EVIDENTIARY REQUIREMENTS IN CLINICAL DEVELOPMENT:
SYNCHRONISING PHASE 3 REQUIREMENTS TO MEET MULTIPLE NEEDS

WORKSHOP
31 March – 1 April 2011
Geneva, Switzerland

WORKSHOP REPORT
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Section 1: Executive Summary

Background to the Workshop
A drug development programme is by its very nature serial, acquiring knowledge and generating evidence about a new medicine through clinical trials that each build upon preceding studies. However, companies today are increasingly obliged to consider more than the traditional requirements of quality, efficacy and safety, as success is now measured by achieving both regulatory approval and reimbursement. In the current environment the regulator and the payer, who make separate decisions, review new medicines at essentially a similar time point and therefore often with the same underlying data. As companies plan future development programmes, the question is how can inclusion of health technology assessment (HTA) requirements be conducted without making the drug development programme overly burdensome or complex?

The key area for debate surrounds phase 3 development, specifically, how practical changes to drug development design might improve efficiency, reduce duplication and mitigate against a potential mismatch of outcome of regulatory and payer approval in terms of the clinical evidence. There are several experiments (pilot projects) in regards to parallel advice from both regulators and payers on the clinical development of a new product. The participants at this Workshop considered whether such advice is leading to better decision making and by discussing the different pilots, sought to identify which aspects of parallel advice programmes are most effective.

The Workshop comprised numerous presentations by topic experts and a discussion of specific topics in the context of Syndicate Discussion Groups.

Objectives
The objectives of this Workshop were to answer several questions:

- **Is there a collective responsibility to develop a high-quality evidence pool?** As drug development is based upon the serial development of evidence, what is the role of the regulatory and HTA agencies in participating in the knowledge build-up and how can industry avoid the temptation to overcomplicate evidence development to try to meet conflicting requirements?

  - **Which phase 3 requirements can be aligned?** The key technical areas within drug development programmes where the differing requirements of the regulator and the payer might be aligned were discussed.

  - **What is the best approach to achieving this alignment?** Discussions were focussed on how such alignment might occur in practice, considering whether this would best occur on a drug-by-drug basis, by therapy area, or in forums.

  - **Does shared scientific advice help?** As payer agencies are now beginning to offer advice on development programmes, the Workshop examined the current experience of pilot joint or parallel scientific advice and sought to identify which approaches to advice work best for all parties.

Presentations
An introduction to the Workshop was provided by Day-1 Chair, **Dr Marcus Müllner**, Head of Agency, Austria Medicines and Medical Devices Agency (AGES PharmMed).

In his presentation “The business case for increased alignment of evidentiary requirements in phase 3: managing uncertainty and balancing risk with return” **Dr Murray Stewart**, Senior Vice President, Head of Metabolic Pathways and Cardiovascular Therapy Area Unit, GlaxoSmithKline, USA explained that the new development paradigm calls for a clear vision of the clinical benefit of new medicines for the patient. Stakeholders must consider the evidence needed to satisfy patient, clinician, regulator and health technology assessment requirements and to communicate and discuss issues pertaining to these requirements, considering clinical evidence beyond that obtained from controlled clinical trials.

Considering the question “why should the regulator and payer wish to align requirements?” **Professor Adrian Towse**, Director, Office of...
Health Economics (OHE), UK said that the easy answer is that it improves the likelihood of bringing health gain to the populations they serve. Although there are multiple reasons not to align, including compromise to their respective missions, difficulty allocating scarce resources, and the unknown chance of success, Professor Towse supported the move towards alignment by quoting a past CIRS Workshop presentation by Martin Backhouse indicating that “The clinical evidence required by payers and regulators could probably be obtained in one comprehensive phase 3 programme and meeting the specific requirements identified would not likely increase costs of development times significantly.”

Because Australia is unusual in the Western world in that its drug regulators and drug reimbursers work for the same level of Government, within the same Department, it is particularly well suited for a pilot programme of advice meetings being undertaken by the Australian Pharmaceutical Benefits Scheme (PBS). Andrew Mitchell, Strategic Adviser, Evaluation, Department of Health and Ageing (DoHA), Australia reported that this pilot, which involves the regulatory agency, Therapeutic Goods Administration (TGA), will be solution focussed, with the objective of improving the quality of dossiers as it relates to the specific needs of the regulator and reimbuser. It will include content experts and sub-committee members and be informed by pre-circulated briefings and questions. Although the pilot is incomplete, preliminary results indicate that clear benefits can be realised including improvements in understanding and trust among stakeholders despite the need to devote significant resources to the process.

In Sweden, a pilot programme of joint advice between the Medical Products Agency (MPA) and the Dental and Pharmaceutical Benefits Agency (TLV) was completed for 12 products in 2010. Bengt Ljungberg, Scientific Director, Pharmacotherapy, (MPA), Sweden provided the details of the pilot assessment. Although the objectives of understanding the methodologies used by the respective agencies, defining the nature of the clinical trial results needed to provide relevant information and the achievement of overall better collaboration between the agencies were achieved, few requests have been made by industry for joint advice since the project concluded. New legislation in Sweden, which will increase requirements for post-authorisation effectiveness studies, however, may lead to an intensified interest in joint advice.

Prof Bruno Flamion, Chairman, Belgian Committee for Reimbursement of Medicines (CTG/CRM), Belgian National Institute for Health and Disability Insurance (INAMI-RIZIV) discussed the European Medicines Agency (EMA) shared advice pilot programme, in which participating companies sought early advice from the EMA and other stakeholders including HTA agencies, payers, patient representatives and clinicians concerning type 2 diabetes or breast cancer therapies under development. Non-sponsor participants assessed the pilot as generally positive and presenting opportunities for increased common understanding. Based on their assessment of the programme, areas that sponsors would approach differently in light of advice received included improving their explanation of the scientific basis for the medicine’s mechanism of action and its link to biomarkers, gaining a clearer understanding of the requested approaches to patient segmentation and having more clarity around the requirements expected from the proof-of-concept study design.

Is it feasible to expect comparators and endpoints to meet the needs of both regulators and the HTA? Dr Greg Rossi, Vice President, Global Health Economics and Pricing, Genentech, USA said overlapping interest of the two groups make such accommodation plausible and suggested some methods for innovation and collaborative change. Standardising comparators would allow the necessary comparisons to inform access decisions. Agreeing on survival endpoints and effect sizes that are both informative and feasible and accepting novel methodologies that accelerate identification of the patients most likely to benefit from therapy would accelerate patient access to new treatment options.

Dr Mira Pavlovic, Deputy Director, Health Technology Assessment Division, Haute Autorité de Santé, (HAS), France outlined some of the tools that may facilitate harmonisation between the needs of regulators and HTA bodies: the European Public Assessment Reports (EPAR), EMA and EUnetHTA guidelines and parallel EMA HTA scientific advice. The new EPAR template was approved by the CHMP in 2010 and an ongoing collaboration provides HTA agencies full access to market authorisation files. The EMA and EUnetHTA are sharing comments on the other group’s guidelines and the pilot programme of shared advice, as reported by Professor Flamion, was concluded in 2010.
Day 2 Chairman, Professor Sir Alasdair Breckenridge, Chairman, Medicines and Healthcare products Regulatory Agency (MHRA), UK introduced Session 5 of the Workshop.

Speaking as a member of the European Federation of Pharmaceutical Industries and Associations (EFPIA) task force, Dr Pierre Sagnier, Vice President, Global Market Access, Development Projects, Bayer Schering Pharma, Germany said that industry stands ready to be held accountable for a new medicine’s value for money and clinical benefit, taking into account patient specificities and the trend toward personalised medicine.

He added that EU-level actions toward standardisation could add value if they tackle unnecessary duplication, enable greater clarity of development requirements, lead to raising standards of methodological and process aspects in HTA, improve predictability of decision making, and contribute to timely access of medicines for patients.

Systematic reviews intended to inform clinical and health policy decisions routinely conclude that the evidence published from over 18,000 randomised clinical trials each year is inadequate to make an informed decision about the real-world value of a medicine. A hypothesis explained by Dr Sean Tunis, Founder and Director, Center for Medical Technology Policy (CMTP), USA proposes that these gaps in evidence would be reduced with greater engagement of decision makers including patients, clinicians, and payers by first identifying those gaps and then by providing guidance for the design of future trials that address recurring deficiencies. The Green Park Collaborative (GPC) was formed to identify the steps needed to produce technology-specific guidance documents with recommendations for the design of clinical studies that address the information needs of payers and HTA bodies from a number of different countries for specific types of therapies. The GPC is currently in the process of selecting a topic for a proof of concept study and securing funding for the initial research.

Dr Thomas Lönngren, Strategic Advisor, NDA Group, UK spoke of the changing needs and dynamics of regulatory agencies, citing significant challenges that include the need for alignment of regulatory and HTA requirements. Inroads toward alignment have been made by regulatory initiatives of the EMA, MHRA, TGA, and Health Canada but more work will be required with other agencies as well as HTA initiatives to develop common methodologies and standards.

Considering the central question addressed in the Workshop, that is, whether it is possible to synchronise clinical evidence requirements to meet the needs of multiple stakeholders, Professor Robert Peterson, Executive Director, Drug Safety and Effectiveness Network, Canadian Institute of Health, Canada offered three suggestions:

1. Seek early scientific advice from both regulatory and HTA organisations
2. Develop post-regulatory approval strategies to acquire evidence for effectiveness as well as safety and
3. Consider a more flexible paradigm of drug development with limited or progressive access to new medicines through the efforts of the key stakeholder
   • Progressive licensing driven by the regulatory authority
   • Coverage with evidence development driven by the payers
   • Managed market entry driven by the company
General Recommendations Across Syndicates

1. Enlist company management understanding and support for the need to address this “industry shift” away from the traditional clinical development model
2. Develop more clarity around the scientific basis for requirements and encourage alignment of these needs across HTA bodies
3. Align incentives between regulators and HTA, considering meaningful input for both parties
4. Influence and educate internal and external stakeholders by undertaking
   a. A CIRS Workshop on coverage with evidence development
   b. An HTA metrics and benchmarking survey
5. Further explore ways to complement good evidence from randomised clinical trials with robust evidence from real-world experiences such as those derived from observational studies
6. Consider ways to more effectively implement predictive science in the approval paradigm
7. Sponsors should be encouraged to make early contact and keep dialogue open with regulatory and HTA authorities
8. Aim to establish clinical practice guidelines with acceptable treatment pathways that illustrate the role of a new medicine in therapy
9. Seek agreement between HTA and regulatory authorities on the choice of endpoints and comparators; indirect comparators should be considered where necessary to expedite a medicine’s review, especially when being considered for critical conditions with few medical alternatives
10. Consider the broader use of follow-up / post-marketing / pragmatic/ real-life study programmes and databases based on agreed standardised endpoints and methodologies
11. Map the current landscape of early HTA and HTA/regulatory advice procedures, including those planned, piloting and established and develop a better understand of the impact of this advice
12. Develop joint HTA/regulatory guidance in important therapy areas to build on regulatory guidance – use “game changing” products as opportunity to drive scientific underpinnings of common ground
13. Identify topics for joint workshops, utilising a case study approach to examine issues, such as methodology alignment and how to address the needs of personalised medicine/diagnostics
14. Proactively explore HTA/regulatory joint/parallel advice in the post-authorisation space, as this may represent an opportunity for greater alignment
## Workshop Programme

### Day 1: Thursday 31 March 2011

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<tr>
<th>Welcome</th>
<th>Lawrence Liberti, Executive Director, Centre for Innovation in Regulatory Science, UK</th>
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<tr>
<td>Chair’s Introduction to Workshop</td>
<td>Dr Marcus Müllner, Head of Agency, Austria Medicines and Medical Devices Agency</td>
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### Session 1: Why is it important to seek ways to align the requirements of both the regulator and the payer in phase 3 clinical development?

| The business case for increased alignment of evidentiary requirements in phase 3: managing uncertainty and balancing risk with return | Dr Murray Stewart, Senior Vice President, Head of Metabolic Pathways and Cardiovascular Therapy Area Unit, GlaxoSmithKline, USA |
| Why should the regulator and payer wish to align requirements; what’s in it for them? | Prof Adrian Towse, Director, Office of Health Economics, UK |

### Session 2: Update on shared activities and accommodating requirements of multiple agencies in drug development programmes

| The Australian pilot (TGA and PBAC) advice programme | Andrew Mitchell, Strategic Adviser, Evaluation, Department of Health and Ageing, Australia |
| The Swedish Presidency pilot (MPA and TLV) advice programme | Bengt Ljungberg, Scientific Director, Pharmacotherapy, Medical Products Agency, Sweden |
| The EMA (EMA and multiple payer) shared advice pilot programme | Prof Bruno Flamion, Chairman, Belgian Committee for Reimbursement of Medicines, Belgian National Institute for Health and Disability Insurance |

### Panel Discussion

| | Dr Rohan Hammett, National Manager, Therapeutic Goods Administration, Australia |
| | Niklas Hedberg, Head of Department, The Dental and Pharmaceutical Benefits Agency, Sweden |
| | Adrian Griffin, Vice President, HTA and International Policy, Johnson & Johnson, UK |
| | Seren Phillips, Associate Director, Scientific Advice Programme, National Institute for Health and Clinical Excellence, UK |
| | Dr Nicola Course, Vice President, Global Regulatory Affairs, Europe, GlaxoSmithKline, UK |

### Session 3: Key barriers to the inclusion of HTA requirements into phase 3: Comparators and endpoints: Is it feasible to expect comparators and endpoints to meet the needs of both the regulator and the HTA?

| Industry viewpoint | Dr Greg Rossi, Vice President, Global Health Economics and Pricing, Genentech, USA |
| Regulatory viewpoint | Dr Mira Pavlovic, Deputy Director, Health Technology Assessment Division, Haute Autorité de Santé, France |
| Recommendations of the 2011 HTAi Policy Forum | Dr Clifford Goodman, Senior Vice President, Lewin Group, USA |
### Syndicate Discussions

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<tr>
<th>Topic</th>
<th>Chair</th>
<th>Rapporteur</th>
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<tr>
<td>How can companies best accommodate both regulatory and HTA requirements into their phase 3 clinical programmes?</td>
<td>Chair: Dr Patrick Keohane, Vice President, Payer Evidence, AstraZeneca, Sweden</td>
<td>Rapporteur: Dr Marie-Christine Minjoulat-Rey, Head, Governance, Global Evidence and Value Development, sanofi aventis R&amp;D, France</td>
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<td>How do we deal with areas of complexity in terms of differing regulatory and HTA needs, focussing on comparators and endpoints?</td>
<td>Chair: Prof Bengt Jonsson, Professor of Health Economics, Stockholm School of Economics, Sweden</td>
<td>Rapporteur: Dr Isaac Odeyemi, Senior Director and Head of Health Economics and Outcomes Research, Astellas Pharma Europe</td>
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<td>What kind of scientific advice model is most effective?</td>
<td>Chair: Dr Petra Dörr, Head of Management Services and Networking, Swissmedic</td>
<td>Rapporteur: Dr Mel Walker, Senior Director, Value Expert Engagement &amp; Collaborations, GlaxoSmithKline, UK</td>
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### Day 2: Friday 1 April 2011

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<td>Dr Pierre Sagnier, Vice President, Global Market Access, Development Projects, Bayer Schering Pharma, Germany</td>
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<td>What is industry looking for from regulatory, HTA and payer agencies; how should roles be defined and where could interaction between these agencies be of use?</td>
<td>Dr Sean Tunis, Founder and Director, Center for Medical Technology Policy, USA</td>
<td>Dr Thomas Löngren, Strategic Advisor, NDA Group, UK</td>
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<td>Is it possible to develop drug development guidelines that encompass HTA requirements?</td>
<td>Dr Sean Tunis, Founder and Director, Center for Medical Technology Policy, USA</td>
<td>Dr Thomas Löngren, Strategic Advisor, NDA Group, UK</td>
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<td>How are the needs and dynamics of regulatory agencies changing?</td>
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**Feedback from Syndicate discussions**

**Panel Discussion**

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<td>Dr Susan Longman, Global Head of Cardiovascular/Metabolic Regulatory Affairs, Novartis, Switzerland</td>
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<td>Wim Goettsch, Deputy Secretary of the Medicinal Products Reimbursement Committee, Dutch Health Care Insurance Board, the Netherlands</td>
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<td>Clare McGrath, Senior Director, HTA Policy, Pfizer, UK</td>
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<td>Seren Phillips, Associate Director, Scientific Advice Programme, National Institute for Health and Clinical Excellence, UK</td>
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**Key outcomes from Workshop**

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**Final word and close of Workshop**

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Section 2: Syndicate Discussions

Three syndicate groups were asked to discuss three different aspects of synchronising clinical development requirements, provide strategies to address the critical issues outlined in their discussions and to arrive at recommendations for change.

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<th>Syndicate 1</th>
<th>Chair: Dr Patrick Keohane, Vice President, Payer Evidence, AstraZeneca, Sweden</th>
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<td>Rapporteur: Dr Isaac Odeyemi, Senior Director and Head of Health Economics and Outcomes Research, Astellas Pharma Europe</td>
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<td>Syndicate 3</td>
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<td>Rapporteur: Dr Mel Walker, Director International Payer Strategies, GlaxoSmithKline, UK</td>
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**Syndicate 1: How can companies best accommodate both regulatory and HTA requirements into their phase 3 clinical programmes? What are the challenges and what approaches are most easily incorporated?**

**Background**

The objective of this Syndicate was to evaluate the challenges of incorporating regulatory and HTA requirements into phase 3 development programmes, considering both pivotal and additional global or regional trials.

The group was asked to discuss how best to accommodate the needs of both of these stakeholder groups in a development plan and to identify the best approaches for this accommodation. In addition to meeting those external requirements, the Syndicate was also charged with consideration of the perspectives of various internal stakeholders in the phase 3 programme within the sponsor company.

**Critical Issues**

The Syndicate began by agreeing that a strict reliance on phase 3 randomised clinical trial results to appropriately and fully characterise a new product was no longer logistically or economically feasible. Rather, the shift in development and launch strategies that has taken place over the last several years means that information requirements and data gathering have assumed importance in earlier clinical development as well as during the post-approval period. Regardless of the stage of development, however, clarity of purpose is central to the incorporation of stakeholder requirements. That is, to align and then address regulatory and HTA requirements externally and internally, it is necessary that these requirements are clearly communicated, understood and actionable. It must be recognised, however, that even with such clarity of purpose, industry’s current vertical structure is not ideally organised to readily accommodate the early incorporation of HTA requirements into integrated development programmes.

**Strategies**

It may be possible to generate good complementary evidence for regulatory and HTA needs from the same randomised clinical trials by using different data elements; however, it is critical that awareness of this new developmental paradigm increase within organisations and that HTA requirements are taken into account early in development. Timely
consideration of the expected requirements needed to justify reimbursement decisions will inform the development strategy, permit agreement on necessary compromises, assist in the definition of evidence packages, and allow the weighting of HTA impact on business plans. However, in addition to achieving an alignment of expectations between regulatory and HTA agencies, it will also be necessary to achieve the same clarity and alignment across multiple and diverse HTA bodies. Based on agreed standardised endpoints and methodologies should be used to more fully characterise a product’s value rather than place an unsustainable emphasis on collecting data during a lengthy per-approval phase.

**Syndicate 2: How do we deal with areas of complexity in terms of differing regulatory and HTA needs, focussing on comparators and endpoints?**

**Background**

The objective of this Syndicate was to discuss how companies, in preparing their phase 3 clinical programmes, should address the potential differing regulatory and HTA needs when it comes to choosing the appropriate endpoints and comparators. They were charged with considering which approaches HTA and regulatory agencies can undertake to help facilitate understanding or align their requirements and examining possible solutions when difference or conflict arises in this complex area.

**Critical issues**

Regulatory and HTA authorities have a common purpose: to serve the public by bringing safe and efficacious medicines and devices to the market. Whilst there is scope for greater collaboration between all stakeholders to speed access to safe and effective medicines, driving this alignment is a major challenge. Clinically relevant endpoints required by regulators and HTAs often are different; prescriber decision making is often associated with treatment standards that vary by region and local market access frameworks differ widely. Furthermore, price and reimbursement decisions are made by payers not by regulators and in some cases not by HTA agencies. Although the scientific requirements that underpin the evaluation of real-world effectiveness lend themselves to a centralised common approach, decisions on pricing and reimbursement will naturally continue to reflect local and political expediencies that drive a jurisdiction’s willingness and ability to pay.

**Strategies**

Early convergence between regulatory and HTA authorities should be sought on the objectives of a product development programme, based on current medical need and the expected unique product characteristics. The development of expert treatment guidelines by disease area can drive the alignment process and the role of a new therapy in those guidelines can be identified and harmonised. Authorities should therefore agree on relevant comparators and the hierarchy of evidence that will be needed to justify the new medicine’s role in the

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**Recommendations**

1. Enlist company management understanding and support for the need to address this “industry shift” away from the traditional clinical development model
2. Develop more clarity around the scientific basis for requirements and encourage alignment of these needs across HTA bodies
3. Align incentives between regulators and HTA, considering meaningful input for both parties
4. Influence and educate internal and external stakeholders by undertaking
   a. A CIRS Workshop on coverage with evidence development
   b. An HTA metrics and benchmarking survey
5. Further explore ways to complement good evidence from randomised clinical trials with robust evidence from real-world experiences such as those derived from observational studies
6. Consider ways to more effectively implement predictive science in the approval paradigm
treatment approach. To this end, establishing clinically meaningful endpoints or surrogate endpoints where appropriate will provide clearer expectations of the utility of the data derived during the development process. HTAs and regulators must agree on those effectiveness measures that can be addressed during clinical development, which can be assessed post-approval, and how these will inform payer decisions.

Stakeholders should be encouraged to reach early aligned agreement on appropriate clinical trial designs (including variables and comparators), appropriate clinical trial endpoints, the use of well-selected populations, the design of special studies for severe and life-threatening conditions and the use of novel analytical methods (including meta-analysis). Where appropriate, follow-up, post-approval, pragmatic study programmes and databases based on agreed standardised endpoints and methodologies should be used to more fully characterise a product’s value rather than place an unsustainable emphasis on collecting data during a lengthy per-approval phase.

**Recommendations**

1. Sponsors should be encouraged to make early contact and keep dialogue open with regulatory and HTA authorities.
2. Aim to establish clinical practice guidelines with acceptable treatment pathways that illustrate the role of a new medicine in therapy.
3. Seek agreement between HTA and regulatory authorities on the choice of endpoints and comparators; indirect comparators should be considered where necessary to expedite a medicine’s review especially when being considered for critical conditions with few medical alternatives.
4. Consider the broader use of follow-up/post-marketing/pragmatic/real-life study programmes and databases based on agreed standardised endpoints and methodologies.

**Syndicate 3: What kind of scientific advice model is most effective?**

**Background**

Now that parallel or joint scientific advice is being given by both HTA and regulatory agencies, the mandate of this Syndicate was to discuss how this collaboration is best achieved, based on the experiences of the various ongoing and completed pilots. Questions to be considered included:

- What are the approaches that companies should use to get scientific advice when developing their phase 3 clinical development plan?
- What would the optimal model for provision of advice be, and would this depend on the advice sought?

**Critical issues**

This Syndicate agreed that there are many and varied interactions when characterising “early advice,” with no consistent view yet on the elements that could form a “best practice.” There is generally a lack of written guidelines, sometimes with the adaptation of regulatory guidance documents for HTA purposes to guide these advice sessions. Adding further complexity, advice may be national and product-specific, or provided by multiple countries, by multiple HTA bodies through an organisation such as the Medical Evaluation Committee (MEDEV) or by multiple stakeholders such as has occurred through the Tapestry Network programme. Additionally, advice may be provided by two agencies in parallel or jointly. Parallel regulatory advice, for example, has involved the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), guiding the development of oncology products; however this parallel regulatory advice has not yet been paired with parallel HTA advice.

Forums such as those conducted by Health Technology Assessment International (HTAi) and CIRS have provided opportunities for high-level discussions to address the possibilities of aligned scientific advice. Aligned advice, however, has been dogged by a number of issues including differences in the political and economic environments within each HTA agency, varied fee structures, goals, missions and perspectives and a relative lack of standardisation in procedures and evaluation methodologies.
The challenge for industry is whether to obtain advice that is representational of most agencies or selective to specific jurisdictions. Moreover, the advice received from HTA agencies may vary and be rapidly influenced by novel therapeutic developments or economic challenges; the quality of the advice is also dependent upon the level of experience of the agency and its staff.

Experience with HTA advice to date reveals that the number of stakeholders involved is important: too many interested parties may make it more difficult to reach consensus or to give detailed recommendations. Furthermore, the timing of advice (phase 1 versus phase 3) may determine the type of dialogue that can be facilitated. The type of advice needed (e.g., study design advice, surrogate recommendations) will determine when advice should be sought; often, this early advice is given verbally and is non-binding, while specific input on trial designs, data collection methodologies would ideally be provided as a written directive.

Just as important is the extent to which sponsors follow the advice. It is clear from the regulatory arena that those companies that follow suggested scientific advice have a greater probability of reaching a positive approval conclusion for their products. Although it is too early to draw conclusions, there may be a parallel with following HTA advice.

Strategies

Industry senior management should drive a company-wide recognition that reimbursement issues are an important component of a development strategy, align internal functions to address this need, and fund mitigation strategies to de-risk clinical development programmes thereby facilitating earlier informed “go” “no-go” decision making. Many would therefore advocate that HTA advice cannot be received too early in a development programme as certain data that can easily be collected during early development phases are crucial to HTA decisions, such as the importance of using dose-finding studies for health economic assessments. Early HTA advice, however, should not be too prescriptive but should be directional yet flexible.

Regulatory agencies can use HTA advice to improve the context of decision making, as health technology assessment may be seen as closer to real-life healthcare delivery. HTA agencies, however, must seek greater alignment locally, nationally and globally, in their scientific approach to decision-making and this alignment may be facilitated by the proactive involvement of groups such as EUnetHTA. Joint HTA-regulatory guidance in important therapy areas or with “game changing” products can be used as an opportunity to reach common ground, and joint or parallel advice in the post-authorisation space will benefit from greater alignment.

Although large groups are appropriate for general advice forums, breakout discussions of smaller numbers of individual stakeholder groups may be more efficient to develop tactical development recommendations for a specific product. In fact, a clear understanding of the source and perspective of the advice is important to facilitate tradeoffs in a global development plan. Whilst there must be a clear identification of commonalities among stakeholders, it is equally important for divergences among the groups to be clearly elucidated. Written advice or minutes should be preferred to ensure accuracy of interpretation and expectation and the development of historical record. Finally, it must be recognised that the aim of all programmes of scientific advice should be to help design a rational, efficient investigational programme whose results will correlate with the ultimate outcome in a real-world setting.

Recommendations

1. Map the current landscape of early HTA and HTA/regulatory advice procedures, including those planned, piloting and established and develop a better understand of the impact of this advice

2. Develop joint HTA/regulatory guidance in important therapy areas to build on regulatory guidance – use “game changing” products as opportunity to drive scientific underpinnings of common ground

3. Identify topics for joint workshops, utilising a case study approach to examine issues, such as methodology alignment and how to address the needs of personalised medicine/diagnostics

4. Proactively explore HTA/regulatory joint/parallel advice in the post-authorisation space, as this may represent an opportunity for greater alignment
The business case for evidentiary requirements in phase 3

Dr Murray Stewart
Senior Vice President, Head of Metabolic Pathways and Cardiovascular Therapy Area Unit, GlaxoSmithKline, USA

Expanding the goals of drug development

Using the development of metabolic and cardiovascular therapies as examples, Dr Stewart discussed the current challenges faced by the pharmaceutical industry in pursuit of its central goal: the improvement of the health and well being of patients.

The incidence of obesity and diabetes is increasing across the world, and industry must rise to the challenge presented by this health crisis by raising the clinical value of new medicines. Medicines developed for patients with these conditions should result in weight loss or reduction of Hba1c levels, clinical effects that will have a significant clinical impact on the prevention of diabetes or reduction of cardiovascular disease and other causes of morbidity, and mortality. Clinical development teams must consider from the time of target selection how a new medicine will be used in the real world and in the context of other drugs being developed, determining what its potential value will be to society. The goal of these research and development teams is no longer solely to submit a new drug application for regulatory approval, but to consider as early as possible what data will make that compound a valuable and reimbursable therapy. Among other things, this consideration results in the planning for regionally appropriate head-to-head clinical trials and the inclusion of relevant testing populations.

In the past, the traditional approach to drug development involved short-term clinical trials in which a new therapy was tested against placebo, with the results then submitted to regulatory authorities along with safety data. Today, however, the designs of randomised clinical trials are improving and most studies of new diabetes therapies extend for at least three years, with improved methods for patient follow-up. Phase 3 programmes now collect comparative data and more elderly patients or patients with concomitant diseases are being included in trials to more accurately reflect real-world conditions.

In addition, developers are considering the incorporation of patient-reported outcome data into trial designs.

Challenges in diabetes trial design

Despite these improvements in pharmaceutical research and development, challenges remain to be addressed, such as the decision as to whether to design clinical trials using surrogates for efficacy or outcomes data. Although there are some recognised and accepted surrogates for efficacy such as a reduction in Hba1c levels in patients with diabetes to indicate a potential improvement in cardiovascular risk, they are regarded by many health technology assessors and some regulators as unreliable indicators. However, because of the time, number of patients and expense required outcomes data such as an actual reduction in rates of microvascular or cardiovascular complications can be challenging to obtain. For example, it has been recently determined that a clinical trial to derive outcomes data comparing a potential osteoporosis treatment with a marketed therapy would require a 40,000-patient study over six to ten years at a cost of $300 to $400 million.

Furthermore, outcome studies may not produce the anticipated results. In the five-year...
Rosiglitazone for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) and the A Diabetes Outcome Progression Trial (ADOPT) trials of sulfonylurea and rosiglitazone, and metformin and rosiglitazone, use of rosiglitazone produced lower glycaemic levels but the magnitude of the reduction was only 2 to 3%. Differences between the occurrences of microvascular events associated with these agents were also minimal and the results may have been confounded by the high level of care received by patients in the trial. Similarly, data from the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE) study also indicated no significant difference between pioglitazone and a placebo control arm on the primary endpoint, which included death from any cause, non-fatal myocardial infarction, stroke, acute coronary syndrome, leg amputation, coronary revascularisation or revascularisation of the leg. In a quote adapted from a report on comparative effectiveness research by John Doyle, Dr Stewart stated that “High value innovation is not merely to develop new medicines, but to develop better ones.”

There are further challenges in designing a clinical trial to determine the efficacy of a medication in the prevention of micro- and macrovascular complications in patients with type 2 diabetes. Although a double-blind design is optimal, any study that involves the use of insulin as part of the strategy has been traditionally open-label. And whilst efficacy superior to the current standard of care is an ideal endpoint, that standard of care for this disease has not been definitively decided and is still variable. Similarly, although trials involving active comparators are considered superior to those using a placebo comparator with regard to providing clinically relevant information, the choice of active comparators can be controversial. Finally, both the EMA and the US FDA have indicated that safety should be the primary endpoint for trials of new diabetes agents, while other authorities require proof of superiority of effectiveness over other available medications. As the results of the previously mentioned trials have indicated, proving the superiority of these agents in reducing the rate of micro- or macrovascular events may be difficult. In fact, although still not well defined, the value of these traditional glucose-lowering agents may lie in their tolerability and efficacy in weight and hypoglycaemia reduction; all of which have significant potential to affect quality of life.

Designing trials for type 1 diabetes agents presents comparable challenges. Using insulin to reduce blood glucose levels is the current standard of care people with this disease. Rather than demonstrating glycaemic control superior to that achieved with the use of insulin, new agents may be able to demonstrate superiority in their effect on C-peptide levels, a surrogate for pancreatic beta cell preservation. The clinical benefit of this preservation, however, may not reveal itself for 10 to 15 years; therefore, the challenge remains to design long-term, real-world analyses.

**Potential solutions and new ways of working**

Developers must create a clear vision of the clinical benefit of a new drug for the patient, considering the evidence, including comparative data and relevant clinical outcomes needed to satisfy patients, regulators and health authorities. Improved communication and discussion of issues relevant to those requirements is essential. To that end, the European Healthcare Innovation Leadership Network has convened working groups from industry and regulators in the therapeutic areas of breast cancer and type 2 diabetes to increase clarity for all parties regarding the evidence required to demonstrate value while providing non-binding advice on the medicinal development plan.

Enhanced interaction and communication with health technology assessors may facilitate their interpretation of clinical trial data. In the sixth Organisation to Assess Strategies in acute
Ischemic Syndromes (OASIS-6), fondaparinux, a synthetic pentasaccharide that selectively binds antithrombin, was tested in a trial of 12,000 patients with ST segment elevation myocardial infarction (STEMI) who were randomised to receive fondaparinux or placebo/unfractionated heparin within 12 hours of symptom onset. Results demonstrated that in comparison to placebo or unfractionated heparin, fondaparinux significantly reduced mortality rates and incidence of subsequent myocardial infarction without increasing the risk of bleeding. However, in patients who underwent primary percutaneous intervention to restore coronary blood flow, which is the standard of care for STEMI in the United States, there was no benefit to fondaparinux and its use was actually associated with increased thrombosis. Consequently, the drug was approved for use in Europe, but not in the United States, although it is now being reconsidered for use there in combination with heparin. Without the necessary stakeholder communication and depending on how these data were analysed, HTA authorities could either conclude that the drug had the potential to save lives or to endanger them.

Standardisation is another vital component of an improved research and development paradigm. Clinical trials should be similar with standard endpoints definitions. Databases should contain information that is uniformly expressed and regulatory authorities and HTAs should have similar requirements for submission.

Early go/no-go decision making in drug development must increase, with timely consideration of the clinical implications of drug target selection and development and therapeutic differentiation and comparators considered in phase 2 studies. Scientific breakthroughs are resulting in the identification of novel targets for drug development, but care must be taken to evaluate the clinical relevance of these novel targets early in their development in a well-defined target population. For example, the over-expression in skeletal muscle of myostatin, a transforming growth factor beta, results in decreased muscle mass, and its inhibition has lead to increased muscle growth in animals and human subjects. However, rather than testing a myostatin inhibitor in a broad population such as the elderly, who are likely to have diverse confounding health issues that underlie their muscle wasting syndromes, developers should specifically target a smaller, more clinically homogenous group of patients who would derive optimum benefit, such as patients who have suffered a hip fracture.

Finally, to effect needed improvements in pharmaceutical development, industry must initiate planning beyond clinical trials using such techniques as modelling and use of risk equations, observational data, pharmacovigilance, registries and patient-reported outcomes.

**Why should the regulator and the payer wish to align requirements? What is in it for them?**

**Professor Adrian Towse**

*Office of Health Economics, UK*

**The need for alignment**

Cooperation between pharmaceutical drug regulatory agencies (DRAs) and health technology assessors (HTAs) including possible alignment on requirements for phase 3 trials potentially improves the likelihood of health gain to the populations that both these groups serve in diverse ways. It could enable expedited access to new innovative medicines and optimise resources through avoidance of duplicative efforts. Attempting such alignment, however, may be regarded as a compromise to the individual missions of each agency and a misuse of scarce resources in pursuit of a goal that is unlikely to be achieved.

DRAs and HTAs have distinct and separate missions in the review of new medicines, and progress toward alignment of requirements between the two groups requires a greater understanding by both parties of the other’s role. Whereas DRAs look to determine the safety and efficacy profile of a new medicine, with a positive benefit-risk balance for a defined group of patients, HTAs expect to see health gains that are associated with the use of the drug at a price that delivers value for money.
Alignment of the outcome measures collected during development is a critical goal that can facilitate patient access. In a CIRS (formerly known as CMR International Institute for Regulatory Science; the Institute) Workshop in March 2010, Dr Supriya Sharma, Director General, Therapeutic Products Directorate, Health Canada, stated “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 ultimately have the medicine not go to market for lack of data to enable a pricing or reimbursement decision.” She went on to say that both groups were learning more about their individual missions. Whilst DRAs sometimes approve drugs on an accelerated or conditional basis, HTA bodies may refuse to approve their use because the price is considered too high, the long-term benefits are too uncertain given the price or there is a lack of sufficient evidence of expected meaningful health gain.

There are requirements, however, that are common to both groups; that is, evidence of efficacy generated by randomised clinical trials and evidence of real-world benefits and harms acquired after launch. In fact, regulators and HTA assessors may be closer to alignment than is commonly acknowledged. In a September 2009 CIRS Workshop, Dr Eric Abadie said the “ever shortening temporal proximity of regulatory and HTA review means that both groups are essentially reviewing the same data.” The best way forward, according to Dr Abadie “may lie in offering sponsors joint scientific advice and identifying ways to introduce some pragmatic measures of value into randomised trials.”

Some of the difficult issues

Results of a 2009 CIRS survey of HTA and DRA agencies revealed opportunities for the two groups to collaborate in drug development including clinical trial design. Respondents indicated that there are “definite dossier requirements that may be amenable to harmonisation, and there are stages of review in which sharing of information and collaboration would be useful.” And that “it’s becoming essential for HTA agencies and drug licensing bodies to collaborate.” Although it was also felt that “such collaboration is very resource intensive.” When asked to anticipate conflicts in potential collaboration, responses included: “HTA agencies need to estimate the impact of health outcomes rather than determine efficacy” and “HTA agencies need comparator trials rather than placebo trials.” Other points of difference included the preference of HTA agencies for direct measurement of patient-relevant outcomes, a difference in selection of appropriate comparators and concerns about the ability to share confidential information across agencies.

The selection of appropriate comparators and the alignment of standards for non-inferiority determination by all stakeholders have been debated at CIRS Workshops. Professor Towsley quoted Professor Robert Peterson from the September 2009 CIRS Workshop: “A three-arm trial with test reference and placebo allows within-trial validation of the choice of non-inferiority margin and should be used wherever possible.” Professor Hans Georg Eichler: explained, however, that “The reality is only a small percentage of medicines are approved based on active comparator trials. Establishing a clinical program whose design can meet the needs of both regulators and HTAs may be challenging.”

The choice of clinical trial endpoints represents another issue of potential conflict between the stakeholders. While both groups want to know if a medicine’s effect on a surrogate outcome can be expected to lead to a change in a real-world health outcome, health technology assessors also want to quantify the change as well as to understand the degree of uncertainty that may surround it.

All of these issues of concern are also relevant in the United States, where although stakeholder requirements are similar to those in Europe, alignment between regulators and HTA bodies is further complicated by the political environment.
Conditional approvals
Whereas regulators may be willing to accept clinical trial evidence demonstrated through intermediate endpoints or the use of placebo, payers generally desire more practical evidence to establish value. A possible solution is for regulators to continue to grant expedited approval for drugs demonstrating significant indication of clinical benefit through progressive authorisation linked to conditional coverage by HTAs with the development of evidence based on outcomes against active comparators.

Discussing conditional approvals, CIRS Workshop presenter Claire McGrath explained that the time gained through a shortened regulatory approval process is frequently lost during reimbursement negotiations and the primary reason for this is that conditionally approved medicines are much more likely to suffer from clinical and financial uncertainty at launch. She proposed a two-part solution: conditional approval should be granted on the basis of an indicator accepted by both payers and DRAs and that conditional pricing using modelling from these indicators be linked to an evidence corridor to get from indicators to real-world clinical outcomes.2

Beyond phase 3
Regulatory agencies including the European Medicine Agency (EMA) have determined that the assessment of benefit and risk should continue throughout a drug’s lifecycle, and the development and communication of evidence must be structured in a way to support that process.3 In fact, both regulatory and HTA agencies require the ongoing assessment post-launch data of effectiveness and should collectively move toward a better understanding of the relationship between efficacy and effectiveness and in the ways they differ under particular circumstances. Because repeating prospective, observational or pragmatic post-approval effectiveness studies in different geographies raises the cost and delays the availability of medicines, international and regional differences in clinical practice need to be anticipated and planned for in the design of post-approval follow-up studies. A tripartite dialogue should be considered to determine to what extent safety, efficacy and effectiveness data can be collected in the same trial and to allow industry to design studies that meet all stakeholder requirements.

Despite potential issues of conflict, concordance among stakeholders is possible. Novartis conducted a series of meetings with DRAs and HTAs to coordinate a development programme for psoriasis medications that they hoped would enable them to deliver clinical trial data that would satisfy the requirements of both groups. Regulatory advisors in Europe were interested in the psoriasis area and severity index scores (PASI) and in the US the Investigator’s Global Assessment (IGA). HTA assessors found those measures useful but also wanted to know the medicine’s health benefit effect. Reporting on the results of the programme at an earlier CIRS Workshop, however, Martin Backhouse, Head, Pricing & Market Access Operations, Novartis Pharma AG, Switzerland observed indications of progress, saying “Far more similarities and differences emerged across countries” and “Clinical evidence required by payers and regulators could probably be obtained in one comprehensive phase 3 program. Meeting the specific requirements identified would not likely increase costs of development times significantly.”2

Another point of view, however, was expressed in the recommendation of one of the Syndicate discussion groups at the March 2010 CIRS Workshop: “The HTA groups and regulators have discrete information needs and desirable designs of studies; to meet these separate needs through a single development program does not mean that all data should be combined into one study and caution should be taken to ensure that the harmonised information requirements do not lead to a development program so large and costly that it inhibits innovation.”

Professor Towse concluded that the investment of time and resources necessary for alignment of the requirements of DRAs and HTA agencies entails confidence that this alignment will deliver improvements in drug development as well as the potential to improve the opportunity for health gains to the patients they serve without compromise to their individual missions.

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The Australian Pilot (TGA and PBAC) Advice Programme

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Australia is unique in the Western world in that its pharmaceutical regulatory (Therapeutic Goods Administration; TGA) and pharmaceutical reimbursement (Pharmaceutical Benefits Scheme; PBS) groups work for the same level of government under the same portfolio Minister of Health and within the same department. These groups operate, however, in different divisions, according to different legislation, using different decision criteria and processes. This atypical organisation means that whilst Australia experiences many of the difficulties that have been associated with the alignment of advice between regulators and payers, they enjoy the advantages of coexistence.

Scientific advice meetings for the TGA and PBS are initiated by industry applicants, and their purpose varies with their temporal proximity to the submission of the dossier. The meetings are mainly divided into:

1. those that occur when phase 3 trials are ongoing or complete, which is typically within a year of dossier submission; and
2. less frequently, but increasingly importantly, those that occur before design of phase 3 trials is finalised, which is typically more than three years before submission.

Meetings are free of charge and the advice is not binding on the eventual decision maker.

Advice given within less than a year to dossier submission
For those advice meetings that occur within a year of dossier submission, evidence generation is typically ongoing or complete. These are mostly bipartite meetings in which applicants meet with TGA and PBS separately, although in one recent tripartite exception, an industry applicant sought both TGA and PBS advice as to the necessary evidence generation to support a drug in a target population for reimbursement.

TGA
In addition to the bipartite meetings, approximately 40 advice meetings take place per year in which only the TGA is consulted, and which are focussed on information to support the proposed dossier submission. In addition, a business process reform programme currently being implemented in Australia has created a new type of meeting that occurs within this timeframe to facilitate predictability of the evaluation process and to improve the efficiency of the dossier assessment. These largely educational meetings, which are chaired by the eventual TGA decision maker, are conducted to promote understanding and acceptance of various regulatory requirements by both the TGA and the industry applicant.

PBS
Advice meetings that take place within a year of submission exclusively with the PBS focus on the strategy of the proposed PBS dossier. Unlike the TGA meetings, however, advice is not provided directly by the decision maker, who in this case is the Pharmaceutical Benefits Action Committee (PBAC). The key issue for the meetings is the translation of the clinical evidence designed for regulatory purposes to meet the needs of the PBAC. Because price setting is governed by both science and other experiences, the meeting inevitably extend beyond scientific discussion and cannot therefore, be considered strictly “scientific advice” meetings.

In an effort to expedite patient access to medicines, the Access to Medicines Working Group (AMWG), which is a forum for multinational pharmaceutical companies and officials from the Australia Department of Health, has proposed a pilot to enhance PBS advice meetings. The proposal included suggestions to include more content experts,
PBS subcommittee members and occasionally to involve TGA representatives. The proposal also specifies that extensive briefings and questions be prepared and circulated in advance of the meeting to optimise the quality of the dossier and reduce the number of resubmissions. This pilot is not yet complete, but a preliminary assessment of its effects reveals that meeting enhancements such as these cannot compensate for missing or weak evidence and that an expansion of the availability of these advice meetings will require more resources from all parties.

Advisory given more than 3 years before submission
The objective of advice meetings that occur more than 3 years before submission is the enhancement of mutual awareness and trust between stakeholders and the facilitation of the more timely and cost-effective generation of evidence for reimbursement without weakening the evidence base for the regulatory decision process.

Since the 1990s, PBS has conducted approximately twelve of these meetings in various therapeutic areas, and since 2008, most have been held in concert with the TGA. The TGA, however, has accumulated more experience and holds approximately six early-stage meetings per year that are independent of the PBS. Largely because of time constraints, it has not been routine for the TGA and PBS to convene before tripartite meetings with the drug company, making the advice truly independent.

The preparation and resources for early advice meeting are much more extensive than those held at a later stage, and there is a more extensive pre-circulated dossier. The meetings themselves are longer in duration and involve a wider range of senior staff. No follow-up meetings have occurred.

An assessment of scientific meetings
TGA and PBS have found the meetings to be useful and hopefully influential, but little feedback from multinational companies has been provided. Similarities between the groups have outweighed differences and the meetings have resulted in an improved mutual understanding and respect for each other’s position, approach and requirements. The separate but extensive advice meeting experience of the two divisions has proved relevant and may demonstrate a similar benefit in cross-jurisdiction liaisons.

An increase in the demand for scientific meetings would necessitate the incorporation of efficiencies to accommodate the increased workload, such as the provision of disease-specific guidelines or the published guidelines of other regulatory agencies, a limit on the number of meetings for an individual product, or the incorporation of multi-jurisdictional advice.

Differences in stakeholder perspective
It must be recognised that intrinsic differences between the role of the regulator and the payer in the provision of scientific advice will remain. Although it is key for the regulators to remain within the scientific realm when providing advice to sponsors, reimbursers must also accommodate the intrinsic negotiation that is part of pricing. These price negotiations are not necessarily scientifically derived but are dependent on cost-effectiveness and budget assessments and are not the purview of regulators.

For example, in a recent pre-phase three meeting, the sponsor proposed a non-inferiority active control design for clinical trials of a new drug. The regulatory contributor to the meeting was primarily concerned with the sensitivity of the assay proposed for use in the trial. The main concern of the reimbursed was that the therapeutic comparator to the new drug cost less than $300 per year and although the evidence generation for the new drug assumed no therapeutic superiority, the applicant was going to propose a much higher price. In another example, the sponsor proposed a superiority active-control design and the use of surrogate outcomes for the clinical trials. The regulator in this case was appropriately concerned with the need for a strong biological rationale to support the chosen surrogate outcomes whilst the reimbursers was also concerned with maximising direct patient relevance of those surrogates, which are typically associated with short time horizons and a weak basis to assess their applicability beyond the explanatory phase to the pragmatic trials.

An emerging issue in scientific advice
Personalised medicine involves a co-dependence between investigative and therapeutic interventions; for example between medicine and a companion diagnostic. This co-dependence can offer the opportunity for coordinated tripartite advice between sponsor, regulator and the funder of the diagnostic, which in Australia is the Medicare Benefits Schedule (MBS). PBS has also approached TGA to see if they would join
in this coordinated advice effort, operating on the principle that the confluence of multiple objectives improves the opportunity to maximise benefit. To date, however, the evidence-base presented at these meetings is typically weak, usually relying on a sub-group analysis that is very rarely pre-specified and that involves multiplicity issues or evidence that is constructed from small phase 1/2 trials, with multiple regression analyses. The way forward for sponsors seeking scientific advice for trials of personalised medicine may be to corroborate evidence with a biologic rationale.

Conclusions

Prior experience in separate advice meetings has helped the TGA and PBS to conduct tripartite scientific advice meetings with greater confidence. Although differences in the roles and objectives between the two advisory groups will continue, there are clear benefits to programmes of shared advice, including the enhancement of understanding and trust. Resource implications may prove to be an impediment that will require shared and improved efficiencies.

Combined scientific advice and product effectiveness guidance meetings – a joint programme by the MPA and TLV in Sweden

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From 2009 until December 2010, the Medical Products Agency (MPA) and Dental and Pharmaceutical Benefits Agency (TLV) of Sweden undertook a pilot project to provide joint scientific advice to industry. The MPA currently offers scientific advice regarding approximately 200 products per year, and this project fit well into its strategy to develop and retain the competencies and resources necessary to provide full regulatory services during the entire life cycle of medicines. Additionally, it was hoped that the programme would create better understanding and improved interaction between the regulatory and health technology agencies.

Twelve joint advice meetings were held during the pilot, primarily with large pharmaceutical companies seeking advice at the initiation of a phase 3 development programme, although some smaller companies working in earlier development programmes also participated. After applying through the MPA website, sponsors were asked to provide briefing material and questions for the agencies well in advance of the meeting, clearly identifying for which agency the questions were intended. The MPA and TLV had a brief discussion prior to the actual meetings, which took place at the MPA in Uppsala. After each meeting, the industry participant was asked to provide feedback.

Pilot results

Regarded as industry’s first significant link to scientific advice from the TLV, the shared advice programme provided industry participants with a better understanding of the evidence base required for the approval and reimbursement of their product and the necessary methods to achieve that evidence. The pilot also facilitated collaboration between the two agencies, although from a practical point of view, implementation required significant planning and time resources.
Although industry responses to the pilot as determined by post-meeting surveys were positive, there have been very few requests for joint scientific advice since January 2011 when the MPA and TLV agreed to provide this service on a regular basis. However, requests for joint advice may be sought at the time of market authorisation or later, and new Swedish legislation that will require more post-authorisation effectiveness studies (PAES) may also lead to an increased interest in joint advice, with PAES advice requested from both agencies.

View from the TLV
At Dr Ljunberg’s request, Dr Nicholas Hedberg, Head of the Department, TLV presented the TLV perspective on the shared advice pilot. Although the TLV engaged in the pilot in support of the MPA rather than in fulfilment of a government mandate, they are prepared to continue the programme, with 10 to 15 shared advice meetings per year.

The formal findings of the pilot evaluation revealed that the MPA answered the most industry questions concerning endpoints, while the majority of TLV questions concerned comparators, and both agencies shared equally in discussions about inclusion and exclusion criteria. In an example of questions concerning the establishment of evidence for reimbursement, several companies asked if in the event that evidence acquired for a drug’s effectiveness in a target population proves insufficient, a drug could be considered reimbursable as last-line therapy. The TLV response has been that there must be clinical trial data showing the effects of the drug on a particular population for treatments for that population to be reimbursable. Participants from the agencies regarded the dossier submissions to be generally of high quality, although the TLV would prefer stronger proof for conditions that were identified by sponsors as “unmet medical needs.”

Dr Hedberg explained that the pilot programme was initiated at the suggestion of industry and reiterated that they had uniformly responded positively to the meetings in which they participated, although not all participants were prepared to follow the advice received. Some companies expressed concern that the MPA might in future require an economic evidence base, which they were assured, is not the case. Other comments centred on the difference in advice received from the two agencies on the same topic, which Dr Hedberg explained was often due to the need of the TLV to consider comparisons with real-life clinical practice. Several companies indicated an interest in receiving TLV-only advice as a complement to the joint advice programme, although such plans would have to be developed by the Swedish government.
The EMA (EMA and multiple stakeholders) shared advice pilot programme

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The need for change
Multiple critical issues have emerged in the development of high-value medicines, including a scarcity of resources available to both industry and national healthcare systems and the cost of late-stage failures in clinical trials. Moreover, pharmaceutical developers are faced with a variety of requirements from regulators, HTAs, payers and clinicians for the approval, endorsement, reimbursement and uptake of new medicines.

According to a survey undertaken by IMS Health for the Belgian government, there is an unacceptable inequality in the access to new medicines in Europe. Between 2005 and 2009, Germany and Spain saw the launch of 45 innovative medicines, two thirds of which were also approved in most of the other countries in Europe. The number of products launched per country within two years of the original approval, however, varied greatly, and an assessment of the actual uptake of medicines revealed as much as a 20-fold difference in the amount of money spent on new medicines in France, Denmark, Spain compared with Latvia, Lithuania and Bulgaria.

In response to these challenges, a pilot programme for shared advice was initiated in 2010 by the EMA and stakeholders from five European countries, including industry, regulators, HTA agencies, clinicians and patients. The overall objective of the pilot was to seek clarity and alignment among stakeholders regarding what constitutes a medicine’s value and what kind of evidence is required to demonstrate that value most effectively. This project was coordinated through the Tapestry Networks, and through the pilot, sponsors sought to identify the projects most likely to result in added value to healthcare systems, to eliminate those that were unlikely to contribute to that value and to consider how to generate data relevant for HTA and payers before marketing authorisation.

The shared advice programme
In this Tapestry Networks programme, three companies engaged in nonbinding group consultative processes for new therapies in type 2 diabetes and breast cancer. Participants operated within their usual legal framework and most agencies either waived their usual fees or kept their total expenses below those currently charged for providing early advice. The consultation process lasted approximately two months. Industry participants delivered a preliminary briefing pack approximately one month before the main meeting and received advisor input on the briefings from clarification meetings or teleconference, before delivering the final briefing pack approximately one month later.

The main consultation meeting lasted approximately four hours and was chaired on a rotating basis by regulators or HTA representatives, with 26 to 28 active participants and several observers. Following its usual procedure, representatives from the Scientific Advice Working Party (SAWP) of the CHMP provided written advice. Although no written advice was available from HTA or payer participants, minutes of the proceedings and a debriefing for all participants were provided.

Comments from non-sponsor participants were generally positive and emphasised the quality of the stakeholder interaction and the resulting increase in common understanding. Although sponsor comments were generally positive,
Is it feasible to expect comparators and endpoints to meet the needs of both regulators and the HTA?

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The need for convergence
Financial analysts believe that too much money is being invested in pharmaceutical research and development and attribute most of the industry’s value to its marketed products rather than to those in the pipeline. In fact, there is an overall success rate of less than ten percent for new medicines, and when that rate of failure is combined with the escalating costs of development and pricing and reimbursement hurdles, it results in the pharmaceutical industry’s ever-declining ability to develop important new medicines. Even a slight improvement in the rate of failure for new medicines, however, would have a significant impact on the cost of development and the resulting costs to the healthcare system and patients. Converging the evidence needs of stakeholders may facilitate the ability of developers to make early decisions as to which medicines have the greatest potential for approval and reimbursement.

early-stage consultation, the long-term effects of the therapies being discussed are unknown. HTA agencies, who are less accustomed to this level of uncertainty than regulators, must decide if the benefits that can potentially accrue from early consultation are worth operating outside of their traditional comfort zones. Similarly, the fact that HTA representatives did not provide written advice in the pilot may lead to a continued limitation to harmonisation and HTA groups must determine if their continued participation in the process might require a stronger commitment. Harmonisation efforts for HTA groups are still in the nascent stages, and it may be that continued participation in programmes of joint advice may in fact assist in these efforts.

Meeting logistics, consultation follow-ups and the potential harmonisation of a European-wide organisation that addresses the increasing diversity in reimbursement systems are all issues that must all be resolved for future initiatives of this type to move forward. Because the relevance of pharmacoeconomic models differs so widely among member states, it may be preferable for each country’s representatives to participate in consultative meetings at different levels.

Drug development is an evolving and iterative process that can no longer be seen as moving from research and development to marketing authorisation to the assessment of health technology. Early scientific consultation programmes are one way to facilitate the application of knowledge concerning the comparative effectiveness and pharmacoeconomics of new medicines during the research and development stages.

Issues and solutions
Direct EMA – HTA meetings might facilitate programmes of shared advice by clarifying individual stakeholder objectives. Because this Tapestry coordinated programme involved there were areas in clinical development of the product that sponsors indicated they might approach differently in light of the advice received, such as clarifying the scientific basis for the medicine’s mechanism of action and its relevance to biomarkers, better defining the approach to patient segmentation and providing more robust rationales for the design of proof-of-concept studies.

An evolving iterative process

1. R&D
2. MA
3. HTA

Comparative effectiveness Pharmacoeconomics
There are significant challenges to such a convergence. The roles and perspectives of regulatory and HTA decision makers are fundamentally different. Regulators look for efficacy based on previously specified objective primary outcomes, whereas HTA evaluators employ a continuous decision framework in which assessments are context specific. Although there is some overlap in the objectives of both of these stakeholders, it remains very difficult to quantitate an estimate of the value of a drug in a common framework.

Other challenges to the establishment of joint regulatory and HTA requirements include choice of comparators and endpoints and the way that personalised medicine will impact the need to develop patient-specific therapies.

Challenges to convergence: comparators
Dr Rossi used the development of bevacizumab in metastatic colorectal cancer to demonstrate the challenge of lengthy phase 3 development in the face of emerging and changing standards of care. The phase 3 trial for bevacizumab was designed to test its efficacy and safety with or without concomitant irinotecan, fluorouracil and leucovorin. However, in the five years that elapsed between the trial design and execution, the preparation of the regulatory dossier and the evaluation of that dossier, five new drugs had been approved for use against the disease: irinotecan, capecitabine, oxaliplatin and cetuximab. At the time of its launch then, the trial results for bevacizumab could not answer the now relevant question posed by healthcare systems: how did its efficacy and safety in the treatment of colorectal cancer compare with that of these new approved therapies?

In addition to changes in the market over time, regional differences in standards of care due to clinical and economic choices, can present challenges to the selection of a single comparator for a phase 3 trial. For example, in 2010, despite the fact that it had not been approved in this indication, trastuzumab was a standard of care for the second-line treatment of metastatic breast cancer in Europe. There was, however, a wide variation among countries as to which drug trastuzumab was paired with, including lapatinib, capecitabine, bevacizumab and other cytotoxics, in a range of combinations.

So when developing a phase 3 trial for trastuzumab in the second-line treatment of metastatic breast cancer, although a head-to-head clinical trial to determine superiority against a comparator would be the preferred trial design, the choice of comparator was problematic.

In a similar example, faced with a wide range of potential comparators, Roche/Genentech used a mixed treatment comparison for applications for the regulatory and HTA approval for tocilizumab in the second-line treatment of moderate-to-severe rheumatoid arthritis for patients who were refractive or intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. The meta-analysis submitted by the company in its application allowed a level of comparisons to the various TNF inhibitors that were used in treatment of this disease that was accepted by the EMA as supportive of the indication. Use of the medicine was also approved by the Scottish Medicines Consortium on the basis of the cost-effectiveness model submitted by the sponsor, in which the clinical efficacy estimates from the indirect comparison was key. To standardise the necessary comparisons to inform market authorisation and reimbursement decisions, however, it is necessary to agree on the technical criteria and supporting data requirements for indirect treatment comparisons as a basis for generating evidence for relative clinical benefit assessment and making decision under conditions of uncertainty.

Challenges to convergence: endpoints
Using another example in oncology, Dr Rossi highlighted the need to bridge the gap between evidence that regulators need in order to perform a risk-benefit analysis of a new drug versus evidence HTA assessors require to decide how much clinical benefit that drug will yield relative to its cost. Metastatic melanoma has a dire prognosis, with only 25%
of patients alive one year after initial diagnosis, a rate that compares unfavourably to all other major epithelial cancers. What level of evidence is necessary to support regulatory and reimbursement decisions in such an illness in which current therapies produce only a 5% to 10% response rate?

Approximately 50% of melanoma tumours have a mutation in their BRAF gene that induces signal transduction and cell proliferation in that disease. Phase 1 trials of verumfaniib, a Roche/Genentech compound that inhibits this kinase demonstrated a partial or complete response rate in 50% of patients and stable disease in an additional 30% of patients with the BRAF gene. Next, two phase 2 trials were initiated, one in patients refractory to the first-line treatment to their metastatic disease and a second, randomised, unblinded, placebo-controlled phase three trial in the front-line setting with a primary endpoint of overall survival (OS).

After a public outcry from patients randomised to the placebo, the US FDA “strongly recommended” that Roche/Genentech change the primary endpoint to progression-free survival (PFS), perform an interim analysis of the results and then allow crossover of patients receiving placebo if the PFS criteria were met. Allowing crossover in the revised trial design, however, will abrogate the magnitude of the treatment effect, and this reduced effect will be associated with HTA challenges in various markets surrounding the price of and the level of access. Dr Rossi suggested a solution that included a reduced reliance on PFS or an unfeasible OS expectation through the qualification of 1-year or 2-year survival as a primary endpoint for certain metastatic cancer settings for which post-progression survival is longer than 2 months or crossover is deemed necessary.

Challenges to convergence: personalised healthcare

Between 2006 and 2009, less than one third of approved therapies were recommended by the National Institute for Health and Clinical Excellence (NICE) for the entire population indicated in the labels and 70% of optimised approvals restricted that treatment population to less than half of potential patients.

For example, trials of trastuzumab plus 5FU or capecitabine plus cisplatin in gastric cancer, a disease with an extremely poor prognosis, resulted in a significant survival benefit for a subset of patients whose positivity level for human epidermal growth factor receptor 2 (HER2) was 3 or greater according to immunohistochemistry (IHC) or who were identified as HER2 positive through fluorescence in situ hybridisation (FISH), which is approximately 22% of patients with this disease. The EU label eventually approved trastuzumab for the treatment of people whose positivity level for HER2 was 3 or greater through IHC or whose level of positivity was identified as 2 or greater with IHC and whose positivity was confirmed through FISH, which is approximately 16% of patients. The eventual recommendation from NICE, however, was for reimbursement only for patients whose HER2 positivity was identified as 3 or greater through IHC, which is approximately 11% of patients.

Dr Rossi concluded his presentation by saying that we must determine what relevant standards are being applied for these sub-group analyses and how our methods and healthcare structure can accelerate rather than stall identification of the correct patients and facilitate access to new treatments. Using pre-specification with appropriate methods and managed entry agreements, infrastructure and pricing will provide the right balance between risk, benefit and access and allow the use of these observations of outcome heterogeneity to provide access for patients. Comparators and endpoints can meet the needs of regulators and HTA evaluators more often than might be assumed, but less often that might be desired and that collaboration and new thinking will be required to effect a sustainable innovative future for the development of medicine.
Is it feasible to expect comparators and endpoints to meet the needs of both regulators and the HTA bodies?

Dr Mira Pavlovic  
Deputy Head, HTA Division, Haute Autorité de Santé, France

Collecting and assessing medical evidence for Health Technology Assessment

In France, a rapid single-technology assessment (STA) is provided by the Haute Autorité de Santé (HAS) for all new drugs. When conducting STAs, the HAS evaluates the dossier submitted by the sponsor, the European Public Assessment Report (EPAR) from the European Medicines Agency (EMA) and data from published scientific literature. Although drug prices are not set by the HAS, they are linked to that organisation’s appraisal of the drug’s clinical value.

The HAS collects and assesses evidence using methods that are similar to other HTA agencies, although there may be some differences regarding issues such as the acceptability of unpublished manufacturer’s data or the criteria employed for literature searches or for the selection of studies. Like other HTA agencies, the HAS assesses efficacy under ideal circumstances (through randomised controlled trials), relative efficacy compared to alternative interventions and effectiveness and relative effectiveness compared to standard healthcare practice. Their aim in evaluating a drug’s efficacy is not only to show that there is a useful trade-off between its benefits and harms, but also to estimate the magnitude of the observed effect and the consequential gain in health. In their assessment of a drug’s effectiveness, they must determine if health benefits are likely to be seen with routine clinical use, as opposed to the ideal conditions of a clinical trial.

What can be shared and with whom

Individual HTA bodies can share methodologies and results of assessment of clinical data with their peers. In addition, each may prepare discrete parts or “bricks” of a combined assessment report. According to The European network for Health Technology Assessment (EUnetHTA) the main “bricks” include the epidemiology of the disease, its diagnosis, alternative therapies, appropriate endpoints and comparators, as well as effectiveness and safety of a drug.

EUnetHTA is an organisation of 34 government-appointed organisations from 23 EU member states, Norway and Croatia that “connects public national/regional HTA agencies, research institutions and health ministries to enable effective exchange of information and support to policy decisions by the member states. The overall aim of EUnetHTA is to establish an effective and sustainable European network for health technology assessment that informs policy decisions.”

One of the goals of the EUnetHTA Joint Action Work Package 5 (JA1 – WP5) has been to develop guidelines concerning 10 methodologic issues encountered in HTA assessment of drugs:

1. Criteria for choice of the most appropriate comparator(s)
2. Direct and indirect comparisons
3. Clinical endpoints
4. Composite endpoints
5. Endpoints relevant to patients
6. Health-related quality of life
7. Internal validity
8. Surrogate markers
9. Safety
10. External Validity

More than 1270 reviewer comments were received on the first drafts of guidelines. The
main observations concerned the scope of the guidelines, the structure of the documents and the consistency between guidelines. Other comments concerned search strategy or ways to develop the supportive bibliography, definitions of the most important concepts and choice of terminology. After WP5 group consultation, second drafts will be developed and in 2012, the EMA and a Scientific Advisory Group will review the material, followed by a public consultation.

**Tools for harmonising requests**
Tools are being developed to harmonise regulatory and HTA requirements, including revised templates for European Public Assessment Reports (EPARs). Both the Medicine Evaluation Group (MEDEV), an unofficial committee of the Social Insurance Platform and EUnetHTA provided the EMA with comments and suggestions for changes to the EPARs, which were incorporated into new EPARs templates approved in November 2010 by the CHMP. The resulting reports provide more information regarding comparators and endpoints used in support of new drug applications as well as the EMA discussion and opinions surrounding regulatory decisions. In fact, the aim of the ongoing collaboration between the EMA and HTA agencies is to result in improved information regarding EMA assessment of marketing authorisation applications.

Guidelines are another possible tool for harmonisation. EMA guidelines are general or disease specific, whilst EUnetHTA guidelines have been developed only in the context of the methodology of assessment of the relative effectiveness of drugs. Regulatory/HTA collaboration regarding both EMA and EUnetHTA guidelines has been recently initiated. As has been mentioned, EMA will comment on the guidelines for HTA assessment currently being developed as part of the EUnetHTA JA-WP5 and HTA agencies have been requested to comment on existing EMA guidelines. It may be useful in the future to examine the use of EUnetHTA and EMA guidelines recommendations in real examples of product development.

Finally, providing scientific advice is an important instrument for harmonisation of regulatory and HTA requirements. In addition to being either regulatory or HTA derived, scientific advice can be national, European, disease specific or general. National HTA scientific advice for new drug applications has been provided by the National Institute for Clinical Excellence (NICE) in the UK, as well as in Sweden, Australia and other countries. The HAS in France has organised pilots for national scientific advice, evaluating three drugs, four devices, two diagnostics, and one therapeutic intervention and is currently planning publication of the results. There have been some instances of combined regulatory and HTA scientific advice in the UK and Sweden as well as the European disease-specific pilot programme of multi-stakeholder consultation in early-stage drug development initiated through the Tapestry Network, which was detailed in Professor Flamion’s presentation. Thus far, the pilot has included three consultations in diabetes and breast cancer. This advice was more parallel than joint, as the EMA gave independent scientific advice, following its typical 70-day procedure, which was not available to the HTA participants, and oral recommendations were provided during the meeting by HTA representatives, with no final written advice available.

The effect of scientific advice from HTA agencies on the development and reimbursement decisions of new medicines has yet to be evaluated. As the EMA has already studied the effect of following regulatory scientific advice on the eventual regulatory decision for a medicine, the effect of following or not an HTA scientific advice on reimbursement decisions is important to be investigated once sufficient number of advices has been provided.

Combined regulatory and HTA scientific advice may provide opportunity to develop an agreement on the choice of comparators and
What is industry looking for from regulatory, HTA and payer agencies, how should roles be defined and where could interaction between these agencies be of use?

Pierre Sagnier
Vice President, Global Market Access, Development Projects, Bayer HealthCare, Germany
Member of the EFPIA HTA Task Force

The European context
As a member of the European Federation of Pharmaceutical Industries and Associations (EFPIA), Dr Sagnier began his presentation by providing background information on pharmaceutical development in Europe.

Most of the 27 European Union (EU) nations have deficits in excess of the European Commission’s permissible 3% of gross domestic product threshold. Furthermore, healthcare is a key aspect of expenditure for all European governments and the pharmaceutical industry is most vulnerable to potential cuts in government spending.

Combined with these external challenges, the pharmaceutical industry is faced with the dilemma of decreasing return on massive research investments, less reward for innovation, exploding development costs, and a decrease in the number of new molecular entities being studied. Short-term measures have been enacted to combat the high cost of medicines, including price-cuts, reference pricing, increased tendering in pharmaceuticals and the introduction of contracting practices. There has also been a significant overhaul of market access systems for new drug therapies in countries such as England and Germany. However, budget silos continue to hinder a holistic approach to healthcare expenditures.

Regional and national differences add additional complexity. Within Europe, in addition to differing evidentiary standards for new medicines, there are different societal values regarding health and the ability and willingness to pay for interventions. A study commissioned by the Belgian presidency of the European community in 2010 showed staggering differences in the ability to access innovative medicines among patients in individual European countries. Despite the drive for the centralisation of value assessment being facilitated by the European Commission and other organisations such as European Network for HTA (EUnetHTA), MEDEV and the EU Network of Pricing Competent Authorities, there is also a fragmentation of payers being brought about by regionalisation, tenders, contracting and reference pricing.

Stakeholder collaboration
Partially, in response to all of these issues, barriers between phases of pharmaceutical
development and between regulator and
reimbuser are beginning to be breached to
create a new development paradigm. As part
of this new paradigm, clinical trial design is
beginning to reflect the evidence needs of
regulator and payer. Market access no longer
begins or ends at launch, and evidence is
being produced throughout the life cycle of a
product to support its continuous benefit-risk
assessment by regulators and its continuous
value assessment by payers. Although this shift
requires more investment for additional data
generation, it also allows a more intelligent
balance to be realised between the amount of
evidence that must be collected in the early
phases of a medicine’s development versus
that which can be collected in the late phases.
In fact, perhaps part of the solution to the
hindrance of access to innovation presented by
the high cost of data collection may be early
market access to select molecules through
strictly enforced conditional approval.

Areas of potential collaboration between
industry, regulators, HTA agencies and payers
exist throughout the product lifecycle and
can be divided into three distinct phases.
Early dialogue and interaction on scientific
advice in the phase 1 and 2 stages of clinical
development are beginning to be seen as
key in the optimisation of resources and
increase in predictability of outcome. Another
emerging point of interaction has become
equally important, however, and this is the
time of implementation of pharmacovigilance
plans, phase 4 postauthorisation studies and
continued data collection to evaluate the
real-world effectiveness of a medicine. The
more “traditional” time for contact between
stakeholders is the late development, early
marketing phase of a product, and this remains
an important phase. Two European initiatives
are planned or ongoing to improve interaction
during this phase. The first is the EUnetHTA
Joint Action, a three-year programme involving
24 member states and a budget of 6 million
Euros. The objectives of the programme are
to develop core HTA frameworks, methods
and modules to address the issue of relative
effectiveness assessment and beyond that, to
initiate a methods management system and
long-term model. In addition, another EUnetHTA
Joint Action is planned for 2012 to 2014 that will
pilot the frameworks developed in the first Joint
Action and collect information on costs and
organisational matters.

The way forward
Industry stands ready to be “held to account”
on medicines’ value for money and clinical
benefit, taking into account patient specificities
and personalised medicine. Regulatory
approvals based on the quality, safety and
efficacy of medicines should remain separate
from assessment of their real-world relative
effectiveness. Sound holistic HTA with proper
involvement of patients, physicians and industry
has the potential to stimulate innovation and
patient access to new medicines.

It is evident that the approach to European
HTA alignment can neither be totally centrally
or regionally driven, but rather a balance of
these two approaches. A common European
evidentiary platform can be built based on
medical need, disease severity and research
and development priorities, while appraisal and
reimbursement decisions remain national or
regional prerogatives. EU-level actions for HTA
standardisation could add value if they tackle
unnecessary duplication, enable greater clarity,
lead to raising standards of methodological and
process aspects in HTA, improve predictability
and contribute to timely access of medicines
to patients. Cost considerations and economic
evaluations, however, should remain at the
national level. Finally and most importantly, the
assessment of medicines should be driven by
patient benefit, including specific needs and
responses.
Methodological guidance for drug development from HTA and payers

Dr Sean Tunis
Founder and Director, Center for Medical Technology Policy (CMTP), USA

The evidence paradox
There is a view that there is a large dearth of evidence to support clinical practice and policy making across the entire spectrum of healthcare in the United States. In fact, a recent systematic review of the clinical trial data for the off-label use of 19 different approved oncology drugs concluded that “because of the paucity of high-quality evidence, the data available, though voluminous, may have little meaning or value for informing clinical practice.” A similar data gap can be observed in cardiology guidelines, where it was found, for example, that 60% of the clinical treatment guidelines for treatment of atrial fibrillation were derived from expert opinion, whilst only 10% were supported by high-quality evidence from clinical trials. This pattern is repeated across the entire domain of major clinical interventions in cardiology.

Statements regarding the insufficiency of clinical trial data supporting treatment guidelines often accompany the guidelines themselves. A clinical treatment guideline from the American College of Physicians for treatment of Alzheimer Disease reviewed five drugs that were approved by the US Food & Drug Administration for dementia based on significant improvement in cognitive function. From the point of view of the committee who developed the guideline, however, evidence for the clinical recommendations was “weak,” because of the short-term, non-comparative nature of the trials. In addition, because most of the outcomes used in the study designs were not employed in routine practice, they could not be considered “clinically important.”

In a recent review of psoriasis treatments by the National Institute for Health and Clinical Excellence (NICE), it was observed that clinical research in this disease tends to measure the extent of total body surface area affected, but interviews of patients affected with psoriasis revealed that face and joint involvement had the biggest impact of their quality of life. This divergence led the appraisal committee to question the relevance of standard psoriasis trial measurements that did not take face and joint involvement into account.

There is an “evidence paradox” in pharmaceutical development in which despite the fact that the results of 18,000 randomised clinical trials are published and tens of thousands of other clinical studies are being conducted each year, virtually every systematic review of those data intended to inform clinical and health policy decisions, routinely conclude that the evidence is inadequate. One hypothesis of comparative effectiveness research in the United States holds that these gaps in evidence arise from a misalignment between the research that is conducted versus the evidence that is required by clinical decision makers such as patients, clinicians and payers. The greater engagement of these stakeholders in selecting research questions and designing research methodologies and protocols would permit the identification of critical deficits in knowledge and the provision of guidance to address recurring deficiencies and evidence in future trials.

CMTP effectiveness guidance documents
The Center for Medical Technology Policy (CMTP) has begun to prepare effectiveness guidance documents in which insights from payers, HTA groups, clinicians and clinical guidelines are incorporated into specific guidance for trial design in individual therapeutic areas. The guidance is targeted to provide specific consistent guidance on the needs of post-regulatory decision makers that builds on existing regulatory guidance. It is hoped that the dialogue from which the guidance is drawn may inform the potential alignment between
The CER Hypothesis

- Gaps in evidence will be reduced with greater engagement of decision makers (patients, clinicians, payers) in:
  - Identifying critical gaps in knowledge
  - Provide guidance for design of future trials that address recurring deficiencies in evidence

regulators and HTA agencies. The work of the CMTP is funded by unrestricted grants.

In the process for guidance development, systematic reviews are conducted to help to identify recurring concerns with existing evidence, after which the CMTP consults with stakeholders to generate initial draft recommendations. Next, a technical working group refines these draft recommendations, and a symposium may be held to explore key issues identify by this group. Revised recommendations are then circulated for public comment and the resulting final recommendations are published.

A CMTP guidance document on patient-reported outcomes (PROs) in trials of the off-label use of oncology drugs has been developed. This focus on off-label use allowed the CMTP to include PROs other than the narrow list of highly validated outcomes specified by the FDA in their guidance on oncology trials. The recommendations include the use of fourteen patient-reported symptoms in trial design such as anorexia, anxiety and constipation. This list, developed through stakeholder input, will eventually be validated by the entire patient advocacy and clinical healthcare community.

Technical and conceptual issues that emerged at the meeting surrounding the development of multinational therapeutic-specific guidance included decisions on guidance focus and process and the timing of clinical development covered in the recommendations. In addition discussions centred on whether the recommendations should be de novo or build on existing regulatory guidance and whether they should be technology or condition specific.

Next steps for the Collaborative are to follow up with participants to determine their level of interest, select a topic for an initial proof-of-concept pilot, develop a more detailed version of guidance development process and secure non-profit funding for the initial phase of work. A presentation on the topic was scheduled for the HTAi meeting in Rio de Janeiro in June 2011.

References


How are the needs and dynamics of regulatory agencies changing?

Dr Thomas Lönngren  
Strategic Advisor, NDA Group, UK

The changing environment
The decline in pharmaceutical productivity combined with unmet public health needs represents a potential crisis in healthcare, and regulators should proactively work toward its resolution. As the Former Director of the European Medicines Agency (EMA), Dr Lönngren was instrumental in the development of the EMA Roadmap to 2015, which outlines strategies that will be employed by the Agency to meet this and other challenges of the rapidly changing environment of pharmaceutical development. He outlined several of those challenges in his presentation, all with significant consequences for regulators.

Regulators must continually balance many different conflicting influences from industry, payer groups, patient advocates and public media set against a backdrop of unmet medical need, compacted timelines and expanding evidence requirements. In the face of all of these issues, regulators are subject to continual public scrutiny for matters of transparency and conflict of interest.

Manufacturing and research and development functions are moving outside of the classic areas of the United States and Western Europe to Eastern Europe, Latin America and Asia, and this shift has led to regulatory concerns surrounding manufacturing standards and the validation of clinical trial results. Ongoing scientific developments such as biomarkers, targeted treatments and stem cell therapy have added additional layers of complexity to the regulation of medicines and governments are reacting to ever increasing drug budgets with more stringent technology assessment requirements.

Regulatory requirements
The time from the submission of dossier to the regulatory decision for a new medicine was relatively short in the past, the amount of evidence required was much lower than today, and very little data were required after product approval. By 2010, however, because of increased awareness of risk, the time to render regulatory decision had increased as had the level of evidence requirements from both regulatory and HTA assessors. Most importantly, the amount of evidence looked for after approval continues to rapidly grow and this rate of growth may be unsustainable.

Increased regulatory and HTA requirements resulting from growing levels of risk awareness may contribute to development gaps in some therapeutic areas such as antibiotics and central nervous system treatments. In fact, one of most significant international health crises today involves the lack of antibiotics to treat resistant strains of bacteria.

In addition, concerns regarding unknown risk have caused wording changes in European legislation that have further increased the responsibility of regulators for benefit-risk decisions. Many products that have been withdrawn for safety concerns during the past ten years have been withdrawn because they were wrongly prescribed or misused. As a result, whereas, regulators were previously responsible to regulate medicines under conditions of “normal” use, they are now accountable for a medicine’s potential “abnormal” utility.

Regulators, who formerly approved medicines that had only been tested in strictly regulated trial populations, must now consider their use outside of label in potentially medically compromised individuals, conditions that both raise the risk and lower the potential benefit of a medicine.

To mitigate these conditions of clinical reality, patient populations must be strictly stratified...
to positively impact the benefit-risk ratio. Risk mitigation programmes and ongoing dialogue with healthcare providers will also ensure that products are used within label conditions and a benefit-risk balance is maintained. Decision making in the face of the spiral of elevated risk awareness must be accommodated with a reasonable level of evidence about which there is a reasonable level of uncertainty.

The HTA influence
The huge challenges for regulators presented by the current pharmaceutical environment can be well met in the coming years by the use of existing experience and competencies integrated with and complemented by the competencies of HTA assessors. HTA bodies must develop common methodologies and standards and although decisions regarding approval and reimbursement must remain separate, all stakeholders must continue to be proactive in the optimisation of resources and alignment of requirements where possible.

Regulators and health technology assessors have already made progress in collaboration toward their common goals. HTA agencies have provided input into the revised EMA European Public Assessment Reports (EPARS). European regulatory agencies together with the Australian Therapeutic Goods Administration, Health Canada and the Medicine and Healthcare products Agency of the UK have investigated the possibility of the alignment of regulatory and HTA payers evidence requirements and scientific advice.

The European Commission stated objectives for HTA are to produce robust evidence on technology and transparency, reduce duplicative efforts and national hurdles to marketing access. Toward that end they have developed a long-term HTA perspective and governance structure, participating in the ELUnetHTA Joint action programmes and other harmonisation pilots.

Key outcomes from Workshop

Professor Robert Peterson
Executive Director, Drug Safety and Effectiveness Network, Canadian Institutes of Health Research

Diverse evidence requirements
The diverse evidence requirements of the various decision-making stakeholders in the development of medicines are driven by their equally diverse informational needs, ranging from the statistics needed by manufacturers to render billion dollar investment decisions to the benefit and harms data that will allow patients to make life and death choices. All of this stakeholder diversity must be represented for meaningful discussions about changes in evidence requirements to take place. However, when considering the evidence requirements of these various groups, the reality that may have to be faced is that simultaneous access to the scope and quality of evidence to meet all decision-making needs may not be possible. Although efforts toward harmonisation of requirements continue, there may, in fact, not be a single path that can accommodate the tremendous global variation in willingness and ability to pay and intended outcomes for healthcare delivery systems.

There are clear challenges associated with HTA evidence requirements. Information about the usefulness of a new drug in the general population is necessary for assessors, including translation of its clinical trial efficacy into real-world effectiveness. It must be determined where the product fits into the therapeutic armamentarium and how to deal with its
unknown long-term safety compared with the safety profile of established therapies. Assessors must decide if a drug should be available for sub-populations not studied in the randomised clinical trials and how limited and appropriate prescribing practices will be. These types of evidence are beyond the traditional regulatory requirements, and if they will be used in making recommendations for product reimbursement, they should be accommodated very early within a drug development programme.

**Pharmacoeconomic models**

Pharmacoeconomic models based upon direct comparison are clearly preferred by those who assess medicines. Direct comparison trials designed to show non-inferiority rather than superiority, however, can present issues surrounding the determination of appropriate margins for measurement, with different standards of comparison frequently assumed by regulator and health technology assessor. Direct comparison models vary based upon an assumption of equal benefit (cost minimisation) or based upon superior benefit (cost effectiveness). Although pharmacoeconomic models based upon indirect comparison are more common, they require stricter rules than simple meta-analysis and it may be difficult to agree upon appropriate assumptions for analysis.

Typical cost-effectiveness models are able to produce rank-ordered decisions with high efficiency. In this model, the cost of a particular health intervention is calculated and divided by quality-adjusted life years (QALYs) gained. To the health technology assessor, however, the cost used in this calculation is an estimate that has not yet been negotiated and the determination of “quality” relies heavily on outcome validation by patient groups. Furthermore, in some disease states, calculations may be of quality-adjusted life weeks or even days.

Once the cost of a therapeutic option for a gain in QALYs has been determined, it can be rank ordered with other therapies and health technology assessors or payers can distribute their budget, with payment going first to the most cost-effective option until the budget is exhausted. This model, however, is insensitive to societal values, and actual budgetary allocations are more likely to be made allowing for certain key interventions such as oncology treatments, which may be very high in cost per QALY gained as compared with the cost-effectiveness of so-called life-style drugs, for example.

Budgetary allocations for key interventions are made after payment thresholds for QALY gains in a disease state are determined. Once payment thresholds for QALY gains have been determined, however, it frequently results in a post-hoc analysis of trial data by the sponsor to determine a subset of patients that can actually be treated at that threshold cost. Unfortunately, post-hoc data analysis creates many problems for the regulator, investigator and clearly for the health technology assessor.

**Stakeholder business models**

Label indications for new therapies invariably undergo narrowing from early phase development, to phase 3, to regulatory approval, and finally to HTA “optimised product listing”. Although patients may interpret this as confusion on the part of decision makers, it is more likely to be related to the conflicting business models of stakeholders. In the past, manufacturer stakeholders have looked for “blockbusters” that can be prescribed to broad populations, or at least products with high early returns on investment, as opposed to medicines that require long development times and shortened times of intellectual property protection.

Because they can pass the cost of premiums onto their subscribers, private payer stakeholders can evaluate the costs of a new medicine in comparison to other expensive treatments in the same therapeutic class. Public payers on the other hand, who must support access based upon proof of value for a necessary treatment...
and cannot easily pass on incremental costs without taxation or cuts elsewhere, must use the most cost-effective therapy as a comparator. This difference in the interpretation of value is a real impediment to international harmonisation of decisions.

Conclusions

Professor Peterson concluded his presentation by stating that there was a clear consensus from participants in this Workshop that a change in evidence requirements is required. Methods for change fall into three broad categories. The first is to obtain scientific advice from both regulatory and HTA organisations as early in the developmental continuum as possible and to merge and harmonise those requirements to the degree that is possible. The second is to include measurements of effectiveness; that is, the benefits and harms of a new medicine in real-world conditions, in post-marketing research. Finally, limited access to new medicines should be considered: progressive licensing controlled by regulatory authorities, coverage with evidence development negotiated by the payers and managed entry, which would be driven by industry. The implications of all of these options should be considered carefully and opportunities for their implementation identified as soon as possible.
Section 4: Panel Discussion Highlights

Workshop participants and eight panelists engaged in an open discussion of the topics covered in the Workshop. A summary of some the points raised in this dialogue follows.

Day 1

Why align evidence requirements?

• Over the next decade there will be a marriage of different responsibilities, brought about by pure practicality. The reality is that regulators will be under increasing pressure to justify regulatory decisions based on real-world data that inform HTA payment and reimbursement decisions.

• Early input from and alignment across HTA bodies is key, and ultimately, industry must meet the challenge of effectively developing one plan to meet the needs of both payers and regulators. However, one of the most insightful aspects of the experience thus far has been not so much the advice coming back to the industry, but the cross-discussion among the stakeholders.

• Rather than alignment around evidence valuation, companies are looking for clarity on evidence requirements across markets for individual assessments of value to take place. That would allow gap analyses and investment decisions based on the feasibility of generating appropriate evidence to meet the requirements of individual markets.

• In Australia, it takes nine months for the regulatory review and 17 weeks for the reimbursement process. If submitted to both agencies in parallel, a drug can be marketed and reimbursed within 11 months.

The role of regulators and HTA

• There is a need for a pragmatic approach to what the ultimate customers are expecting of HTA and regulatory processes. The ultimate role of regulators is to ensure that patients have access to effective medicines; legislation in some countries have also made it clear that they also have the responsibility to make sure that that access is provided in a timely manner.

• The role of HTA bodies, reimbursers and payers, is not to control cost, but rather to distribute available resources between patients and companies.

• Funding decisions must always be made in local and regional context. Equity in access cannot be achieved unless prices are set at levels linked to the purchasing parity of individual markets.

Formal versus informal advice

• It wasn’t clear from the individual presentations regarding joint advice programmes to what extent these led to formal or written advice. Certainly within NICE, informal advice is distinct from formal written advice, which requires a full meeting at which there is detailed discussion with companies in order to fully understand their development plans. More general advice, similar to the Tapestry process is partly a reflection of the logistical difficulties of conducting a meaningful discussion with a very large number of stakeholders.

The value of early advice

• The goal of early advice for industry is to understand which potential new medicines are viable candidates as early as possible, reduce uncertainties and late-stage failures, potentially delivering value to the payers or the reimbursement agencies.

• Surely the point of early advice is to result in changes in the way the industry develops its drugs, in order to improve patient access by meeting the needs of all stakeholders within the healthcare system.

• Although it’s very early in our experience with joint advice to identify any real tangible benefits, early input from and joint discussion with both regulators and HTA bodies has allowed a change in study designs moving forward.

Uncertainty and scientific advice

• Scientific advice has to reduce the uncertainty in the evidence eventually generated; that is, not only how cost effective a new innovation will be, but how confident we are that the potentials being claimed will be realised when we invest in the technology. However, to what extent should not just health outcomes and cost offsets be valued, but this confidence? And how do you put those two metrics on the one decision-making paradigm?
**The way forward toward alignment**

- The key to uptake of this new paradigm is internal education and changing of mindsets within companies.
- Most scientific advice today is provided in order to get an approval or a first reimbursement or pricing decision. Ideally, however, it should also include discussion about the design of postapproval studies to generate more information about the efficacy and effectiveness of a product. New ways of doing some kind of continuous evaluation over a medicine’s life cycle must be examined, re-evaluating outcomes data when they become available over that lifetime. Information that is being developed as part of risk management plans and post-marketing approval studies should be of interest to reimbursement authorities and, more particularly, to governments who are interested in the costs of their health systems.
- Aligning regulatory and HTA evidentiary standards, cannot be done at a high generic level, but rather at a fairly specific, therapeutic level and really examine specific issues about the way regulators look at evidence versus the way HTA assessors looks at evidence.
- Many people say that this process of alignment or harmonisation will not happen in the next 5 or 10 years. But that was exactly what was said about the EMA. It remains to be decided who will drive or facilitate the process, but candidates include such organisations as the EMA, the Drug Information Association or CIRS.

**Positive results of collaboration**

- Recent changes in the European Public Assessment Report (EPAR) have provided assistance in the process of daily assessments and represent an important development in the collaboration between the EMA and EUnetHTA.
- Individual HTA agencies who are working toward alignment, increase consistency and also increase the quality of work.

**Perspectives from the United States**

- The hope and expectation is that stakeholders in the United States will learn new methodologies and better ways of evaluating multiple technologies and healthcare delivery.
- The USFDA recognises that they must respect and interact with CMS and other the other payer bodies. In fact, some of the healthcare decision-makers, like Kaiser Permanente, are exerting significant pressure on the system, with the result that some members of industry are now saying Kaiser Permanente is the only payer with which that they really need to deal.

**Postmarketing data collection**

- Moving forward, data will become available throughout the whole lifecycle of a product, with a continuous reassessment of benefit-risk.
- There are systems for post-marketing data collection within industry risk management plans and the EMA has a very well-developed programme of post-marketing data collection as well.

**The way forward toward alignment**

- There’s an excellent possibility that all evidence requirements can be met within the framework of trials for regulatory approval, which can generate truly useful information for other decision makers.
- There’s huge scope for common ground in evidentiary requirements. To move the whole field forward, all constituents have identified and need to execute some game-changing new methodologies toward harmonisation.
- Moving this discussion into a pre-competitive environment would preclude discussion about a specific product. A disease-level approach could be used to reconcile HTA and regulatory evidentiary requirements, providing methodological standards, for a disease.
### Appendix: Workshop Attendees

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<thead>
<tr>
<th>Regulatory and Government Agencies</th>
<th>Industry</th>
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<tr>
<td><strong>Prof Sir Alasdair Breckenridge</strong></td>
<td><strong>Eoma Anderau</strong></td>
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<tr>
<td>Chairman</td>
<td>DRA Manager</td>
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<td><strong>Dr Petra Dörr</strong></td>
<td><strong>Frederik Andersson</strong></td>
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<td>Head of Management Services and Networking</td>
<td>Director of Health Economics and Epidemiology</td>
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<td><strong>Prof Bruno Flamion</strong></td>
<td><strong>Dr Stephane Andre</strong></td>
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<td>Chairman</td>
<td>Head of EU/ROW Regulatory Affairs</td>
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<td><strong>Dr Katrine Frønsdal</strong></td>
<td><strong>Dr Nicola Course</strong></td>
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<tr>
<td>Senior Researcher</td>
<td>Vice President, Europe Global Regulatory Affairs</td>
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<td><strong>Wim Goettsch</strong></td>
<td><strong>Moira Daniels</strong></td>
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<tr>
<td>Deputy Secretary, Medicinal Products Reimbursement Committee</td>
<td>Vice President Regulatory Policy, Intelligence and Labelling</td>
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<td><strong>Dr Rohan Hammett</strong></td>
<td><strong>Dr Susan Forda</strong></td>
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<td>National Manager</td>
<td>Vice President, International Regulatory Affairs (EU and Intercontinental)</td>
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<td><strong>Niklas Hedberg</strong></td>
<td><strong>Edward Godber</strong></td>
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<tr>
<td>Head of Department</td>
<td>Vice President and Head of Access to Medicines Centre of Excellence</td>
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<td><strong>Dr John Lim</strong></td>
<td><strong>Dr Angus Grant</strong></td>
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<td>Chief Executive Officer</td>
<td>Vice President, Head of Regulatory Affairs Europe</td>
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<td><strong>Bengt Ljungberg</strong></td>
<td><strong>Adrian Griffin</strong></td>
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<tr>
<td>Scientific Director, Pharmacotherapy</td>
<td>Vice President, HTA and International Policy</td>
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<td><strong>Dr Huei-Xin Lou</strong></td>
<td><strong>Dr David Guez</strong></td>
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<tr>
<td>Acting Director, Pharmaceuticals and Biologics Branch</td>
<td>Director, Medical Innovation and R&amp;D Coordination</td>
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<td><strong>Prof Adrian Towse</strong></td>
<td><strong>Sanjay Gupta</strong></td>
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<td>Linda Harpole</td>
<td>Vice President, Global Health Outcomes</td>
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<td>Stefan Holmstrom</td>
<td>Director, HEOR</td>
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<td>Dr Patrick Keohane</td>
<td>Vice President, Payer Evidence</td>
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<td>Dr Susan Longman</td>
<td>Global Head of Cardiovascular / Metabolic</td>
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<td>Desirée Luthman</td>
<td>Director, Regulatory Affairs Europe</td>
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<tr>
<td>Clare McGrath</td>
<td>Senior Director, HTA Policy</td>
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<td>Dr Catherine Melfi</td>
<td>Senior Director, Global Health Outcomes</td>
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<tr>
<td>Dr Marie-Christine Minjoulat-Rey</td>
<td>Head, Governance, Global Evidence and Value Development (EVD)</td>
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<td>Dr Brigitta Monz</td>
<td>Head, Global Health Economics &amp; Outcomes</td>
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<td>Dr Patrizia Nestby</td>
<td>Global Regulatory Lead</td>
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<td>Siobhan Nolan</td>
<td>Senior Manager – Global Study Management</td>
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<tr>
<td>Dr Isaac Odeyemi</td>
<td>Senior Director and Head of Health Economics</td>
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<td>Dr Greg Rossi</td>
<td>Vice President, Global Health Economics and</td>
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<td>Dr Pierre Sagnier</td>
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<td>Dr Joseph Scheeren</td>
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<td>Dr Murray Stewart</td>
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<td>Dr Janet Tobian</td>
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<td>Ruud van Tol</td>
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<td>Dr Mel Walker</td>
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<td>Dr Sean Tunis</td>
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<td>Centre for Innovation in Regulatory Science</td>
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<td>Patricia Connelly</td>
<td>Manager, Communications</td>
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<td>Lawrence Liberti</td>
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<td>Dr Franz Pichler</td>
<td>Manager, HTA Programmes</td>
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<td>Prof Stuart Walker</td>
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<td>Tina Wang</td>
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