions made for the treatment of patients with rare or orphan diseases.

Key elements for success

All stakeholders (mainly payers and manufacturers, but also regulatory authorities, legislators, healthcare providers and patients) must collaborate towards patient-centric, value models and a climate of mutual trust and respect is essential to accomplish this end. Early, proactive involvement and engagement, fairness and transparency are aspects of the risk-sharing process.

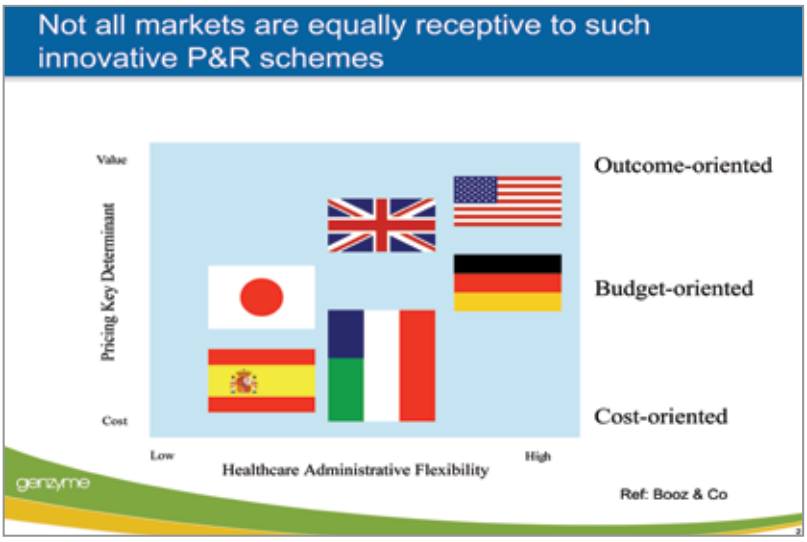
These must especially be recognised by investors and financial markets which must embrace the long-term, "win-win" scheme of "benefits-maximisation", instead of the short-term, single-

Examples of Patient & Population Level Outcome Based Schemes

Country/Manufacturer	Product	Issue	Strategy
Italy Bayer	Nexavar (sarofenib)	Refusal to reimburse products for broad range of patients	Performance risk-sharing agreements – 50% discount to the hospital for the first two months – For responding patients, the treatment is reimbursed by AIFA and the manufacturer no longer has to grant the 50% discount
Canada Sanofi-Aventis	Taxotere (docetaxel)	Provincial formulary authorities were concerned about efficacy and cost of Taxotere for oncology	Efficacy guarantee – Patients were tested for six months of treatment for agreed responder levels – If a certain level of progression was not reached, the company paid back the regional payers the reimbursed cost of the drug – The programme lasted six months for Taxotere to gain market/formulary access
UK Janssen-Cilag	Velcade (bortezmab)	Product not covered	Performance risk-sharing agreements (*proposed*) – Patients showing a full or partial response to the drug after a maximum of four cycles of treatment would be kept on therapy, with the treatment funded by the NHS – Patients showing minimal or no response would be taken off therapy with costs refunded by the manufacturer

genzyme

Source: IMS Health



sided approach to profit maximisation. Cost, time to return on investment and uncertainty all impact pharmaceutical development. We can value and reward innovation with a focus on all aspects of healthcare costs rather than just on drug budgets and on controlling new technologies. Reimbursement systems should be structured on the basis of the overall approach to treatment of the disease rather than in terms of the cost-value assessment of the use of a certain number of pharmaceutical units. In the future, innovative treatments such as gene therapy may transform chronic diseases and payers must develop the ability to value a technology's lifetime impact rather than base the decision on a point-of-delivery cost assessment.

We need to develop global standards and harmonised approaches to clinical development as well as the opportunity for all stakeholders to provide early advice on establishing parameters of clinical evidence, implementing optimal trial design and collecting data to fulfil post-approval requirements. Sustainable global medical progress and innovation will depend on our capability to match the fast pace of scientific advances with equally creative economic, regulatory and administrative schemes.

Reference

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Why is risk-sharing largely a non-US phenomenon?

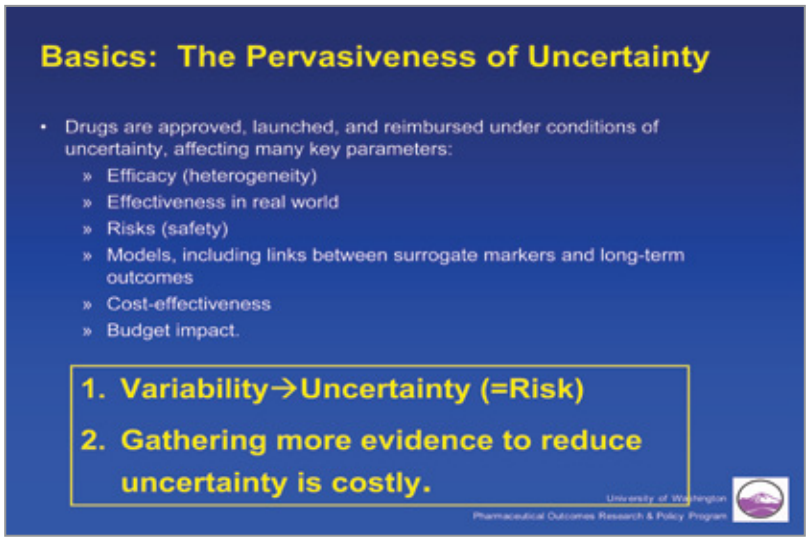
Professor Lou Garrison

Associate Director, Pharmaceutical Outcomes Research and Policy Program, University of Washington

Increasing healthcare expenditures are contributing to the global interest in developing novel risk-sharing approaches to medicines development and access. This focus can be attributed to the use of high-cost biopharmaceuticals for common, chronic conditions such as rheumatoid arthritis, asthma, and psoriasis; the use of expensive, combination biopharmaceutical treatments in treatment of neoplastic and infectious disease; and the practice of prescribing often costly products in ways that go beyond the body of common evidence and approved indications. All of these are compounded by the need to manage ageing populations with fewer financial resources.

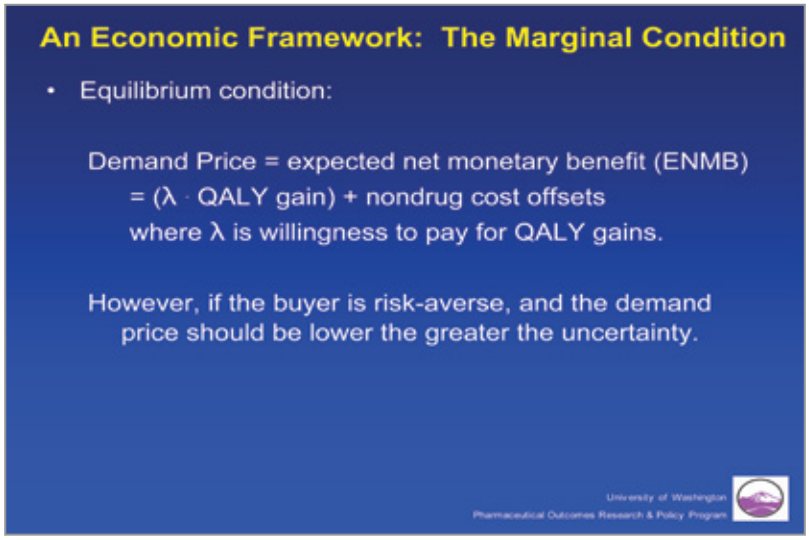
An understanding of the current interest in risk-based release agreements should be helpful to predict their long-term adoption and impact. Two analytic approaches can be applied to facilitate this understanding: firstly, empirical or inductive practice, which asks what examples of risk sharing have arisen in the real world and what their characteristics tell us about their potential impact. Alternatively the economic or deductive approach assesses the historical risk-sharing approaches used by manufacturers and payers and asks why these approaches are undergoing scrutiny and change.

Drugs are approved, launched, and reimbursed under conditions of uncertainty; many parameters influence the degree of uncertainty that must be assessed by stakeholders: efficacy in clinical trials; effectiveness in the real world; expected risks; models used to predict outcomes; including confirming the links between surrogate markers and long-term outcomes; cost-effectiveness and budget impact. Variability in any of these parameters contributes to uncertainty and may overestimate risk. If great uncertainty surrounds a new product, a risk-averse payer will expect the price for the technology to be lower in the face of this uncertainty. As evidence is gathered, uncertainty



about the product decreases and its value can be more completely characterised. Gathering the evidence to reduce uncertainty, however, is costly and the value received for the investment will play a role in how quickly evidence can be collected to support a risk-sharing approach.

According to Gerard de Pouvourville, there are certain elements that are central to all outcomes-based risk sharing agreements. The agreements can be focused on effects on health outcomes and cost-effectiveness or may focus on the payer's budget restrictions. In either case, they must include a prospective or retrospective programme of data collection to reduce uncertainty about the expected cost-effectiveness of the technology. Pricing for the technology must be linked by formula to the outcome of the data collection. Finally, the agreement must distribute the risk between the payer and the manufacturer, which may differ from conventional contractual payment arrangements.[1]



Conventional risk-sharing has been largely based on the "blockbuster" financing model for research and development in which the protection of a sponsor's intellectual property following market authorisation of the product incentivises investment and risk-taking for manufacturers and in which there is no prior agreement with a payer to share the innovation costs. In this model, the payer negotiates the price and bears the risk that the incremental health benefits of the new technology are in fact not worth the additional cost. The payer is free to collect post-launch data, but to date, manufacturers have primarily done so as part of post-marketing commitments or if it is in their competitive interests. Individual countries negotiate different types of reimbursement programmes with sponsors and the range of environments lead to negotiated or free pricing. This incentivises manufacturers to seek the highest justifiable price at the time of launch of the product. In a true risk-sharing scheme, this incentive would not be in effect.

Despite the potential benefits of risk-sharing schemes, there are barriers to overcome. Six such barriers identified by Carlson and colleagues[2] are:

1. Associated transaction and administration costs
2. Limitations of current information systems to track performance
3. Agreeing on the scheme details (eg, the appropriate outcome measure or the financial adjudication process)
4. Physician push-back to administer the schemes
5. "Free-rider" problem (other manufacturer or payer competitors may benefit from the information or schemes developed), and
6. Scepticism between payers and the technology developers.

Risk-sharing schemes are more prevalent with public payers for whom risk aversion takes on a different role, but changes in regulatory or HTA policies can shift the risk-sharing equilibrium. Therefore, risk sharing has been largely a non-US phenomenon because of the public goods nature (nonexclusive and nonreducible) of information, the monopsony power of central

payers and lower transaction costs in non-US countries. Many ex-US agreements may in fact be simply disguised price discounts aimed to limit the impact of reference pricing. Finally, US manufacturers typically use non-outcomes based contracting policies to fashion buyer incentives and discounts. In the future, the role of CER in the US may becoming increasingly important in influencing pricing strategies and increasing interest in risk-sharing approaches, in particular if CER is publicly subsidised. It is not clear, however, whether private payers will fund the research needed to underpin outcome guarantees without public subsidisation and the development of the necessary infrastructure to collect, monitor, interpret and apply the results of CER to their risk sharing payment paradigms.

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