



BUILDING THE BENEFIT-RISK TOOLBOX:

Are there enough common elements across the different methodologies to enable a consensus on a scientifically acceptable framework for making benefit-risk decisions?

20-21 JUNE 2012
WASHINGTON, DC

WORKSHOP REPORT

Workshop report authors

Stuart Walker, BSc, PhD, MFPM, FRSC, FIBiol, FRCPath

Neil McAuslane, PhD

Lawrence Liberti, MSc, RPh, RAC

Patricia Connelly, BA, ELS

CIRS - The Centre for Innovation in Regulatory Science - is a neutral, independent UK-based subsidiary company, forming part of the Intellectual Property and 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.

Centre for Innovation in Regulatory Science (CIRS)
The Johnson Building, 77 Hatton Garden, London, EC1N8JS, UK

Email: centre@cirsci.org

Website: www.cirsci.org

Section 1: Executive Summary

Background to the Workshop

A survey undertaken by CIRS in 2011 identified the most significant barrier to implementing a formal benefit-risk framework within companies and agencies as the lack of a scientifically accepted model. This barrier exists despite the fact that there is generally good agreement as to the need and function of an appropriate framework as well as to the perceived advantages for implementing a framework as a tool for communication, structured discussion and enhancing transparency and accountability. A consensus is emerging that rather than a single benefit-risk methodology, a toolbox of methodologies derived from a common framework may be required that are flexible and adaptable for different situations. However, for this concept to be taken forward, agreement must be reached amongst the major stakeholders on a general scientifically acceptable benefit-risk framework.

Over the last five years, a number of initiatives have emerged from regulatory agencies such as the EMA, FDA and members of the Consortium on Benefit-Risk Assessment (COBRA) and from individual companies and industry consortia such as the Benefit-Risk Action Team. These initiatives have developed qualitative and semi-quantitative methodologies, all of which have a number of common elements and which are being undertaken as pilot projects to test their application in real-world cases. In 2012, as the development of benefit-risk methodologies moves forward through these initiatives, this Workshop was designed to bring together the various stakeholders to discuss case studies in the context of the common elements of the various methodologies. The question is whether the stakeholders agree on a scientifically acceptable overarching framework for the benefit-risk assessment of medicines?

Workshop Objectives

- **Discuss the progress** made since 2011 by different groups on defining and implementing a benefit-risk framework and specific methodologies within their organisations
- **Further the thinking as to what can be learnt** from case studies and from each

other about the different methodologies that can be used to make explicit benefit-risk decisions.

- **Identify the common elements** across methodologies and discuss how to achieve a consensus on a scientifically acceptable overarching framework for making benefit-risk decisions

Introduction

Lawrence Liberti, Executive Director, CIRS, London, opened the Workshop with an update on the evolution of benefit-risk assessment activities at CIRS. CIRS undertakes its various benefit-risk assessment activities under its UMBRA – Unified Methodologies for Benefit-Risk Assessment - initiative. UMBRA provides the platform for the development, assessment, implementation and ongoing refinement of an internationally acceptable, structured, systematic, standardised approach for the benefit-risk assessment of medicines. CIRS established the UMBRA initiative to serve as the information-sharing and -coordinating entity for global benefit-risk activities, to work cooperatively with all stakeholders to develop the science and art of benefit-risk decision making and communication and to help centralise the development and dissemination of a globally acceptable framework. To this end, CIRS will look for best practices from which companies, agencies and other stakeholders can develop and evolve a toolbox of specialised methodologies to make and communicate benefit-risk assessments.

Key points from presentations

SESSION: DEVELOPMENT OF A FRAMEWORK FOR BENEFIT-RISK: WHAT HAS BEEN LEARNT THROUGH CASE STUDIES?

Day 1 Chairman, Dr Murray Lumpkin, *Commissioner's Senior Advisor and Representative for Global Issues, US Food and Drug Administration (FDA)* welcomed participants to the annual CIRS Benefit-Risk Workshop in Washington DC, remarking that as this Workshop took place, legislators in Washington were making final refinements to the fifth Prescription Drug User Fee Act (PDUFA V) submitted for consideration by the FDA. He invited one of the Act's primary developers, **Dr Theresa Mullin**, *Director, Office*

of Planning and Informatics, Center for Drug Evaluation and Research (CDER), FDA, USA, to further discuss this legislation.

Dr Mullin explained that PDUFA provides more than 60% of support for the review of drugs in the United States. It has been recognised within the FDA that a framework that accurately and concisely describes benefit and risk considerations would help reviewers apply a structured approach in regulatory decision making and product assessment and a more systematic and open discussion with all stakeholders. In particular, informed patients could provide valuable insights regarding a given disease and the potential gaps or limitations in available therapies. Accordingly, PDUFA V includes recommendations to develop and implement a plan to integrate a benefit-risk framework in the drug review process and to conduct public meetings with relevant patient advocacy communities within specific disease states.

In addition to the benefit-risk framework being developed at the US FDA, **Dr Tim Garnett**, *Chief Medical Officer and Senior Vice President, Eli Lilly and Company, USA*, cited three other frameworks that represent a significant step forward in developing a consistent, transparent and structured approach to benefit-risk assessment: those developed by the European Medicines Agency (EMA), the Consortium on Benefit-Risk Assessment (COBRA) and the Benefit-Risk Action Team (BRAT). Each of these four frameworks recognises that a structured and systematic process plays an essential and fundamental role in assisting and improving decision making. Dr Garnett called for next steps that included the accumulation of additional stakeholder input, collaboration toward a common framework and the ongoing use of a forum such as the CIRS-coordinated Benefit-Risk Taskforce to share implementation experiences and best practices.

Calling the framework being developed by the EMA a simple qualitative tool, **Prof Hans-Georg Eichler**, *Senior Medical Officer, European Medicines Agency* considers implementation of such tools among the next steps in the development of a benefit-risk "toolbox." After this implementation, he recommended that stakeholders explore and familiarise assessors and decision makers with more complex quantitative tools and address how the values of the various stakeholders are being considered in benefit-risk assessments by developing methods that combine the technical expertise of regulatory scientists and patients to address the diverse spectrum of value judgements.

Australia's Therapeutic Goods Administration (TGA), Singapore's Health Sciences Authority (HSA), Health Canada and Swissmedic are the four agencies making up the Consortium on Benefit-Risk Assessment (COBRA). **Dr Jason Ferla**, *Director, Prescription Medicines Clinical Unit 3, Office of Medicines Authorisation, Therapeutic Goods Administration, Australia* provided an update on the work of COBRA. This aims to develop a systematic qualitative approach for the benefit-risk assessment of medicines in order to facilitate the opportunity for joint or shared reviews by the four agencies. Having developed a framework "proforma", the consortium is currently reviewing the results of a retrospective study employing its use with plans for making the template more reflective of actual practice, integrating the ability to graphically visualise the data and initiating a prospective study.

Dr Francesco Pignatti, *Head of Section Oncology Safety and Efficacy of Medicines, European Medicines Agency* reported on an EMA field test of PROACT-URL, a qualitative framework for structured decision making. In this test, the identified Problem was medullary thyroid cancer; the Objectives were to determine the effect of treatment on overall and progression-free survival and toxicity. The Alternatives (available therapies) were vandetanib and placebo and the Consequences of the treatments were presented in an effects table (a tabular summary of the favourable and unfavourable events associated with treatment) with Tradeoffs determined through swing weighting of those events. Data were subjected to a sensitivity analysis to determine the level of Uncertainty. Risk tolerance for vandetanib was reflected in the restricted approval granted to the product for use in a limited controlled set of patients. Links to other decisions will be determined by the long-term use of the effects table in regulatory assessments. The EMA hopes to implement the effects table through a pilot programme to determine if its use is generally fit for purpose.

Field tests of the US FDA benefit-risk framework are ongoing for six products being assessed in the Center for Drug Evaluation and Research (CDER). **Patrick Frey**, *Director, Office of Planning and Analysis, CDER, FDA, USA* said that it is hoped that these tests will help evaluate and further refine the framework and support its implementation into the CDER review process. Additional FDA benefit-risk initiatives planned as part of PDUFA V include the publication of a five-year plan for the implementation of the framework and an evaluation of its impact as

well as public workshops on benefit-risk from the perspective of regulators and other stakeholders.

A case study of the use of the benefit-risk framework developed by the Benefit-Risk Action Team (BRAT) revealed that such methodology can add rigour and transparency to the decision-making process, seems appropriate for most benefit-risk decisions and can be easily used, especially in regulatory settings such as FDA Advisory Committee meetings. Although progress has been made through the development of this methodology and others, **Dr Filip Mussen**, *Head, Global Labeling Center of Excellence, Janssen Research and Development, Belgium*, believes that there is currently no common set of terms, definitions or agreed methodology for capturing “values” that can be applied in these methodologies and additional discussion, application and piloting is required for the further development of globally acceptable methodologies.

The objective of the EMA Work Package V is to develop methods for use in benefit-risk assessment, including both the underpinning modelling and the presentation of the results, with a particular emphasis on graphical methods. In fulfilment of that objective **Dr Diana Hughes**, *Vice President, Worldwide Safety Strategy, Primary Care Business Unit Lead, Pfizer Inc, USA* reported that the members of the Innovative Medicine Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (IMI PROTECT) reviewed benefit-risk frameworks and tested a first wave of thirteen methodologies using a case study approach. The group deliberately selected more complex cases for evaluation to stretch the use of the methodologies and explore the use of visual representation. A summary report being developed will critically appraise the methodologies and a second wave of case studies has begun.

Jean Mossman, *Policy Lead, European Federation of Neurological Associations* reminded Workshop participants that in addition to the risk of adverse effects from medication, illness can represent many types of risk to patients, all of which may influence their decision making. These include the risk of not getting the correct diagnosis or of not getting a diagnosis in a timely manner: the risk of not getting treatment, of not getting treatment from an expert or even of getting the wrong treatment. Patients also run the risk of not taking the treatment as scheduled. In fact, for a variety of reasons, patients often do not take medicines as prescribed and industry,

regulators and clinicians should work harder to help patients understand the potential benefits and risk of taking – or not taking medicines. They should also work harder at understanding that the benefits of treatment, important to patients, may not be captured as clinical trial endpoints and ensuring that the people who must live every day with the potential of associated benefits and harms of medicines are involved in decisions about those medicines throughout the product life cycle. Perhaps the most obvious consideration is that patients should be informed of the results of their input and of the ongoing status of a therapy’s development, as they often feel left out of the information loop despite their key contribution of time and effort to research programmes.

Patients and FDA regulators are engaged early and often when the Amyotrophic Lateral Sclerosis (ALS) Association is developing new clinical or preclinical trials. **Dr Lucie Bruijn**, *Chief Scientist, ALS Association, USA* explained that the work of the ALS association is divided into research, public policy and care services, with patients at the centre. The Association’s Clinical Research Learning Program, for example, is geared toward patients to help ameliorate concerns that benefits of certain treatments and study results may be over-interpreted. ALS affects 30,000 Americans at any given time; worldwide, there are two cases per 100,000. Most patients die within two to five years of diagnosis. However, recent years have seen an improved understanding of disease and care and one therapy has already been approved and many others are in the development pipeline. The patient’s role in helping to develop novel ALS therapies can serve as a model for other disease areas.

In her second Workshop presentation, **Dr Diana Hughes** provided an industry perspective on involving patients in benefit-risk assessments, emphasising that patients want to be heard and to have their perspectives incorporated into the decision-making process. Work toward that end within the pharmaceutical industry is ongoing, with organised patient input to help identify key facets of disease targets, to inform on the collection of patient-centric views for development programmes and to provide insights into the assessment of the disease and the symptoms that are of most value to patients. For their part, patients and patient advocacy groups recognise the need to better organise, establish credibility and productively contribute to the discussion

based on scientific merits and to develop an understanding of the growing role of health technology assessment in the availability of novel medicines. Next steps should include continued outreach to and collaboration with advocacy groups; the formation of an industry consortium to understand unmet medical need and patient experience; the development of patient educational programmes to help elicit information on the most relevant aspects of the disease and methodological work to advance a common approach to valuing and weighting (relative importance).

Patient input regarding the real-world effectiveness and tolerability of currently available therapy can help to establish if an unmet medical need exists. Furthermore, the largely untapped ability of patients to provide insights and help identify important dimensions of benefit not adequately captured in current studies points to the need for validated tools for patient-reported outcomes (PROs).

Dr Theresa Mullin reiterated the FDA's ongoing commitment to enable more patient-focused drug development, illustrated by such initiatives as its Patient Representative Program in which selected patients receive training for participation in disease state advisory committees and involvement in the drug review process. Among several patient-centred activities planned for 2012, the FDA expects to develop a basic roadmap that could be used by patient groups interested in pursuing the development of PRO measures in a specific disease area.

Although there is an increasing use of decision-support frameworks including benefit-risk frameworks as well as simulation and modelling to aid decision-making in drug development, this process can be subjective and as such is influenced by an individual's knowledge, ability and motivation. As part of a doctoral research programme, under the sponsorship of the Welsh School of Pharmacy at Cardiff University and CIRS, **Ronan Donelan**, *Head of Regulatory Affairs EMEA and ANZ, Quintiles, Ireland* is investigating how individuals and organisations manage decision making within the drug development arena. The Quality of Decision-Making Orientation Scheme (QoDoS)[®] is an instrument being developed in the doctoral programme through qualitative research and validation with key opinion leaders, regulatory agencies, pharmaceutical companies and contract research organisations, which aims to improve the linkage of the science and art components of decision making.

At GlaxoSmithKline (GSK) as at other major pharmaceutical companies, complex decisions are made at multiple levels on a continual basis. **Dr Paul Huckle**, *Chief Regulatory Officer, GlaxoSmithKline, USA* described the key factors that assist industry in meeting this challenge and ensuring good decision making, including clarity of accountability, timeliness and the establishment of mechanisms to ensure objectivity such as peer review by specialised advisory groups. Most importantly, consistency of decision making at GSK is accomplished through adherence to its corporate values of patient focus, transparency, respect and integrity.

Sponsors and regulators have committed to safeguard public health through the formal assessment of the benefit-risk balance of medicines. **Prof Sir Alasdair Breckenridge**, *Chairman, Medicines and Healthcare products Regulatory Agency, UK* reported that there has been a convergence of thought by global regulators regarding the necessity to make this assessment an ongoing process throughout a medicine's life cycle. For example, the European Pharmacovigilance regulation in force as of July 2012 emphasises the importance of ongoing risk management plans for all newly approved products, improves the legal basis for post-authorisation studies of safety and effectiveness and seeks to enhance transparency of and access to long-term safety data. Similarly, it has been recommended that benefit-risk assessment management plans become part of regulatory submissions to the US FDA and must be approved by FDA and updated over the life cycle of the medicine.

According to **Day 2 Chairman, Dr Frank Rockhold**, *Senior Vice President, Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline, USA*, the content of the first day's presentations and discussions were a good preparation for the Syndicate discussions that would occur on day 2. That is, irrespective of whether a qualitative or semi-quantitative methodology is used, stakeholders in the development of medicines have agreed that a structured, disciplined thought process is needed to apply the right information and perspectives to benefit-risk decisions.

Considerations in methodologies to assess benefit-risk in Canada were presented by **Barbara Sabourin**, *Director General, Therapeutic Products Directorate, Health Canada* who provided the regulatory viewpoint and **Dr Chander Sehgal**, *Director of the Common*

Drug Review (CDR) program, Canadian Agency for Drugs and Technologies in Health (CADTH), who discussed the health technology assessment perspective. Ms Sabourin explained that evaluation processes at Health Canada are continuing to evolve as they seek to meet the challenges presented by the need for more rigorous, analytical standards and a desire for consistency of decision processes by developing a qualitative or semi-quantitative framework for benefit-risk analysis. The agency has also embarked on a programme of increasing collaboration with CADTH, including shared information and understanding of requirements.

Dr Sehgal said that whilst regulators evaluate safety, efficacy and quality, with comparisons frequently solely made to placebos, health technology assessors must evaluate the medicine's comparative effectiveness, cost and cost-effectiveness and relevance to patient input compared with the best publicly funded alternative. Indeed, patient input plays an important role in CADTH evaluations and this input is reflected in CADTH recommendations to Canadian payer agencies. Future CADTH plans include making CDR review reports publicly available and the exploration of parallel review mechanisms with Health Canada.

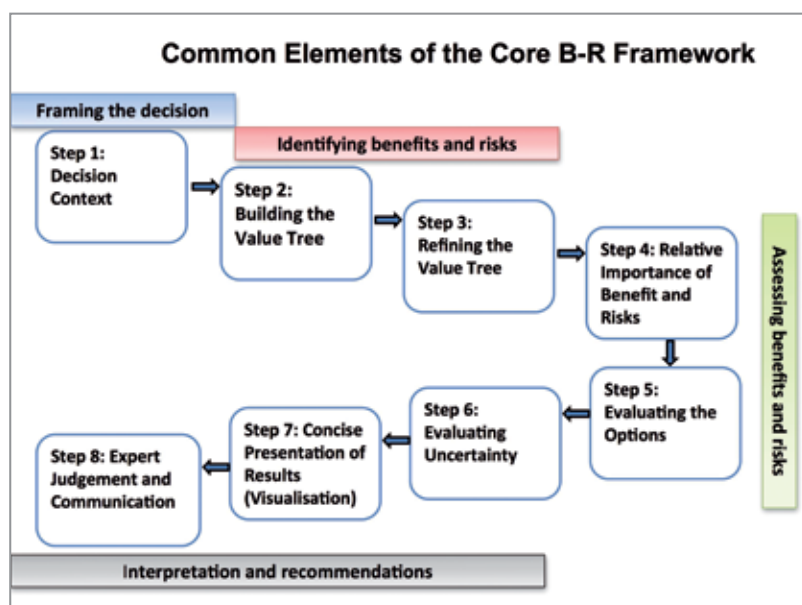
Prof Sir Alasdair Breckenridge informed the group of the activities of the CIRS Benefit-Risk Task Force. Chaired by Sir Alasdair, the Taskforce comprises representatives from all the major benefit-risk initiatives, including eight regulatory agencies and eight pharmaceutical

companies. Its purpose is to facilitate knowledge exchange in the area of benefit-risk and to make recommendations for workshops, surveys and research that should be undertaken to develop the appropriate toolbox for benefit-risk assessment.

A final reflection was provided by CIRS founder **Professor Stuart Walker** who underlined the importance of the consensus that had been achieved at this Workshop in agreeing the UMBRA eight-step Benefit-Risk Framework (Figure 1).

He also reviewed the recent progress made in the area of benefit-risk and discussed CIRS activities planned for the near future including proposed pilots using the UMBRA framework in select agencies in South East Asia and Europe. In addition, CIRS Senior Research Fellow Art Gertel will perform research in valuing and weighting benefit-risk parameters and a focussed technical Workshop has been planned for 13 December 2012 to discuss the research results and to develop relevant recommendations. Finally, CIRS will also seek to conduct two surveys, one of regulatory agencies and industry examining the role of patients in clinical development and regulatory assessment and the second to elucidate the current use of benefit-risk assessment frameworks by health technology assessment agencies.

Figure 1. The 2012 UMBRA benefit-risk framework



Recommendations from across the Syndicates

- Develop usage and implementation guides based on the common framework
- Adopt a lexicon that emphasises “prioritisation” or “relative importance” rather than “weighting” and document the rationale behind the prioritisation
- Employ a “change management” approach to promote framework uptake and adoption, using a staged approach to promote organisational change and demonstrate value; this approach must be of value, compatible with current thinking and understandable and visible
- Ensure quality information and analyses to support the decision
- Develop a structured, living database for benefit-risk assessments
- Develop a cross-functional forum for decision makers within organisations
- Establish decision-training programmes in agencies and companies
- Encourage the use of a framework and toolbox for decision-making methodologies both general and benefit-risk specific
- Learn from QoDOS pilot experience (page 39); further assess its value for baseline and ongoing analysis of the quality of decision making and to define training needs
- CIRS should conduct a detailed analysis of regulatory outcomes as a measure of quality decisions
- Industry should appoint a single individual from outside the commercial organisation to engage with patients and representative groups at set points throughout the development process
- Consortia of academics, regulators, industry, payers and patients should be established and leveraged in different disease areas to clarify unmet needs, areas of concern and clinical trial endpoints to consider
- Preferences of a broad patient population should be included as part of phase 3 or pivotal testing
- CIRS should sponsor a Workshop on *The patient voice in clinical development* with discussion topics to include process and methodology

Workshop Programme

DAY 1: 20 JUNE 2012	
Session: Development of a framework for benefit-risk: what has been learnt through case studies?	
Welcome	Lawrence Liberti , Executive Director, CIRS
Chairman's welcome and introduction	Dr Murray Lumpkin , Commissioner's Senior Advisor and Representative for Global Issues, US Food and Drug Administration
The role PDUFA V will play in delivering a benefit-risk framework for FDA by 2013	Dr Theresa Mullin , Director, Office of Planning and Informatics, Center for Drug Evaluation and Research, Food and Drug Administration, USA
Achieving a scientifically acceptable framework for benefit-risk decision making: Should this be based around a toolbox of methodologies underpinned by common elements?	
Industry viewpoint	Dr Tim Garnett , Chief Medical Officer and Senior Vice President, Eli Lilly and Company, USA
Regulatory viewpoint	Prof Hans-Georg Eichler , Senior Medical Officer, European Medicines Agency
Benefit-risk framework development: Case studies and forward plans	
Four Agency Consortium	Dr Jason Ferla , Director, Prescription Medicines Clinical Unit 3, Office of Medicines Authorisation, Therapeutic Goods Administration, Australia
EMA case study	Dr Francesco Pignatti , Head of Section Oncology Safety and Efficacy of Medicines, European Medicines Agency
FDA case study	Patrick Frey , Director, Office of Planning and Analysis, Center for Drug Evaluation and Research, Food and Drug Administration, USA
Company case study using the BRAT methodology	Dr Filip Mussen , Head, Global Labelling Center of Excellence, Janssen Research and Development, Belgium
Session: How and when to involve patients to help inform benefit-risk decision making in companies and agencies	
Update on the IMI initiative	Dr Diana Hughes , Vice President, Worldwide Safety Strategy, Primary Care Business Unit Lead, Pfizer Inc, USA
How and when should patients be involved in making benefit-risk decisions	
European patient viewpoint	Jean Mossman , Policy Lead, European Federation of Neurological Associations
USA patient viewpoint	Dr Lucie Bruijn , Chief Scientist, ALS Association, USA

Company viewpoint	Dr Diana Hughes , Vice President, Worldwide Safety Strategy, Primary Care Business Unit Lead, Pfizer Inc, USA
Patients' perspectives on benefit and risks in drug development	Dr Theresa Mullin , Director, Office of Planning and Informatics, Center for Drug Evaluation and Research, Food and Drug Administration, USA
Decision making: what are the challenges in making quality decisions?	Ronan Donelan , Head of Regulatory Affairs EMEA and ANZ, Quintiles, Ireland
Reflections from a company	Dr Paul Huckle , Chief Regulatory Officer, GlaxoSmithKline, USA
Reflections from an agency	Prof Sir Alasdair Breckenridge , Chairman, Medicines and Healthcare products Regulatory Agency, UK

DAY 2: 21 JUNE 2012

Session: Syndicates

Chairman's introduction	Dr Frank Rockhold , Senior Vice President, Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline, USA
Methodologies to assess benefit-risk in the context of licensing and in relation to HTA: What can be learnt and do the similarities outweigh the differences?	
Health Canada	Barbara Sabourin , Director General, Therapeutic Products Directorate, Health Canada
Canadian Agency for Drugs and Technologies in Health	Dr Chander Sehgal , Director of the Common Drug Review program, Canadian Agency for Drugs and Technologies in Health
Syndicate sessions	
Syndicate A: Can there be alignment on the various components that should be included in any ideal framework?	
Chair	Prof Sir Alasdair Breckenridge , Chairman, Medicines and Healthcare products Regulatory Agency, UK
Rapporteur	Dr Becky Noel , Senior Research Scientist, Eli Lilly and Company, USA
Syndicate B: What are the challenges and the processes/procedures which would enable agencies and companies to make quality decisions in benefit-risk assessments?	
Chair	Professor Sam Salek , Director, Centre for Socioeconomic Research, Cardiff University, UK
Rapporteur	Dr Mark Goldberger , Divisional Vice President, Regulatory Policy and Intelligence, Abbott USA
Syndicate C: When and how should patients be involved and what would facilitate their involvement with regard to the benefit-risk assessment of new medicines?	
Chair	Dr Paul Huckle , Chief Regulatory Officer, GlaxoSmithKline, USA
Rapporteur	Dr Nadine Cohen , Senior Vice President, Regulatory Affairs, Biogen Idec, USA

Session: Challenges and difficulties of presenting benefit-risk information to stakeholders – is alignment the key to informed decision making and information symmetry?	
Panel viewpoint following syndicate discussion feedback	
Company representatives	Dr Carmen Bozic, <i>Senior Vice President and Global Head, Drug Safety and Benefit-Risk Management, Biogen Idec, USA</i> Dr Susan Welsh, <i>Vice President, Global Pharmacovigilance and Epidemiology, Medical Safety Assessment Therapeutic Area Head, Oncology & Immunology, Bristol-Myers Squibb, USA</i>
Licensing body, European and USA representatives	Prof Hans-Georg Eichler, <i>Senior Medical Officer, European Medicines Agency</i> Dr Theresa Mullin, <i>Director, Office of Planning and Informatics, Center for Drug Evaluation and Research, Food and Drug Administration, USA</i>
Patient representative	Jean Mossman, <i>Policy Lead, European Federation of Neurological Associations</i>
Benefit-Risk Taskforce Chairman	Prof Sir Alasdair Breckenridge, <i>Chairman, Medicines and Healthcare products Regulatory Agency, UK</i>
Final reflections	
CIRS	Prof Stuart Walker, <i>Founder CIRS</i>

Section 2: Syndicate Discussions

Three Syndicate Discussion Groups were asked to discuss aspects of benefit-risk decision making in the development and regulation of new medicines, including the advancement of a scientifically acceptable benefit-risk

framework, quality decision making and patient participation.

Syndicate Discussion A

Can there be agreement (alignment) on the various components that should be included in any ideal model/framework?

Chair	Professor Sir Alasdair Breckenridge , <i>Medicines and Healthcare products Regulatory Agency, UK</i>
Rapporteur	Dr Becky Noel , <i>Senior Research Scientist, Eli Lilly and Company, USA</i>

Background

There is generally a good agreement among regulatory agencies and pharmaceutical companies on the need and function of an appropriate benefit-risk framework as well as the perception that implementing such an approach would serve as the basis for tools for communication, structured discussion and enhanced transparency and accountability. A toolbox of methodologies that are flexible and adaptable for different situations seems to be required, although for this to be taken forward, a consensus must be reached amongst the major stakeholders on a general scientifically accepted overarching common framework.

The development of an overarching framework would enable the consideration of different qualitative or quantitative methodologies that have encapsulated the agreed-upon decision steps for making a benefit-risk assessment. Over the last five years, a number of initiatives at regulatory agencies and at individual companies and across companies have developed qualitative, semi-quantitative and quantitative benefit-risk approaches, all of which have a number of common elements. For purposes of this Syndicate Discussion, CIRS has drawn up a potential alignment of the main methodologies under a possible overarching framework. The question for this Syndicate Discussion is *can agencies and companies agree on an alignment of the common elements and principles for making a consistent, systematic, transparent and accountable benefit risk assessment?*

Questions for consideration

- Can the common elements be aligned under the suggested steps if not, what would the group suggest as an alternative?
- If agreement is reached in principle – How should this be taken forward to ensure buy-in from the different stakeholders working on benefit risk methodologies and achieve recognition as the accepted framework? What are the issues that need to be considered?
- Can the different methodologies being developed be organised within the suggested overarching framework?

Critical issues and strategies

This Syndicate concluded that differences and commonalities among stakeholders in benefit-risk decision making must be recognised and respected. As in many past Syndicate discussions of activity harmonisation, the group agreed on the need for a common lexicon as a prerequisite to the alignment of the components of various benefit-risk frameworks. That is, a common understanding must be developed of the meanings of terms such as *framework*, *methodology*, *model* and *weighting*. However, because the acceptance of explicit weighting of benefit-risk parameters varies widely among agencies, differences in regional regulatory and cultural viewpoints must also be considered.

It should also be recognised that the alignment of methodologies should not be rushed. Rather, following the agreement of a common framework, time should be allowed for pragmatic

methodological approaches to be developed including adequate timing for feedback on best practices to emerge. Further, it should be understood that developing these aligned methodologies will require resources from many stakeholders and the establishment of processes for the management and archiving of information to support iterative improvements in techniques for benefit-risk assessments.

The Syndicate also agreed that uncertainty must be formally incorporated into any benefit-risk framework. Ideally, this parameter should not be limited solely to statistical uncertainty but should encompass the entire process.

An overarching framework

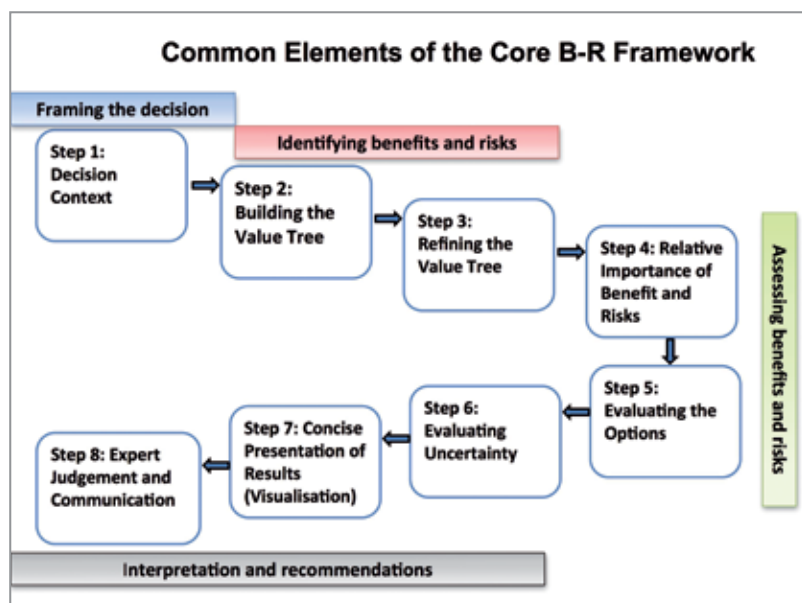
A key milestone was accomplished at this Workshop: As part of its recommendations, this Syndicate proposed and the Workshop attendees later agreed on the common elements of an overarching, internationally acceptable, standardised benefit-risk framework (Figure 1). Furthermore, this framework was endorsed following the Workshop by the Benefit-Risk Taskforce and will serve as the

ongoing basis for discussions around the development of novel, dynamic methodological tools to address the diverse needs of benefit-risk assessment throughout a product's life cycle by diverse stakeholders. CIRS envisions an ongoing discussion and assessment of the framework components to ensure it reflects the dynamic nature of this area of science.

Recommendations

- Develop usage and implementation guides based on the common framework
- Adopt a lexicon that emphasises “prioritisation” or “relative importance” rather than “weighting” and document the rationale behind the prioritisation
- Employ a “change management” approach to promote framework uptake and adoption, using a staged approach to promote organisational change and demonstrate value; this approach must be of value, compatible with current thinking and understandable and visible

Figure 1. The 2012 UMBRA benefit-risk framework



Syndicate Discussion B

What are the challenges and the processes/procedures which would enable agencies and companies to make quality decisions in benefit-risk assessments?

Chair	Professor Sam Salek , Director, Centre for Socioeconomic Research, Cardiff University, UK
Rapporteur	Dr Mark Goldberger , Divisional Vice President, Regulatory Policy and Intelligence, Abbott USA

Background

At the April 2005 CIRS Workshop *Building quality into regulatory dossiers and the review process*, Professor Larry Phillips, Professor of Decision Analysis at the London School of Economics discussed the science of quality decision making:

"Many people find it hard to believe that there can be a 'science of decision-making'. There is such a science and it is based on a very coherent theory about how to make better decisions... Contrary to expectations, a quality decision and decision-making process should not be tested by looking at the outcomes and consequences. In an uncertain world, it is perfectly possible to take a good decision that has poor consequences and equally, to make a bad decision and come up with a good outcome. On balance, however, the long-running use of good systems for making decisions will generally give better outcomes."

Although companies and agencies are working to develop methodologies for making consistent, systematic, transparent and accountable benefit-risk decisions, systems, enablers and barriers for quality decision making within companies and agencies remain to be defined. One way of testing quality decision making is to look at how individuals and organisations make decisions based on custom and practice and map performance against best practice decision making.

To focus the discussion on how to build quality into the benefit-risk decision-making process within companies and agencies, this Syndicate was provided with highlights from the pre-meeting survey and resulting Workshop presentation evaluating how agencies and companies make decisions.

Questions for consideration

- What are the characteristics of a quality decision?
 - In their publication *Smart Choices, A Practical Guide to Making Better Life Decisions*, JS Hammond and colleagues

state that good decision making is supported by the use of a systematic approach and may include aspects such as framing and clarifying issues and deciding the criteria and goals for the decision as well as developing different scenarios, controlling divergent aims, anticipating the results and comprehending the intrinsic risks.

- What are the major obstacles within companies and agencies to making good-quality decisions and how should these be overcome or handled?
- What are the major enablers within companies and agencies for making good-quality decisions and how should these be encouraged?
- Is it possible to establish a set of principles/practices that companies and agencies should consider that will build quality into the benefit-risk decision-making process?
- How might organisations measure the quality of their decision making and monitor the outcome of their decisions?

Critical issues

This Syndicate specified that internal organisational challenges to making quality decisions that are specific to benefit-risk decisions include difficulties inherent in valuing and weighting specific elements in the decisions, in communicating problem statements and in defining or explaining uncertainties around specific benefits and harms.

It should further be remembered that stakeholders may have incentives that differ according to their responsibilities and be influenced by contexts that may be institutional, regional or global. However, Syndicate members agreed that regardless of individual perspectives or contexts, these decision makers must apply validated decision tools that are appropriate to individual circumstances and to the stage of the

medicine's life cycle.

It was the consensus of this group that benefit-risk evaluators need to learn from prior decisions and experiences. Processes must be transparent, rigorously documented and clearly communicated. Training that is supported by standard operating procedure documents and guidelines is also key. Organisational roles and responsibilities need to be clearly defined, with a person within the organisation designated as being accountable for senior decision making coupled with a defined escalation process.

Although a common framework encourages standard decision making, independent objective points of view within an organisation should be encouraged and a "devil's advocate" assigned to challenge assumptions or proposals. Teams need to offer a primary solution but an accepting environment should be created for alternative strategies and out-of-the-box ideas. It has been the experience of members of the group that analysis of such alternative options often leads to better decisions. The long-term impact of decisions should be considered in addition to short-term effects.

Strategies

Quality of decision making within organisations can be measured based on a comparison of the desired versus the actual impact of decisions and by evaluating the adherence to process. A repetition of this analysis over time verifies or

qualifies initial decisions and demonstrates the value of the process. It must be understood that asking the right questions at the beginning of the decision-making process allows the development of a question database that informs good-quality decisions. Finally, quality decisions should also include communication of the rationale underpinning the evaluation.

Recommendations

- Ensure quality information and analyses to support the decision
- Develop a structured, living database for benefit-risk assessments
- Develop a cross-functional forum for decision makers within organisations
- Establish decision-training programmes in agencies and companies
- Encourage the use of a framework and toolbox for decision-making methodologies both general and benefit-risk specific
- Learn from QoDOS pilot experience (page 39); further assess its value for baseline and ongoing analysis of the quality of decision making and to define training needs
- CIRS should conduct a detailed analysis of regulatory outcomes as a measure of quality decisions

Syndicate Discussion B

When and how should patients be involved and what would facilitate their involvement with regard to the benefit-risk assessment of new medicines?

Chair	Dr Paul Huckle , <i>Chief Regulatory Officer, GlaxoSmithKline, USA</i>
Rapporteur	Dr Nadine Cohen , <i>Senior Vice President, Regulatory Affairs, Biogen Idec, USA</i>

Background

As companies and agencies work on methodologies to develop methods for undertaking benefit-risk decisions surrounding new medicines and to communicate those decisions to stakeholders, there has been a growing awareness that the most important stakeholder's voice, the patient, is a critical if often absent component. This is true in both the developmental phase where this voice would ensure that companies are developing

medicines of value to patients as well as in the regulatory review phase, where there may be a difference in perspective between patients and regulators as to the maximum acceptable risk and minimum acceptable efficacy for new medicines.

In April 2012 CIRS held a Workshop, *The Patient's Role in the Benefit-Risk Assessment for the Submission and Review of New Medicines* and the consensus from this meeting was that patients should be involved in providing information

to inform the benefit-risk decision throughout the life cycle of a new medicine, including the early and late stages of development and the regulatory review. This Syndicate was challenged to make recommendations on the possible methodologies and approaches that companies and agencies should take or require to be developed to ensure that patients' needs are well characterised and pivotal to informing benefit risk decision making within the companies and agencies. They were to discuss when and how patients should be involved and what would facilitate their involvement with regard to the benefit-risk assessment of new medicines.

Critical issues and strategies

Along with other Workshop Syndicates, this Syndicate agreed that patient engagement should occur throughout the development of medicines. However, patient advocacy groups report that engagement has been intermittent at best. More effective forums are needed for industry, regulators, academics and payers to hear the voice of the patient.

However, patient engagement must be carefully planned and monitored. Industry's traditional engagement with patients through its commercial divisions has created an often negative perception of the potential influence of a company's marketing department on patient decision making. Sponsors therefore need to ensure that patient advocacy is separated from product advocacy in the sponsorship of patient groups. Furthermore, the content, format and timing of questions to be addressed by patients need to be clarified. Examples of questions that may be appropriate include:

- What matters to you and how can we measure that reliably?
- What benefits and risks are you willing to trade?
- (and simply) What do you want to tell us?

This patient input should play a substantial and formalised role in clinical development, which often relies on well-established endpoints, but which may not adequately or correctly address patients' needs. New endpoints and methodologies for their development and validation must be considered to address the patient voice in the development process. The regulatory and health technology assessment implications of using such patient-related outcomes need to be assessed during the earliest phases of a medicine's development.

Recommendations

- Industry should appoint a single individual from outside the commercial organisation to engage with patients and representative groups at set points throughout the development process
- Consortia of academics, regulators, industry, payers and patients should be established and leveraged in different disease areas to clarify unmet needs, areas of concern and clinical trial endpoints to consider
- Preferences of a broad patient population should be included as part of phase 3 or pivotal testing
- CIRS should sponsor a workshop on the patient voice in clinical development with discussion topics to include process and methodology

Panel Discussion of Syndicate Results: Key points

Following the presentation of the results of the Syndicate Discussion by the Rapporteurs, representatives from industry and licensing bodies discussed these conclusions and recommendations as well as other topics that emerged during the Workshop.

- Harmonisation
 - Existing benefit-risk approaches have enough commonalities that their alignment and the development of a common framework was accepted by the Workshop participants.
 - The common framework such as the UMBRA Framework developed at this Workshop provides a solid basis for the ongoing evolution of novel assessment methodological tools.
 - While most tools now rely on descriptive or qualitative assessments, it was noted that the use of varying supplementary quantitative models and elements, especially quantitative visualisation tools, can be considered for more complex evaluations. However, others feel that complex issues do not necessarily require complex decision-making methodologies. Rather, the use of simple tools such as an effects table can serve as the basis for an organised and structured benefit-risk discussion.
- Benefit-risk frameworks and industry
 - Industry recognises the value of benefit-risk methodologies based on a common framework and these methodologies should continue to be developed through consortia to avoid duplication of effort and to encourage shared learnings. They should be applicable to all phases of medicines development.
- Patient input
 - Rules of engagement with patients must be established to avoid misperceptions around conflict of interest and to ensure a methodology for consistent, scheduled and balanced input.
 - Patients should be informed of the results of their input as they often feel left out of the loop when they contribute time and effort to research programmes.
 - Patients will benefit from education regarding the inherent nature of uncertainty in benefit-risk decisions.
 - Successful patient input into the development, regulation and coverage of new medicines will be directly connected to the use of the most clinically relevant patient-reported outcomes as part of clinical trial design.
 - The value of patient input appears implicit, but needs to be demonstrated to a wider audience through further research and communication.

Section 3: Presentations

Prescription Drug User Fee Act Reauthorization (PDUFA) V

Dr Theresa Mullin

*Associate Director for Planning and Informatics,
FDA Center for Drug Evaluation and Research*

Continuous process improvement enabled by the Prescription Drug User Fee Act

In 1992, in response to public concerns regarding the timeliness of the review of medicines at the US Food and Drug Administration, the United States Congress enacted the first version of the Prescription Drug User Fee Act (PDUFA). As part of this legislation, the FDA was able to institute a fee-for-service programme and to receive public funding in exchange for an agreement to meet specific performance goals.

The financial support generated by this law made it possible for the FDA to increase the number of review staff and to eliminate the backlog of applications, thereby achieving a more predictable, streamlined process and improving timeliness. In fact, after PDUFA approval, average clinical development time decreased by 10% and the time to marketing approval was reduced by nearly 60%. Because of these PDUFA-funded improvements, patients

have gained earlier access to over 1,500 new drugs and biologics approved since 1992.

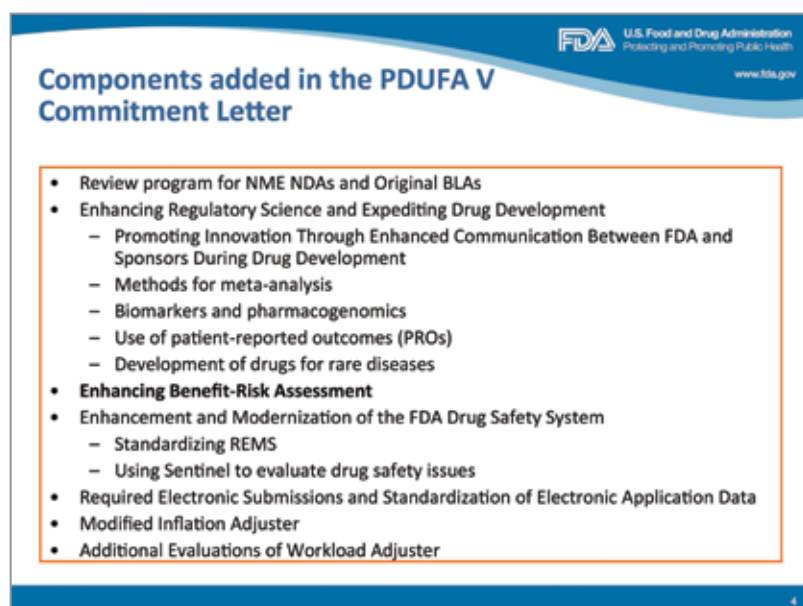
Subsequent iterations of PDUFA legislated over the past two decades have enabled additional developmental and review process improvements throughout the agency as well as enhancements in sponsor-agency interactions. In order to continue this important work, the FDA has recently engaged extensively with stakeholders to develop recommendations for PDUFA reauthorisation. These recommendations were proposed to the US Congress in January 2012 as part of PDUFA V, which is expected to pass into law before 30 September, when the current version of PDUFA is set to expire [Editor Note: PDUFA was re-authorised by Congress on 9 July 2012]. PDUFA currently provides annual fee revenues that support the review of new human medicines.

Among other components of PDUFA V (Figure 2) the FDA has committed to embark on a programme of improved regulatory science and expedited drug development and promoting innovation through enhanced communication with sponsors during the process of drug development. The agency has also pledged to expand its efforts in developing best practices in meta-analysis methodology and to increase its capacity to manage pharmacogenomics in clinical studies and in review packages including the review and qualification of biomarkers. The post-marketing drug safety system will also be enhanced at the FDA and initiatives related to standards for electronic data submission are expected to improve agency efficiency over time.

Benefit-risk in PDUFA V

An essential element of the commitments made by the FDA in PDUFA V is the enhancement of benefit-risk assessment at the agency. The FDA acknowledges that an important consideration in the evaluation of a medicine's potential benefits and harms is the context in which the decision is made, including an understanding of the condition treated and the unmet medical need. Accordingly, since a more systematic and open discussion with informed patients could provide valuable insight on a given disease and the potential gaps or limitations in available therapies, the FDA plans to conduct public meetings between review divisions and the relevant patient advocacy communities

Figure 2. FDA commitments in PDUFA V.



... a framework that accurately and concisely describes the benefit and risk considerations associated with medicines will help [FDA] reviewers apply a structured approach in regulatory decision making ...

to review the armamentarium for specific indications or disease states.

It is the FDA's position that a framework that accurately and concisely describes the benefit and risk considerations associated with medicines will help reviewers apply a structured approach in regulatory decision making (see page 26). Accordingly, during PDUFA V implementation, the agency will develop and implement a plan to integrate a benefit-risk framework into the drug review process; this process will be supported by two public workshops on benefit

and risk from the regulator's perspective. The first of these workshops will be primarily informational, focussing discussion on the various frameworks and methods available and their application to regulatory decision-making. The second workshop will centre on the results and lessons learned in implementing frameworks at regulatory agencies in the pre- and post-market drug review process.

Dr Mullin informed Workshop participants that the FDA will publish a five-year plan for public comment that describes their approach to implement a structured benefit-risk framework in the new drug approval process and will begin implementation of the plan during 2013, including a revision of review and decision memo templates. Finally, an evaluation plan will be developed to ascertain the impact of the benefit-risk framework in the drug review process.

A framework for benefit-risk decision making: An industry perspective

Dr Tim Garnett

Chief Medical Officer and Senior Vice President. Eli Lilly and Company

The expeditious and efficient delivery of innovative medicines to patients is a goal for stakeholders across the pharmaceutical industry. To achieve this goal, submission packages are required that clearly and succinctly communicate the benefit-risk profile of new molecules to each of the stakeholder groups, including regulators, clinicians, patients and payers as well as act as a common platform for benefit-risk assessment across multiple geographies. Once approved, the benefit-risk profile of medicines must be optimised through the design and delivery of effective benefit-risk management and communication programmes.

However, whilst benefit-risk assessments are at the core of development and regulatory decisions, decision-making in the current environment has predominantly been based on a system of expert judgement. As a result, a common, systematic and transparent framework and processes to support higher quality benefit-risk decision making that can be easily explained and communicated is lacking. Multiple initiatives have been developed over the past few years to

address this benefit-risk framework gap.

As discussed by Dr Mullin (p 18) benefit-risk assessment is a key component of PDUFA V. FDA commitments contained within the legislation include the hosting of informational workshops on the various frameworks and their application to regulatory decision making. The agency additionally plans to develop a plan to ascertain the impact of the implementation its approach and to assess how to better provide for the inclusion of the patient perspective into FDA decision making. The FDA has reported that they are using the assessment process being developed by the agency in a pilot programme using six applications for new molecular entities under review.

Similarly, the EMA has also committed to making its opinions on the balance of benefits and risks as consistent and transparent as possible and began a three-year project on benefit-risk methodology in early 2009. The project aimed to identify decision-making models that could be employed by the EMA to make the assessment of the benefits and risks of medicines more consistent, more transparent and easier to audit.

The project consists of five work packages, which include:

1. Describing the benefit-risk assessment models already being used in the European Union's regulatory network (Completed March 2010)
2. Assessing the suitability of the current tools and processes used in benefit-risk

assessments (Completed August 2010)

- 3. Field-testing the most appropriate models in five European medicine regulatory agencies (Completed June 2011)
- 4. Refining the most suitable models for use in medicines regulation to create a new benefit-risk tool (Completed February 2012)
- 5. Training European assessors to use the final tool (Started March 2012)

In addition to the FDA and EMA programmes, two other key initiatives are investigating the development of methodologies rooted in the common benefit-risk framework, the CIRS Consortium on Benefit-Risk Assessment (COBRA) and the Pharmaceutical Research and Manufacturers of America Benefit-Risk Assessment Team (PhRMA BRAT).

Each of the four approaches recognises that a structured and systematic process plays an essential and fundamental role in assisting and improving human decision making. They share a set of common principles that assist, supplement and enhance human judgement, because cognitive psychology has shown that approaches such as these assist but cannot replace, but enhance the complex process of translating data into useable evidence.

All methodologies express a consistent, coherent approach designed to assist rational thinking and judgement and provide a practical and transparent approach to benefit-risk decision making (Figure 3). Most methodologies are based on a qualitative approach rooted in

... a structured and systematic process plays an essential and fundamental role in assisting and improving human decision making.

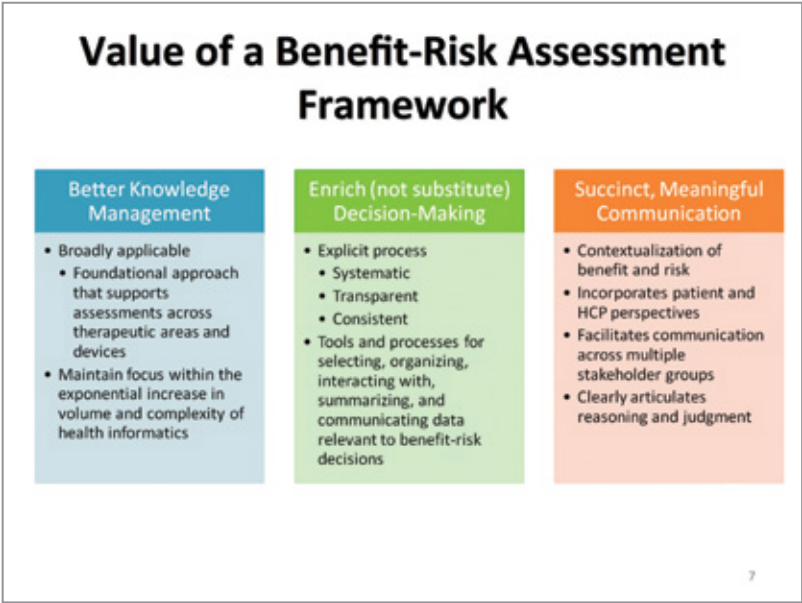
decision science. Their goal is not to drive toward a single, summary statistic, or to express a benefit-risk ratio, rather they reflect the reality that benefit-risk assessment is a qualitative exercise grounded in quantification of various data. In this way, they serve as decision tools that help to structure the evaluation, by addressing key considerations:

- Which benefits and risk were considered most relevant?
- What was the evidence? How was the evidence interpreted?
- How were the benefits and risks weighed or prioritised?
- What can be done to manage and mitigate the risks? What can be done to optimise the benefits?

In using these methodologies, decision makers frame the decision context through consideration of several critical issues: the population being treated, the severity of the indication, the current treatments for the condition and associated unmet medical need and the perspective from which the decision is being made. Methodology developers share the recognition that there must be an articulation of the importance of the benefit and risk criteria and rationale for that importance. Some of the models include embedded processes that assist with summarising, visualising and otherwise communicating the data considered most relevant to the benefit-risk decision. Importantly, the methods also highlight the need to specify the uncertainties surrounding the data used to make the assessment. Finally, each approach has the capacity to rigorously document decision making, which serves to help communicate the rationale of the decision.

As these multiple initiatives begin to coalesce around common themes, it is now opportune to collaborate to establish a common overarching decision-making framework. A forum to share implementation experiences and best practices would be especially useful and stakeholder input beyond industry and regulators must be sought, specifically identifying and reinforcing the perspective of the patient.

Figure 3. Benefit-risk frameworks assist and improve decision making.



Building the benefit-risk toolbox: An EMA perspective

Professor Hans-Georg Eichler

Senior Medical Officer, European Medicines Agency

Regulators are surrogate decision makers who are accountable to their stakeholders and who should respond to reasonable questions and criticism from patients, academics and payers. In recent years, such questions and criticisms have surrounded issues such as the comparative data on which EMA decisions are based, the inconsistency of those decisions with those made by other agencies and the lack of patient participation in their formation.

Advancing the construction of a benefit-risk decision "toolbox" should address some of these important concerns and improve accountability for example, through the development of a more auditable decision-making process. In addition, transparency, that is, the transformation of value judgements from implicit into explicit decisions, will be achieved and the predictability of decisions and their congruence with patients' values will be enhanced. Professor Eichler explained that although these improvements would not necessarily obviate criticism or debate, they would likely increase the value of such discourse. He quoted Dr Baruch Fischhoff, who said "We should not expect if we have better methodology that we would have fewer conflicts, no, but we will have better conflicts and we will increase the light-heat ratio in decision making."¹

Figure 4. The effects table is a simple qualitative benefit-risk tool.

Effects Table						
	Name	Description	Best	Worst	Units	Placebo 300 mg
Favourable Effects	Progression-free survival Ratio	Date of randomization to the date of objective progression or death (blinded independent review)	0	1	-	1
	Progression-free survival (median)	Date of randomization to the date of objective progression or death (Weibull model)	60	0	months	19.3
	Objective Response (RECIST)	Proportion of complete or partial responders (at least a 30% decrease in the sum of the longest diameter of target lesions compared to baseline)	100	0	%	13
	Overall survival	Proportion surviving at 2 years	100	80	%	83
Unfavourable Effects	Diarrhoea Grade 3-4	Increase of ≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living; Life-threatening consequences	0	100	%	2.0
	QTc events Grade 3-4	QTc > 0.50 second; life threatening signs or symptoms; Torsade de pointes	0	100	%	1.0
	Infections Grade 3-4	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated; Life threatening consequences	0	100	%	36.4

... a benefit-risk decision "toolbox" should address some of these important concerns and improve accountability for example, through the development of a more auditable decision-making process.

Because regulatory decisions often involve varying degrees of complexity, a toolbox rather than a single methodologic approach may be required for efficient decision making, with the use of the more complex methodologies such as multi-criteria decision analysis reserved for more intricate decisions. In addition, in an organisation that is resistant to change, it may be more expedient to implement smaller changes or "tools," gradually building to the use of more significant, complex benefit-risk methodologies. These tools will include qualitative models that can improve transparency, communication and consistency in the benefit-risk assessment of medicines and quantitative (decision-theory) models that can accommodate any form of data and help make explicit the assessors' judgments of clinical relevance.

Sensitivity and scenario analyses can explore different assumptions and sets of values in the use of quantitative models.² As appropriate methodologies are developed, adapted and adopted, decision makers will need to incorporate these value judgements and preferences into benefit-risk evaluations and it will become necessary to elicit the values of patients in addition to those of statisticians and scientists to avoid a disconnect between regulators and their primary customers.

Professor Eichler concluded that the implementation of a simple qualitative benefit-risk decision-making tool within agencies such as the EMA effects table (Figure 4) is key in order that regulators may explore and familiarise themselves with these tools before agreeing to the use of more complex models.

References

1. Fischhoff B. "Risk perception and communication." In Detels R, Beaglehole R, Lansang MA, Gulliford M (Eds), Oxford Textbook of Public Health, Fifth Edition:940-952. Oxford: Oxford University Press, 2009
2. Phillips L D, Fasolo B, Zafropoulos N., Beyer, A. Is quantitative benefit-risk modelling of drugs desirable or possible? *Drug Discov Today Technol.* 2011;8:e3-e10.

Benefit-risk framework: case study and forward plans

The consortium of four agencies

Dr Jason Ferla

Director, Prescription Medicines Clinical Unit 3,
Office of Medicines Authorisation, Therapeutic
Goods Administration, Australia

The COBRA framework

Although many regulatory agencies have instituted their own tailored approach for assessing the benefits and risks of new medicines, by 2009 no well-established, standardised models had yet been developed. Therefore, in April of that year CIRS and regulators from Australia's Therapeutic Goods Administration, Singapore's Health Sciences Authority, Health Canada and Swissmedic began an initiative to develop a unified qualitative approach to the benefit-risk assessment that could be used by these agencies to enhance their benefit-risk decision-making processes. These four mid-sized agencies, which together have become known as the Consortium for Benefit-Risk Assessment (COBRA), had previously enacted a series of bilateral agreements and had engaged in information sharing and pilot projects for joint or shared reviews that allowed them to share resources while maintaining independence.

It was envisioned that the implementation of a structured, standardised, systematic approach to benefit-risk assessment would facilitate further work and information sharing among the group. It was additionally hoped that such a framework would be flexible enough to accommodate the needs of all stakeholders while enhancing the predictability, transparency, accountability and usability of evaluations throughout a product's life cycle.

Using a qualitative or semi-quantitative approach, a template was developed by CIRS based on the CHMP guidance document of 2008.¹ The template, which includes consideration of uncertainties, is divided into two sections, the "pro forma" or comprehensive main section and the abbreviated Summary section.

The pro forma elements allow the reviewer to describe specific aspects of the medicine under review, including:

- Background
- Quality overall summary
 - Non clinical overall summary
 - Human pharmacology overall summary
 - Clinical overall summary
- Identified benefits and risks together with the main reason for inclusion or exclusion
- Benefits and risks – study information
- Benefit-risk summary table and expert judgement including weighting and valuing
- Benefit-risk conclusions

Using this template, the potential benefits and risks of a medicine can be listed and the rationale behind inclusion or exclusion of those parameters specified. The studies containing data supporting the medicine's benefits are described, including the population studied and the data's clinical and statistical significance, effect size and comparative efficacy versus placebo or other therapies. To evaluate risks of the medicine, the incidence of adverse events are catalogued along with their severity and association with treatment discontinuation. Throughout these evaluations, uncertainties that surround data are also carefully considered. Benefits and risks are then weighted simply through a subjective rank order or categorised as high, medium or low and then valued relative to a comparator or placebo.

Figure 5. The hypothetical benefits of a fictionalised medicine listed on the COBRA benefit-risk template.

				
Example: New cardiovascular medicine				
Benefits	Weighting	Valuing		
		Active	Comparator	Placebo
1. Reduction in the frequency of cardiovascular events	High	40%	20%	10%
2. Improved walking distance				
Strength and Uncertainty of each benefit				
Strength: Statistically and clinically significant. Uncertainty: Reduction in cardiovascular death not proven.				

Benefit risk framework development: CIRS Workshop June 2012

Example: New cardiovascular medicine

Risks	Weighting	Valuing			Strength and Uncertainty of each risk
		Active	Comparator	Placebo	
1. Increase in muscle disorders	Medium	20%	5%	2%	Strength: Statistically and clinically significant. Uncertainty: Limited short term data.
2. Increase in nausea					

Benefit risk framework development: CIRS Workshop June 2012

Figure 6. The hypothetical risks of a fictionalised medicine listed on the COBRA benefit-risk template.

Other benefit-risk considerations include the potential for harm from using and also abusing or misusing the product, the potential change of the benefit-risk balance over time and describing any outstanding issues or further studies that might reduce some of the uncertainties that have been identified. Paediatric development and pharmacovigilance and risk-management plans and options to communicate those plans must also be considered. The Consortium is additionally currently considering a methodology for incorporating the input of advisory committees and patient group and consumer groups into the template.

Hypothetical case study

Using the example of a hypothetical cardiovascular therapy, Dr Ferla demonstrated the use of the template, showing how benefits such as a reduction in cardiovascular events and improved walking distance might be weighted relative to each other and valued relative to other therapies or a placebo. The strength or uncertainty of the data supporting each benefit is also a significant part of the analysis (Figure 5). Similarly, risks were weighed, valued and evaluated relative to the uncertainty or strengths of the evidence (Figure 6).

... such a framework would be flexible enough to accommodate the needs of all stakeholders while enhancing the predictability, transparency, accountability and usability of evaluations throughout a product's life cycle.

This hypothetical case study highlighted the benefits and disadvantages that are associated with the use of the COBRA methodology. The structured nature of the process allows a shared approach among agencies in which the rationale and supporting documentation for benefits and risks are clearly listed. Access to an abbreviated Summary of the benefit-risk evaluation in addition to the more comprehensive pro forma can provide a tool to tailor the level of communication regarding agency decisions to different stakeholders according to their needs. The template also permits the systematic articulation of each benefit and risk as well as their weighting and provides consistency of comparison with other therapies to support regulatory decision making, enabling it as a tool for collaborative work across agencies. The case study also elucidated the template's value as both a platform for peer review discussion and a vehicle through which members of a therapeutic class can be compared. Finally, it allows the clear communication and visualisation of benefits and risks to various stakeholders.

Challenges for the approach exist, however, such as establishing the role the template will assume within the agencies; that is, whether it will replace or add to existing documentation. That role will in turn dictate whether the level of information included in the pro forma must be increased or decreased. Individual agency validation of the template, its incorporation into product life cycle management, the subjective nature of weighting and valuing and methods for optimal visualisation are issues that all remain to be resolved.

Forward plans

Having obtained permission from the sponsor to share data with CIRS, the Consortium recently applied the template in the retrospective benefit-risk evaluation of a dossier submitted to all four jurisdictions for a new indication for an approved medicine. Based on the results of this study, the group will consider any necessary modifications to the template prior to its next use which will be in a prospective evaluation of the benefits and risks of a dossier for a new medicine submitted to all four agencies.

Reference

1. Committee for Medicinal Products for Human Use. *Reflection paper on benefit-risk assessment methods in the context of the evaluation of marketing authorization applications of medical products for human use*. Found at http://www.emea.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500069634.pdf. Accessed November 2012.

EMA case study and forward plans

Dr Francesco Pignatti

Head, Section Oncology, Haematology and Diagnostics, Safety and Efficacy Sector, European Medicines Agency, London, UK

Based on a recommendation published by a working group of the Committee for Medicinal Products for Human Use¹, the European Medicines Agency initiated the Benefit-Risk Methodology Project in 2009 to “identify decision-making models that can be used in the Agency’s work, to make the assessment of the benefits and risks of medicines more consistent, more transparent and easier to audit.”² The project consists of five consecutive Work Packages. The first four Work Packages form a research phase that aims to develop and test tools and methods for balancing benefits and risks of medicinal products. The fifth Work Package is intended for training and initial implementation. The results of Work Package four were recently published³ and the last Work Package was begun in March 2012.

As part of Work Package three, five regulatory agencies participated in field testing the most appropriate methods. The field tests were performed in the context of a facilitated workshop with the generic decision framework ProACT-URL (problems, objective, alternatives, consequences, trade-offs, uncertainties, risk tolerance and linked decisions) supporting the

decision process. A table of the main criteria, the Effects Table, was created that provided criteria definitions, the clinical trial data, the units as well as upper and lower limits of the scoring scales. Specialised software for Multi Criteria Decision Analysis (MCDA) was used to incorporate linear and non-linear value functions, provide extensive sensitivity analysis and generate graphical displays to support the representation of the final results. Dr Pignatti presented a case study of the use of this methodology in the evaluation of vandetanib for medullary thyroid cancer (MTC).

Problem

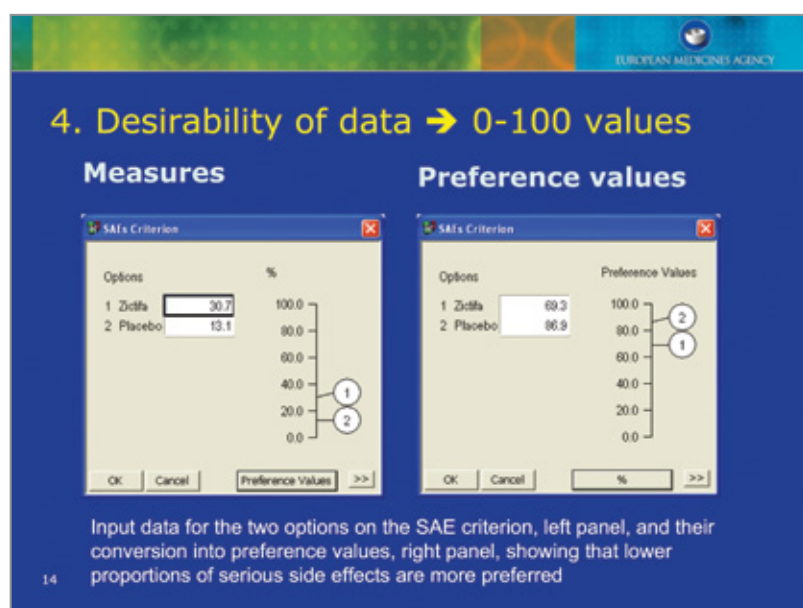
Vandetanib (Caprelsa, Zictifa) was submitted for approval for treatment of medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease, which represents approximately 2.5% to 10% of thyroid cancers. Although MTC is associated with a five-year survival rate of 78%, surgery is the only option for progressive disease, which is unresponsive to conventional doses of radiation therapy or chemotherapeutic regimens.

The phase 3 randomised, placebo-controlled trial of vandetanib resulted in a statistically significant, 20% difference in the number of events for progression-free survival (PFS), the primary endpoint. The clinical significance, however, of PFS can be controversial and an evaluation of results for the secondary endpoint of overall survival revealed little or no difference between the placebo and vandetanib treatment arms. The most commonly reported adverse drug reactions in the trial were diarrhoea, rash, nausea, hypertension and headache. Substantial and concentration-dependent prolongation in QTc (mean 28 msec, median 35 msec) also occurred. QTc prolongation particularly increased in patients with hypertension (20%), diarrhoea (>20%), serum Mg less than the lower limit of normal (31.3%) and with baseline cardiac impairment (32.1%).

Objectives

An Effects Tree was created to graphically present the most important favourable and unfavourable treatment effects. Favourable effects included progression-free and overall survival, overall response and duration of response. Unfavourable effects were general adverse events, QTc prolongation and treatment-related deaths. The dynamic nature of the model was critical to the evaluation as the relative importance of these effects changed throughout the assessment process.

Figure 7. Clinical trial data were converted into preference values.



Alternatives

Vandetanib is an orally administered tyrosine kinase inhibitor with activity against the rearranged during transfection (RET) proto-oncogene, the vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR). As there was no alternative treatment for MTC, the comparator treatment in the clinical trial was placebo.

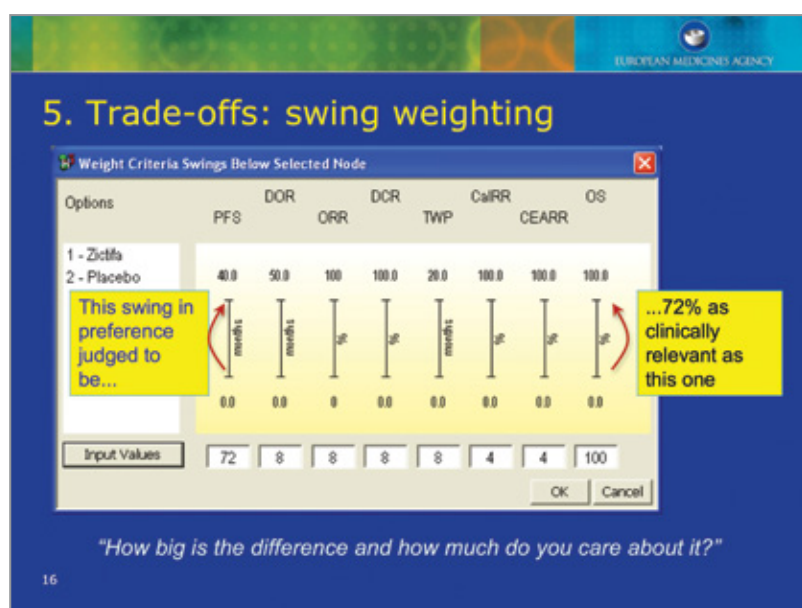
Consequences

The values from the trial data were displayed in an Effects Table that showed the range of favourable and unfavourable effects for vandetanib relative to those associated with placebo. The range of data for each effect was translated into preference scales (Figure 7). One of the assets of the methodology tested is its ability to allow the use of linear and non-linear value functions. In this case, a non-linear value function was considered appropriate as the potential occurrence of more than one percent of treatment-related deaths resulted in an exponential decrease in the preference value of the treatment.

Tradeoffs

The relative value of treatment effects was determined through iterative discussion among the evaluators regarding the size of each effect and its importance. For example, a 40-month gain in PFS was judged to be 72% as clinically relevant as a 0% to 100% difference in percentage of patients surviving at two years (Figure 8). In this model, the value of all favourable and unfavourable effects can be

Figure 8. The relative value of treatment effects was determined through iterative discussion.



cumulatively calculated and various visual displays can be created to show the relationship of safety and efficacy toward each other as well as toward other therapies.

Uncertainty

A sensitivity analysis allowed an exploration of the uncertainties in weighting and valuing the treatment effects. For example, the total weight given to the unfavourable effects associated with vandetanib was 40. A sensitivity analysis showed that if that weight were raised to 50, the balance would still be in favour of the drug over placebo. If the weight was over 50, however, the balance would shift in favour of the placebo.

Risk tolerance

Vandetanib was granted conditional marketing authorisation, with the indication restricted to patients who are in urgent need of treatment for symptomatic and progressive MTC. That is, the risk associated with vandetanib treatment was acceptable to patients in whom the disease was currently progressing and for whom no other treatment options existed. In addition, the granted indication specified that patients could not test positive for a particular gene mutation for which the medicine's effectiveness was not conclusively demonstrated.

Dr Pignatti explained that this modelling exercise for vandetanib was constructed for a general population and that if it were to be reconstructed in this restricted population the benefit-risk ratio would be likely to favour vandetanib to a greater degree.

Linked decisions

Although this was the first drug approved for MTC, the effects table (p 21), which clearly describes the criteria used to judge the therapy's efficacy and safety could be used for comparison and consistency in the evaluation of future drugs.

Lessons learned and forward plans

Data from questionnaires completed by assessors before and after the exercise were favourable for the model.⁴ Respondents indicated that the approach:

- Can easily test different perspectives for their impact on the results
- Helps to see the impact of uncertainties on the benefit-risk balance
- Has an overt and clear structure
- Helps combine data about value and

Because MCDA modelling requires substantial training and resources, its implementation across the EU regulatory network poses some practical challenges. The use of the effects table (page 21) is considered the logical first step in integrating a benefit-risk methodology within the drug evaluation process.

uncertainty into an overall balance between favourable and unfavourable events

- Helps make assumptions, multiple objectives and trade-offs explicit

Although the value of more quantitative models based on MCDA may lie in their ability to accommodate the perspective of multiple stakeholders, they may be best reserved for more complex decisions requiring even greater precision. Because MCDA modelling requires substantial training and resources, its implementation across the EU regulatory network poses some practical challenges. The use of the effects table (page 21) is considered the logical first step in integrating

a benefit-risk methodology within the drug evaluation process. This simple tool can be expanded to accommodate the evidence from multiple studies, to include risk management solutions or to focus on benefit optimisation in specific subpopulations as well as improve the transparency and consistency regulatory decision making.

References

1. Committee for Medicinal Products for Human Use. *Reflection paper on benefit-risk assessment methods in the context of the evaluation of marketing authorization applications of medical products for human use*. Found at http://www.emea.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500069634.pdf. Accessed November 2012.
2. European Medicines Agency. *Benefit-risk methodology*. Found at http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000314.jsp&mid=WC0b01ac0580223ed6. Accessed August 2012.
3. The Benefit-Risk Methodology Project Team. *Work package four report: Benefit-risk tools and processes*. Found at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/03/WC500123819.pdf. Accessed August 2012.
4. Phillips LD, Fasolo B, Zafiropoulos N, Beyer A. Is quantitative benefit-risk modelling of drugs desirable or possible? *Drug Discov Today Technol*. 2011;8:e3-e10.

The CDER benefit-risk framework

Patrick Frey

Director, Office of Planning and Analysis (OPA), FDA/Center for Drug Evaluation and Research (CDER)

Rationale for a benefit-risk framework

In 2009, the Center for Drug Evaluation and Research (CDER) at the US Food and Drug Administration (FDA) identified the need for a more structured benefit-risk assessment in the review process. The rationale behind this need was twofold. First, it is believed that a structured process could better communicate the reasoning behind CDER decisions, advising stakeholders which benefits, risks and other factors are considered; how evidence is interpreted and which methodology is used to weigh risks and benefits. Second, it is the CDER position that a structured approach would ensure that the “big picture” is kept in mind during a complex, detailed review. Therefore, this effort was initiated and has continued with the support of internal and external decision science and drug regulatory experts.

It was understood within CDER that the approach would need to achieve a balance between expert judgement and quantitative analysis. Although formal quantitative methods were considered, it was believed that reducing complex considerations into a single scale could not capture the nuanced assessments in FDA decisions and that quantitative analysis risked obscuring subjective expert judgement. Accordingly, it was determined that a structured qualitative approach best fitted the agency's needs. This approach reflects the reality that benefit-risk assessment is a qualitative exercise grounded in the quantification of various data and is flexible to accommodate more complex supporting quantitative analyses that can aid, rather than replace, expert judgement. Additionally, the qualitative approach permits the rigorous communication of the basis for decisions in words.

Development of the approach

The key goals and design principles envisioned for the FDA's “framework” centred on its ability to provide support for review staff and signatory authorities. Specifically, it was believed that the approach would facilitate identification of critical issues regarding a product's benefits and risks, faithfully capture the review team's

careful deliberations and represent expert views transparently while ensuring that the benefit-risk balance is kept in mind throughout the review. In addition, the model would recognise the dynamic nature of benefit-risk assessment over a product life cycle and efficiently align with a review team's existing processes. Importantly, the model would provide an internal communication vehicle between the review team and the signatory authority and assist in communications about the decision.

CDER developed and tested a conceptual model exploring six case studies of past regulatory decisions to understand the range of benefits and risks that were considered. They conducted one-on-one interviews of key reviewers in different disciplines, determining the relevant issues that surrounded each decision. The draft model was tested in more recent regulatory decisions and explored two additional case studies using a focus group process, incorporating all resulting revisions into the model. In recognition that effective decision support must begin with an understanding of how decision makers think, the overall development process was guided by senior management at the Offices of New Drugs, Surveillance and Epidemiology and Biostatistics.

The model is structured as a table (Figure 9) for the input of information regarding five decision factors for a new medicine. The first two rows concern the therapeutic area to be treated by the drug under evaluation. The entry of information into these rows regarding the condition and the currently unmet medical need provides clinical

... a structured process could better . . . [advise] stakeholders which benefits, risks and other factors should be considered; how evidence is interpreted and which methodology is used to weigh risks and benefits.

context for evaluating a medicine's benefits and risks. The last three rows are to enter product-specific information about the medicine's benefits and risks and the risk management plan that has been proposed. This information allows the reviewer to assess potential benefits and harms to a population and to judge the expected impact of risk management to reduce or further characterise safety concerns. The columns organise the evidence and uncertainties for each of these five decision factors and the conclusions based on the evidence. The final row of the table is to provide a summary of the benefit-risk analysis and the resulting decision.

CDER also developed a series of instructions and questions for each of the five decision factors for consideration by the review team. These instructions and questions are designed to elicit the information required to complete the benefit-risk evaluation.

Analysis of Condition

- Describe the condition that is treated or prevented by the drug.
- What are the clinical manifestations of the condition, what is known about its natural history and how does severity vary across sub-populations?

Unmet Medical Need

- Describe the other therapies used to treat the condition, including approved and off-label pharmacological therapies and non-pharmacological therapies.
- How effective and how well-tolerated are these alternatives and what evidence is available to support these conclusions?

Benefit

- Describe the trials (including strengths and weaknesses) that were conducted to establish efficacy.
- What endpoints were evaluated and how are they clinically meaningful? How did the benefits vary across sub-populations of responders?

Figure 9. The FDA Benefit-Risk Framework is constructed as a table.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Summary of evidence:	Conclusions (implications for decision):
Unmet Medical Need	Summary of evidence:	Conclusions (implications for decision):
Benefit	Summary of evidence:	Conclusions (implications for decision):
Risk	Summary of evidence:	Conclusions (implications for decision):
Risk Management	Summary of evidence:	Conclusions (implications for decision):
Benefit-Risk Summary and Assessment		

Risk

- Characterise the safety concerns identified in the clinical trials. What was the incidence of the risk in the study population and does the incidence vary by sub-population? Is there a range in the severity of the risk, does it change with continued exposure and is it reversible when treatment is stopped?
- How might the incidence change in the post-market setting? Is additional work needed to further characterise the risk?

Risk Management

- Which risks (if any) require mitigation or further characterisation? What tools are recommended to address the risks and what is the expected contribution of each tool to the overall risk management plan.
- What would constitute a successful risk management plan, how that might be measured, and if the desired impact is not achieved at what point should the risk management plan be re-evaluated?

Ongoing work and future plans

A pilot is ongoing within six different divisions of the Office of New Drugs with the key goal of the further refinement and improvement of

the framework to increase its utility and value to reviewers and signatory authorities. The implementation of the model into the CDER review process is also being explored including such issues as the alignment of the model with current processes and the identity of the responsible party. As mentioned by Dr Mullin (p 18) the enhancement of benefit-risk evaluation at the FDA represents a significant aspect of the agency's commitments proposed for PDUFA V.

The FDA's benefit-risk model now in development is a key feature of that enhancement. It provides a high-level snapshot as well as a concise bottom-line description of the issues relevant to a regulatory decision. It is sufficiently flexible to accommodate a wide range of considerations through a question-based approach within a standard structure. Additionally, it facilitates greater explicitness of the issues identified in a review and discussion of what is of most importance in regulatory decisions. Finally, it clearly articulates the clinical reasoning and judgement behind regulatory decisions, which ultimately can improve transparency in the decision-making process.

Company case study using the BRAT methodology

Dr Filip Mussen

Head, Global Labelling Center of Excellence, Janssen Research and Development, Belgium

Background

From an industry perspective, there are several key advantages to using a structured benefit-risk approach in the development of a new medicine. Constructing a value tree to identify key benefit and risk attributes before phase 3 can enhance the developmental

focus for the product and act as an excellent vehicle to promote prospective dialogue between companies and health authorities. This ongoing communication may anticipate regulatory hurdles and foster the creation of a better informed phase 3 programme, with a positive impact on product labelling and risk management plans. In addition, use of framework-based models may ultimately assist sponsors in the use of appropriate benefit-risk tools in the Clinical Overview section of the dossier and in the development of a better articulated and communicated benefit-risk profile.

From the point of view of a regulatory authority, the use of appropriate benefit-risk tools in regulatory evaluations and assessment reports can result in the development of clear and coherent benefit-risk profiles that facilitate the decision-making process. Furthermore, the use of these tools in agency presentations and discussions such as advisory committees

... the use of these tools in agency presentations and discussions such as advisory committees permits the comprehensive and transparent communication of the benefits and risks of a medicine ...

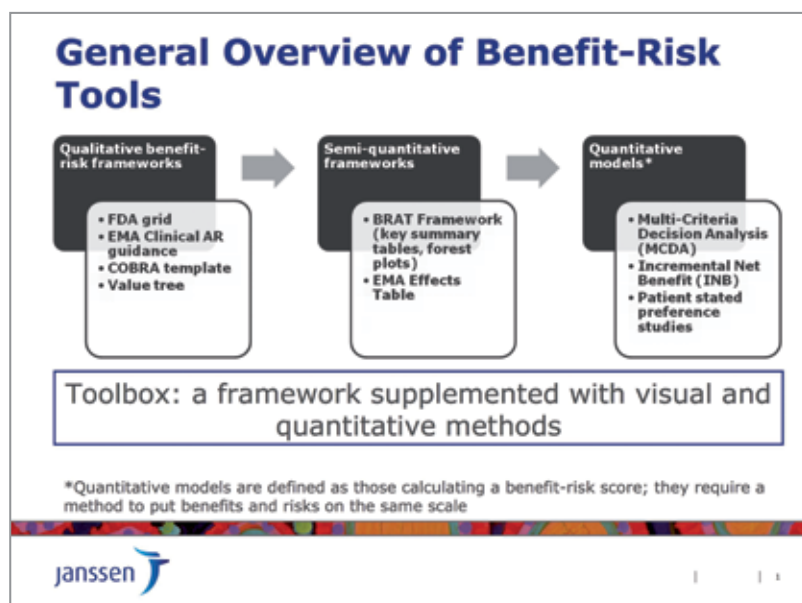


Figure 10. A toolbox of approaches may prove most useful in benefit-risk evaluations.

permits the comprehensive and transparent communication of the benefits and risks of a medicine and paves the way to a more systematic consideration of all relevant benefit and risk attributes by decision makers.

The benefit-risk tools that have been developed to date range from the qualitative examples from the US FDA and COBRA; semi-quantitative models such as the BRAT framework and the EMA effects table; and quantitative examples such as multi-criteria decision analysis (MCDA) and the incremental net benefit and patient-stated preference models. All of these approaches have certain common features defined by a common framework: it is first necessary to establish the decision context, to select and define the benefit and risk outcomes and metrics and then to quantify efficacy and safety outcomes. All of the methods are also challenged by the incorporation of uncertainty and values into assessments. Because it is imperative that evaluators are comfortable with the methods of analysis used, a toolbox of qualitative approaches supplemented with visual and quantitative methods may prove most useful in benefit-risk evaluation (Figure 10).

Use of relatively simple visual tools such as forest plots in benefit-risk evaluation, which were

developed for this use by the Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team (PhRMA BRAT), can make a significant impact by helping the sponsor to better understand and articulate all aspects of the benefit-risk evaluation, while also assisting decision makers in their deliberations. However, challenges remain. There are currently no common set of terms or definitions, no agreed methodology for capturing values and no appropriate methodology to capture non-statistical uncertainty such as gaps in efficacy and safety data or in the level of evidence.

Possible methods for establishing the value or weight of benefits and risks have been suggested such as the ranking process used in the rivaroxaban exercise, zero-one rating (in which a component is either included in evaluation or not), categorical weighting, point allocation, preference weighting, swing weighting, health utilities and conjoint analysis. Issues surround the use of these techniques; for example, the use of refined weighting scales can be controversial as they may provide a false sense of accuracy. Furthermore, healthcare stakeholders continue to question whose values should be captured.

Conclusions and a path forward

Quantitative or semi-quantitative methods seem appropriate for most benefit-risk decisions, add rigour and transparency to the decision-making process and can be easily used, especially in regulatory settings such as FDA Advisory Committee meetings. However, a common set of principles, standards and a toolbox of methods are still required. Progress is being made by such organisation as the EMA, the US FDA and CIRS and although further discussion, application and piloting of benefit-risk methodology are still required, eventually, a common and global benefit-risk toolbox should emerge.

Update on IMI PROTECT Work Package 5

Dr Diana Hughes

Vice President, Worldwide Safety Strategy, Primary Care Business Unit Lead, Pfizer Inc, USA

The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) project is the collaboration of 33 international partners including academic, regulators and industry members, aiming to "improve and strengthen the monitoring of the benefit-risk of medicines marketed in the EU."¹ PROTECT is coordinated by the European Medicines Agency (EMA) and funded through the Innovative Medicine Initiative (IMI) "Europe's largest public-private partnership aiming to improve the drug development process by supporting a more efficient discovery and development of better and safer medicines for patients."²

Planned output for PROTECT consists of seven Work Packages, one for the project's organisation and management, four targeting specific objectives and methodologic developments and two concerned with the communication, validation and integration of the scientific work into an integrated and cohesive European activity. Dr Hughes' provided a status update for Work Package 5 (WP 5), a public/private partnership formed to develop methods for benefit-risk assessment including both the

underpinning modelling and the presentation of results.

In furtherance of this goal, members of WP 5 tested key methods currently being used in benefit-risk assessment via a case study approach and reviewed the graphic or visual representations that could be used in presenting benefit-risk information. Taking the perspectives of regulators, patients and prescribers, case studies of some complexity were deliberately selected to further stretch the capabilities of the methodologies and visual representations. A systematic review of the literature on benefit-risk approaches in medicine was combined with member experience and information drawn from other parallel initiatives. Elements of the methods that were evaluated included their Principles, Features, Accessibility and Visualisation. Cost-effectiveness and other health technology assessment issues were not considered. Methodological approach classifications included metric indices, estimation techniques and utility survey techniques.

Thirteen methodologies and linked graphic representations were tested in the first wave of case studies of Raptiva (efalizumab; Genentech/Merck Serono); Tysabri (natalizumab; Biogen Idec/Elan Pharmaceuticals); Ketek (telitromycin; sanofi aventis) and Acomplia (rimonabant; sanofi aventis; Figure 11).

Raptiva (efalizumab) is a drug approved for the treatment of psoriasis in 2004 and withdrawn from the market due to concerns regarding progressive multifocal leukoencephalopathy (PML). Four different methodologies for benefit-risk assessment were evaluated using the Raptiva case study, including PROACT-URL. As discussed by Dr Pignatti (page 24) PROACT-URL is a generic benefit-risk framework that serves to structure the evaluation by outlining the Problem, Objective, Alternative, Consequences, Tradeoff, Uncertainty, Risk tolerance and Linked Decisions. In this assessment, evaluators used the methodology to create a value tree and effects table comparing benefits and risks of Raptiva with placebo. Favourable effects were input based on the scales used in clinical trials and patient ratings and the unfavourable effects were based on the results of clinical trials and post-marketing observational data.

In addition to PROACT-URL, the methodology developed by the Benefit-Risk Action Team (BRAT) as discussed by Dr Mussen (page 18) was used to create a graphic representation of the benefits and risks associated with Raptiva in the form of a forest plot. Additionally, multi-criteria

Figure 11. Work Package 5 members tested 13 methodologies for evaluating benefit-risk using a case study approach.

PROTECT				
Wave 1 Case studies: Methodologies				
	Acomplia	Ketek	Raptiva	Tysabri
PROACT-URL	✓	✓	✓	✓
BRAT	✓	✓	✓	✓
MCDA	✓	✓	✓	✓
SMAA	✓	✓		
NNT & NNH	✓			✓
Impact Number	✓			
QALY				
Q-TWIST				
INHB	✓			
BRR	✓	✓	✓	✓
PSM	✓	✓		✓
MTC				✓
DCE				
Other:	Direct utility elicitation	SBRAM, Swing-weighting	Decision conferencing	Decision conferencing

16

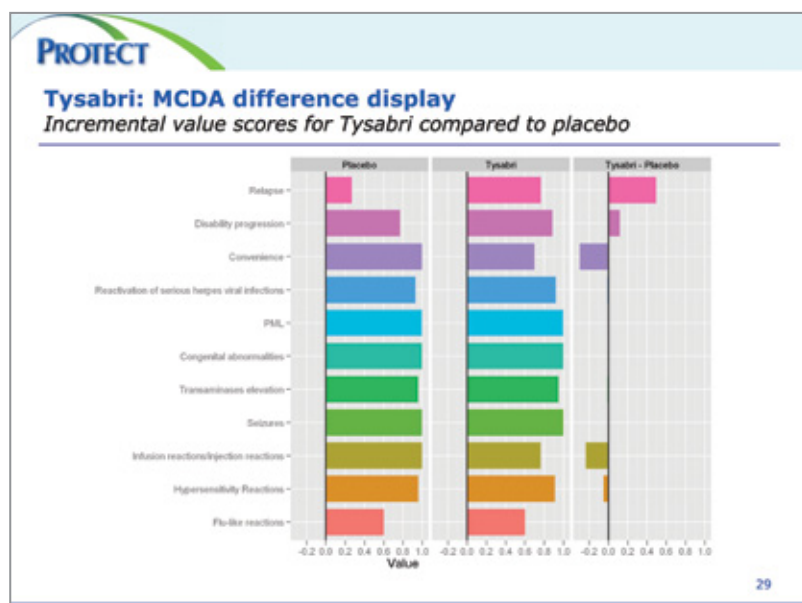


Figure 12. Multi-criteria decision analysis graphically showed that Tysabri's effects on prevention of the relapse of multiple sclerosis was the most important parameter in its benefit-risk assessment.

decision analysis (MCDA) was utilised to derive swing weighting and value functioning and to visually display the contribution of the benefit and risk parameters to the overall ratio for Raptiva.

Tysabri (natalizumab) was approved for relapsing remitting multiple sclerosis in 2004, withdrawn from the market in 2005 because of concerns regarding progressive multifocal leukoencephalopathy and subsequently reintroduced because of patient demand in 2006. The Committee for Medicinal products for Human Use (CHMP) reassessed the PML risk associated with Tysabri in 2009 and continued its approval. The Work Package 5 team evaluated eight methodologies for benefit-risk assessment using the case study of Tysabri, including MCDA.

Using MCDA it was possible to graphically depict through bar and waterfall charts and tornado diagrams, the contribution of selected outcomes for determining the benefits and risks of Tysabri compared with placebo as well as the degree of uncertainty surrounding the evaluation. Results showed that Tysabri's effects on preventing relapse exerted the most influence on the benefit-risk assessment for the medicine.

Ketek (telithromycin) was approved for community-acquired pneumonia, acute exacerbation of chronic bronchitis, acute

bacterial sinusitis and tonsillitis/pharyngitis in 2001. Despite concerns regarding potential cardiac syncope and liver failure restrictions that resulted in warnings and restrictions for Ketek in 2007, licensing for the medication was renewed in 2011. Five methodologies were evaluated by the Work Package 5 team using Ketek as a case study, including Stochastic Multi-attribute Acceptability Analysis (SMAA). SMAA extends the use of MCDA when there are uncertainties regarding the performances of a medicine against selected criteria or when there are diversified opinions on the choices of weights. To accommodate uncertainties, probabilities for distribution of data can be used instead of discrete data points.

Acomplia (rimonabant) was approved for weight loss in obese and overweight adults with co-morbidities in 2006. It was voluntarily withdrawn from the market in 2009 because of concerns regarding the increased risk of anxiety and depression associated with its use. Nine methodologies were evaluated using Acomplia as a case study. Among them, Population Impact Numbers of Eliminating a Risk Factor over 1 Year (PIN-ER-1) allowed the graphic demonstration of the fact that approximately 3.2 million people in England and Wales could achieve 10% weight loss at one year with Acomplia, whilst approximately 463,000 would experience anxiety. These numbers could then be assessed over a range of value preferences of benefit to risk.

Conclusions and next steps

Methods such as those evaluated by the members of Work Package 5 are important to govern the benefit-risk assessment process and to ensure transparency, but benefits and risks need to be on common scales to be evaluated against one another. Furthermore, stakeholder value preferences may influence the benefit-risk assessments reached through these methodologies and the incorporation of uncertainties remains a necessary component. Finally, it must be recognised that benefit-risk approaches can only act as tools for decision-makers whose expert judgement is ultimately required.

A summary report is being developed by members of Work Package 5 that draws together and critically appraises the methodologies and a second wave of studies with a strong focus on visualisation methods has been initiated.

... stakeholder value preferences may influence the benefit-risk assessments reached through these methodologies and the incorporation of uncertainties remains a necessary component

References

1. *The Pharmacoeconomic Research on Outcomes of Therapeutics by a European Consortium*. Found at <http://www.imi-protect.eu/index.html>. Accessed August 2012.
2. *The Innovative Medicines Initiative*. Found at <http://www.imi.europa.eu/>. Accessed August 2012.

How and when should patients be involved in making benefit-risk decisions?

Jean Mossman

Policy Lead, European Federation of Neurological Associations

Because medicines are not developed for regulators, health economists or even the prescribers, but rather for patients who require treatment for illness, patient input should be solicited when a new compound is discovered and throughout its development and use. Discovering what patients hope to achieve from a treatment for their illness and what problems they are willing to tolerate to achieve benefits can help inform registrational trials. Furthermore, patient perspectives should be incorporated into national reimbursement decisions and even into clinician prescribing practice guidelines (Figure 13).

People who have been newly diagnosed with an illness are faced with a maze of treatment options and uncertain outcomes and need support, particularly in the interpretation of the benefits, risks and uncertainties of treatment and of non-treatment. Having an illness is not a straightforward proposition but is fraught with many and varied risks, all of which may influence patient decision making. In addition to the risk of adverse effects from medication these

risks include the risk of not getting the correct diagnosis or of not getting a diagnosis in a timely manner; the risk of not getting treatment, of not getting treatment from an expert or even of getting the wrong treatment. Moreover, the benefits and risks of multiple medicines considered singly and in interaction with one another add additional complexity for patients with comorbidities as well as for the regulators and prescribers of their medicines.

Regulators have been surprised by the degree of risk that some patients are willing to assume. Tysabri (natalizumab; Biogen Idec; Elan Pharmaceuticals) is the treatment for multiple sclerosis that was withdrawn from the market due to safety concerns only to be reintroduced as a result of a reanalysis of its role in therapy spurred by patient demand. In discussing Tysabri, Dr Ian Hudson of the UK Committee for Medicinal products for Human Use (CHMP) said "The level of risk patients were prepared to take was quite illuminating. It may be that patients' acceptance of risk is higher than the regulators and when you look at individual patients' situations you might understand it."

Patients themselves have spoken out about their willingness to accept risk to achieve the benefit of survival. Professor Albert Jovell, who runs the Spanish Patients Forum, has been living with metastatic cancer for four years. It is his view that "safety is the concern of consumers not patients ... [as a patient he is] "living in an unsafe place and a little more unsafeness doesn't matter to me. What does matter is I want to see my kids grow up."

From the patient perspective, benefits frequently may be multifactorial. Ms Mossman's cited the personal example of the positive effects that medical treatment for metastatic colorectal cancer provided her own husband. Although he eventually succumbed to the disease, his treatment resulted in a period of progression-free survival that allowed he and his family to experience enhanced quality of life.

However, it is often questionable as to whether all patients fully understand the risks that may be associated with treatment. These risks may be presented to them using highly variable or technical terminology such as relative risk, absolute risk or hazard ratio, whose obscure meaning serves to exclude patient participation in decision making. Using sophisticated methods of graphic presentation such as forest or waterfall plots or Kaplan Meier curves may confuse rather than elucidate (Figure 14)

Figure 13. Patient input should be solicited throughout the life cycle of medicine development.

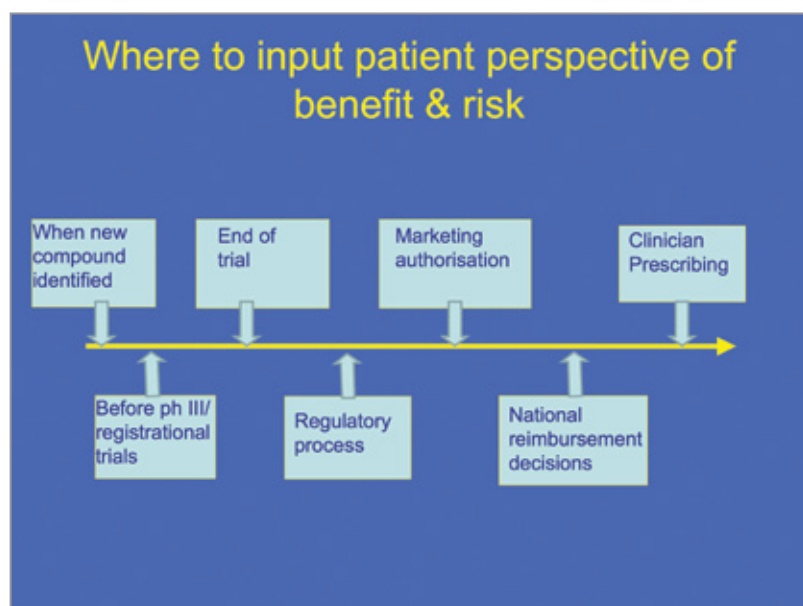




Figure 14. The many methods of graphically representing benefit-risk may be confusing to patients.

options. Patient decisions can also be influenced by the manner in which benefits and risks are presented; that is, being informed of the treatment's effect on the likelihood of living versus the likelihood of dying.

Patients also run the risk of not taking the treatment as scheduled. In fact, for a variety of reasons, patients often do not take medicines as prescribed. For example, they may have many competing priorities in their lives that might interfere with drug schedules or they may want to minimise the amount of drugs they take. The list of unwanted effects or unclear instructions may deter them from taking the medicine or the cost of medicines may make them pick only some from a range of prescribed drugs.

Treatment non-adherence is prevalent even among patients with life-threatening conditions. Feng and colleagues reported that approximately 30% of patients interrupted treatment for at least 30 days in their first year of imatinib treatment.¹ Member of the European Parliament, Linda McAvan detailed the results of noncompliance in treatment: "In the EU alone, 194,500 deaths each year are due to misdose of and non-adherence to prescribed medication. Poor adherence carries a huge cost, both in terms of patient safety and quality of life. It also

presents a serious problem for health systems, both in terms of inferior health outcomes, unnecessary treatments and hospitalisations".² With these costs in mind, industry, regulators and clinicians should work harder to help patients understand the potential benefits and risk and short- and long-term implications of taking – or not taking medicines.

Working to increase the transparency and comprehension of benefit and risk information and engaging patients throughout the development of new medicines may produce benefits for multiple stakeholders: the regulatory process may be more straightforward, HTA activities may be more relevant and the patients will get the benefit that they need with the risk they understand.

References

1. Feng W, Henk H, Thomas S et al. Compliance and persistency with imatinib. *J Clin Oncol Ann ASCO Proc*.2006; 24s:6038.
2. McAvan L. 21st September lunch debate at the EU Parliament on 'Medical Adherence' Available at http://www.cpme.be/news_eunews.php?id=1193. Accessed September 2012.

Working to increase the transparency and comprehension of benefit and risk information and engaging patients throughout the development of new medicines may produce benefits for multiple stakeholders ...

How and when should patients be involved in benefit-risk decisions:

A US patient perspective

Dr Lucie Bruijn

Chief Scientist, ALS Association, USA

Amyotrophic Lateral Sclerosis (ALS) affects 30,000 Americans and worldwide two out of 100,000 people are afflicted with this disease. Only 5 to 10% of cases are familial in origin and for the majority of patients, ALS is sporadic. Onset and progression are variable, but the hallmarks of denervation and atrophy of muscle due to loss of spinal motor neurons, usually beginning focally with degeneration of upper motor neurons causing spasticity are characteristic. Most patients die within two to five years of diagnosis and those with familial ALS may succumb within six months.

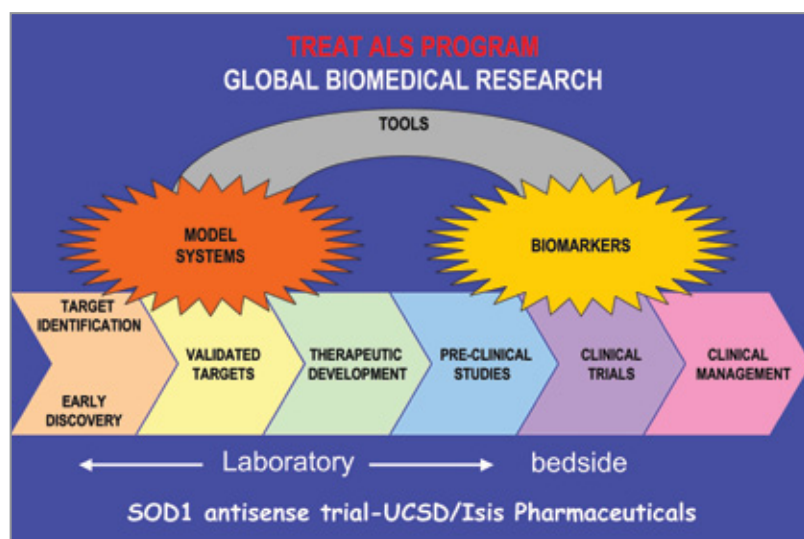
The work of the ALS Association is divided into research, public policy and care services, with patients at the centre. Although the Association has a limited budget, it works closely with the government and others to drive research, from the identification of appropriate research targets, through preclinical and clinical trials (Figure 15).

Major strides have taken place in ALS research in recent years, resulting in an improved understanding of the disease and its care. One drug, riluzole (Rilutek; Sanofi) has been approved and has been shown to increase survival by approximately two months in some patients;

many others are in the development pipeline. In particular, phase 2 trials with pramipexole, which is marketed as Mirapex for the treatment of Parkinson's disease (Boehringer Ingelheim), have shown promising results. Other ongoing ALS research includes phase 1 stem cell trials, in which stem cells are injected to replace motor neurons or surrounding cells and the injection of anti-sense molecules to down-regulate production of the main gene responsible for ALS. Because of the dire prognosis associated with ALS, however, patients are eager for immediate access to potential treatments and developing clinical trials with valid control groups can be challenging.

The Association has also played a role in building a national disease registry and supports a network of clinical centres throughout the United States that has been proactive in standardising and improving clinical trial enrolment. The Association liaises early and often in the preclinical trial process with patients as well as with the US Food and Drug Administration to help develop much needed safe, controlled and meaningful research. This is particularly critical in a disease such as ALS whose diagnosis may cause many patients to accept risks that may be out of proportion to any benefit they may receive. In addition to developing research, the Association's Clinical Research Learning Program provides patients with necessary background information concerning clinical trials, helping to ameliorate concerns that the benefits of certain treatments and study results may be over-interpreted. The patient's role in helping to develop novel ALS therapies through the work of the ALS Association can serve as a model for other disease areas.

Figure 15. The ALS Association plays a central role in developing new therapies.



... safe, controlled and meaningful research. ... is particularly critical in a disease such as ALS whose diagnosis may cause many patients to accept risks that may be out of proportion to any benefit they may receive.

How and when to involve patients in benefit-risk decision making:

An industry perspective

Dr Diana Hughes

Vice President, Worldwide Safety Strategy, Primary Care Business Unit Lead, Pfizer Inc, USA

Why, when and how to involve patients

In the development, review and reimbursement of a new medicine, eliciting the perspective of patients who will be using that medicine is integral to its value proposition. Patient input may help determine the benefit-risk balance for individuals rather than entire populations and may impact eventual adherence to medicines, which is critical for their safe and effective use.

Individually and as part of organisations, industry, regulators and HTA assessors recognise the need to establish validated methodologies for the benefit-risk evaluation of medicines. Accordingly, methods have been developed by the US FDA, the EMA, the Consortium for Benefit-Risk Assessment (COBRA) and the Pharmaceutical Research and Manufacturers of America BRAT (now being developed under the CIRS UMBRA initiative; page 3). Each of these approaches recognises that benefit-risk assessment is relative and that the importance placed on the benefits, risks and outcomes is dependent on the perspective. Patients want to ensure that their perspective is incorporated into the decision-making process.

Furthermore, as detailed by others at this Workshop, patients should be involved throughout a medicine's life cycle and the types of input required will differ according to the time point. Their perspective regarding unmet treatment needs may be of value in determining early investment priorities and selecting candidate therapies for development. They may provide relevant information to assist in trial protocol development, helping to determine proof of concept criteria, relevant endpoints and clinically meaningful effect size and in selecting

and refining patient-reported outcomes; during clinical trials, patients provide obvious assistance in the collection of data.

The evaluation of medicines for purposes of reimbursement is another important point for patient involvement. In *Who has the say in HTA Assessment?* a 2010 Hill & Knowlton survey of 100 patient groups in western Europe, respondents recommended that patients be educated in health technology assessment and that they be given the ability to dispute assessor decisions. They further advised that HTA agencies should embrace the quality of life of patients and caregivers, including a patient's ability to return to work as part of their evaluation of new therapies.¹ For their part, patient advocacy groups have realised that they must become better organised and establish credibility by developing an understanding of health technology assessment and productively contributing to the discussion based on scientific merits.

There are multiple pathways to obtain patient involvement in decision making for new medicines, including the use of patient groups, social media, focus groups, market research consortia, physician-mediated surveys, representative samples and "professional" patient input. The use of more traditional methods for obtaining patient viewpoints such as patient-reported outcomes and utilities is clear but a focus on more novel approaches such as social media and advanced data mining is required.

There are challenges, however, to involving patients in decision making for new therapies. First, the wide range of geographic and cultural backgrounds of potential patients may add complexity to the determination of which patients' viewpoints to include. Second, it must be determined what type of media is used to foster their inclusion and whether the inclusion methodology is scientific and acceptable to regulators and payers. Finally, better methods of effective communication with patient representatives must be developed.

Current initiatives

Industry is making inroads with patient involvement, soliciting the viewpoints of this critical stakeholder throughout the continuum of medicines' development (Figure 16). Regulators are also making connections with patients. The FDA has established the FDA Patient Network, the inaugural meeting for which was held 18 May of this year. A periodic newsletter will

Patient input may help determine the benefit-risk balance for individuals rather than entire populations and may impact eventual adherence to medicines, which is critical for their safe and effective use.

contain FDA-related information on a variety of topics, including new product approvals, significant labelling changes, safety warnings, notices of upcoming public meetings, proposed regulatory guidances and opportunity to comment and other information of interest to patients and patient advocates. In Europe, the European Patients Academy on Therapeutic Innovation (EUPATI) was also launched in 2012. It is a five-year programme to develop educational material, training courses and a public Internet library to educate patient representatives and the lay public about all processes involved in medicines development. Regulators are also testing methodologies through mechanisms such as the Patient Risk Tolerance Survey for Obesity Devices, a conjoint analysis Internet survey to elicit patient preferences for medical devices to reduce weight. As Dr Hughes discussed in her previous presentation at this Workshop (page 30) the Innovative Medicine Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (IMI PROTECT) is also exploring methodologies for incorporation of patient perspective.

Likewise, associations and academia are playing a role in patient involvement. In collaboration with the London School of Economics, the European Federation of Neurological Association has established a Health Technology Assessment Summer School for patient groups to help patient representatives understand topics such as benefit-risk and patient-reported outcomes and to generally improve their health literacy.

The European Healthcare Innovation Leadership Network has developed disease-specific working groups in type 2 diabetes and breast cancer as well as pilot consultations for patient input into new, early-stage medicine.

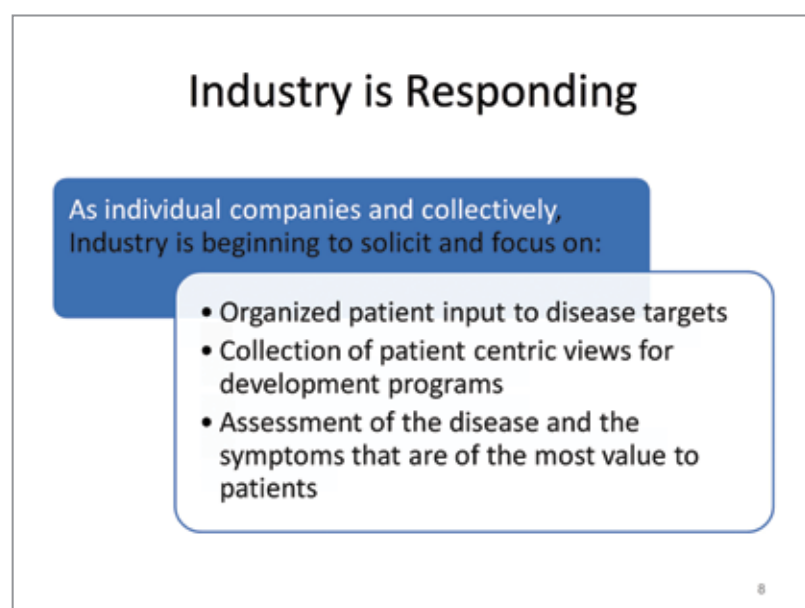
Moving forward

Dr Hughes concluded her presentation with several recommendations to advance patient involvement in drug research, regulation and reimbursement, including increased industry and agency outreach and collaboration with patient advocacy groups and the development of additional educational programmes for patient advocacy education. In addition, the formation of industry consortia in the precompetitive space would advance understanding of unmet medical need and patient experience and methodological work, perhaps in the form of white papers, would advance a common approach to weighting benefit and risk parameters and developing patient-reported outcomes and utilities. Finally, learnings from other sectors such as over-the-counter drugs should be incorporated into patient involvement initiatives and legislative bodies should also be engaged around this important topic.

Reference

1. Ossenberg K. *Who has the say in health technology assessment*. 2012; Found at <http://www.hillandknowlton.be/news/who-has-say-health-technology-assessment> Accessed October 2012.

Figure 16. The pharmaceutical industry has made inroads in patient participation in the development of medicines.



Patient-focussed drug development

Dr Theresa Mullin

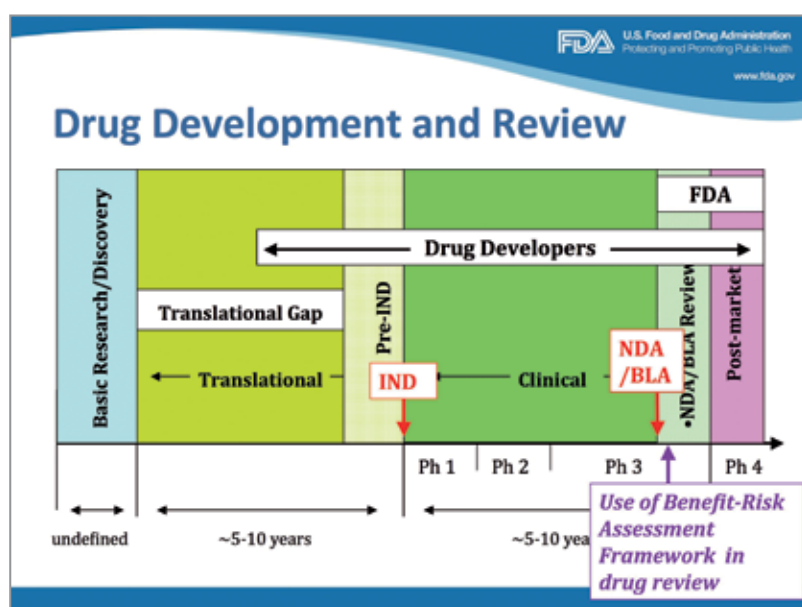
*Associate Director for Planning and Informatics,
FDA Center for Drug Evaluation and Research*

The patient viewpoint on the severity of a condition and unmet medical need

Assessment of a medicine's benefits and risks involves an analysis of the severity of condition that it treats as well as the current state of the treatment armamentarium for that condition, two of the five considerations identified in the benefit-risk framework currently in development at the US FDA (p 26). This framework has been developed to be used during the process of regulatory review of a new medicine (Figure 17).

However, because patients who live with a disease have a direct stake in the drug review process and are in a unique position to contribute to drug development, the review process could also benefit from a systematic approach to obtaining patient perspective on disease severity or unmet medical need. Accordingly, the programme of patient focus in drug development proposed by the FDA as part of its PDUFA V commitments (p 18) centres on eliciting those perspectives. PDUFA-funded resources are expected to support additional programme staff to expand activities dedicated to providing review divisions with patient input.

Figure 17. The benefit-risk framework in development at the FDA is designed to be used as part of regulatory review.



... the review process could also benefit from a systematic approach to obtaining patient perspective on disease severity or unmet medical need.

As part of this programme, the FDA will convene meetings with participation from review divisions, the relevant patient advocacy community and other interested parties. In addition, the FDA will hold four public workshops per year—a total of 20 meetings over 5 years. It is anticipated that each meeting will focus on a different disease area, reviewing the armamentarium for that indication and identifying areas of unmet need, dimensions of living with a disease that have not yet been adequately captured in clinical studies (Figure 18).

Patient-reported outcomes

It will be also necessary to develop instruments to measure a medicine's effectiveness for those dimensions that are also validated for regulatory review before clinical trials are initiated. One such potential instrument is patient-reported outcomes (PROs). As defined by the FDA, PROs are any report of the status of a patient's health condition coming directly from the patient, without interpretation by physicians or others, about how the patient functions or feels in relation to a health condition and its treatment. In their review of PRO instruments, FDA assessors must judge if the instrument measures the concept it is supposed to measure, if it is well specified and reliable, if it is specific for a target population and target indication and if its measurement properties are adequate.

Qualitative research can be used to establish PRO content validity and might include focus groups to generate a pool of PRO-related domains and their components, asking what symptoms and functions or activities impacted by disease are most important to patients. Another type of validation involves surveys that include a larger and more diverse sample of patients with a given condition. These surveys might examine the importance and relevance of domains identified by literature review, expert opinion or among a smaller set of patients, to validate PROs items and potentially explore other measurement characteristics.

Patient Representation Program

The Patient Representation Program is another method employed by the FDA to elicit patient

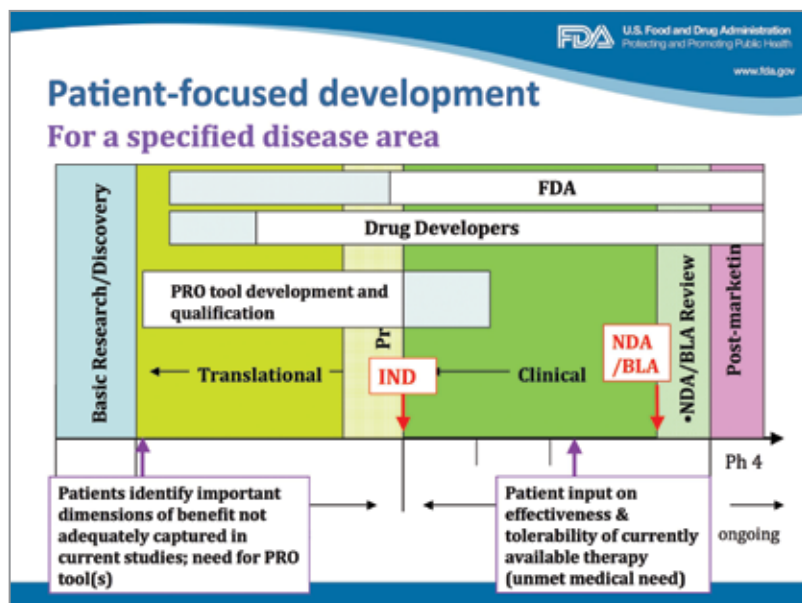


Figure 18. Patient-focused drug development at the FDA will provide the opportunity for patients to identify areas of unmet need.

input. In this programme, the role of the Patient Representative is to provide the FDA with the unique perspective of patients and family members directly affected by a serious or life-threatening disease. Representatives may serve in several ways, including on Advisory Committees, where they offer the patient perspective, ask questions and give comments to assist the committee in making recommendations; as consultants for review divisions assisting clinicians and scientists who review data submitted to determine whether the product's benefits outweigh the potential

risks and as presenters at FDA meetings and workshops on disease-specific or regulatory and health policy issues. Training for these representative consists of a programme of individual learning, monthly webinars and an annual workshop for newly recruited patient representatives

Next steps

It is anticipated that the FDA will next develop a preliminary list of 20 disease areas for public comment to inform planning for the public meetings proposed in PDUFA-V. It will also develop a basic roadmap or toolkit that could be used by patient groups interested in pursuing the need for and development of PRO measures in a specific disease area and identify important but currently unaddressed aspects of their disease experience to potentially be considered in evaluating new therapies.

A preliminary list of the 20 disease areas will next be published for public comment. A public meeting will then be convened to discuss the proposed list of disease areas for the PDUFA meetings and to discuss strategies for getting broader public input and to develop a basic roadmap for identification of important patient outcomes and strategies for collaborative development PRO measures. It is expected that the FDA Patient-Focused Drug Development initiative will add to the existing FDA programmes designed to integrate patients' perspectives.

Decision making: what are the challenges in making quality decisions?

Ronan Donelan

*Head of Regulatory Affairs EMEA and ANZ,
Quintiles, Ireland*

Drivers, challenges and frameworks for decision making

Not surprisingly, decision making among the regulators of medicines and members of the pharmaceutical industry is driven by differing factors. Regulators must adhere to a remit to positively impact public health whilst remaining mindful of precedents and adhering to laws, regulations and policies. Pharmaceutical industry members, on the other hand, are motivated by the need to predictably and transparently develop medicines that will fulfil patient needs and regulatory requirements whilst delivering profit to shareholders.

Meanwhile, the challenges to medicines development for both regulators and industry have been well documented and include increasing dossier complexity, the need for expedited approval timing, escalating costs in the face of constraints on capital, patent expiries, dwindling pipelines and stakeholder scrutiny with resulting demands for access, proven value, productivity and return on investment. Any support for quality decision making in the

QoDoS . . . aims to improve the link between the science and art of decision making, with a structured and systematic approach that incorporates human awareness and provides the basis to achieve better practice.

face of these sometimes conflicting drivers and challenges would benefit all stakeholders.

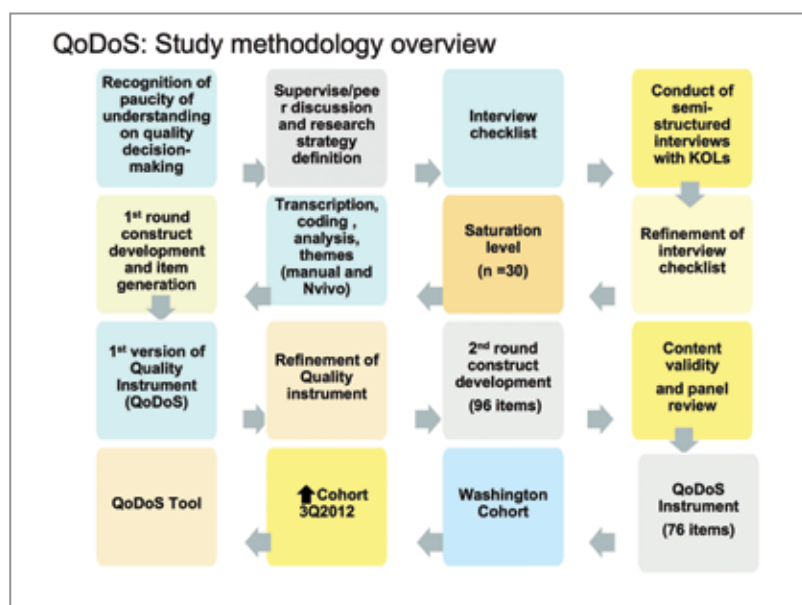
There are four basic decision-making styles: subjective, objective, analytical and non-analytical, with numerous academic sub-styles such as directive, analytical, conceptual and behavioural. Linked to these styles, numerous qualitative, semi-quantitative and quantitative decision approaches have evolved such as the PROACT-URL, Multi-criteria Decision Analysis, EMA, FDA and UMBRA frameworks discussed at this Workshop. However, decision making is part science and part art, with art in this case being the subjective human component within the decision-making process. This subjective decision-making style reflects the combination of how an individual perceives and comprehends stimuli and the general manner in which he chooses to respond to it. It is linked to an individual's knowledge, ability and motivation plus their value orientation and tolerance for ambiguity.

Doctoral research: QoDoS®

In recognition of the paucity of understanding regarding quality decision making in medicines development and regulation, Mr Donelan initiated a programme of doctoral research in 2011, undertaken under the sponsorship of Cardiff University and CIRS to investigate how individuals and organisations manage decision making within the drug development arena. The goal of this research is to develop and refine the Quality of Decision-Making Orientation Scheme (QoDoS), an instrument that will facilitate quality decision making and that involves both a structured and systematic approach but also includes human elements. To construct this instrument a robust, scientific protocol was employed in which semi-structured, face-to-face interviews were conducted with a variety of key opinion leaders from the EMA and national European regulatory agencies as well as from pharmaceutical companies and some contract research organisations (Figure 19).

The initial phase of the research involved conducting interviews of between 40 and 90 minutes with 30 key opinion leaders and coding

Figure 19. A robust scientific protocol was used in the development of the QoDoS tool.



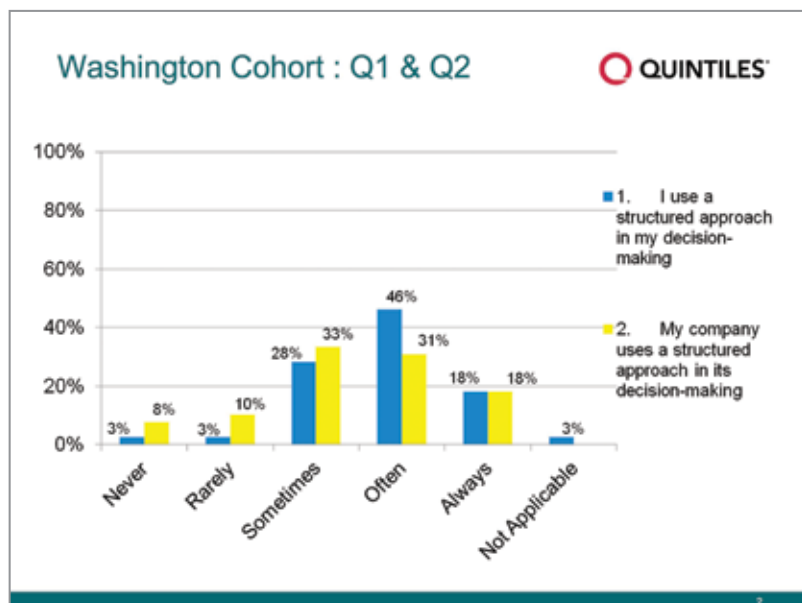


Figure 20. Preliminary results of the first cohort to use the QoDoS instrument.

the results using nVivo software. After content validation and expert panel review, 76 themes emerged from these interviews, allowing the construction of the survey instrument. Specific insights were also gained; for example, responses revealed that decision making is a complex space with multi-factorial considerations such as expectations, influences and individual values, intuition, biases and preferences that may not be obvious within a structured, quantitative decision-making process. In turn, those insights can result in specific actions, allowing decision makers to promote discipline, self-awareness and better practice. It was also possible to identify twelve hallmarks of quality decision making that can be linked to decision-making drivers and that if put into practice may increase confidence in decision making:

1. Understand the decision context
2. Apply knowledge, experience, ability and motivation
3. Employ sound scientific principles
4. Seek information integrity for validity and trust
5. Be objective and maintain awareness of your

biases and preferences

6. Employ uncertainty and alternatives screening
7. Assign values
8. Re-evaluation as needs evolve
9. Appreciation and management of internal and external influences
10. Transparency and record trail
11. Effective communication
12. Perform impact analysis $t_{1/2}$

Over 70% of attendees at this Workshop (the Washington Cohort) completed the pilot questionnaire using the QoDoS tool and preliminary results reveal how individuals and companies approach decision making (Figure 20). This research is a work in progress and a larger cohort investigation with factorial analysis and modelling for validity and reliability will take place later in 2012.

Conclusions

Although there is an increasing use of framework-based simulation and modelling to aid decision making within drug development, this process is subjective in nature and QoDoS is a tool to enrich and enhance its quality. QoDoS, which is complementary to other ongoing research in this area, aims to improve the link between the science and art of decision making, with a structured and systematic approach that incorporates human awareness and provides the basis to achieve better practice.

Decision making: Reflections from a company

Dr Paul Huckle

Chief Regulatory Officer, GlaxoSmithKline, USA

The pharmaceutical industry is engaged in the very important enterprise of bringing new and effective medicines to patients to improve public health. To achieve that goal, decisions made at pharmaceutical companies occur at multiple levels on a continual basis. At the highest level, company strategy drives the direction in which human and financial resources are invested and potentially determines corporate success or failure. At the portfolio level, decision makers choose which therapeutic areas will be investigated and which will be excluded, whilst at the project level, decisions are made on an almost hourly basis around the ways in which individual products are advanced. Regardless of the level, however, mechanisms must be built into corporate decisions to ensure their timeliness, accountability and objectivity and most importantly, that they are value driven.

Within companies, clarity around the information and timing requirements for decisions that are scheduled to occur at various milestones of product development allow for the careful integration of those decisions into company processes. However, the complex nature of pharmaceutical companies can have a direct impact on the speed and effectiveness of decision making, emphasising the necessity for the thoughtful selection of decision participants. Establishing at the initiation of a project the level at which decisions must occur, the accountability for those decisions, whether at the individual or committee level and the mechanism for reaching the decisions is key to timely and effective decision making.

The objectivity and accountability of project teams who are incentivised to bring a particular medicine to market must be counterbalanced within their organisation. This can be accomplished by the peer review of their decisions by a team with experience in

the field but no personal involvement in the development of that medicine, who consider all data in the context of the company's portfolio. Another method of counterbalance is the establishment of arbiter groups in governance areas such as safety, pharmacovigilance, regulatory review and product quality who are empowered to step in and change decisions or to halt or redirect programmes. This function can extend to the more senior company decision making, for which separate internal and external expert scientific panels might review and opine on the robustness of the science underlying a particular programme.

The methodology used for decision making that has not been routinely planned or scheduled should be consistent with the methodology for planned decision making. To manage an unexpected issue and come to a decision regarding its resolution, a specific team is created to operate for a discrete amount of time as a standalone group of expertise. To drive efficiency, this team is given access to relevant key stakeholders who are empowered to provide information and made decisions for the issue in question and balanced oversight is also provided for these decisions.

In addition to mechanisms for the provision of oversight, a clear set of corporate values will ensure consistency of decision making across an organisation. At GlaxoSmithKline, patient focus, transparency, respect and integrity are imbued into all activities and decisions are evaluated according to their alignment to those values.

Finally, the right expertise and experience is key to effective decision making. Although many decisions in the pharmaceutical industry may be influenced by biases, biases based on experience should not be routinely discounted. Dr Huckle cited a well-known quotation from an anonymous source, "Good decisions come from experience and experience comes from bad decisions" stating that the challenge both for individuals and for organisations is to learn from bad decisions so that better decisions can be made going forward.

Establishing at the initiation of a project the level at which decisions must occur, the accountability for those decisions. . . and the mechanism for reaching the decisions is key to timely and effective decision making.

Decision making: reflections from an agency

Prof Sir Alasdair Breckenridge

Chairman, Medicines and Healthcare products Regulatory Agency, UK

The unknown in the regulation of medicine

The regulation of medicines is based in law, is driven by science and is meaningless unless it protects the public health. Unfortunately, major changes in this area have resulted from the disastrous, unanticipated effects on the public health exerted by some medicines. For example, because of a lack of clinical testing requirements, hundreds of people were poisoned in the United States through the contamination of sulphadimidine with ethylene glycol, leading to the passage of the Food and Drugs Cosmetic Act in United States in 1938. In 1962, after thousands of children whose mothers had used thalidomide were born with birth defects, the United States and other countries enacted legislation requiring the testing of the teratogenic potential of new medicines. More recently, changes in British regulatory law were passed after six test subjects experienced major organ failure in the phase 1 testing of the monoclonal antibody TGN 1412 in 2006.

The unknown also plays a role in clinical trials used for regulatory submissions. Although much data are accumulated about a new medicine's

quality, pharmacology and efficacy at the time of its approval, efficacy data in a highly select clinical trial population may provide an incomplete and in fact, misleading account of the drug's effectiveness in the population at large. Likewise, rare adverse events may occur with the use of an approved medicine, which were undetectable in the small number of participants in the clinical trial used to demonstrate the medicine's efficacy and safety. Both of these factors underscore the need for ongoing assessment of both effectiveness and safety in the post-market setting.

The press, the public and politicians may be overwhelmed with misplaced concerns about drug safety, when in reality a drug's value is determined by its benefit-risk balance. In fact, while the most favourable benefit-risk profile for a new medicine involves low potential for risk of harm and high potential of benefit, many drugs approved to treat conditions such as cancer and HIV disease, have extremely negative safety profiles but their effectiveness causes their benefit-risk profile to be deemed favourable.

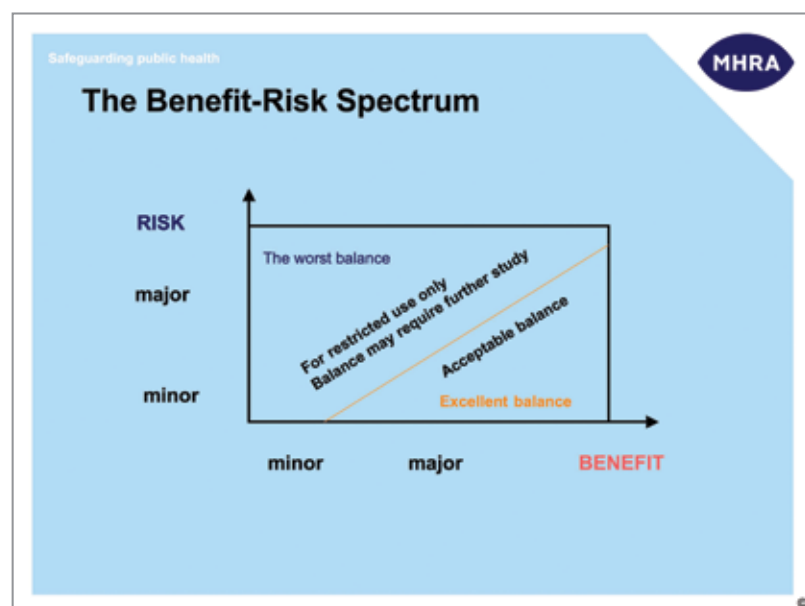
Legislating a life cycle approach to regulation

Although the number of new molecular entities is decreasing despite increasing investment in research and development, the proportion of new medicines that are biological entities is increasing (Figure 21). What is more, many of these new medicines offer potential cures or the amelioration of outcomes for serious disease states, leading to increased patient advocacy for access to these medications in a shorter-than-traditional timeframe and a change in regulatory practice that focuses strongly on post-approval safety and effectiveness surveillance studies.

In 2007 after examining the approach to drug safety in the United States, the Institute of Medicine (IOM) concluded that a life cycle approach to regulation was key. This conclusion was substantiated that year when Avandia (rosiglitazone) was withdrawn from the market. Avandia had been licensed in 1999 using surrogate endpoints of fasting blood sugar and haemoglobin A1c levels. Unfortunately, the medicine also causes an increase in low-density lipid cholesterol and in weight and a 2007 meta-analysis suggested an increase rather than a decrease in heart disease among users.

The USA Food and Drug Administration Amendments Act was passed that year, which detailed the post-marketing requirements

Figure 21. The proportion of new medicines classified as biological entities is increasing.



Regulatory decision making in Europe and the United States is converging, as both groups become increasingly aware of the importance of a robust assessment of a new medicine's benefit-risk balance throughout that medicine's life cycle.

and commitments that the FDA could require of sponsors of new medicines, including adverse event surveillance, observational studies and clinical trials. Additionally, the Act allowed the agency to request risk evaluation and minimisation strategies, outlining the importance of active safety surveillance. Subsequently, at the request of the US FDA, the IOM investigated the science and ethics supporting safety study requirements for new medicines after their approval. Among the 23 recommendations in the resulting report, the IOM advised that the FDA require a benefit-risk action management plan (BRAMP) be implemented during the life cycle of a new medicine. It was recommended that this BRAMP be part of the regulatory submission, be initiated by the sponsor of the new drug, discussed with and approved by the FDA and updated over the medicine's life cycle.

Meanwhile, in 2005 the European Commission

also passed a regulation calling for mandatory risk management plans, including pharmacovigilance plans for determining what is unknown about new medicines as well as plans for risk minimisation and risk communication. This regulation was further strengthened by the European Pharmacovigilance regulations of 2012 which stressed the importance of risk management plans for all newly approved products, improves the legal basis for post authorisation studies of safety and effectiveness and seeks to enhance the transparency of and access to safety data.

Conclusions

Regulatory decision making in Europe and the United States is converging, as both groups become increasingly aware of the importance of a robust assessment of a new medicine's benefit-risk balance throughout that medicine's life cycle. Although new regulations are seldom welcome and may be costly to implement, inadequate response to the safety signals for a new medicine can have public health and economic consequences for the patients and society and the vision for drug safety requires the commitment of both those who produce and those who regulate new medicines.

Methodologies to assess benefit-risk: Regulatory and HTA considerations in Canada

Barbara Sabourin

Director General, Therapeutic Products Directorate, Health Canada

Dr Chander Sehgal

Director of the Common Drug Review program, Canadian Agency for Drugs and Technologies in Health

Benefit-risk at Health Canada

A *benefit* is a measure of both the benefit to human health that results from being exposed to a product under specific conditions of use, together with the likelihood that the benefit will occur. A *risk* is a measure of both the harm to human health that results from being exposed to a product under specific conditions of use,

together with the likelihood that the harm will occur

Newly approved medicines, however, do not have benefit-risk profiles – they acquire them in the context of their use, which is why labelling and informed use by the prescriber are so important. Furthermore, the likely evolution of a product's benefit-risk profile over time and use necessitates post-marketing surveillance.

During the assessment process Health Canada reviewers consider information from sponsors regarding a product's efficacy, defined as "substantial evidence of the clinical effectiveness of the new drug for the purpose and under the conditions of use recommended." This evidence includes pivotal clinical studies and under some circumstances supportive clinical studies and phase I data. Assessors also evaluate evidence for the product's safety, defined as "detailed reports of the tests made to establish the safety of the new drug for the purpose and under the conditions of use recommended." This information includes all relevant clinical studies when at least one dose of study drug

was administered, all relevant non-clinical data, phase I data and post-marketing data if available. Canadian Food and Drug regulations specify the terms efficacy and safety rather than benefit and risk and although reviewers sometimes use these terms interchangeably, the nuances of difference are important to note.

Health Canada reviewers also consider information outside of the dossier and that includes expert advice, medical literature, treatment guidelines and more recently, information from other regulatory groups. Mechanisms for these collaborations include work with

- Foreign regulatory scientific committees, which are run by other regulatory authorities to form policies, practices and guidance for industry
- Foreign reviews, which are scientific reports from other agencies with regard to safety, efficacy and quality, upon which marketing authorisation decisions are based
- Parallel reviews, which are separate independent reviews conducted on the same application at the same time by two or more regulatory authorities
- Joint reviews, which consist of reviews of sections conducted by different regulatory authorities and consolidated at the end of the process
- Scientific advice, which is regulatory authority assistance to applicants regarding

the conduct of the studies and the proposed content of specific applications or submissions for marketing authorisation

- Inter-regulatory discussion groups, which are expert panels run jointly by two or more regulatory authorities

Health Canada has four methods for using foreign reports in the review of dossiers. The first, in which the Canadian decision is based on a critical assessment of the foreign review, the second, in which the Canadian review is based on a critical assessment of the foreign review and referring to the data filed in Canada as necessary, the third, in which the Canadian review is based on a critical assessment of the data filed in Canada, with the foreign review as an added reference and the fourth, in which the Canadian review is based on a critical assessment of the data filed in Canada, with no use of the foreign review. Any of these methods can be applied separately or in combination to different segments of a dossier review.

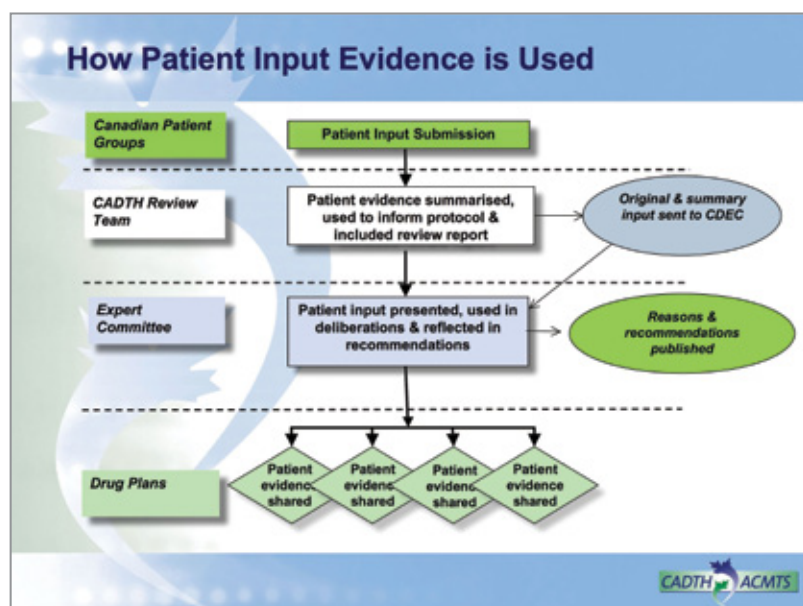
In the evaluation of the benefits and risks of a medicine, reviewers must summarise the background of the disease and its treatments, being explicit about the importance of benefits and risks in a specific therapeutic context and describing the sources of uncertainty and variability and their impact on the assessment. Benefits are estimated according to the weight of the statistical and clinical evidence to support dosage and efficacy in the target population and risks are calculated from the incidence, seriousness and duration of specific adverse effects according to the weight of clinical trial and post-marketing surveillance results.

In cases in which the level of risk must be managed following approval, risk mitigation options must be discussed and evaluated including modification of the proposed dosage regimen, restriction of the drug population, modification of the drug labelling to reflect potential safety concerns regarding drug-drug or drug-disease interactions or to indicate the need for monitoring for signs or adverse events, recommendations for surveillance or post-marketing studies.

An important point to consider in the evaluation is the need for a separate benefit-risk assessment for each requested indication. All available data should be considered and the nature of the disease and the benefit-risk balance relative to other therapies must be taken into account.

Key documents used in the evaluation are

Figure 22. Patient input is incorporated throughout the CADTH review process.



quality and clinical review reports, including the Pharmaceutical Safety and Efficacy Assessment Template and Manager's Memo, the Executive Summary, Product monograph, Authorization document and Summary Basis of Decision.

Product Monographs and Summary Basis of Decision documents can also be found on the Health Canada website.

Three types of regulatory decision are possible: 1) a Notice of Compliance or Notice of Compliance with Conditions, which results in market authorisation and the issuance of a product monograph with appropriate risk management plan and labelling for risk mitigation; 2) A Notice of Non-Compliance provides the sponsor with concerns or issues, which if not addressed can result in NON-Withdrawal; or 3) a Notice of Deficiency, which stops the review and which is typically issued well before the benefit-risk assessment phase

Challenges and strengths

Like other agencies, Health Canada faces challenges. Because the analysis process encompasses many considerations, review outcomes are not always consistent with other regulatory agencies even when reviewing the same data package. A potential solution to this issue is the use of a qualitative or semi-quantitative framework for benefit-risk assessment of medicines that is currently under evaluation by Health Canada.

Health Canada is also rising to meet the challenge of recommendations that sometimes differ with those of the health technology assessment decisions. Increased collaboration with the Canadian Agency for Drug Technology and Health (CADTH), allows both groups to share information regarding the basis for decisions and understand both sets of requirements. CADTH has also been invited to observe pre-submission, pipeline and scientific advisory meetings.

Health Canada reviewers are measured against seven areas of competency: computer skills, the drug development process, scientific communications, critical thinking and evaluation, Canadian and international regulatory context, organisational awareness and most importantly, as representatives of a public agency they are expected to exhibit ethics and values.

Future directions for CADTH involve enhancement to the transparency initiatives. . . and parallel review mechanisms with Health Canada are being explored.

To maintain relevance to the patients they serve, evaluation processes and practices continue to evolve at Health Canada, but experience, expertise and judgement will continue to be key competencies.

Benefit-risk at CADTH

CADTH is a pan-Canadian health technology assessment agency that performs evidence-based reviews of pharmaceuticals, medical devices and procedures, to provide decision makers with relevant information on which to base resource allocations. CADTH is a not-for-profit, independent agency funded by federal, provincial and territorial Canadian governments, with the exception of Quebec, which has its own process.

The market access continuum is sequential in Canada, with Health Canada decisions followed by submissions to CADTH for evaluations through the Common Drug Review process. Approximately 260 recommendations for new drugs have been issued since the Interim Common Drug Review process was established in 2002. CADTH, however, does not make decisions for reimbursement but rather makes recommendations to drug plan administrators in local jurisdictions.

At Health Canada where the mandate is for market authorisation of new medicines, safety and efficacy are the key drivers of benefit-risk evaluation and in many cases, the new interventions are compared with placebo. During the health technology assessment for those drugs, the common drug review process is by definition a single technology assessment, that is, one drug and one indication at one time. The common drug review process differs from the therapeutic review or optimal use process in which drug class and disease indications are reviewed; for example, CADTH recently completed evaluation of anticoagulants in atrial fibrillation. CADTH examined competitive and cost effectiveness and patient group input.

Starting with the process of regulatory review, uncertainty permeates the review of new medicines. At the time of their health technology assessment, evaluators are faced with the clinical uncertainty that results from randomised clinical trials that may employ a placebo rather than appropriate clinically relevant comparator, a targeted rather than general population or a surrogate rather than clinical endpoint. This trial data, which is often short term, often suffers from a lack of generalisability. In addition, economic

uncertainty results from a lack of head-to-head trials, complex translations from surrogate to clinical endpoints, or inappropriate comparators or patient groups, resulting in limited or poor-quality data and assumptions built on models that are not necessarily evidence based.

Patient input

Patient input evidence has been incorporated into all aspects of the CADTH review process in the majority of evaluations over the past several years; however, although dialogue is open and ongoing with patient groups, it is still an evolving process and input has been absent from some reviews and of mixed quality in others. Patient evidence is summarised and becomes an integral part of the review process and the material sent to the Canadian Drug Expert Committee, where it is discussed and taken into account during the development of the clinical and economic review reports. In addition, two of the fourteen committee members are lay participants with equal voting rights (Figure 22).

CADTH recommendations

Final recommendations are based on established criteria of the safety, efficacy and effectiveness of a medicine compared to alternatives and the therapeutic advantages, disadvantages and cost-effectiveness relative to current accepted therapy as well as the patient and public perspectives on impact of the drug. Because of the complexities of assigning value across

disease areas and across types of input or data, weights are not applied to these criteria. In this transparent process, the sponsor has the opportunity to comment before final deliberations are made.

Regional Drug Plan reimbursement decisions are based on regulatory reviews, health technology assessment recommendations, the current funding status of comparators and ultimately, on affordability or the budget impact and local resource limitations. Also factored in are local context and other factors such as ethical, legal and societal preferences, meaning that each jurisdictions may make different reimbursement decisions based on variable constraints.

Future directions

Future directions for CADTH involve enhancement to the transparency initiatives. It is the intent of the agency to make CDR review reports available to the public and dialogue is ongoing to make all submission information disclosable (except for price and manufacturing processes). An evaluation of patient groups input is underway and parallel review mechanisms with Health Canada are being explored.

Appendix: CIRS Benefit-Risk Activities

CIRS Benefit-Risk Workshops 2004-2012

Synopses and reports for these Workshops are available at <http://cirsci.org/past-workshops-and-publications>

2012	Building the benefit-risk toolbox: Are there enough common elements across the different methodologies to enable a consensus on a scientifically acceptable framework for making benefit-risk decisions? Washington, DC, USA: 20-21 June 2012
2012	The patient's role in the benefit-risk assessment for the submission and review of new medicines; Hampshire, UK, 25-26 April 2012
2011	Visualising Benefit-Risk: The key to developing a framework that informs stakeholder perspective and clarity of decision making; Washington, DC, US: 16-17 June 2011
2010	Refining the benefit-risk framework for the assessment of medicines: Valuing and weighting benefit and risk parameters; Washington, DC, US: 17-18 June 2010
2009	Strategies for Communicating Benefit-Risk to Decision Makers: Explaining Methods, Findings and Conclusions Through a Common Approach Washington, DC, US: 17-19 June 2009
2008	Measuring Benefit and Balancing Risk: Strategies for the benefit-risk assessment of new medicines in a risk-averse environment Washington, DC, US: 19-20 June 2008
2005	Benefit-risk assessment model for medicines: Developing a structured approach to decision making, Washington DC, USA: 13-14 June 2005
2004	Benefit-Risk Assessment: The Development of a Model for Benefit-Risk Assessment of Medicines Based on Multi-Criteria Decision Analysis London, UK: 29-30 March 2004

Journal articles

Walker S, McAuslane N, Liberti L. Refining the benefit-risk framework for assessing medicines: valuing and weighting the parameters: a report on progress by regulators and industry on the development of a common benefit-risk assessment framework. *Reg Affairs J.* 2011;March:14-17.

Liberti L, McAuslane N, Walker S. Standardising the benefit-risk assessment of new medicines: practical applications for the pharmaceutical healthcare professional. *Pharm Med.* 2011;25:139-146.

Liberti L, McAuslane N, Walker SRW. Progress on the development of a benefit/risk framework for evaluating medicines. *Regulatory Focus.* 2010: March.

Brizmohun N. Standardising Benefit: Risk Assessment Heads DIA EuroMeeting News. *Regulatory Affairs J.* 2010; 21:221-224.

Walker S, McAuslane N, Liberti L, Salek S. Measuring benefit and balancing risk: strategies for the benefit-risk assessment of new medicines in a risk-averse environment. *Clin Pharmacol Ther.* 2009; 85:241-246.

Mussen F, Salek S, Walker S, Phillips L. A quantitative approach to benefit-risk assessment of medicines - part 2: the practical application of a new model. *Pharmacoepidemiol Drug Saf.* 2007;16 Suppl 1:S16-41.

Mussen F, Salek S, Walker S. A quantitative approach to benefit-risk assessment of medicines - part 1: the development of a new model using multi-criteria decision analysis. *Pharmacoepidemiol Drug Saf.* 2007;16 Suppl 1:S2-S15.

Book

Benefit-Risk Appraisal of Medicines: A Systematic Approach to Decision Making. Mussen F, Salek S and Walker SR, eds. John Wiley: Surrey, UK. 2009.

Appendix: Workshop Attendees

Patient and disease advocacy organisations and academic and research institutions		
Dr Lucie Bruijn	Chief Scientific Officer	ALSA, USA
Dr Gregory Daniel	Fellow, Economic Studies, Managing Director, Engelberg Center for Health Care Reform	The Brookings Institution, USA
Robert Guidos	Vice President, Public Policy and Government Relations	Infectious Diseases Society of America, USA
Marjana Marinac	Director, Regulatory Affairs – Drugs & Biologics	JDRF, USA
Jean Mossman	Policy Lead	European Federation of Neurological Associations
Professor Sam Salek	Director, Centre for Socioeconomic Research	Cardiff University, UK
Dr Jessica Walrath	Science Policy Analyst	Friends of Cancer Research, USA
Regulatory and government agencies		
Mohammed Hamdan Al-Rubaie	Director of Drug Control	Ministry of Health, Oman
Prof Sir Alasdair Breckenridge	Chairman	Medicines and Healthcare products Regulatory Agency, UK
Professor Hans-Georg Eichler	Senior Medical Officer	European Medicines Agency, UK
Dr Jason Ferla	Director, Prescription Medicines Clinical Unit 3, Office of Medicines Authorisation	Therapeutic Goods Administration, Australia
Patrick Frey	Director, Office of Planning and Analysis, Center for Drug Evaluation and Research	Food and Drug Administration, USA
Dr John Jenkins	Director, Office of New Drugs, Center for Drug Evaluation and Research	Food and Drug Administration, USA
Dr Joyce Korvick	Deputy Director of Safety, Division of Gastroenterology and Inborn Errors Products	Center for Research and Evaluation, Food and Drug Administration, USA
Cordula Landgraf	Head of Networking	Swissmedic
James Leong	Senior Regulatory Specialist	Health Sciences Authority, Singapore
Dr Huei-Xin Lou	Director, Pre-Marketing Division, Health Products Regulatory Group	Health Sciences Authority, Singapore
Dr Murray Lumpkin	Commissioner's Senior Advisor and Representative for Global Issues	Food and Drug Administration, USA
Ginette Michaud	Deputy Director, Office of Blood Research and Review, Center for Biologics Evaluation and Research	Food and Drug Administration, USA
Dr Theresa Mullin	Associate Director, Office of Planning and Informatics, CDER	Food and Drug Administration, USA
Prof Robert Peterson	Executive Director	Drug Safety and Effectiveness Network/Canadian Institutes of Health Research
Dr Francesco Pignatti	Head of Section Oncology Safety and Efficacy of Medicines	European Medicines Agency, UK
Barbara Sabourin	Director General, Therapeutic Products Directorate	Health Canada
Dr Chander Sehgal	Director, Common Drug Review Program	Canadian Agency for Drugs and Technologies in Health (CADTH)

Dr Mark Walderhaug	Associate Office Director for Risk Assessment, CBER	Food and Drug Administration, USA
Zhimin Yang	Deputy Office Director(acting), Office of Clinical Evaluation	Center for Drug Evaluation, - SFDA, China
Pharmaceutical industry and contract research and manufacturing associations		
Dr Nayan Acharya	Senior Director, Office of Risk Management and Pharmacoepidemiology	Eli Lilly and Company, USA
Dr Stephane Andre	Head of EU/ROW Regulatory Affairs	F. Hoffmann-La Roche Ltd, Switzerland
Dr Fabrice Bancken	Expert Statistician in Quantitative Safety	Novartis Pharma AG, Switzerland
Dr Gary Bloomgren	Vice President, Safety and Benefit-Risk Management	Biogen Idec, USA
Dr Graham Burton	Senior Vice President, Regulatory Affairs Pharmacovigilance and Corporate QA Compliance	Celgene Corporation, USA
Dr Nadine Cohen	Senior Vice President, Regulatory Affairs	Biogen Idec, USA
Ronan Donelan	Head of Regulatory Affairs EMEA and ANZ	Quintiles, Ireland
Dr Eva Essig	Executive Director, US Regulatory Affairs	Astellas Pharma Global Development Inc, USA
Allen Feldman	Vice President, Clinical Safety and Pharmacovigilance	Daiichi Sankyo, USA
Dr John Ferguson	Senior Vice President, Global Regulatory Affairs, Pharmacovigilance and Corporate QA Compliance	Celgene, USA
Veronique Frechin	R&D Strategic Foresight Director	Institut de Recherches Internationales Servier, France
Dr Tim Garnett	Chief Medical Officer and Senior Vice President	Eli Lilly and Company, USA
Dr Mark Goldberger	Divisional Vice President, Regulatory Policy and Intelligence	Abbott, USA
Dr Christine Hallgreen	Post Doc	Novo Nordisk A/S, Denmark
Dr Richard Hermann	Safety Science Physician	AstraZeneca, USA
Dr Paul Huckle	Chief Regulatory Officer	GlaxoSmithKline, USA
Dr Diana Hughes	Vice President, Worldwide Safety Strategy, Primary Care Business Unit Lead	Pfizer Inc, USA
Qi Jiang	Executive Director	Amgen Inc, USA
Dr Hiroki Kato	Director	Zeria Pharmaceutical Co Ltd, Japan
Dr Shuji Kondo	Science and Regulatory Representative	PhRMA, Japan
Dr Elias Kouchiakji	Executive Director, Therapeutic Area Head, Nephrology/Cardio-Renal, Global Safety	Amgen Inc, USA
Dr Bennett Levitan	Director	Janssen, USA
Dr Marilyn Metcalf	Director, Benefit Risk Analysis USA	GlaxoSmithKline, USA
Steven Miller	Vice President, Regulatory Affairs	Janssen Research & Development, LLC, USA
Dr Filip Mussen	Head, Global Labeling Center of Excellence	Janssen Research and Development, Belgium
Dr Becky Noel	Senior Research Scientist	Eli Lilly & Company, USA
Kinnari Patel	Associate Director, Global Regulatory Sciences, US	Bristol-Myers Squibb Company, USA
Dr Jitesh Rana	Medical Director, Safety and Benefit-Risk Management	Biogen Idec, USA

Dr Tjark Reblin	Head, UK SERM Development	GlaxoSmithKline, UK
Dr Frank Rockhold	Senior Vice President, Global Clinical Safety and Pharmacovigilance	GlaxoSmithKline, USA
Dr Meredith Smith	Senior Scientific Director, Risk Management	Abbott Laboratories, USA
Dr Richard Spivey	Senior Vice President, Global Regulatory Affairs	Allergan Inc, USA
Dr Kristin Van Goor	Senior Director, Scientific and Regulatory Affairs	PhRMA, USA
Allison Villinski	Director, Regulatory Affairs Strategy	Takeda Global Research and Development Center Inc, USA
Dr Ulrich Vogel	Head, Strategic Data Analysis	Boehringer Ingelheim GmbH, Germany
Dr Douglas Watson	Senior Director	Merck & Co Inc, USA
Cheryl Watton	Vice President, Global Safety and Epidemiology	Allergan Inc, USA
Dr Max Wegner	Vice President, Head Global Regulatory Affairs, General Medicine	Bayer HealthCare Pharmaceuticals, Germany
Dr Susan Welsh	Vice President, Global Pharmacovigilance & Epidemiology, Medical Safety Assessment Therapeutic Area Head - Oncology & Immunology	Bristol-Myers Squibb Company, USA
Centre for Innovation in Regulatory Science		
Patricia Connelly	Manager, Communications	
Art Gertel	Senior Research Fellow	
Lawrence Liberti	Executive Director	
Dr Neil McAuslane	Director	
Prisha Patel	Portfolio Manager	
Professor Stuart Walker	Founder	