CIRS WORKSHOP

Commonality in evidentiary requirements across regulatory and HTA stakeholders

21-22 SEPTEMBER 2016

SURREY, UK

A BRIEF SUMMARY

CIRS Centre for Innovation in Regulatory Science

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CIRS - The Centre for Innovation in Regulatory Science - is a neutral, independent UK-based subsidiary company, forming part of Clarivate Analytics, formerly the IP & Science business of Thomson Reuters. The mission of CIRS is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities and grants.

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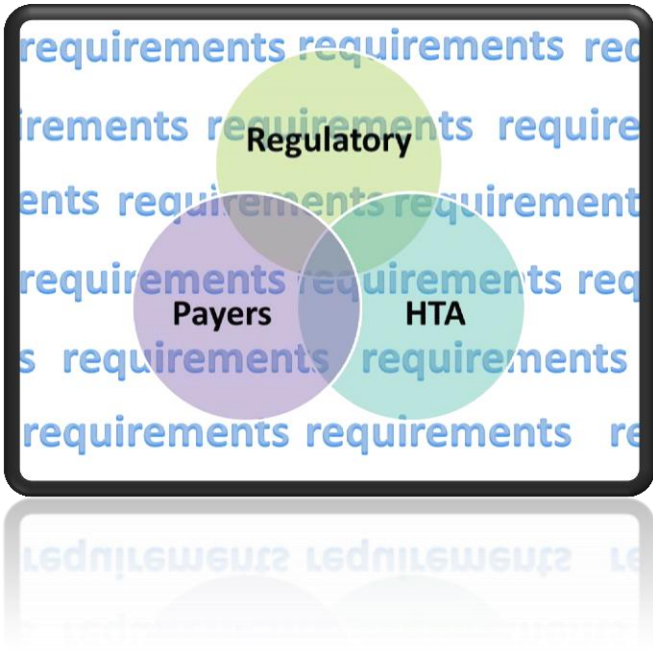
Report date: December 2016

BACKGROUND

The dynamics of bringing new medicines to market are influenced by conflicts between the agendas of regulators, health technology assessors and payers. Regulators are under pressure to develop methods to speed the approval process, including mechanisms such as flexible accelerated approval pathways, while maintaining an emphasis on safety, quality and efficacy. By contrast, there is an increasing pressure on payers to control spiralling healthcare costs via the heath technology assessment (HTA) of the clinical and cost effectiveness of new interventions. Whilst historically, regulatory review and HTA have been entirely separate, the current dialogue around comparative effectiveness research may lead to a closer relationship between the two.



Over the last five years, alignment of complementary evidence generation for regulatory and HTA decision making has been seen as critical for effective and efficient development. Indeed, recommendations from the March 2011 CIRS Workshop, "Evidentiary requirements in clinical development: Synchronising phase III requirements to meet multiple needs", included the undertaking of a HTA metrics and benchmarking survey; that HTA and regulatory authorities should seek agreement on the choice of endpoints and comparators and the development of more clarity around scientific issues that can be aligned with increased early dialogue both between HTA agencies and HTA and regulators. Since this Workshop, a number of initiatives involving scientific advice in early development have begun; these have included pilots for companies to receive joint regulatory and HTA advice to initiatives providing multi-stakeholder advice (multiple HTAs). In addition, companies themselves are benchmarking the activities they conduct during early development to identify how best to align the needs of HTA in Europe and payer organisations in the US and licensing agencies to ensure both an effective and efficient development programme. This is complemented by initiatives at the policy level within regions to ensure reduction in duplication of effort and at the research level to understand the decision-making processes and to determine if divergent regulatory and HTA decisions are due primarily to differences in the evidentiary requirements or other factors.

The aim of this Workshop was to discuss the direction of change toward alignment and more synchronised decision making between agencies, how agencies are managing uncertainty by determining key differences among stakeholders and the implications of these changes to evolving development and approval models that seek increased flexibility in regulatory and access pathways.

WORKSHOP OBJECTIVES

- **Discuss the progress made to align evidentiary requirements**, what the drivers have been and if this has improved the efficiency and effectiveness of the development, approval and reimbursement processes
- **Identify the areas where there are still major differences** that impede efficient and non-divergent regulatory and HTA decision making
- **Make further concrete recommendations as to how to ensure complementary evidence generation** and what is needed to mitigate the risk of mismatch of outcomes that can occur when a regulatory authority grants an approval that is not compatible with current HTA decision-making requirements

WORKSHOP CHAIRS

Prof Hubert Leufkens, *Chairman, Medicines Evaluation Board, Netherlands*

Dr Sean Tunis, *Founder and CEO, Center for Medical Technology Policy, USA*

Professor Sir Alasdair Breckenridge, *Former Chair, Medicines and Healthcare Products Regulatory Agency, UK*

WORKSHOP PROGRAMME

SESSION: MEETING REGULATORY AND HTA EVIDENTIARY REQUIREMENTS DURING NEW MEDICINE DEVELOPMENT: WHAT ARE THE KEY CONSIDERATIONS?

Welcome and opening remarks	**Lawrence Liberti,** *Executive Director, CIRS*
Chair's welcome and introduction	**Prof Hubert Leufkens,** *Chairman, Medicines Evaluation Board, Netherlands*
Has the gap between regulatory and HTA evidence requirements narrowed?	**Tina Wang**, *Manager, HTA Programme, CIRS*
Getting to the right evidence during development to support both the registration and reimbursement decision: An achievable endpoint?	
Regulatory agency viewpoint	**Dr Tomas Salmonson,** *Chair, CHMP, European Medicines Agency*
HTA viewpoint	**Niklas Hedberg,** *Chief Pharmacist, TLV, Sweden*
Industry viewpoint	**Pam Smith,** *Vice President –Europe & Emerging Markets Regulatory Affairs, AstraZeneca, UK*
Discussion: Potential benefits of early advice and dialogue	
Multiple HTA advice: Past learnings and future development of multiple HTA agency early dialogue within Europe	**Wim Goettsch,** *Director, EUnetHTA JA3 Directorate, Zorginstituut Nederland*
Joint HTA and regulatory scientific advice –– Is this helping align regulatory and HTA thinking in the development space?	**Rob Hemmings,** *Head of Licensing Division's Statistics Unit, MHRA, UK*
Company perspective: Are industry's needs best served by current dialogue models and, if not, what changes would be helpful?	**Francesca Caprari,** *Head of Payer Intelligence and HTA, Sanofi SA, Italy*
What types of interactions beyond scientific advice between regulatory and HTA agencies can be of use?	**Dr Brian O'Rourke,** *President and CEO, Canadian Agency for Drugs and Technologies in Health*
Internal company alignment/dialogue (between regulatory and health outcomes) – Is this being achieved and does this enable better scientific advice requests?	**Christine Mayer-Nicolai,** *Head Global Regulatory and Scientific Policy, Merck KGaA, Germany*
SESSION: FIT-FOR-PURPOSE LIFE-CYCLE MANAGEMENT - HOW TO BEST COORDINATE REGULATORY AND HTA NEEDS PRE- AND POST-LAUNCH	
Chairman's introduction	**Dr Sean Tunis,** *Founder and CEO, Center for Medical Technology Policy, USA*
Ensuring there is a collective responsibility for the development of a high-quality evidence pool -IMI Adapt Smart	**Prof Sarah Garner,** *Associate Director, Science Policy and Research, National Institute of Health and Care Excellence (NICE) UK*
Synchronisation of regulatory and HTA decision making – How do systems need to change to meet this goal?	
HTA viewpoint	**Andrew Mitchell,** *Strategic Adviser, Evaluation, Department of Health, Australia*
Regulatory viewpoint	**Marion Law,** *Director General, Therapeutic Products Directorate, Health Canada*
Company viewpoint	**Adam Heathfield,** *Senior Director, Global Health and Value Innovation Centre, Pfizer, UK*

SESSION: SYNDICATE DISCUSSIONS	
Topic A: Early dialogue: How to use input from a variety of stakeholders to effectively ensure a development plan that best meets regulatory and HTA needs	**Chair: Dr Thomas Lonngren,** Independent Strategy Advisor, PharmaExec Consulting Filial SE, Sweden **Rapporteur: Louise Gill,** Regulatory Head – Europe and Canada, Global Regulatory Affairs, GlaxoSmithKline, UK
Topic B: Integrating regulatory and HTA evidence requirements into clinical programmes for standard and novel products – How can this best be achieved?	**Chair: Prof Jonathan Fox,** Chair, SMC **Rapporteur: Marci English,** Director HEOR, Astellas Pharma US Inc, USA
Topic C: Post-licensing evidence generation to support accelerated regulatory pathways and HTA decision-making needs - How do we narrow the uncertainty gap?	**Chair: Dr Sandra Kweder,** Deputy Director, Europe Office, FDA, USA **Rapporteur: Claudine Sapede,** Global HTA and Payment Policy Lead, **F**. Hoffmann-La Roche Ltd, Switzerland
SESSION: SYNDICATE FEEDBACK AND PRESENTATIONS	
Chairman's introduction	**Prof Sir Alastair Breckenridge**
How are patients focusing their activities to use their voice to inform both the regulatory and HTA decision making?	
Overarching patient group activities	**Nicola Bedlington,** Secretary General, European Patients Forum, Belgium
Disease-specific patient activities - melanoma	**Dr Bettina Ryll,** Founder, Melanoma Patient Network Europe
Company perspective	**Sonja Pumplün,** Head, Global Regulatory Affairs, Actelion, Switzerland
SESSION: BEYOND HTA AND REGULATORY COORDINATION	
Panel discussion: Enabling effective and efficient drug development: Where are companies, regulatory agencies, licensing authorities and HTA agencies going in the next 10 years and what is the pathway to the future?	
European regulatory agency perspective	**Prof Hans-Georg Eichler,** *Senior Medical Officer, European Medicines Agency*
European HTA agency perspective	**Meindert Boysen,** *Director, Technology Appraisals Programme, NICE, UK*
Academic perspective	**Prof Adrian Towse,** Director, Office of Health Economics, UK
Company perspective	**Shane Kavanagh,** *Vice President, Health Economics, Janssen NV, Belgium*
Patient perspective	**Jean Mossman,** *Senior Associate Director (Honorary), London School of Economics, UK*

SYNDICATE SESSION RECOMMENDATIONS

Topic A: Early dialogue: How to use input from a variety of stakeholders to effectively ensure a development plan that best meets the needs of regulatory and HTA agencies?

Chair: **Dr Thomas Lonngren** *Independent Strategy Advisor, PharmaExec Consulting, Sweden*
Rapporteur: **Dr Louise Gill,** *Regulatory Head – Europe and Canada, Global Regulatory Affairs, GlaxoSmithKline, UK*

Recommendations

- To enable time to support validation of new patient-reported outcomes, stakeholders should create a framework supporting pre-competitive collaboration to consider regulatory and HTA development needs for key therapeutic area or new scientific breakthroughs
- CIRS should study decision-making frameworks of various HTA agencies to potentially group agencies according to their evidential requirements
- Industry should consider communicating commercial drivers and trade-offs to HTA agencies to inform strategies and choices
- EMA should continue leading parallel advice for early development
- Stakeholders should continue to strengthen patient input into early stakeholder dialogue and development
- Companies should share output from CIRS meetings with local affiliates to help inform local development strategies
- To enable greater transparency, stakeholders should convene an industry-HTA forum with a focus on sharing of methodologies
- Some HTA agencies should increase capacity and capability to enable participation and substantive input into early scientific advice discussions, specifically for cutting-edge therapies

Topic B: Integrating regulatory and HTA evidence requirements into clinical programmes for standard and novel products – How can this best be achieved?

Chair: **Prof Jonathan Fox,** Chair, Scottish Medicines Consortium
Rapporteur: **Marci English,** Director, HEOR, Astellas Pharma Inc, USA

Recommendations

- Although important differences between jurisdictions in clinical practice and societal preferences make full international standardisation unrealistic, efforts to internationally harmonise HTA processes and evidentiary requirements should be supported
- While regulatory and HTA alignment on specific evidence strategies may not be feasible, transparency in evidence optimisation and provision of HTA guidances, frameworks or core models may facilitate efforts toward convergence of HTA evidence strategies.
- To facilitate how patient engagement can inform discussions and decision making by regulatory and HTA agencies, stakeholders should develop guidance around this engagement
- Stakeholders should undertake efforts to identify critical gaps and divergences in regulatory and HTA information needs and identify a mechanism by which these can be addressed

Topic C: Post-licensing evidence generation to support accelerated regulatory pathways and HTA decision making needs - How do we narrow the uncertainty gap?

Chair: **Dr Sandra Kweder**, Deputy Director, Europe Office, FDA, USA
Rapporteur: **Claudine Sapede,** Global HTA and Payment Policy Lead, F. Hoffmann-La Roche Ltd, Switzerland

Recommendations

- Stakeholders should further investigate toolbox/methods/sources for post-approval evidence generation to complement standard randomised clinical trials
- To ensure a development programme that meets all pre- and post-licensing needs, regulators, HTA bodies, patients, healthcare providers and payers should continue to develop and pilot models or processes that include early engagement and opportunities for stakeholders to reconvene along milestones in the product life cycle; these programmes should focus on the early development in products with transformative potential

PRESENTATION HIGHLIGHTS

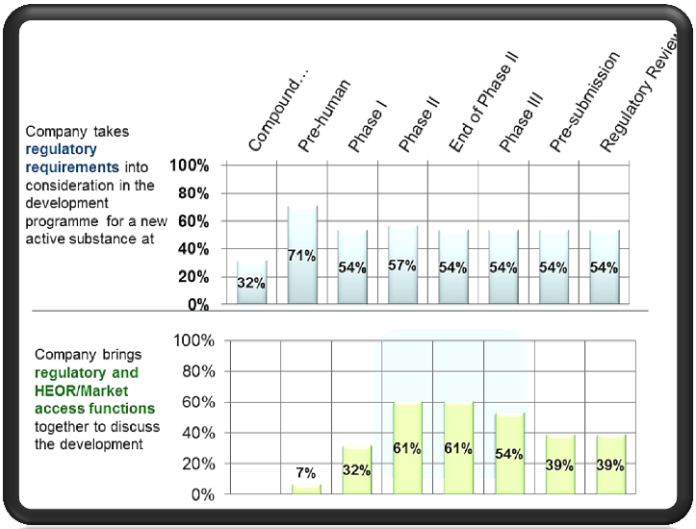
INTRODUCTION: HAS THE GAP BETWEEN REGULATORY AND HTA EVIDENCE REQUIREMENTS NARROWED?

Setting the scene for the Workshop, **Tina Wang**, *Manager, HTA Programme, CIRS,* presented the results of a 2016 CIRS focus survey to explore multiple stakeholder views on alignment of regulatory and HTA requirements. A similar 2009 CIRS survey revealed that although industry was interested in harmonising regulatory and HTA requirements and regulators felt that some requirements were amenable to sharing, all participants agreed that better alignment was required.

Current landscape

In this current survey, conducted among 28 industry participants from regulatory and health economics outcomes research functions at 19 companies and 8 regulatory and 9 health technology agencies, 100% of industry respondents agreed that "*There is an increasing need today for my company to include HTA requirements earlier in development compared to 5 years ago."*

Despite this agreement, regulatory and HEOR/Market Access functions were rated as fully integrated in the decision-making process during development by only 4 of 28 participants, whilst they majority of respondents indicated that although there may a move toward integration, it is mostly ad hoc and inconsistent and regulatory requirements are given priority when designing development programmes.



Industry strategy for internal interaction; from the presentation of T Wang, CIRS.

Evidence and technical requirements

Survey respondents indicated that the greatest divergence in regulatory and HTA requirements occurs for medicines receiving a conditional or accelerated approval, oncology, orphan, or high-cost drugs or those associated with a small incremental improvement or in a crowded therapeutic class. The area that most industry, regulatory and HTA agency survey participants agreed represented the highest potential for divergence and the greatest potential for alignment between HTA and regulatory agencies was agreement on the choice of research endpoints and specifically the choice and use of surrogate endpoints.

Indeed, there were differences between industry, regulatory and HTA perceptions regarding surrogates. For example, surrogate endpoints previously accepted by one HTA agency would be considered adequate for use in regulatory submission by 43% of industry but only 14% of regulatory agency survey respondents and the use of those previously accepted endpoints would be satisfactory for HTA submissions according to 96% of industry and only 22% of HTA agency respondents. Ms Wang noted that HTA views on surrogate endpoint criteria appeared to be context related, need to be clinically relevant and may be decided on a case-by-case basis.

Future trends

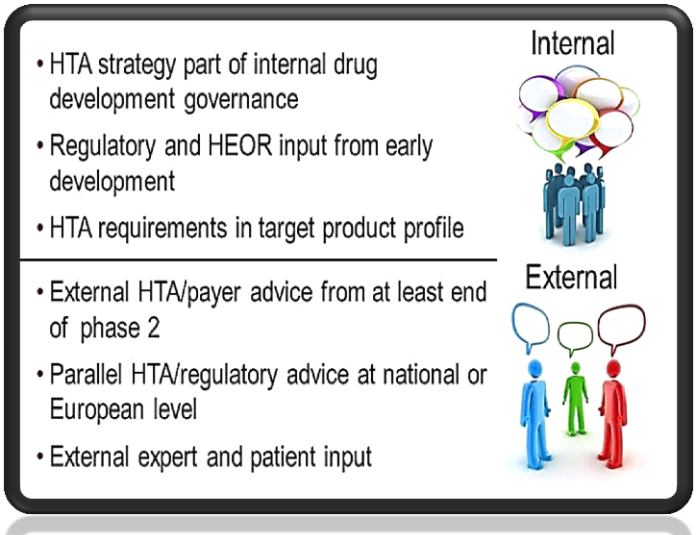
Joint scientific advice from regulatory and HTA agencies was regarded as being the best mechanism to reach consensus across regulatory and HTA stakeholders for a drug development plan by just 36% of industry participants; however, 61% felt that this advice had the potential to achieve consensus. Early understanding of regulatory and HTA insights rather than full alignment might be the ultimate goal. All three stakeholder groups felt that step-wise convergence, shared best practice and the promotion of the patient-centred approach represent the "ideal world" of the convergence of regulatory and HTA needs.

SESSION: MEETING REGULATORY AND HTA EVIDENTIARY REQUIREMENTS DURING NEW MEDICINE DEVELOPMENT: WHAT ARE THE KEY CONSIDERATIONS?

In this session, presenters provided regulatory, health technology assessment and industry perspectives regarding the rationale for and possibility of obtaining evidence to support regulatory and reimbursement decision making.

According to the recent report of the outcome of the three-year work plan for EMA-EUnetHTA collaboration, there are three important areas for cooperation between these two groups: creating synergies and avoiding duplication, sharing experience and the increasing transparency. **Dr Tomas Salmonson,** *Chair, CHMP, European Medicines Agency* reported that an expert working group for the International Conference on Harmonization (ICH) is developing an addendum to the ICH E9 guideline that will result in an improved framework for clinical trial planning, conduct, analysis and interpretation. This guideline will focus on estimands and sensitivity analyses, particularly after randomisation, to deal with issues that include data for add-on or rescue medication and missing information such as that which results when patients are lost to follow up. In addition, because of a perceived lack of clarity among stakeholders surrounding some therapeutic indications, the EMA CHMP endorsed a reflection paper in 2016 containing principles on how to define the wording of these indications.

Despite a high degree of openness, an efficient generic substitution system and good conditions for real-world studies,



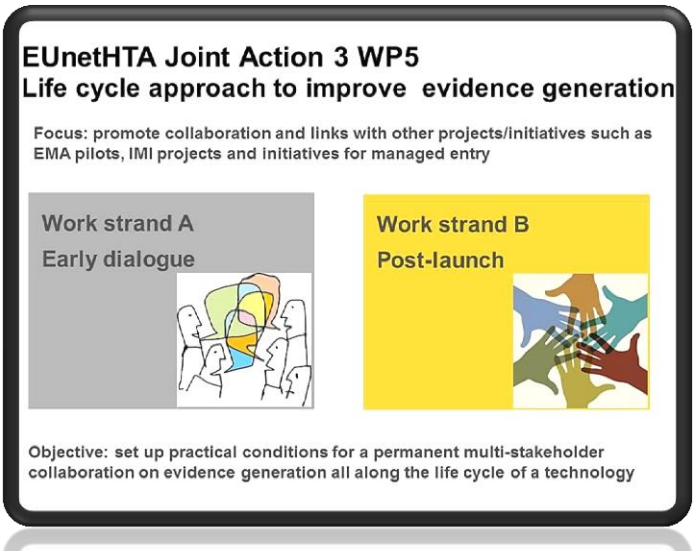
Industry tactics for managing divergent regulatory HTA evidence needs. Adapted from the presentation of P Smith, AstraZeneca.

Tandvårds- och läkemedelsförmånsverket (TLV), the Dental and Pharmaceutical Benefits Agency in Sweden has experienced challenges in its use of value-based pricing. **Niklas Hedberg,** *Chief Pharmacist, TLV, Sweden,* detailed those challenges, including increasing difficulties for HTA bodies to appraise value and identify relevant patient group as new medicines come to market in earlier phases, with pricing based on small subgroups and discrepancies between the value estimated based on randomised clinical trials and that observed in real life. In addition, prices on new and innovative pharmaceuticals are often very high, which increase the payer's uncertainty about the true value of the intervention. In response to these challenges, there has been extensive use of real-world data by companies in their applications to TLV as a basis for many of the assumptions in the health economic model (such as the use of resources and risk estimates). Despite methodologic and interpretation issues, the use of real-world data is likely to increase, facilitated by collaborations among stakeholders in such projects as the Innovative Medicines Initiative Get Real Project.

Pam Smith, *Vice President –Europe & Emerging Markets Regulatory Affairs, AstraZeneca, UK* explained that differing focuses of regulators and health technology assessors lead to differing evidence needs. This can result in differing decisions by the two groups, especially in disease areas with treatment standards of care that vary across markets, for products undergoing accelerated assessments or conditional approvals, and products for which the generation of real-life data is expected to be challenging. Industry strategies to meet these challenges include providing details of the regulatory plan together with input from HEOR on potential pricing from early development; the inclusion of HTA and payer requirements in the target product profiles and clinical development plans, the use of external HTA and payer advice from at least the end of phase 2; the consideration of parallel HTA and regulatory advice at the national or European level; and the solicitation of external expert and patient input – particularly in areas of unmet need or where there is limited experience.

On behalf of **Dr François Meyer,** Advisor to the President and Director of International Affairs, Haute Autorité de Santé, **Wim Goettsch,** *Director, EUnetHTA JA3 Directorate, Zorginstituut Nederland* outlined the progress of the EUnetHTA Joint Action 1 and 2 (JA 1, 2) and the European Commission Shaping Early European Dialogues for health technology assessment (SEED) programme. Starting with pilot programmes of early scientific advice in JA1through revised procedures in JA2 and SEED, 19 sessions of early advice were conducted for medicines and 5 for medical devices with multiple HTA agencies, sometimes with the participation of the regulatory agencies. These pilots were considered to be successful but a more solid structure and standing committee of experienced partners is likely required, with more effective way or providing consolidated answers and advice to industry. Therefore two work strands have been developed to continue early dialogue programmes for JA3. Strand A will cover early dialogues and Strand B will cover post-launch evidence generation.

The recent EMA report on parallel regulatory HTA scientific advice stated that "The pilot of parallel regulatory-HTA advice under the draft Best Practice Guide has demonstrated positive outcomes and should now continue on an operational basis*"* **Rob Hemmings,** *Head of Licensing Division's Statistics Unit, MHRA, UK* cited Tarfuri and colleagues who reported a relatively high level of agreement between regulators and HTA assessors in 31 of these joint procedures (77% on population; 59% on endpoints; 60% on other study design characteristics and 59% on overall efficacy and safety package; 44% on comparators;). The results of the pilots indicate that parallel scientific advice contributes positively to drug development but flexible licensing and reimbursement for innovative or needed products will result in increased challenges for all as will consideration of the efficacy or benefit-risk uncertainty trade-off. Lifecycle thinking and scenario planning will be required and procedures and outputs are evolving but increased experience will enhance dialogue and understanding, promoting efficient evidence generation.



EUnetHTA Joint Action 3. Adapted from the presentation of W Goettsch, EUnetHTA.

Experience from early advice pilots has contributed to gradually building mutual understanding amongst HTA bodies and regulators. **Francesca Caprari,** *Head of Payer Intelligence and HTA, Sanofi SA, Italy* related that the Sanofi team participating in the SEED project was largely satisfied with the usefulness of the advice received and their ability to incorporate it into the evidence generation plan. In all cases, the advice was followed to some extent and reflected in the evidence generation plan; similarly, the market authorisation application filing strategy was fine-tuned in some cases. Because alignment is a key criterion of success in joint scientific advice at the EU level, improved alignment of evidentiary requirements between different HTA bodies and between HTA bodies and the EMA should be sought on all aspects of a company evidence generation plan. Companies need to reduce areas of uncertainty by better anticipating evidentiary needs for coverage decision making by national authorities while bridging the evidentiary requirements for HTA bodies and regulatory approval. Increased cooperation will help address the prevailing heterogeneity in data requirements from national authorities and in their respective added clinical benefit assessments for pharmaceuticals. These divergences contribute to fragmentation of patient access conditions within the EU.

Dr Brian O'Rourke, *President and CEO, Canadian Agency for Drugs and Technologies in Health* said that regulatory and HTA interactions such as information sharing, parallel reviews and post-market surveillance and assessment contribute to early patient access to medicines as well as to sustainability of health systems. Information that is shared between the two groups includes pipeline information, drugs under review, technical requirements such as surrogate outcomes, non-inferiority margins and safety concerns. Furthermore, the Canadian regulator and CADTH share information on processes and initiatives such as application fees, legislation and stakeholder engagement and major change initiatives such as the EU Medicines Adaptive Pathways to Patients (MAPPs). Parallel reviews are already being conducted in Australia by the TGA and PBAC and in Canada by Health Canada and CADTH to better align the timing of licencing and reimbursement decisions. Post-market surveillance and assessment for safety is being conducted in the US by the FDA through its Sentinel programme and in the EU by the EMA through its European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). It is also being carried out for effectiveness, which is primarily the health technology assessor or payer's role through initiatives such as AIFA registries, and Canada's Drug Safety and Effectiveness Network (DSEN). However, there is a growing need to capture real-world evidence and to enable big data approaches, potentially through public-private partnerships.

Commenting on the EMA pilot of parallel regulatory-HTA advice, **Christine Mayer-Nicolai,** *Head Global Regulatory and Scientific Policy, Merck KGaA, Germany* agreed that this initiative has had a positive outcome. The overall aim of the pilot was to achieve greater alignment and synchronised decision making between agencies, whilst industry specifically hoped the programme would inform drug development and reduce risks linked to investment. Overall lessons learned from participation in the pilots included the understanding that ideally, global development should integrate the requirements of regulatory and HTA agencies world-wide. Greater alignment between regulators and HTA bodies necessitates alignment of commercial, regulatory and clinical internal interests and that it is important to ensure fully informed R&D decisions prior to requesting parallel regulatory HTA scientific advice. Applications should be comprehensive and include a conclusive company position and close cooperation with agencies during preparation of the submissions should be ensured. It is currently challenging to meet all specific HTA requirements from different agencies because of development costs and timelines and an internal contingency plan is needed for situations in which regulatory and HTA advice are contradictory. Despite early dialogue, uncertainty remains and currently, HTA advice helps to understand the risks associated with drug development.

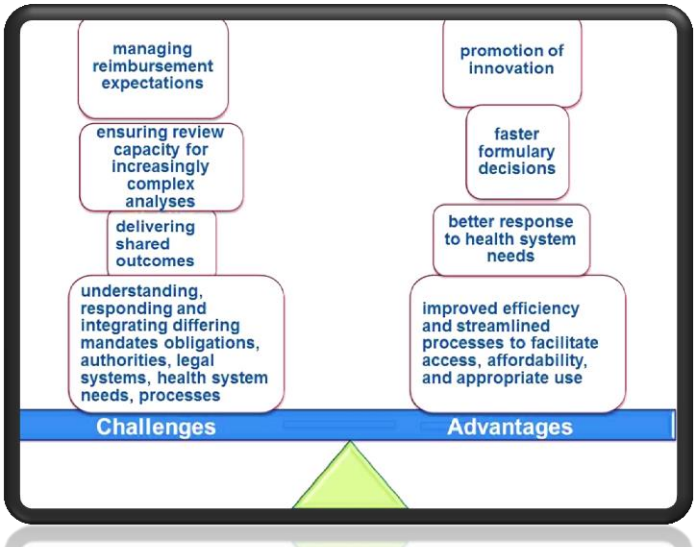
SESSION: FIT-FOR-PURPOSE LIFE-CYCLE MANAGEMENT - HOW TO BEST COORDINATE REGULATORY AND HTA NEEDS PRE- AND POST-LAUNCH

In this session, speakers discussed the role of the regulator and the health technology assessor in participating in the knowledge build-up that will foster the development of innovative medicines that will meet healthcare needs.

Prof Sarah Garner, *Associate Director, Science Policy and Research, National Institute of Health and Care Excellence (NICE) UK* discussed the development of and roles and responsibilities for of high-quality evidence pools. The current framework for regulatory and HTA evidence generation is associated with challenges such as the limited availability of head-to-head clinical trials with all clinically relevant comparators, trials often focus on meeting regulatory requirements, there is often little or no follow up for post-authorisation data collection for conditional approvals and limited data are available to support indication sub-group analyses. Challenges for complementary regulatory and HTA evidence generation include a lack of skills to design appropriate studies, and understand potential methodologies, misaligned incentives to meet regulatory and HTA needs, lack of consensus on appropriate approaches to alignment, and consortium fatigue from so many groups trying to address similar alignment questions. However, efforts to ensure full stakeholder participation have been mandated through legislation and encouraged through the creation of safe harbours and the development of financial incentives. Opportunities for collaboration have been developed and successful programmes have been launched. The Innovative Medicines Initiative Get Real project, an educational resource

to investigate the potential use of real-world data to support the development of new medicines, is one such project. Get Real outputs include software, checklists and templates and design options for pragmatic clinical trials.

Although there is a mostly common foundation of clinical evidence for new medicines, **Andrew Mitchell,** *Strategic Adviser, Evaluation, Department of Health, Australia* pointed out that evidence for HTA more explicitly quantifies net clinical benefit, is more often in the "grey zone" of "translation", is more tolerant of reduced confidence in clinical evidence for decision making and is influenced by other relevant factors for decisions. There are areas between the regulators and HTA agencies that should be synchronised such as building a common foundation and guidelines to address clinical evidence, providing parallel advice to design pivotal studies, promoting alignment of evidence generation where feasible, facilitating the preparation of dossiers, offering parallel regulatory and HTA reviews with overlapping assessment periods. Decisions for medicines made with less mature and less patient-relevant clinical evidence will pose challenges that can be overcome and common foundations to interpret this type of clinical evidence are likely to expand where feasible. Although important differences in decisions will always remain because of different decision criteria and goals, company, regulatory and HTA systems can all continue to optimise toward a common clinical evidence foundation. Respect for the differences in the use and interpretation of the common clinical evidence foundation; however, remains essential.



Rationale for aligning regulatory and HTA evidence generation. Adapted from the presentation of M Law, Health Canada

Health is an area of shared jurisdiction among federal, provincial and territorial governments in Canada. **Marion Law,** *Director General, Therapeutic Products Directorate, Health Canada* outlined challenges and benefits to the adaption of the system to enhance interactions between the regulatory agency Health Canada, the health technology assessment agency Canadian Agency for Drugs and Technologies in Health and the Federal, provincial and territorial payers. Challenges include understanding, responding to and integrating differing mandates and obligations; addressing the needs of diverse authorities, legal systems, health system needs, and processes; ensuring review capacity for increasingly complex analyses; delivering outcomes that can be shared in a relevant way by all stakeholders; and managing reimbursement expectations; Benefits of adapting the current system include better response to health system needs; faster formulary decisions; streamlined processes to facilitate access and affordability, and appropriate use and promotion of innovation.

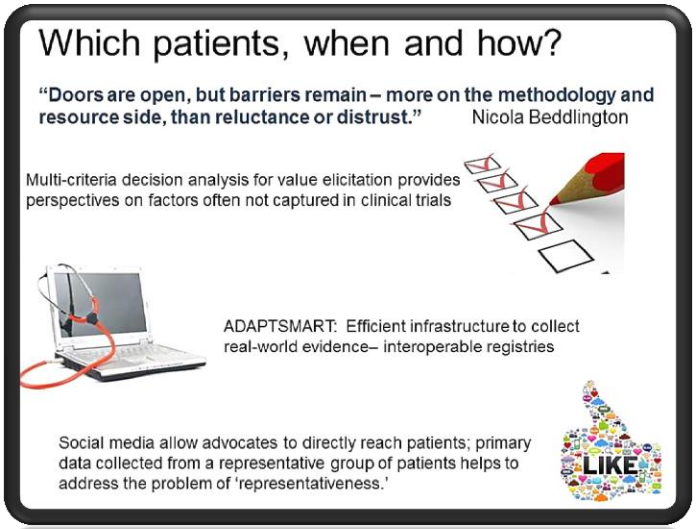
Adam Heathfield, *Senior Director, Global Health and Value Innovation Centre, Pfizer, UK* observed that regulatory and HTA agencies have different objectives and a complete alignment may not be feasible or realistic. Furthermore, the current fragmented system, with its growing multitude of requests from different stakeholders, may be impossible to satisfy and detrimental for patient access to medicines. Whilst coordination and synchronisation of these diverse systems may be desirable, he pointed out that industry should not compromise to meet the least flexible standards. The ongoing good work to accelerate regulatory approval for very novel medicines highlights the divergence between EMA and national HTA agencies with the former accelerating decisions based on earlier data and the latter finding difficulty in using the same data to create a value model. However, there is considerable untapped potential in EMA/HTA parallel advice and this advice also represent an opportunity to incorporate the patient voice in trade-offs involved in accelerating development. In addition, greater availability and acceptance of real -world data might offer potential solutions for evidence generation; alignment on relative efficacy assessment methods among health technology assessment agencies is a route to alignment with EMA on essential elements of a clinical programme.

SESSION: HOW ARE PATIENTS USING THEIR VOICE TO INFORM REGULATORY AND HTA DECISION MAKING?

In this session, speakers discussed challenges to and solutions for identifying appropriate patients, developing effective methodologies and implementing patient input into decision making.

The European Patients Forum (EPF) is an independent umbrella group of 67 patient organisations formed to achieve equitable access to high-quality, patient-centred health and social care for all patients in the EU. Patient interactions are important catalysts to ensure connectivity and trust across the product life cycle and EPF and other key patient organisations focus on meaningful patient engagement in the regulatory, HTA and pricing and reimbursement environment. **Nicola Bedlington,** *Secretary General, European Patients Forum, Belgium* reported that doors are open and the barriers that remain are based on methodology rather than reluctance or distrust. The patients' voice at the individual and collective level is critical and multi-stakeholder initiatives, patient education, and structured, systematic engagement of patients is a vital part of the future of medicines' development.

Speaking about integrating patient perspectives into regulatory and HTA processes, **Dr Bettina Ryll,** *Founder, Melanoma Patient Network* cited several working definitions coined by the European Society for Medical Oncology Patient Advocate Working Group: a *patient* is concerned with their own disease; *patient advocates* are concerned with a widened focus on the patient group in exchange with peers; a *patient advocate expert* is an advocate who engages on a professional level. Unfortunately for these groups, the questionable "representative" nature of representatives combined with selection and confirmation biases and knowledge gaps can make the evidence that they provide easy to disregard. Although plotting the distribution of individual preferences may seem to overcome the "representativeness" issue of patient advocacy, it is important to ensure that the relevant stakeholder voice is heard. *Evidence-based advocacy* is based on evidence that can inform and direct efforts so that advocates truly act in patients' best interests. Because single experiences are often discounted as 'anecdotes' even when valid and relevant, the systematic collection of broader set of data can bolster the validity of individual experiences. Social media allow advocates to directly reach patients. Primary data collected from a representative group of patients through these novel media approaches helps to address the issue of 'representativeness.'



Methodology and guidance for patient input is needed. Adapted from the presentations of N Beddlington, EPF; B Ryll, MPN; S Pumplün, Actelion.

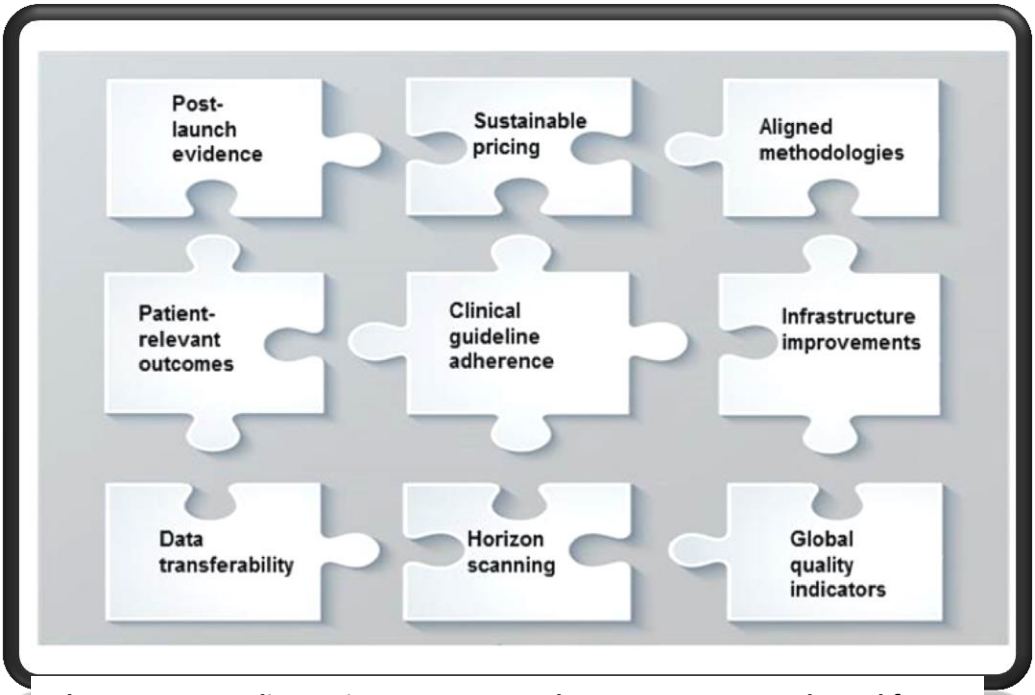
Sonja Pumplün, *Head, Global Regulatory Affairs, Actelion, Switzerland* reported on a recent patient preference study in multiple sclerosis. In the study, data will be collected in 18 countries, with target enrolment of more than 360 patients. Patients will be asked to give preferences for 7 benefit or risk outcomes. Preferences will be elicited at baseline and at the end of the study, with the difference between the measures expected to show the impact of treatment on patient preferences. Data will be collected on a hand-held device given to patients. Patient training will be provided at screening and online. It is expected that researchers will be able to rank the importance of the outcomes from the patients' perspective, use regression analyses to estimate predictive models for preferences and that demographic and disease characteristics may predict preferences for treatment outcomes. This type of research may allow clinical results used in marketing authorisation reviews to be complemented by quantitative perspective of patients and relevant patient information can also inform health technology assessors.

SESSION: BEYOND HTA AND REGULATORY COORDINATION

A panel discussion was conducted to determine what needs to be changed or considered from a strategic, technical and process view point to enable companies, licensing authorities, and HTA agencies to ensure patient access to innovative medicines in the next ten years. What is the pathway to the future?

Prof Hans-Georg Eichler, *Senior Medical Officer, European Medicines Agency* predicted that changes would occur within the next ten years in the areas of **methodology, infrastructure, pricing for sustainability** and **process.** Although different roles may require different methodologies, hopefully, the cultural shift occurring amongst stakeholders will allow the gulfs among methodologies to be bridged. Infrastructure will continue to advance, with better electronic databases and healthcare systems, improvements in usability, readability and interoperability. These improvements will facilitate online access to data, enabling rapid-cycle analyses of safety and efficacy signals. These data will also enable dynamic and pay-for-performance pricing. Dynamic, value-based and affordability-based pricing will come to pass as payers are brought more into the development dialogue. Indications will narrow and freedom of prescribing may disappear as niche indications and specialty prescribing centres come to the fore. Rapporteurship and other methods for work sharing will be enabled through the establishment of mutual trust among HTA agencies.. In order to develop necessary resources, HTA agencies will come to grips with the need for cost recovery and develop mechanisms to deal with conflict of interest as regulators have in the past.

The four themes of importance for the next decade according to **Meindert Boysen,** *Director, Technology Appraisals Programme, NICE, UK* are ***accelerate, adapt, afford*** **and** ***austere****.* Horizon scanning by all stakeholders is a key element to acceleration. Early scientific advice is a cornerstone of the work at NICE, which has also organised safe harbour meetings for therapeutic area discussions with industry. Acceleration efforts, however, should concentrate on transformative products. All stakeholders should be willing to embrace the use of RWE and the use of digital health records to supported managed entry access schemes, especially for critical new products for unmet medical need. An example of a NICE contract for managed access, which patients have been instrumental in establishing, is for the elosulfase alfa for treating mucopolysaccharidosis type IVa. NICE is also interested in adapting its methods to company value propositions in order to effectively evaluate product portfolios. Although affordability should not factor into NICE decisions, products with a sizable budgetary impact must ensure cost effectiveness. The Cancer Drugs Fund is an example of the management of the affordability issue. Austerity and the efficient use of its resources are important factors that NICE will have to address over the coming years.



Changes to expedite patient access over the next ten years. Adapted from H-G Eichler, EMA, M Boysen, NICE, A Towse, OHE; S Kavanagh, Jannsen.

Prof Adrian Towse, Director, Office of Health Economics, UK presented a vision of the pathway to the future that calls for the evolution of pre-launch dialogue from separate but equal stakeholders, to learning, to compromise of differences. To move forward, there also must be a shift of evidence generation to the post–launch setting, with the use of observational, pragmatic trials as well as large simple and randomised controlled trials. Payers must develop the willingness or ability to recognise the value of data used to support conditional regulatory approval. Costs associated with post-approval data collection will decrease with the use of better and wider methods for data collection including electronic registries and the transferability of data across jurisdictions and health systems. Companies must look at evidence generation on a pan-Atlantic basis and all parties must be willing to accept such data. Adaptive pathways will require intensive stakeholder planning and the integration of pre- and post-launch data collection. In the US, the separation of the FDA and payers is a barrier to change. The "brutal but simple" US market place will become more evidence based, particularly if capitation becomes widespread.

Shane Kavanagh, *Vice President, Health Economics, Janssen NV, Belgium* drew attention to several issues in pharmaceutical development at play in the United States, which is arguably the key driver of growth in income for the pharmaceutical industry: 1) the growing importance of patient-reported outcomes, 2) a potential movement by payers toward an insistence on indication-specific evaluations, with resulting built-in quality indicators and performance agreements; and 3) the importance of clinical guidelines in the US, where they may directly or indirectly drive access decisions. He added that the window between early and later development phases is growing smaller, which means that industry is asking for early scientific advice around issues such comparators and the validation of endpoints and are asking their early development teams to consider these factors as potential regulatory success issues as well. For products granted early access, teams must consider the feasibility of generating the real-world evidence that will satisfy international health technology assessors, especially those in Germany and France, where alignment with label indications is key.

Jean Mossman, *Senior Associate Director (Honorary), London School of Economics, UK* reminded Workshop participants that as we look toward the potential for long-term change in the ways that stakeholders will align in the next decade, the importance of the incremental gains observed to date should not be overlooked. She noted that at a recent meeting of approximately 200 patient groups from 45 countries, 80% of patients agreed that pharmaceutical development is too slow. To these patients, the process for the development of medicines that incorporates the perspectives of multiple stakeholders does not adequately represent the patient need for access. There are many opportunities to effectively gather patient input for this process such as the use of smart phones to collect real world data, but the most important steps forward can only be achieved by gathering all stakeholders together to determine the goals of improvement and then to design a system that is fit for purpose to achieve those goals.

"... the most important step toward improvement in the next ten years can only be achieved by gathering all stakeholders together to determine the goals of improvement and then to design a system that is fit for purpose to achieve those goals."

J Mossman, LSE

WORKSHOP ATTENDEES

Regulatory agencies		
Prof Sir Alasdair Breckenridge	Former Chair	**MHRA, UK**
Prof Hans-Georg Eichler	Senior Medical Officer	**European Medicines Agency, UK**
Rob Hemmings	Statistics and Pharmacokinetics Unit Manager	**MHRA, UK**
Dr Esa Heinonen	Head of Sector Marketing Authorisation	**Swissmedic**
Dr Sandra Kweder	Deputy Director, Europe Office	**Food and Drug Administration, USA**
Marion Law	Director General, Therapeutic Products Directorate	**Health Canada**
Prof Hubert Leufkens	Chairman	**Medicines Evaluation Board, the Netherlands**
Jane Moseley	Senior Scientific Officer	**European Medicines Agency, UK**
Dr Tomas Salmonson	Chair	**CHMP, EMA**
Dr Giovanni Tafuri	National Expert on Secondment, Scientific Advice	**European Medicines Agency, UK**
Industry and consultancy groups		
Dr Shagufta Ahmad	EU Regulatory Affairs TA Head Oncology	**Amgen, UK**
Ana Filipa Alexandre	Director, HEOR	**Astellas Pharma Europe BV, The Netherlands**
Dr James Barnes	Director, Regulatory Policy and Advocacy	**Vertex Pharmaceuticals (Europe) Ltd, UK**
Dr Birge Berns	Senior Director, Global Regulatory Leader Immunology	**Janssen Research & Development, UK**
Francesca Caprari	Global Head of Payer Intelligence and HTA Strategy	**Sanofi SA, Italy**
Dr Nicola Course	Vice President, Global Regulatory Affairs, Region	**GlaxoSmithKline, UK**
Moira Daniels	Head of GRA Neurology and New Medicines	**UCB Biopharma SPRL, Belgium**
Nicholas Drago	Operational Manager	**Bayer Consumer Care AG, Switzerland**
Emma Du Four	Senior Director	**AbbVie Ltd, UK**
Marci English	Director HEOR	**Astellas Pharma US Inc, USA**
Dr Bruno Flamion	Vice President, Head Strategic Development	**Actelion, Switzerland**
Dr Louise Gill	Regulatory Head – Europe and Canada, Global Regulatory Affairs	**GlaxoSmithKline Ltd, UK**
Sharon Gorman	Director, EU and International Regulatory Policy	**Pfizer, UK**
Dr Michael Happich	HTA director, EuCan BioMeds	**Eli Lilly and Company, Germany**
Vibeke Hatorp	Senior Director	**Novo Nordisk A/S, Denmark**
Adam Heathfield	Senior Director, Global Health and Value Innovation Centre	**Pfizer, UK**
Dr Tony Hebden	Vice President of Health Economics and Outcomes Research	**AbbVie, USA**

Dr Peter Honig	Senior Vice President, Worldwide Safety and Regulatory, Worldwide Research and Development	**Pfizer Inc, USA**
Dr Christopher Hoyle	Director Payer and HTA Policy	**AstraZeneca, UK**
Dr David Jefferys	Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety	**Eisai Europe Ltd, UK**
Shane Kavanagh	Vice-President Health Economics	**Janssen Pharmaceutica NV, Belgium**
Nadege Le Roux	Senior Director Regulatory Affairs	**Celgene, Switzerland**
Dr Thomas Lönngren	Independent Strategy Advisor	**PharmaExec Consulting Filial SE, Sweden**
Dr Olivia Maurel	Vice-President, Therapeutic Area head, Global Regulatory Affairs	**Shire, Switzerland**
Dr Christine Mayer-Nicolai	Head Global Regulatory and Scientific Policy (GRASP)	**Merck KGaA, Germany**
Bharti Navsariwala	Senior Director, Regulatory Affairs	**Takeda, UK**
Dr Marta Parmar	EU Regulatory Policy Lead	**F. Hoffmann La Roche, Switzerland**
Eric Peress	World Wide Patient Access Head, Respiratory	**Novartis, Switzerland**
Marie-Laure Prud'homme	Payer intelligence and HTA strategy	**Sanofi, France**
Sonja Pumplün	Head, Global Regulatory Affairs	**Actelion, Switzerland**
Dr Catherine Reed	Senior Research Scientist, Global Patient Outcomes and Real World Evidence	**Eli Lilly and Company, UK**
Claudine Sapede	Global HTA and Payment Policy Lead	**F. Hoffmann-La Roche Ltd, Switzerland**
Pam Smith	Vice President – Europe & Emerging Markets Regulatory Affairs	**AstraZeneca, UK**
Dr Robin Thompson	Director	**Biogen, Switzerland**
Renu Vaish	Executive Director, Global Regulatory Affairs	**Merck & Co, USA**
Dr Pauline Walstra	Director, Regulatory Affairs	**Astellas, The Netherlands**
Dr John Way	International Regulatory Development	**Biogen, UK**
Health technology assessment agencies		
Luc Boileau	President and CEO	**Institut national d'excellence en santé et en services sociaux (NESSS), Canada**
Meindert Boysen	Director, Technology Appraisals Programme	**National Institute of Health and Care Excellence (NICE) UK**
Prof Jonathan Fox	Chairman	**Scottish Medicines Consortium, UK**
Prof Sarah Garner	Associate Director, Science Policy and Research	**National Institute of Health and Care Excellence (NICE) UK**
Wim Goettsch	Director, EUnetHTA JA3 Directorate	**Zorginstituut Nederland**
Dr Caroline Hind	Deputy Director of Pharmacy and Medicines Management/ Co-vice Chair of NDC	**NHS Grampian, UK**
Andrew Mitchell	Strategic Adviser, Evaluation	**Department of Health, Australia**
Dr Brian O'Rourke	President and CEO	**Canadian Agency for Drugs and Technologies in Health**

Patient groups and academic and non-profit institutions		
Dr Mary Baker	Past President	**European Brain Council**
Nicola Bedlington	Secretary General	**European Patients Forum**
Prof Finn Boerlum Kristensen	Professor	**Faculty of Health Sciences, University of Southern Denmark**
Jean Mossman	Senior Associate Director (Honorary)	**London School of Economics, UK**
Dr Bettina Ryll	Founder	**Melanoma Patient Network Europe, Sweden**
Prof Sam Salek	Professor of Pharmacoepidemiology	**University of Hertfordshire, UK**
Prof Adrian Towse	Director	**Office of Health Economics, UK**
Dr Sean Tunis	President and CEO	**Center for Medical Technology Policy, USA**