



Evidentiary requirements in clinical development: Synchronising phase III requirements to meet multiple needs

WORKSHOP SYNOPSIS
31 March – 1 April 2011
Geneva, Switzerland

The following is a high-level summary of key points from a Workshop conducted by the Centre for Innovation in Regulatory Science (CIRS) on 31 March – 1 April, 2011, in Geneva, Switzerland. A complete Workshop Report including full presentation summaries and syndicate recommendations will be forthcoming.

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 III 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 III 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

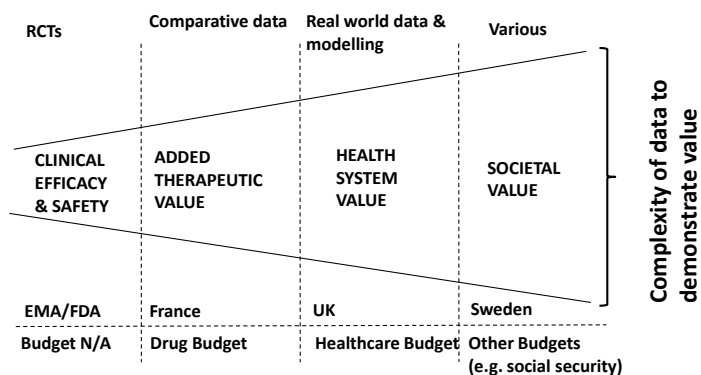
Key points from presentations

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)*.

Session: Why is it important to seek ways to align the requirements of both the regulator and the payer in Phase III clinical development?

In his presentation “The business case for increased alignment of evidentiary requirements in phase III: managing uncertainty and balancing risk with return” **Dr Murray Stewart**, *Senior Vice President, Head of Metabolic Pathways and Cardiovascular Therapy Area Unit, GlaxoSmithKline* 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.

Understand where and how value can be demonstrated



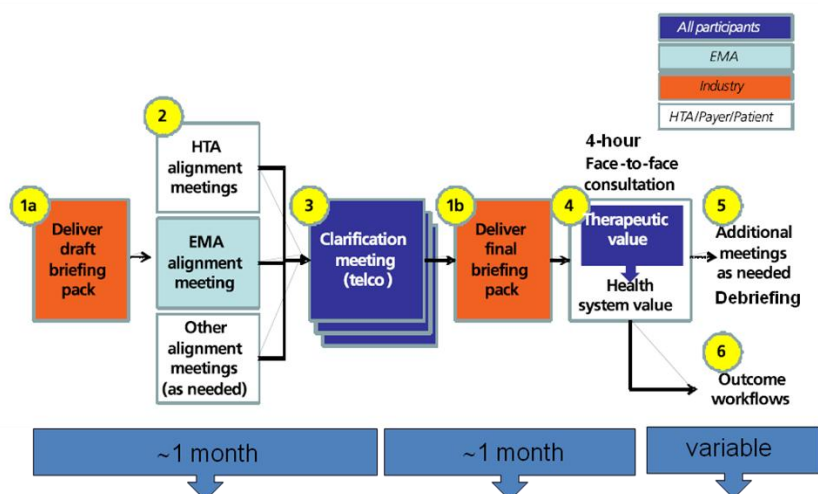
Considering the question “why should the regulator and payer wish to align requirements?” **Professor Adrian Towse**, *Director, Office of Health Economics (OHE), UK* said that the easy answer is that it improves the likelihood of bringing health gain to the populations they serve. Although there are 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 III programme and meeting the specific requirements identified would not likely increase costs of development times significantly.”

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

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 reimbursers. 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.

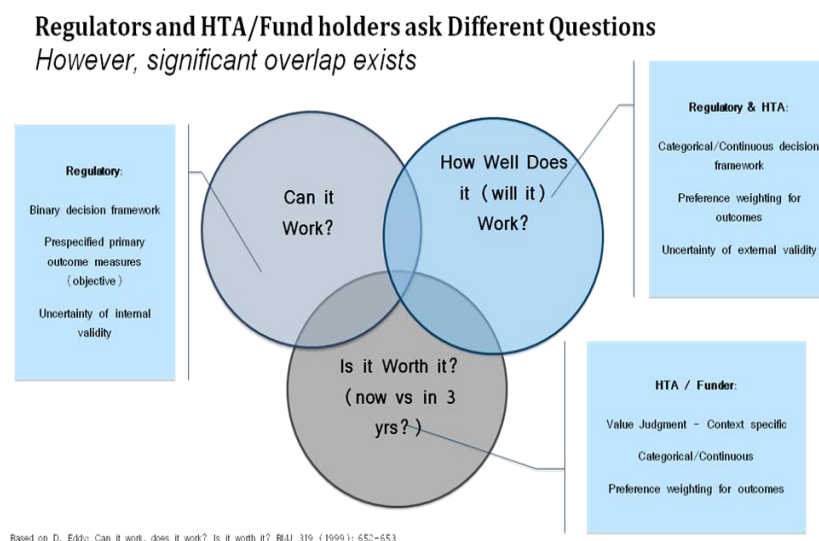
In Sweden, a pilot programme of joint advice between the Medical Products Agency (MPA) and the Dental and Pharmaceutical Benefits Agency (TLV) was completed for 12 products in 2010. **Bengt Ljungberg**, *Scientific Director, Pharmacotherapy, (MPA)* provided the details of the pilot assessment. Although 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.



Session: Key barriers to the inclusion of HTA requirements into phase III: Comparators and endpoints

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* 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.

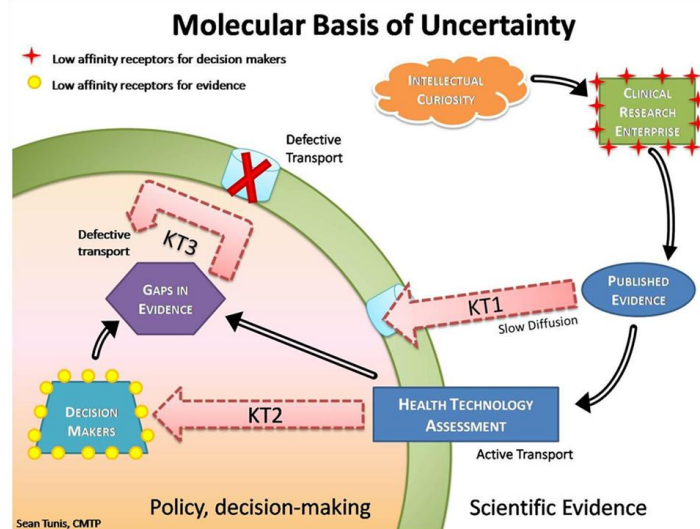
Day 2 Chairman, Professor Sir Alasdair Breckenridge, Chairman, Medicines and Healthcare products Regulatory Agency (MHRA), UK introduced Session 5 of the Workshop.

Session: Working towards greater clarity of roles

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* 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.

Session: Syndicate Discussions

As a lead in to the Syndicate discussions, Dr Franz Pichler, Manager HTA Programmes, Centre for Innovation in Regulatory Science provided the background and objectives for the discussions and Dr Clifford Goodman, Senior Vice President, Lewin Group, USA discussed the relevant recommendations of the 2011 HTAi Policy Forum. Health Technology International (HTAi) is a global professional society of members who produce, use, or encounter HTA for collaboration and the sharing of information and expertise. Dr Goodman reported that the Forum identified possible goals, opportunities, principles and challenges for improved interactions as well as national and international activities that could build on progress to date and help to address some of those challenges. One suggested approach is to develop joint regulator/HTA/coverage scientific advice for industry on the design of pre- and post-market evaluations for specific therapeutic conditions, addressing such matters as appropriate comparators, outcome measures, study populations and subgroups.

Key Points from the Syndicate Discussions

How can companies best accommodate both regulatory and HTA requirements into their Phase III clinical programmes? What are the challenges and what approaches are most easily incorporated?

- To align and then address regulatory and HTA requirements externally and internally, it is necessary that these requirements are clearly communicated, understood and actionable
- Industry's current vertical structure is not ideally organised to readily accommodate the early incorporation of HTA requirements into integrated development programmes; it is critical that awareness of this new developmental paradigm increase within organisations and that HTA requirements are considered early in development to:
 - Inform decision making
 - Define evidence packages and agree on necessary compromises
 - Consider the HTA impact on business plans (value optimisation)
- It may be possible to generate good complementary evidence for regulatory and HTA needs from the same randomised clinical trials, however, by using different data elements
- In addition to achieving an alignment of expectations between regulatory and HTA agencies, it is also necessary to achieve clarity and alignment across HTA bodies; to that end, it will be useful for CIRS to conduct a survey on HTA metrics and benchmarking

Key Points from the Syndicate Discussions

How do we deal with areas of complexity in terms of differing regulatory and HTA needs, focusing on comparators and endpoints?

- Regulatory and HTA authorities have a common purpose: to serve the public by bringing safe and efficacious drugs and devices to the market. Whilst there is scope for greater collaboration between all stakeholders to improve access to medicines, driving this alignment is a major challenge because:

- Clinically relevant endpoints required by regulators and HTAs may be different
- Prescriber decision making is often associated with treatment standards that vary by region
- Local market access frameworks differ
- Price and reimbursement decisions are made by payers not regulators (nor in some cases 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 reflect local and political expediencies that drive willingness and ability to pay
- Early convergence between regulatory and HTA authorities on the objectives of a product development programme can be based on the medical and 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:
 - Agree on relevant comparators /hierarchy of evidence
 - Establish clinically meaningful endpoints / surrogates where appropriate
 - Agree on those effectiveness measures that can be addressed during clinical development and that will inform the payer decision
- 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 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 the product's value

Key Points from the Syndicate Discussions

What kind of scientific advice model is most effective?

- There are many and varied interactions when characterising “early advice,” with no consistent view on best practice. There is generally a lack of written guidelines, sometimes with the adaptation of regulatory guidance documents for HTA purposes; to complicate matters, advice may be national and product-specific, or relevant to multi-country, multi-HTA, multi-stakeholder. This advice may be provided 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. Discussion forums such as those conducted by Health Technology Assessment International (HTAi) and CIRS provide opportunities for high-level discussions to address the possibilities of aligned scientific advice
- Aligned advice is dogged by a number of issues including: differences in the political/economic environments within each HTA works, non-standardised procedures, fee structures, differences in

goals, missions and perspectives and a relative lack of standardisation among their 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; 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 I versus phase III) may determine the type of dialogue that can be facilitated. The type of advice needed (ie study design advice, surrogate recommendations) will determine when advice should be sought; often, this early advice is given verbally and non-binding, while specific input on trial designs, data collection methodologies would ideally be provided as a written directive
- Industry senior management should drive a company-wide recognition of reimbursement issues, 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
- HTA advice cannot be received too early in a development programme as certain data are crucial, such as the importance of 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 HTA may be seen as closer to real-life healthcare delivery
- 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

Conclusion

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

SPECIAL THANKS TO

The Workshop Chairs

Dr Marcus Müller, Head of Agency, Austria Medicines and Medical Devices Agency (AGES PharmMed)

Prof Sir Alasdair Breckenridge, Chairman, Medicines and Healthcare products Regulatory Agency (MHRA), UK

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

Professor Adrian Towse, Director, Office of Health Economics (OHE), UK

Andrew Mitchell, Strategic Adviser, Evaluation, Department of Health and Ageing (DoHA), Australia

Bengt Ljungberg, Scientific Director, Pharmacotherapy, (MPA), Sweden

Prof Bruno Flamion, Chairman, Belgian Committee for Reimbursement of Medicines (CTG/CRM), Belgian National Institute for Health and Disability Insurance (INAMI-RIZIV)

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Seren Phillips, Associate Director, Scientific Advice Programme, National Institute for Health and Clinical Excellence (NICE), UK