VISUALISING BENEFIT-RISK: THE KEY TO DEVELOPING A FRAMEWORK THAT INFORMS STAKEHOLDER PERSPECTIVE AND CLARITY OF DECISION MAKING

WORKSHOP REPORT
16 – 17 JUNE 2011
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WORKSHOP REPORT
The Centre for Innovation in Regulatory Science (CIRS) is an independent UK-based subsidiary company, forming part of the Intellectual and Science business of Thomson Reuters. CIRS is operated as a not-for-profit with its own dedicated management and advisory boards, and its funding is derived from membership dues and related activities. The organisation provides a neutral, independent international forum for industry, regulators, health technology agencies and other stakeholders to identify and apply scientific principles for the purpose of advancing regulatory and HTA coverage policies and processes in medicines development.

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Section 1: Executive Summary

Background to the Workshop

In 2010 the Centre held its annual meeting on benefit-risk in Washington, DC to discuss weightings and values within frameworks for the benefit-risk assessment of medicines. It was agreed at that meeting that one way of ensuring the development of the most effective framework is through undertaking scenarios with different stakeholders and products. This method allows the identification of ways in which agencies and companies will use the framework and establish practical methodologies to be used in the review of new medicines.

That Workshop also identified a number of barriers to acceptance of a benefit-risk framework and possible solutions, which included continuing dialogue between agencies and companies and working through case study examples as a way of both evolving the thinking and gaining acceptance of the value of a process for articulating benefit-risk in a transparent manner.

In 2011, as the development of a benefit-risk framework moves forward through US Food and Drug Administration, the European Medicines Agency, the Benefit-Risk Action Team of the Pharmaceutical Research and Manufacturers of America and the consortium of four agencies being facilitated by CIRS, this Workshop again brought these groups together with industry, many of whom are developing their own methodology with common objectives.

Workshop Objectives

- Discussing the progress made since 2010 by the different groups on defining and implementing a benefit-risk framework within their organisations
- Furthering the thinking regarding how to undertake weightings and valuing within the framework using worked examples/ scenarios and testing the difference between industry and agencies using practical examples
- Identifying how and what visualisation techniques can aid both the inputs and outputs of the process of describing benefits and risks and how this enables stakeholders to a better articulation, understanding and clarity of the benefit-risk decision

Key points from presentations

SESSION: DEVELOPMENT OF A FRAMEWORK FOR BENEFIT-RISK: CHALLENGES AND ARE WE THERE YET?

Is there a need for an internationally accepted approach for the systematic routine and standardised documentation of decision making in the benefit-risk assessment of medicines?

Day 1 Chairman, Professor Bruno Flamion, Chairman, Belgian Committee for Reimbursement of Medicines, Belgian National Institute for Health and Disability Insurance, opened the Workshop with a challenge to participants to demonstrate that the development of a standardised benefit-risk (BR) framework will improve the three most important aspects of regulatory decision making: transparency, consistency and communication.

Those three aspects of decision making are indeed being enhanced by the movement toward an internationally accepted, systematic, routine and standardised documentation of BR decisions, according to Professor Hans-Georg Eichler, Senior Medical Officer, European Medicines Agency. As methodology and presentation evolve from providing implicit to explicit value judgements and from being a reflection of regulators’ values to those of patients, the development of a toolkit for BR assessment will further enhance the predictability and audibility of regulatory decisions.

Those sentiments were echoed by Dr Theresa Mullin, Director, Office of Planning and Informatics, Center for Drug Evaluation and Research, Food and Drug Administration, USA, who, in her presentation of the BR framework under development at the FDA, said that this framework had the potential to improve the predictability and consistency of decision-making through a standardised structure. The power of the framework to clearly outline both the available evidence and the uncertainties and articulate the thinking and judgement behind regulatory decisions can improve transparency of the decision-making process.

Although Dr Ellen Strahlman, Chief Medical Officer GlaxoSmithKline, USA, wholeheartedly...
agreed that a standardised framework for BR assessment is necessary, she outlined some of the challenges to its development, including international and regional differences in available tools, rigor of application, regulatory processes, criteria, clinical guidelines and labelling. Dr Strahlman emphasised the need to extend BR assessment as early and as late as possible in the development continuum and to examine benefits as closely as harms, tracking their impact over time.

Dr Neil McAuslane, Director, Centre for Innovation in Regulatory Science (CIRS), UK reported on the preliminary results of a survey conducted by CIRS to determine, among other things, pharmaceutical companies’ and regulatory agencies’ current approaches and attitudes toward BR assessment. The key perceived advantages identified for implementing a BR framework were as a tool for communication, structured discussion and enhancement of transparency and accountability. Although there is generally a good agreement between agencies and companies on the need and function of an appropriate BR framework, development of visualisation tools for communicating benefit-risk balance within companies and agencies seems currently limited to a few companies.

**Benefit-Risk framework development and visualisation: Current status and forward plans**

The status of the development of the European Medicines Agency (EMA) BR framework was provided by Dr Lawrence D. Phillips, Professor, London School of Economics and Political Science, UK. The first of three work packages of the EMA BR Project: **Description of current practice, Applicability of current tools and methods and Field tests of tools and methods** have been completed and the last two: **Tools and methods for BR assessment and Training modules for assessors** are currently being developed:

To facilitate the opportunity for shared or joint review, the Four-Agency Consortium comprising Health Canada, Swissmedic, Australia’s Therapeutic Goods Administration and Singapore’s Health Science Authority has thus far developed a draft pro forma for a qualitative BR framework. Dr Supriya Sharma, Director General, Therapeutic Products Directorate, Health Canada reported that although certain topics such as the weighting of risks and benefits and visualisation tools are still under discussion, a pilot study is planned for 2012.

Dr Diana Hughes, Vice President, Worldwide Safety Strategy, Primary Care Business Unit Lead, Pfizer Inc, USA explained that the Soft Pilot Program (SPP) of the Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team (PhRMA BRAT) was developed and implemented to gain experience with the BRAT BR framework in a real-world environment. To date, ten companies are participating in the SPP and findings and accomplishments of the programme will be disseminated after its completion in 2011.

Work Package 5 of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) project is to develop methods for continuous benefit-risk monitoring of medicines, by integrating data on benefits and risks from clinical trials, observational studies and spontaneous reports, including both the underpinning, modelling and the presentation of the results, with a particular emphasis on graphical methods.

Dr Alain Micaleff, Senior Medical Safety Advisor, MerckSerono SA, Switzerland, reported that ongoing activities of the programme, which is a project of the Innovative Medicines Initiative (IMI), include the planned publication of their review of benefit-risk methodologies and visualisation methods and the selection of a second wave of products for case study evaluation.

**SESSION: CHALLENGES AND DIFFICULTIES OF PRESENTING BENEFIT-RISK INFORMATION TO STAKEHOLDERS – IS VISUALISATION THE KEY TO INFORMED DECISION MAKING AND INFORMATION SYMMETRY?**

Day 2 Chairman, Professor Sir Alasdair Breckenridge, Chairman, Medicines and Healthcare products Regulatory Agency, UK summarised the first day’s proceedings and introduced this session’s presentations, saying that he would add a fourth item to the three most important aspects of regulatory decision making proposed by Professor Flamion on Day 1: defining and clarifying treatment populations.

The size of a medicine’s beneficial and harmful effects are revealed by data and described and scored for decision makers, whose interpretation is subject to individual perspective and willingness to trade off risks and benefits. The power of visualisation tools to integrate data and to communicate the implications of these tradeoffs was discussed by Dr James Felli, Research Fellow, Eli Lilly and Co, USA.

Using the integrated computing system
Mathematica® Dr Mark Walderhaug, Associate Office Director for Risk Assessment, Center for Biologics Evaluation and Research, Food and Drug Administration, USA and colleagues developed a theoretical model that represents the benefit-risk-uncertainty profile of a medical product, highlights key properties of distributions that may affect decision-making; integrates and unifies data on multiple properties and allows the comparison of two products.

The Medical Products Agency (MPA) of Sweden produces national product monographs containing unbiased information regarding new medicines used by health technology assessors and health authorities. Dr Jane Ahlqvist-Rastad, Senior Expert, MPA, presented case studies of two MPA product monographs that demonstrated negative benefit-risk balances and the consequences of those evaluations.

To learn about the ways in which benefit-risk is communicated to patients and healthcare professionals (HCPs), Professor Sam Salek, Professor of Pharmacoepidemiology, Cardiff University, Wales, posted the benefit-risk Communication Index to a random sampling of physicians, nurses and pharmacists. As a result of the responses of 1167 of these HCPs, Professor Salek’s recommendations include additional research and training in the communication of benefit-risk and the adoption of a systematic approach to risk communication by the government and industry.

Professor Ruth Day, Director, Medical Cognition Laboratory, Duke University, USA, explained that although challenges to effective BR communication such as violations to cognitive accessibility must be overcome, small changes to written communication such as chunking, clustering and coding can result in major positive consequences for comprehension, memory and decision making.

Stating that pharmacovigilance in clinical practice with community pharmacists can improve data collection from patients’ perspectives in real clinical practice, Professor Sylvie Perreault, Faculty of Pharmacy, University of Montreal, Canada, explained that this active surveillance programme, which builds upon multiple existing resources, will monitor clinical signs and symptoms, determine whether anticipated health outcomes are attained and capture information regarding positive or negative unanticipated health related events.

Prof Stuart Walker, Founder, Centre for Innovation in Regulatory Science concluded the presentations, informing Workshop participants that next year’s annual benefit-risk Workshop would likely be somewhat extended to accommodate the vast influx of new material emerging on this important topic. He additionally reported that seven companies and seven agencies have expressed interest in joining a CIRS Benefit-Risk Taskforce. The goal of this group will be the facilitation of productivity and the avoidance of duplicative efforts though ongoing knowledge sharing and the dissemination of reports and other learnings in the critical field of benefit and risk.

Syndicate groups at the Workshop conducted a structured benefit-risk discussion as to whether a hypothetical triptan submitted for approval in the acute treatment of migraine in patients with one or two cardiovascular risk factors should be approved at a high or low dosage or not at all. Before the discussions, scenario designer Dr Bennett Levitan, Director, Epidemiology, Johnson & Johnson PRD, USA, provided background information regarding triptans and migraine as well as an orientation to data on the mock triptan.

**Overall conclusions from the syndicates**

- Assessment tools, be they more qualitative or quantitative in their approach, help provide a transparent structure for the discussion of multifactorial elements of the benefit-risk assessment of a medicine
- Visualisation tools help to focus benefit-risk discussions on critical issues, identifying gaps and exposing overlapping benefits and harms and providing a succinct summary of the information needed to make benefit risk decisions
- In addition to transparency, consistency and communication, articulating and reaching consensus on research questions and meticulously delineating target populations are essential to benefit-risk evaluation
- For conditions involving subjective benefits and harms, patient input is invaluable in informing the thinking of decision makers such as regulators and researchers
- Communicating decision rationales reached through multi-criteria decision analysis to prescribing physicians may require some education on methodology. Results could be simplified for patients by providing a graphically displayed quantification of tradeoffs.
## Workshop Programme

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### Chair’s Introduction

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

### Session 3: Challenges and difficulties of presenting benefit-risk information to stakeholders – Is visualisation the key to informed decision making and information symmetry?

#### Feedback of day one Syndicate discussion

- **Visualisation options for presenting benefit-risk information on new medicines to agencies: Does this need to be improved?**
  - Dr Thomas Lönngren, Strategic Advisor, NDA Group, UK

- **How are the needs and dynamics of regulatory agencies changing?**
  - Dr Thomas Lönngren, Strategic Advisor, NDA Group, UK

#### Feedback from Syndicate discussions

- **Industry viewpoint**
  - Dr James Felli, Research Fellow, Eli Lilly and Co, USA

- **Agency viewpoint**
  - Dr Mark Walderhaug, Associate Office Director for Risk Assessment, Center for Biologics Evaluation and Research, Food and Drug Administration, USA

- **Presenting the regulatory decision on the benefit-risk of a new medicine to physicians: What are the visualisation techniques agencies think are best and do physicians find them useful?**
  - Dr Jane Ahlqvist-Rastad, Senior Expert, Medical Products Agency, Sweden

- **Communication of benefit-risk information to patients by physicians, pharmacists and nurses for shared decision making**
  - Prof Sam Salek, Professor of Pharmacoepidemiology, Cardiff University, Wales

- **Presenting benefit-risk information on a new medicine to patients: What are the challenges and can visualisation improve understanding?**
  - Prof Ruth Day, Director, Medical Cognition Laboratory, Duke University, USA

- **What role has perception in communicating and understanding benefit-risk assessment of medicines?**
  - Prof Sylvie Perreault, Faculty of Pharmacy, University of Montreal, Canada

- **Possible next steps**
  - Prof Stuart Walker, Founder, Centre for Innovation in Regulatory Science, UK
Is there a need for an internationally accepted approach for the systematic routine and standardised documentation of decision making in the benefit-risk assessment of medicines?

Professor Hans-Georg Eichler
Senior Medical Officer, European Medicines Agency

The need for structure in decision making
Whilst most regulators would agree that a benefit-risk framework is a requirement for the evaluation of new medicines, deciding which framework is best suited for a particular type of decision is an additional challenge. Although most current regulatory decisions are rendered through the use of templates that apply qualitative criteria to decision making, the more complex the decision, the less useful this approach may be. For decisions that represent a higher degree of complexity or importance, a quantitative framework, that is, one that combines treatment options with external realities, uncertainties, and value judgements, may prove to be more useful (Figure 1).

Benefit-risk assessment: art or science?
The ingredients of regulatory decision making are data, uncertainties and values. Every regulatory judgement is driven by the probability of an event occurring or not occurring as the result of the use of a medicine and the positive or negative value that is assigned to that event, otherwise known as the "expected utilities." In this equation, however, it is the values of the patients, who will reap the benefits and incur the risks associated with medicine, which must be considered rather than those of the regulator (Figure 2).

In a recent article in the New England Journal of Medicine, Beasley and colleagues clearly explained why the US FDA authorised a higher dose of a certain drug:

“If stroke or systemic embolism and major haemorrhage were considered equally undesirable these rates would indicate similar benefit-risk assessments for the two doses. Most people would agree, however, that the irreversible effects of strokes and systemic emboli have greater clinical significance than non-fatal bleeding. Any benefit-risk assessment in which strokes and systemic emboli are given more weight than non-fatal bleeding would find the higher dose more favorable in elderly patients”

This observation leads to the question whose values should be taken on board to inform regulatory decisions – most likely, it should be patients’ values.

Moving forward
Benefit-risk methodology and presentation is currently evolving to that CIRS-stated goal of “an internationally accepted, systematic, routine and standardised documentation of BR decisions.” The regulatory community has moved to its current state of experimentation with different models by a number of groups and agencies. It will next seek to implement the knowledge gleaned from this experimentation. It is likely that this continued evolution will incorporate both qualitative and quantitative...
assessments moving from implicit to explicit value judgements, adding to regulator’s values that of the patients. In the future, benefit-risk decisions will be graphically demonstrable in a patient-understandable way. A toolkit for benefit-risk assessment must be developed that will make regulatory decisions predictable and auditable, with differing models for individual situations. Using the same detailed and systematic tools should permit the correlation of regulatory opinion regionally, nationally and internationally.

Reference

Figure 2. In the benefit-risk equation, the values of the patients must be considered.

Is there a need for an internationally accepted approach for the systematic routine and standardised documentation of decision making in the benefit-risk assessment of medicines?

The US FDA Viewpoint

Dr Theresa Mullin
Director, Office of Planning and Informatics, Center for Drug Evaluation and Research, US Food and Drug Administration

The evolution of the FDA benefit-risk framework

Dr Mullin presented an update of the FDA’s evolving assessment framework, which, by addressing in more detail an analysis of the condition to be treated and the unmet medical needs surrounding that condition, strives to find a place for the patient’s perspective to inform the agency’s assessment (Figure 3).

Although obviously functioning under different legislations, the FDA framework is conceptually similar to that under construction at the European Medicines Association (EMA) in terms of the elements being considered for inclusion. Despite similarities, cultural differences underpin the frameworks (such as variations in the acceptability of risk among US and European populations) as do practical differences in the nature of the data received by each agency upon which to form their decision (i.e., the availability of patient-level data to the FDA). These differences may in part underscore the divergences in approvals that sometimes occur between the two agencies rather than a difference in the underlying approach to scientific assessment.

The framework, which allows the review team to succinctly summarise in a few pages the key points of a much larger documentation of the review of a new medicine, is intended to function as a facilitator of internal dialogue amongst reviewers and to facilitate public communications about FDA decisions. It has been
piloted using case studies of previous regulatory decisions and facilitates the evaluation of the benefit and risks of a new medicine using five parameters: analysis of the condition assesses the potential morbidity and mortality of the untreated disease or condition; unmet medical need describes the benefits and potential harms of currently available therapies for the disease or condition, including consideration of untreated subpopulations, an area where patient input can be valuable; clinical benefit evaluates data supporting the efficacy of the drug in terms of decreased morbidity or mortality or the alleviation of symptoms; risk considers the occurrence of adverse events associated with the drug, including their frequency, severity and reversibility; and risk management documents the sponsor’s plans for post-marketing studies and other measures designed to ensure the minimisation of potential harm to treated populations.

In addition to the evaluation of available evidence, that is, that which is explicitly known regarding a new medicine, including the submission data from controlled clinical trials and disease state and therapeutic class information from published literature, the framework has evolved for the enhanced consideration of the uncertainties that may surround a drug. These unknown factors include the drug’s potential use and misuse in larger populations as yet unstudied in clinical trials.

**The patient perspective**

In order to more effectively consider the ramifications of patient perspectives to inform the Prescription Drug User Fee Act (PDUFA)-V negotiation process, the agency has been meeting with patient groups and has provided the opportunity for patients to receive education and communication regarding FDA plans, policies and procedures as well to provide their diverse perspectives on the regulation of medicines to the agency.

Because of this diversity in perspective and the extreme variation in risk tolerance even among patients with the same disease, the FDA has been encouraged by a number these patient groups to ensure that the agency continues to serve as the arbiter of adequate efficacy and risk for new therapies. However, rather than wait to incorporate the patient perspective at the time of the review of a new medicine and as part of its long-term plan to facilitate patient-focussed drug development, the FDA plans to convene public quarterly meetings to engage patients, physicians, researchers, and industry members with interest in each of approximately 20 specific serious disease areas. It is anticipated that discussions at these meetings will address measuring disease severity, the merits and flaws of current therapies and unmet medical needs, including underserved populations.

In addition to these efforts, industry resources and support is being sought for the development of reliable, validated patient-reported outcome tools that can form part of a comprehensive development strategy.

**Other benefit-risk assessment initiatives**

Moving forward, the FDA plans to systematically and consistently evaluate the effectiveness of various risk management strategies in use by industry to enhance the limited amount of information that may be available for a particular patient population for a specific disease at the time of regulatory review.

Finally, the FDA will be pressing industry for electronic submission and for the standardisation of data and terminology for purposes of easier input into modelling tools for analysis and for the quantification of benefits and risks and the characterisation of their associated uncertainties. These efforts will support FDA efforts to optimise the transparent and explicit nature of their decision making.
Visualising benefit-risk: An industry perspective

Dr Ellen Strahlman
Chief Medical Officer GlaxoSmithKline, USA

Benefit-risk assessment at GlaxoSmithKline

Operating in 85 different countries, with approximately 50,000 licenses worldwide, GlaxoSmithKline (GSK) currently has 30 new medicines in late-stage development and approximately 44,000 subjects participating in clinical trials in 2011. Somewhere in the world, a GSK facility is hosting a regulatory inspection every working day of the year, and each year, one GSK product is terminated for safety reasons. In order to keep the benefit-risk balance as positive as possible throughout its products’ life cycles across such a large and diverse organisation, GSK has a systematic, routine and standardised system of medical governance that allows early, targeted and informed examination of benefit-risk issues (Figure 4).

As the Chief Medical Officer of GlaxoSmithKline, Dr Strahlman identified herself as the benefit-risk “owner” of its products and pipeline on behalf of the ultimate GSK stakeholders, its patients. Dr Strahlman leads the regulatory, safety and compliance groups at GSK, which are deliberately kept separate from GSK commercialisation. Part of the medical governance at GSK, the Global Safety Board reviews products throughout their lifecycle.

Guidance given to GSK teams from the Board includes advice to provide a clear explanation of how the medicine will meet the needs of patients, regulators, and payers; list go/no go criteria, surrogates for clinical benefit and unfavourable effects of the medicine; and describe how the medicine fits within its therapeutic area and within the class of compounds.

In addition to the multiple internal efforts to manage benefit and risk, GSK is involved externally in a number of activities taking place through groups such as the Pharmaceutical Research and Manufacturers of America (PhRMA BRAT) the European Federation of Pharmaceutical Industries and Associations (EFPIA), The Innovative Medicines Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (IMI PROTECT), and the Next Steps Working Group. In addition, in an effort to achieve external transparency regarding its data, GSK has made a commitment to publish or post data from all its clinical trials on publicly available websites.

Despite ongoing group efforts, however, there are multiple challenges inherent in the international assessment of benefit and risk. Labelling is not consistent across the world and the level of rigour in evaluation and the availability of necessary tools to do so vary by country and region. Review processes, terminology, principles, criteria and guidelines differ among regulators, and even within agencies, advice with regards to benefit-risk assessment can vary by reviewing department.

Key elements of a benefit-risk framework

The methodologies derived from a successful benefit-risk framework share certain important features (Figure 5). A certain level of structure, standards and governance is required, even though a high degree of flexibility should surround these rules and procedures. Graphics are an important element of the process, allowing transparent visualisation of the juxtaposition of the key benefits and risks of a product in the same chart or graph. Quantified measurement serves two purposes: creating graphic visualisations and ensuring objectivity. Scientific insight ascertains the application of objective and clinically meaningful standards, allowing implicit assumptions to be made explicit. Finally, within an effective methodology, unfavourable effects should be able to be monitored and managed, and the extent of
Another ongoing issue among benefit-risk stakeholders is the unequal concentration on the monitoring of potential risks associated with a medicine at the expense of the consideration of its benefits.

Favourable effects calculated. Understanding the effects of a treatment, particularly a chronic or long-term treatment, helps better quantify the experience of patients.

Challenges to consider
Several recent studies have found an association between the GSK anti-epilepsy drug lamotrigine and sudden unexplained death from epilepsy (SUDEP). The results of these studies are not conclusive. When looking at the range of evidence for benefit-risk evaluation, such as occupational data, clinical data, clinical trials and case controls studies, reasonable people can come to very different opinions regarding the association of therapy with SUDEP and the results of a pooled analysis of several case control studies are subject to interpretation. However, the emergence of these data almost 20 years after the medicine’s approval points to the fact that benefit-risk evaluation should not only begin earlier in a product lifecycle but extend far beyond obligatory post-marketing milestones.

Another ongoing issue among benefit-risk stakeholders is the unequal concentration on the monitoring of potential risks associated with a medicine at the expense of the consideration of its benefits. It would be advantageous to improve our willingness and ability to track the impact of a medicine’s benefits over time and evaluate long-term changes in the benefit picture. In the past 20 years, treatments for cardiovascular and HIV disease, cancer, rheumatoid arthritis, and diabetes have had a tremendous impact, turning formerly fatal conditions into chronic but treatable illnesses. By applying a benefit-risk assessment to an evaluation of these therapies, it may be possible to learn from past examples of disease area benefits.

Dr Strahlman concluded by remarking that the generation of evidence and the development of a model framework and scientifically valid methodologies for the evaluation of safe and effective medicines to fulfil unmet medical needs is a societal obligation for all healthcare stakeholders.

Framework for benefit-risk assessment: Current approaches and future directions

Dr Neil McAuslane
Director, Centre for Innovation in Regulatory Science

Dr McAuslane presented the preliminary results of a survey of 20 companies and 11 agencies that was conducted in order to develop a collective understanding of the current status of the development of benefit-risk systems, criteria for their use, and the advantages and disadvantages of the various models. The survey additionally aimed to identify internal and external barriers and possible solutions to the incorporation of a benefit-risk framework and methodologies into the development, regulatory review and ongoing assessment of medicines.

Systems and satisfaction
In the first survey question, respondents were asked to identify the type of system being used by their organisation to assess
benefit-risk: qualitative, semi-quantitative, or quantitative. Results indicated that companies and agencies were both approximately evenly divided between use of qualitative and semi-quantitative methodology while no company or agency employed a fully quantitative framework. For those groups not using a semi-quantitative or quantitative system, the reasons most frequently cited were the lack of agreement on the underlying common benefit-risk framework among peers and stakeholders, the fact that such a framework was not required for current product development, the need for a scientifically validated framework and a dearth of knowledge about benefit-risk frameworks and methodologies in general. However, three of the ten companies and three of the five agencies using a fully qualitative model planned to develop a semi-quantitative model within the next three years.

The majority of respondents from both agencies (4 of 6) and companies (6 of 9) using semi-quantitative frameworks were not satisfied with that model for reasons including a lack of internal validation and a general need for improvement in its methodology. Respondents from both groups indicated that within their methodologies, they sometimes but not routinely assigned values and weights to benefit and risk parameters. When asked if certain specific parameters i.e. incremental net benefit, quality-adjusted life years, patient preferences, number needed to treat and number needed to harm were used in their evaluations, respondents again indicated that these parameters were sometimes, but not routinely, used with agency respondents indicating a primary use of the number-needed-to-treat and the number-needed-to-harm parameters.

Advantages and barriers
When provided with a list of nine potential advantages to using a common benefit-risk framework, the three advantages that were rated highest by both agencies and companies were the potential for a framework to act as the basis for a tool for communication among peers within organisation, for it to act as a tool for communication between organisation and stakeholders, and for it to provide documentation for structured discussion. There was a difference between company and agency perception for one of the listed advantage: the potential for the framework to act as a training tool was rated highly by 54% of agency respondents whilst none of the company respondents regarded this as a highly advantageous characteristic.

Companies and agencies were also asked to rate the significance of eight potential barriers to the use of a benefit-risk framework. The four barriers rated highest by company respondents were the lack of a framework accepted or recognised by stakeholders both within and outside the company, the lack of a scientifically validated set of methodologies, resource limitations to implement a benefit-risk assessment programme and a lack of knowledge and expertise to execute the framework. Two other barriers, cultural change within companies and significant change to work processes were also indicated as medium-level challenges by a significant number of company respondents. Agency responses also indicated that the lack of a framework accepted or recognised by stakeholders was rated as a high-level challenge, but the lack of a scientifically validated framework, lack of knowledge or expertise within the agencies to execute the framework and its methodologies and the significant retraining of staff were also rated as medium-level challenges by a majority of respondents.

Perceptions of need for the framework
Thirteen statements were provided regarding the need for an appropriate benefit-risk framework covering its value as a communication tool, the benefit-risk framework itself and the functions of the benefit-risk framework. Companies and agencies were asked to rate the statements as strongly agree, agree, indifferent, disagree or strongly disagree.
Responses related to the communication of benefit and risk indicated that the majority of both agencies and companies agreed that the purposes of establishing an appropriate benefit-risk framework and methodologies include the improvement of the transparency, communication and the consistency of the decision.

For the purpose of this preliminary analysis, Dr. McAuslane grouped the data into two categories, agree/strongly agree and indifferent/disagree/strongly disagree.

Responses related to the need for a benefit-risk framework indicated that the majority of both agencies and companies agreed that there is an overall need for a benefit-risk framework to be used by both groups, that it is possible to develop an overarching benefit-risk framework that will drive the use of specific methodologies and that the framework and its methodologies should be used at all stages of drug development from drug development through post approval. However, whilst the majority of companies agreed that the framework should also be applicable to health technology assessment groups and that there is a need for therapeutic area-specific benefit-risk frameworks, the majority of agency respondents were indifferent or disagreed (Figure 6).

Responses related to the function of the benefit-risk framework indicated that the majority of both agencies and companies agreed that benefit-risk frameworks can be utilised across regulatory divisions within an agency, they enable assessments and development of benefit-risk management plans and that all stakeholders should be part of the development and validation of these benefit-risk assessment tools. However, whilst the majority of companies agreed that the framework should be utilised across agencies world-wide, the majority of agencies were indifferent or disagreed. Regulators agreed that their preference would be to use a quantitative rather than a purely qualitative approach to benefit-risk assessment but company responses indicated that they wanted to reserve the opportunity to use both qualitative and quantitative methodologies. But both agencies and companies disagreed that the purpose of an appropriate benefit-risk framework is to define a number that translates the benefit or balance in absolute terms and can be used to measure its sensitivity to various parameters.

Responses related to the communication of benefit and risk indicated that the majority of both agencies and companies agreed that the purposes of establishing an appropriate benefit-risk framework and methodologies include the improvement of the transparency, communication and the consistency of the decision. Further there is a need for a coordinating group including representatives from most relevant stakeholders to ensure the appropriate direction and application of the appropriate benefit-risk systematic standardised framework (Figure 7).

When asked to rate seven criteria for reviewing benefit-risk models and methodological approaches as highly significant, less significant or not relevant, there was general agreement between both groups of respondents regarding the significance of logical soundness, acceptability of results and practicality and presentation, whereas the scope, comprehensiveness and specificity and sensitivity were rated slightly less important.

The top three hurdles to the use of a benefit-risk framework specified by all respondents were divergent stakeholder perspectives, disagreement on what is an appropriate methodology(ies) and lack of alignment or buy-in by agencies and stakeholders. The top solutions specified were

- Better dialogue between stakeholders to develop consensus/agreement on a general validated framework focusing on a toolbox of methodologies adaptable for different situations
- Training and education
The final question concerned visualisation: Has your organisation developed an effective visualisation tool for communicating benefit and risk internally, to agencies/companies, to healthcare professionals and to patients? Responses indicated that although some companies have developed tools for communication with some of the groups named, no agency respondents indicated that such a tool had been developed within their organisation.

Summary
Although no company or agency that responded to the survey is currently using a fully quantitative model for benefit-risk assessment, agencies and companies are both looking to improve on their existing methodologies or systems of assessment and some of those using qualitative frameworks are looking to move to a semi-quantitative or quantitative model. In all likelihood, the methodology(ies) that an organisation will settle on will incorporate elements of both qualitative and quantitative decision making.

The key perceived advantages identified for implementing a benefit-risk framework, particularly for companies, were as a tool for communication, structured discussion and enhanced transparency and accountability, whereas the biggest barrier named was a lack of a scientifically accepted or recognised framework or methodologies. There is generally good agreement, however, between agencies and companies on the need and function of an appropriate benefit-risk framework and the key hurdles to its implementation mainly relate to the divergent stakeholder perspectives and lack of accepted methodologies and solutions. Finally, development of visualisation tools for communicating benefit-risk balance within companies and agencies seems to be in its earliest stages.

Dr McAuslane emphasised that these were the preliminary findings of a detailed study and that a full report will be produced and sent to respondents to the survey.

Status of EMA benefit-risk framework development

Dr Lawrence D. Phillips
Professor, London School of Economics and Political Science, UK

Benefit-risk framework Work Package 1

Because there is currently no standard methodology for evaluating the benefits and risks of new medicines, the European Medicines Agency (EMA) embarked on a three-year project consisting of five Work Packages (WPs) to “develop and test tools and processes for balancing multiple benefits and risks as an aid to informed regulatory decisions about medicinal products.”

Begun in 2009, WP1 was undertaken to describe the current practice of benefit-risk assessment throughout Europe. Members of the project team participated in a series of interviews and observation sessions at five volunteer agencies in Sweden, France, The Netherlands, the UK and Spain.

Along with information such as each agency’s history, governmental relationships and organisational structure, the final report of this Work Package detailed processes and models used by these agencies for assessing the benefits and risks of new medicines and described the meanings assigned by participants to the terms benefit and risk. Results detailed in the completed report for this Work Package demonstrated that despite varying structures, organisational systems and informational flow, all five agencies arrived at benefit-risk decisions “intuitively” through a process of discussion, and no agency employed a formal model for benefit-risk assessment.

Interpretations of the terms benefit and risk varied widely, with more disparity noted in participants’ characterisation of risk (51 definitions) compared with characterisation of benefit (37 responses; Figure 8). Based on this lack of consensus for terminology, the project team recommended that the EMA adapt the benefit-risk assessment portion of its 80-day guidance document to specify that assessors identify a product’s favourable and unfavourable effects, describe any uncertainties surrounding those effects and then decide if the favourable...
effects with their uncertainties outweigh the unfavourable effects with their uncertainties (Figure 9).

**Work Package 2**

Completed in August 2010, WP2 was an extensive review of the applicability of current tools and methods for benefit-risk evaluation. Dr Phillips and his team reviewed three qualitative and eighteen quantitative approaches to benefit-risk assessment. Of these approaches three were found to quantify effects and uncertainties: 1) Bayesian statistics, which can revise beliefs in the light of new data, making it particularly useful in post-marketing analysis; 2) decision trees or influence diagrams, which can model uncertainty, and 3) multi-criteria decision analysis (MCDA), which can model benefit-risk trade-offs, and which is the only theoretical system that provides for both values and uncertainties. Dr Phillips expressed his belief that whatever future quantitative method for benefit-risk assessment is adopted, it will be based on MCDA and its further development to accommodate multiple conflicting objectives. The review team found that five other approaches demonstrated supplementary modelling attributes: probabilistic simulation for modelling effect uncertainty; Markov processes and Kaplan-Meier estimators for assessing health-state changes over time; quality-adjusted life years for modelling health outcomes; and conjoint analysis for assessing trade-offs among effects.3

**PrOACT URL**

After discussing the currently available benefit-risk models reviewed in WP2, Dr Phillips outlined a type of MCDA framework, the Problem, Objectives, Alternatives, Consequences, Tradeoffs (PrOACT) Uncertainty, Risk tolerance, Linked decisions (URL) decision framework developed by Hammond and colleagues4 that would be used in the Syndicate discussion session for which he would act as facilitator (see page 43). In the first five steps of the PrOACT model, the user determines the nature of the problem and its context; establishes the objectives and the criteria for favourable and unfavourable effects; identifies the options to be evaluated against the criteria; considers how each option performs for the criteria; and assesses the balance between favourable and unfavourable effects, allowing the creation of an “effects table.”

Although these first five steps may assist in creating a benefit-risk profile, at this point, only issues concerning the favourable and unfavourable effects, and their balance, have been considered. The next three steps are relevant in considering how the benefit-risk balance is affected by taking account of uncertainties. First, the user considers how the benefit-risk balance would be affected by uncertainty; second, judges the relative importance of the decision maker’s risk attitude for this product and indicates how this affects the balance; and finally, links decisions, that is, considers the consistency of this decision with similar past decisions, and assesses whether this decision could impact future decisions.

**Work Package 3**

WP3, which was initiated in September 2010 and is currently being implemented, consists of field tests of the most appropriate benefit-risk models in five European regulatory agencies through the conduct of facilitated workshops called decision conferences at which the benefit-risk balance of five drugs were evaluated by experts representing diverse perspectives and experiences.

Before and after these conference attendees answered a series of questions concerning the utility of those processes, tools and organisational structures used at the meeting.
The status of the Four-Agency Benefit-Risk Consortium

Dr Supriya Sharma

Director General, Therapeutic Products Directorate, Health Canada

Background to the Consortium

In April 2009, representatives from four similar sized, “like-minded” agencies met for the first time with Professor Stuart Walker and Dr Neil McAuslane of CIRS to develop a qualitative methodology based on a common framework for the benefit-risk assessment of medicines. The “Four-Agency Consortium”, represented by Drs Jason Ferla from the Therapeutic Goods Administration in Australia, Huei-Xin Lou from the Health Sciences Authority of Singapore, Petra Dörr from Swissmedic and Supriya Sharma from Health Canada hoped that such an approach would facilitate the opportunity for joint or shared reviews.

The Consortium approached this plan with a record of prior collaboration. There were a series of existing bilateral agreements for work sharing, quarterly Heads of Agencies teleconferences and regular face-to-face connections during other meetings. Additionally, the agencies had a history of information sharing through vehicles such as assessment reports and safety information. Pilot projects of parallel reviews had taken place as well as other exercises that built mutual confidence in one another’s processes.

Questionnaire results revealed that when considering the post-meeting change in attendee perspective on the modelling process used at the conference on a seven-point scale, the biggest alterations in responses concerned the model’s ability to

• easily test different perspectives for their impact on the results;
• assist in the exploration of how the overall balance is affected by a reduction or increase in uncertainty;
• help evaluators to see the impact of uncertainties on the benefit-risk balance;
• provide a clear structure;
• assist in the combination of data about value and uncertainty into an overall balance between favourable and unfavourable events; and
• help make assumptions, multiple objectives and trade-offs explicit.

Dr Phillips concluded by remarking that It is the combination of decision analysis and social process that creates intelligent decisions. The final two Work Packages of the EMA benefit-risk project are currently in development.

References


and expertise. Through these projects, the agencies gradually moved toward the goal of true work sharing, while retaining the privileges of independent decision-making. All of these prior experiences highlighted the need for common IT platforms, templates and processes, in particular, the need for a common benefit-risk assessment template.

The project was initiated with a feasibility study in 2009, followed by a pilot study begun in 2010 (Figure 10). In the pilot study, a draft framework or "pro forma" was developed through a two-team retrospective analysis of a product approved by Australia and Canada and a product approved by Switzerland and Singapore. In this process, the teams found that although there were differences in the representation of certain sections of the assessment reports, such as preclinical toxicology or chemistry manufacturing, comments made on the clinical portions of the reports were remarkably similar among the groups. The group will continue to refine the pro forma through the team analysis of additional products. The pro forma is currently being adapted for an electronic platform.

The Consortium expects to accrue specific benefits through the use of a benefit-risk template. Evaluators using such a tool will be required to think and articulate each benefit and risk clearly. Templates can act as efficient checklists for items to consider in an evaluation, an attribute which may be especially important for new evaluators. Templates carry the potential for the standardisation of approaches to benefit-risk evaluation across agencies as well as for the in-class comparisons of drugs. It is additionally hoped that the use of benefit-risk frameworks will optimise internal consistency in regulatory decision making and the clear and consistent communication of the potential harms and benefits for new medicines.

**Topics under discussion**

Among issues still to be determined, Consortium members must decide if the finalised template will replace existing documents at their agencies or function as an alternative or additional document for purposes of work sharing among the group. When complete, the template is expected to be large and comprehensive, and the amount of time that may be required for its completion may present a significant obstacle to reviewers with timelines that are already compressed and who ultimately must be convinced that use of a benefit-risk template will contribute positively to the health and safety of the patients they serve. It will be necessary to be clear that completion of the entire template, or completion in a particular order is not mandatory.

Weighting individual parameters continues to present the most challenging aspect of benefit-risk evaluation. Consortium members must decide if parameters are to be weighted according to, among other things, their severity or relevance and the Consortium needs to establish how allocated weights will be assigned to specific patient populations. Reviewers who may implicitly know an appropriate weight to assign to a benefit-risk parameter must translate that process into an explicit evaluation that can be communicated to all stakeholders. When the pro forma is complete, the Consortium hopes to begin the incorporation of a visualisation aspect such as the use of Forrest plots, which will further assist in that communication.

**Next steps**

It is anticipated that the electronic pro forma will be completed by September 2011 (Figure 11) and that a retrospective pilot study will be then initiated, ideally with one industry and two agency participants. Between December 2011 and early 2012, the groups will conduct follow-
up discussions on the outcomes of the study and a member of the Consortium will report the results of the pilot study at the 2012 CIRS Benefit-Risk Workshop. Although a lengthy and iterative process, the Consortium feels strongly that the development of this template will prove beneficial to the four agencies involved and ultimately to patients everywhere.

PhRMA Benefit-Risk Soft Pilot Program Update

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

The PhRMA BRAT Benefit-Risk Framework

The Pharmaceutical Research and Manufacturers Association (PhRMA) Benefit-Risk Action Team (BRAT) initiative was begun in 2006 when it was adopted as a key element of innovation for the PhRMA five-year strategy plan. The overarching mission of the initiative is to improve benefit-risk assessment during drug development and the regulatory approval process, increasing the transparency, predictability and consistency with which benefit-risk assessments are conducted and improving the communication of benefit-risk information to patients and healthcare professionals and other stakeholders. In order to accomplish these strategic goals, the BRAT mandate is to develop a structured, transparent framework for benefit-risk assessments with the idea of facilitating its use within PhRMA member companies and eventually integrating it into the regulatory decision-making process.

In addition to keeping abreast of the activities within the policy and the regulatory environment, BRAT conducted interviews with 16 companies to build a baseline of industry perspectives on benefit-risk and benefit-risk assessments to support policy advocacy. The consolidated and blinded results of these interviews revealed that most companies engage with regulatory agencies in discussions of benefit-risk profiles, but only some do so consistently throughout the development of a medicine, and few companies leverage explicit benefit-risk frameworks during FDA and EMA approval discussions. Interview respondents reported challenges specific to benefit-risk assessments when interacting with regulatory agencies as well as within internal discussions and as a result, voiced interest in developing a common benefit-risk language and approach.

As a result of this research as well as its own mandate, the benefit-risk framework developed by BRAT enables a structured and transparent approach to benefit-risk assessments. It is designed to supplement rather than substitute for expert judgement and to facilitate a balanced approach. Although the framework focuses on qualitative elements, it has the
The ability to incorporate any available quantitative methodologies necessary to introduce weighting based on conjoint or other studies. In 2010, the BRAT framework was applied to three hypothetical example medicines, a triptan, a statin and a tumour necrosis factor inhibitor to examine its use in three different disease area paradigms.1

The BRAT framework is not a model but rather a set of flexible principle guidelines and tools that help a decision-maker select, organise, understand and eventually summarise the key data relevant to a particular benefit-risk decision and promote the transparency of the decision-making process. The framework embraces the complexity of real-world data, representing and accounting for uncertainty and missing information and allowing the concurrent consideration of multiple benefit-risk parameters. It also accounts for the nature and differing importance of benefits and risks, enabling the use of weighting methodologies and examination from the perspective of multiple stakeholders. In addition, the framework is applicable in multiple contexts and accounts for the comparative nature of benefit-risk either from the use of trial comparators or therapeutic standards of care.

The six steps of the BRAT framework each consist of a set of specific activities (Figure 12). In step one, define the decision context. the dose formulation, indication, patient population, comparators, decision perspective and time horizon for benefit and risk outcomes will be determined. In step two, identify and select benefit and risk outcomes, creation of an initial value tree will determine the preliminary set of outcome measures. In step three, identify and extract source data, data sources to support outcome measures will be determined and data extracted and input into data summary tables in readiness for creating summary visualisations. In step four, customise the framework, the value tree is re-examined and revised to incorporate additional clinical context. In step five, assess the outcome importance, informal or formal weighting methodologies are employed to determine the relative importance of all outcomes. Finally, in step six, display and interpret the key measures, data are summarised in a visual format to aid in interpretation and decision, information gaps are filled in and sensitivity analyses are conducted.

The Soft Pilot Programme

To obtain real-world experience with use of the BRAT benefit-risk framework, PhRMA commissioned the Soft Pilot programme, which will be executed through BRAT under the guidance of Dr Becky Noel from Eli Lilly. The goals for this programme are to gain member company experience with the framework process and tools, to use that experience to further refine and develop the framework and to help facilitate increased use across the member companies. The collective feedback from the pilot programme will also be used by PhRMA to further advocacy efforts regarding benefit-risk.

In the Soft Pilot programme, volunteer companies will independently select assets for framework implementation, without limitations on drug, therapeutic area or stage of development. Companies will apply the framework into existing processes at their own discretion, customising it to fit individual benefit-risk approaches, preferred methodologies and available data.

Interested companies were encouraged to begin participating in the pilot beginning in February 2011, but are welcome to do so at during the first three quarters of 2011. The pilot was initiated with a global webinar and enrolled companies have been given free access to a number of tools that facilitate the application of
The Innovative Medicines Initiative (IMI) is “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. IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe.”

Each year since 2008, IMI has called for proposals for research on topics in medicine such as safety, efficacy, communication, training and education. One such research project, the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) was initiated in September 2009 as a five-year project, with an overall budget of over 21 million Euros.

The objective of PROTECT is to “strengthen the monitoring of the benefit-risk of medicines in Europe.” PROTECT has been designed as a comprehensive and integrated project aiming to develop and validate a set of innovative tools and methods that will 1) enhance data collection directly from consumers in their natural language; 2) improve early and proactive signal detection; 3) develop methodological standards for the design of pharmacoepidemiological studies; 4) develop methods for continuous benefit-risk monitoring of medicines; and 5) test and validate various methods developed in PROTECT.

Seven Work Packages (WPs) have been designed to fulfil these objectives. One WP is concerned with all aspects of the organisation and management of PROTECT, two “horizontal” WPs are concerned with the communication,
validation and integration of the scientific work into an integrated and cohesive European activity and four “vertical” WPs target specific objectives and methodological developments. Work for the WPs is guided by a Steering Committee consisting of WP co-Leaders and the Deputy Coordinator, with additional guidance and recommendations provided by an external Advisory Board composed of members with backgrounds in pharmacoepidemiology, pharmacovigilance and benefit-risk management. (Figures 14 and 15).

Work Package 5

Dr Micaleff reported on the status of Work Package 5, one of the vertical WPs targeting a specific PROTECT objective, that is, objective 4: to develop methods for the continuous benefit-risk monitoring of medicines, by integrating data on benefits and risks from clinical trials, observational studies and spontaneous reports, including both the underpinning modelling and the presentation of the results, with a particular emphasis on graphical presentation.

While recognizing the relevance of pre-approval benefit-risk assessment, the scope of WP5 only covers the benefit-risk assessment during the submission and post-approval periods. The project addresses individual and population-based decision-making and considers the perspectives of multiple stakeholders including patients, physicians, regulators and industry as well as the societal views necessary for health technology assessment (HTA). There may be some possible dependencies with other PROTECT Work Packages and other relevant external programmes. The WP will incorporate the review and selection of methodologies and of visualisation methods, the choice and implementation of case studies, and the visualisation and communication of benefit-risk.

The WP5 project team includes representatives from regulatory agencies, industry, academia and patient groups, some of whom are also involved with other Work Packages. Six work streams have been developed to fulfil the charter of the WP: the charter, the review of methodologies and graphical tools, the choice of case studies in two waves, the collection of data required for running these case studies, software to support application of the methodologies and graphical tools and finally application to case studies.

Much was achieved during the project’s first year including completion of the charter, development of the protocol for the review of all benefit-risk methodologies and the selection of products for the first wave of case studies, all medicines that have been withdrawn or returned to the market and which have already been the subject of some benefit-risk assessment by regulators. Additionally, the ProACT URL framework discussed by Professor Phillips (see page 16) has been selected for preparation of case studies and data collection. Members of WP5 also had interaction with the Observational Medical Outcomes Partnership (OMOP), the US FDA’s Sentinel Initiative, and PhRMA BRAT as well as made numerous presentations at congresses,
conferences and other meetings. Ongoing activities in this second year include work toward expected finalisation of the review of the benefit-risk methodologies and visualisation methods with a possible publication of the results. Finally, the criteria for and selection of wave two case studies is being determined and data for these studies will be gathered.

References

Visualisation options for presenting benefit-risk information: Can these be improved?

Dr James Felli
Research Fellow, Eli Lilly and Co., USA

Product labels: perspective
Using a typical package insert to illustrate the representation of benefit and risk for a new product, Dr Felli demonstrated the potential effects of this type of communication for consumers and other healthcare stakeholders. In the sample insert illustrated in his exercise, the concepts of benefit and risk were most often represented by the words “relief” and “adverse events,” with words representing risks occurring far more frequently throughout the document. This repeated interjection of descriptions of potential adverse events among the descriptions of the potential aspects of effectiveness of the medicine made it difficult for the reader to form a balanced conclusion as to whether the risks of that drug are worth its benefits. In this illustration, non-committal pairings of statement of benefits and harms did not appear to provide a balance with which a reader could form an informed opinion.

The sample insert used relatively broad statements to describe the degree of risk; for example, “incidents of reported reaction between three and nine percent in those reactions occurring in less than three percent of patients” or “the following adverse experience have also been reported in approximately one to ten percent of patients.” Deciding if these numbers or that degree of risk are clinically important, however, can be challenging without the assistance of relative concepts.

The common phrase “one in 1000,” is more meaningful when examples of the likelihood of the occurrence of specific events are tied to the statistic. For example, by one account a person in the United States has an average one in 1000 chance of getting rabies from a bat bite. The number also approximates the chance that someone drawing four playing cards from a deck will select all face cards or that ten tossed coins in a row will land heads up. Marrying these types of common observations to the incidence of clinical rare adverse events may provide context within which patients and other stakeholders can make a more informed decision about the risk of incurring that event.

Visual representation of risk can provide an aid to comprehension, especially if presented from a perspective of relative incidence. One recent publication reported that one in 1000 patients would die from Torsades des Pointes, given a continuous QTc prolongation of 25 over the course of one year. Representing this as a point risk visually, as one dot in a field of one thousand may provide a different perspective than if it were represented as a thousand dots in a much larger field of a million.
Product labels and the visualisation of supportive data

Product label data, whether presented as raw or scaled information or utility scores can focus conversation on differences and lead to a more complete understanding of weights. Sparklines are simple focused linear graphics developed by Edward Tufte that are meant to appear as part of text.\(^2\) Rather than being the visual depiction of the data, sparklines are meant to represent the differentiation of or trends for information and can foster dialogue about differences in benefit and risk.

Data can be described, scored or valued, singly or in combination. Description allows the categorisation of data, whereas activities such as valuing, scoring, or placing a benefit or harm parameter in a hierarchy enables relationships and preferences to be communicated. For example, using numerical categories to describe the degree of hepatobiliary toxicity of a drug permits the stakeholder to differentiate treatments on the basis of hepatobiliary toxicity and lays the groundwork for scoring the relative potential risks. The initial categorisation of severity permits a more open discussion of how one values the risk and degree of an event.

Scatterplot graphics, in which the potential effects of a drug can be plotted on a chart using axes of favourable and unfavourable effects, can also facilitate the calculation and communication of the overall balance of benefits and risks of a particular treatment as well as its comparison with other treatments (Figure 16).

Representing the unfavourable and favourable effects of a drug as hues of colour is another visual method of allowing a stakeholder to assess the degree of benefit and harm and therefore be more informed about selecting the trade off between risk and benefit with which they are most comfortable (Figure 17).

For example, if the potential benefits of a cancer therapy were shown in a graphic as progressing from lightest to darkest blue and the incidence of its harms were portrayed using lightest to darkest red, a physician or patient would ideally choose the therapy represented with the lightest red, which represented the lowest chance of a harm accompanied by the darkest blue, which represented the greatest chance of tumour reduction. More importantly, this form of representation allows each stakeholder to more clearly define their level of benefit expectation and risk tolerance.

Dr Felli concluded by remarking that the emergence of novel diagnostic and therapy optimisation technologies and the development of socio-medical networks should greatly facilitate doctor-patient communication and therapeutic decision making.

References

There is a strong interest in developing more formal, quantitative methods of benefit-risk analysis for medical products, and new technologies have enabled the creation of visualisation tools that can stimulate creative new thinking and dialogue in this area.

Dr Mark Walderhaug
Associate Office Director for Risk Assessment CBER, Food and Drug Administration, USA

There is a strong interest in developing more formal, quantitative methods of benefit-risk analysis for medical products, and new technologies have enabled the creation of visualisation tools that can stimulate creative new thinking and dialogue in this area. Dr Mark Walderhaug presented one such tool, which he is currently developing along with colleagues from the US Food and Drug Administration Center for Biologics Evaluation and Research and Norfolk State University. Dr Walderhaug emphasised that the findings and conclusions in this presentation have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy.

Through the use of Mathematica software, the team has created a theoretical model that represents the benefit-risk-uncertainty profile of a medical product as a bivariate normal distribution. In this model, which assumes that risks and benefits can be represented as a common metric, they are denoted as points on a two-dimensional surface. However, the uncertainty about those parameters means that the exact coordinates are unknown, and this uncertainty is depicted in the model as a three-dimensional surface in which the height of the surface represents the probability that a treatment has a particular risk-benefit coordinate.

The concepts of risks, benefits and uncertainties can be extended to a comparison of two products or a comparison of a new product versus the status quo and users can interactively manipulate the parameters of both distributions. Depending on differences in risks and benefits between the two options, and the variances of the two distributions, the choice between the two can be obvious or extremely difficult to observe (Figures 18 and 19).

The evolution of benefit-risk
The understanding of risks and benefits of a new medicine evolves over time. Although phase 3 trials provide important data regarding a drug’s safety and efficacy, they may not be large enough or long enough to detect rare adverse events. Dr Walderhaug provided a realistic but fictionalised example of the ability of the model to map this evolution with the case of a hypothetical vaccine to protect against a common virus that causes severe diarrhoea in children. The benefits of the vaccine’s use in developed countries included reduced disease burden and hospitalisation for children and reduced burdens on caregivers; whilst the primary risk was intussusception, a serious and potentially life-threatening condition in which the intestine becomes blocked or twisted.

Because the occurrence of this adverse event is very rare, it was not discovered during clinical trials. Using binomial distribution to simulate the occurrence of adverse events, the model was able to show no increased risk for the use of a second vaccine using the assumptions that vaccines prevented an average of 91.5% (85%-98%) of hospitalisations and 1 in 15,000 children receiving the first vaccine had a severe adverse event caused by the vaccine.

Advantages and limitation of the model
The use of this tool allows key properties of distributions that may affect decision-making...
Presenting the regulatory decision on the benefit-risk of a new medicine to healthcare professionals

Dr Jane Ahlqvist-Rastad  
Senior Expert, Medical Products Agency, Sweden

MPA monographs  
The Swedish Medical Products Agency (MPA) routinely compiles national monographs assessing new drugs, which are informed by the local treatment tradition and healthcare system. These monographs are used by a variety of Swedish healthcare stakeholders including regional drug advisory committees, the national health technology agency, prescribers and other health authorities.

After positive opinions for new medicines are issued through the Centrally Authorised Procedure (CAP) by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) or when a drug has been approved through other national non-CAP European procedures, the MPA prioritises their preparation of national product monographs for these medicines based on their importance and the size of the potential treatment populations in Sweden. The resulting monographs directly refer to the European Public Assessment Reports (EPARs) for CAP drugs and the Public Assessment Reports for non-CAP drugs and when available, to publications of clinical trials which were included in the application dossier. The language of those reference documents does not present a barrier to Swedish healthcare professionals, who are typically proficient in English. Resulting MPA monographs describe efficacy and safety data available at the time of authorisation and are not updated on an ongoing basis. Treatment guidelines prepared with the guidance of Swedish healthcare professionals help monograph users evaluate the place of the medicine in the therapy armamentarium.

An important part of the new drug monographs, MPA benefit-risk evaluations are conducted using a structured, mainly qualitative approach. In the evaluation, emphasis is placed on local medical need, and benefits and risks are evaluated in a specific therapeutic context, with the benefit-risk balance estimated for each major patient subpopulation over time. The most
to be highlighted. Additionally it integrates and unifies data on multiple properties of a product and encourages stakeholders to interact with the visualisation to explore “what-if” scenarios. The model does have some inherent limitations.

Results still require expert judgement to make a final decision and currently, only statistical uncertainty can be considered with this tool. The conversion of benefits and risks to a common unit represents a significant challenge. However, as an extension to this work, Dr Walderhaug and colleagues are developing examples using hypothetical and actual data to map multiple risks and benefits to three-dimensional surfaces employing a user-defined weight matrix to put risks and benefits in a common unit.

*Copyright, 2011: Wolfram.
important source of data for the evaluation is randomised clinical trials, although data from observational studies may also be applied to safety evaluations. As part of the evaluation, a comparison of gains or harms associated with the medicine is made, for example, lives saved or lost or the occurrence of specific clinical events. Sources of uncertainty for the data and the impact of that uncertainty on the assessment are also described.

In addition to information such as approved indications and dosages, monographs contain a summary of efficacy and safety from clinical studies, as well as a more in-depth section with the actual data and references. Draft monographs are provided to the marketing authorisation holders for their comment.

Example MPA monographs
Dr Ahlqvist-Rastad presented core messages from the 2009 product monograph for agomelatin as an example of the use of an MPA monograph to place a medicine in the context of available treatments. The monograph first provided background information on depression: "Major depression is a heterogeneous disease for which no treatment could be uniformly best for all patients." Next, agomelatin was identified in the monograph as "a new antidepressant with a new mode of action" with a different and potentially advantageous safety profile." Informed by other therapeutic options, however, agomelatin was identified as potentially less desirable than the gold standard: "The anti-depressive effect [at the] population level can be somewhat less than the alternatives on the market" and furthermore, "its value can be limited due to need for liver monitoring."

In another example, the 2001 MPA monograph for sibutramine, details concerns regarding the known and unknown risks of the medicine compared with its potential benefits. "Reductil (sibutramine) implies a new pharmacological principle for treatment of obesity. Potentially favourable effects on blood lipids and blood sugar control [are] indicated. However, treatment with sibutramine entails a risk of increased pulse and blood pressure which can have negative effects on cardiovascular disease in the target population. Further studies are needed to elucidate the clinical value of Reductil in the treatment of obesity." These concerns were eventually borne out when, after the results of the Sibutramine Cardiovascular OUTcome Study were released, the medicine was withdrawn from the market in 2010 (Figure 20).

Summary
There is a need to provide information to healthcare professionals concerning the grounds for approval of new medicines, including their benefits, risks and uncertainties; and this information should be presented in a national context. Although healthcare professionals in Sweden are now accustomed to receiving this information in the form of a monograph, the monographs could be improved, highlighting uncertainties and using methods for visualisation such as benefit-risk value trees.

Citing a recent article in the British Medical Journal, Dr Ahlqvist-Rastad explained that shared decision making in which healthcare professionals and patients work together will herald the “Century of the Patient.” This shared decision making, however, will require the ongoing communication of knowledge surrounding the benefits and known and unknown risks of new and existing medicines not only to patients but also to healthcare professionals.

Reference
Communication of benefit-risk information to patients by physicians, pharmacists and nurses for shared decision making

Professor Sam Salek
Professor of Pharmacoepidemiology, Cardiff University

Background
Adverse reactions to medicines exact a huge financial and human cost each year, resulting in as many as 5% of hospital deaths and 197,000 overall deaths per year in Europe and expenses of 79 billion Euros. Even small improvements in pharmacovigilance have the potential to result in a reduction of the occurrence of these adverse events, thereby creating a significant impact on public health and society. One method of creating such an improvement is the clear communication of the benefits and risks of medicines, translating population-level information to that of the individual user.

To learn how benefit-risk is communicated to patients and to healthcare professionals (HCPs) and to report the benefit and risk information needs of these groups to industry and regulatory stakeholders, a questionnaire was posted to a random sample of general practitioners, pharmacists and nurses, with 1,167 responses (778 GPs, 134 nurses, and 255 pharmacists). The questionnaire, or Benefit and Risk Communication Index (BRIC), was divided into questions that measured benefit-risk communication of medicines to HCPs and the information source for that communication (Figure 21) and questions that explored communication of benefit-risk balance to patients by HCPs (Figure 22). Professor Salek presented the preliminary results of this study, cautioning that excerpted comments from the survey quoted in his presentation should be regarded as individual opinions that are supplementary to the amalgamated responses.

How benefit-risk information is communicated to healthcare professionals
Most healthcare stakeholders consider the sources, quality, and reliability of benefit-risk information for new medicines to be extremely variable. Of the HCP respondents to the BRIC questionnaire, 54% indicated that a more systematic approach to risk communication by the government and industry is needed, with 58% reporting that they often research the risks of medicines independently. However, at least one survey respondent did not want to receive benefit and risk information from pharmaceutical companies at all, saying “drug companies have proven themselves to be untrustworthy; they cannot be relied on” while another commented “the government needs to do more when it comes to risk communication, because company reps are sadly not doing so.” In fact, the government was named as the preferred source of pharmaceutical benefit-risk information by the majority of respondents, and a government or independent website dedicated to the communication of the risks of medicines was suggested as a useful tool by 50%. One other source of benefit-risk information, The Drug and Therapeutics Bulletin, is an independent publication containing evidence-based evaluations of medicines, which was formerly provided free to physicians. However, one individual survey response said that its current cost stood in the way of its use.

Some HCPs responding to the questionnaire reported that more perspective is required from providers of benefit-risk information, with 51% specifying that the risks of medicines should not be conveyed independent of their benefits. One respondent indicated that whilst the British National Formulary was his/her primary source of benefit-risk information, “It should provide more information on the likelihood of each risk for example, 10%, 1%, 0.1% etc…” For some HCPs, the visualisation methods that are being used are not effective: “I believe information about drug risks is being introduced in a very confusing format.”
How benefit-risk information is communicated to patients

Although full disclosure of all relevant information surrounding a new medicine to its ultimate user is regarded by many healthcare stakeholders as a requirement of patient empowerment, the communication of the risks of medicines to all patients was considered important by only 56% of BRIC respondents. Conveying the possible advantages and harms associated with medicines to all patients was obviously not considered by all respondents as entirely advantageous, with one commenting “I am surprised there are no [survey] questions about the detrimental effects of communicating the risks of medications to patients.”

Even though 98% of BRIC respondents indicated that communicating benefit-risk to patients is primarily the physician’s responsibility, and 70% considered their patients to be very responsive to such information, fewer physicians who completed the survey explain the benefit-risk balance to patients than the nurses or pharmacists who responded, and overall, only 47% of HCP respondents actually do explain the benefit-risk balance. Of those HCPs who do communicate benefit-risk to their patients, verbal interaction was considered the most effective method by 98%, although 62% refer their patients to other information sources such as the Internet.

The product information leaflet (PIL) was not widely recommended as a source of benefit-risk information for patients; only 35% of HCPs refer their patients to this resource, and one respondent specified that “A lot of patients refuse to take the medicines when reading the PIL. Patient information in choosing the right medication is important for compliance.”

Recommendations

The preliminary results of the study have allowed Professor Salek and his team to develop several recommendations for action. More training for physicians in developing and implementing strategies and tactics for the communication of risk to patients is clearly needed. Additional research is required regarding how different methods, particularly the use of visual aids, help patients to understand risk; and an update on existing research is needed as to how differences in factors such as culture, age and gender affect patients’ perceptions.

The provision of benefit-risk information in an understandable manner as part of patient information leaflets would be highly beneficial as would the involvement of patients, and HCPs in the development of relevant information.

Finally the development of an independent, government-managed website dedicated to risk of medicines and the adoption of a systematic approach to communicating risk by governments and industry both have the potential to positively affect benefit-risk communication and ultimately, public health.
Presenting benefit-risk information on a new medicine to patients: What are the challenges and can visualisation improve understanding?

Professor Ruth S. Day  
Director, Medical Cognition Laboratory, Duke University, USA

Cognitive accessibility  
The “cognitive accessibility” of drug information is defined as the ease with which healthcare stakeholders can find, understand, remember and use information about medicines in a safe and effective manner. Unfortunately, however, information about new drugs is often complex and technical in nature, making it difficult to present in cognitively accessible ways.

As the Director of the Medical Cognition Laboratory at Duke University, Professor Ruth Day and her team study the perception, comprehension, memory and use of drug information. They examine information from a variety of sources, including direct-to-consumer television advertising, internet web sites and hard copy materials such as professional labels, patient package inserts, pharmacy leaflets, medication guides, magazine advertisements and even over-the-counter packaging.

In the first phase of the Medical Cognition Laboratory’s evaluation of medical information, a cognitive analysis is performed, quantitative measures are determined and cognitive accessibility is calculated. After developing enhanced displays of the information using accepted cognitive principles, cognitive experiments are performed in which the effects of both the original version of information and the enhanced version of the same information are tested on processes such as attention, comprehension, memory, problem-solving, decision-making and ultimately, on health outcomes.

Many cognitive principles underlie this analysis, including the contrast between “information load” (the sheer amount of information provided), vs. “cognitive load” (the mental effort needed to process the information). One persistent finding of the Medical Cognition Laboratory’s experiments has been that subjects who are exposed to medical information remember approximately 80% of the information concerning a drug’s benefits and only approximately 20% of the information concerning its risks. Although there may be several reasons for this phenomenon, including fear of risk information on the part of the subjects, the cognitive inaccessibility of the information’s presentation may be the most powerful cause. That is, whereas information regarding a medicine’s benefits is often presented with high cognitive accessibility through techniques such as repetition, simple language, normal speaking speed and lack of distraction, risk information is often presented in ways that violate these principles. Therefore risk information may be physically present for legal and regulatory purposes, but functionally absent to the users. This results in an unfair balance in cognitive accessibility, but one which can be improved.

Before improving the balance in benefit-risk presentation, however, it is important to define what is meant by “benefit” and “risk.” When thinking of a medicine’s potential benefits, patients want to know what effect the medicine will have on their health (its outcome), how likely it is that the effect will take place (its probability), and the degree of the effect (its magnitude). When thinking of a medicine’s risks, patients want to know which adverse events could happen, how serious the events would be and how likely they would be to occur. If the events do occur they want to know how to recognise them and what they should do about them. For most users of medical information, however, this information may be difficult to identify.

Cognitive accessibility affects all groups of...
stakeholders to a surprisingly equal degree. In one Medical Cognition Laboratory experiment, consumers (non-patients) who were exposed to actual risk information for a drug retained less than 10% of that information. Somewhat surprisingly, physician specialists who actually prescribed this drug retained a similarly low percentage of the risk data. When presented with enhanced versions of this information based on cognitive principles, however, both groups were able to approximately double the amount of information retained.

**Benefit-risk representation**

The results of tests on the effects of alternative representation of risk information on different cognitive processes have demonstrated that lay persons understand and remember side effects more effectively when the effects are categorised according to severity or probability. Pictograms can be used to represent this linear relationship for persons with low literacy. The presentation of side effect information in a simple text paragraph format can be cognitively enhanced through the addition of words that categorise the effects on a linear scale according to their severity, such as serious, moderate, or mild; or according to their frequency, such as common, less common, or rare. Further enhancements can be effected through techniques such as placing the side effects in a list rather than a paragraph and through “chunking” the list or separating it into those specific categories of severity or frequency. Matrix representation of a drug’s risks, in which potential side effects are grouped according to any or all of these linear categories can show the interaction of two of the categories; that is, it can demonstrate those adverse events that while serious, are also rare. Matrix presentations also permit the easy comparison of risks associated with multiple drugs in the same therapeutic class.

Professor Day provided an example of the effect of the cognitive inaccessibility of the product information for aspirin. In the original presentation reviewed by Medical Cognition Laboratory subjects, the risk for stomach bleeding associated with the use of aspirin was included at the end of a “chunk” of information labelled “alcohol use” where it could be potentially ignored by subjects who do not consider themselves users or abusers of alcohol. Consequently, potential stomach bleeding was not recalled by test subjects as one of the risks associated with the use of aspirin. When this risk was separated into its own labelled “chunk”; however, the comprehension and retention of this information doubled (from only 33% correct to almost 70% correct).

**Conclusions**

The use of these alternative representations, whether they are lists, chunking, linear categorisation or matrices have all demonstrated positive effects on perception, attention, comprehension, memory, problem solving and ultimately, on behaviour and health for users of medical information. Those who develop risk information should choose the format for presentation best suited for the primary cognitive task they envision for the user; whether that is decision making, retention or understanding, tasks that are sometimes but not always correlated.

The generality of Professor Day’s research extends across many types of people, information sources and cognitive tasks. Small changes in the presentation of information, such as categorising risks can result in major improvements in comprehension, retention and use of that information. Although various “new” visual displays of benefit-risk information such as forest plots and value trees can prove extremely useful, Professor Day cautioned that these displays should be individually tested to determine their effects on cognitive tasks.

... subjects who are exposed to medical information remember approximately 80% of the information concerning a drug’s benefits and only approximately 20% of the information concerning its risks.
What is the role of “perception” in communicating and understanding the benefit-risk assessment of medicines?

Professor Sylvie Perreault
Faculty of Pharmacy, University of Montreal, Canada

Benefit-risk perception
The communication and understanding of the benefits and risks of medicines is greatly affected by the perceptions of healthcare stakeholders, and these perceptions differ based on their varying needs. Manufacturers, for example, need the information that will allow them to make investment decisions; regulators require data on the efficacy, safety and quality of a medicine; health technology assessors need to have proof of its value and payers must position it within an established formulary. Prescribers are required to make judgements and recommendations in which they reduce the results of population studies to a single patient, whereas patients simply want access to affordable medicines that yield the greatest benefit with the smallest potential for harm.

Benefit-risk in the real world
Although the balance of benefit-risk of a new medicine is key in the initial regulatory authorisation decision, unknown factors can still affect this balance after approval. These unknowns include the effectiveness of the product in normal clinical practice, the vagaries of patient compliance and concomitant treatments prescribed to populations not included in the randomised clinical trials. In addition, full safety profiles have not yet been developed including the occurrence of rare or delayed adverse drug reactions as well as those that may occur through chronic exposure, pregnancy or off-label use.

Information about the usefulness of a new drug in the general population must be developed, that is, its efficacy in randomised clinical trials needs to be translated into real-world effectiveness. It must be determined where the product fits into standard clinical practice, including the use of pharmacologic and non-pharmacologic therapies and with consideration of the uncertainty around its unknown risks compared to drugs with established safety profiles. The limitations and appropriateness of prescribing practices and the drug’s use in populations not studied in randomised clinical trials must be estimated and its pharmacoeconomic value in untested patient groups validated.

The dossiers for new medicines are developed largely to meet the decision-making needs of regulatory agencies, and thus often do not have the required data to meet the needs of other decision makers. Industry, regulators, health technology bodies and other stakeholders need to develop an early mutual understanding of each other’s needs, with each contributing to the design of the data package, which is available at launch and at the time of health technology assessment. Industry should seek early scientific advice from both regulatory and health technology assessment groups and the movement to establish robust post-approval strategies to determine a drug’s effectiveness.
and safety using adaptive trial designs and observational studies should be accelerated. Pharmacoeconomic studies in real-world clinical settings must be developed, validated and implemented to provide scientific data that are not susceptible to misperception.

**Benefit-risk and orphan drugs**

Applications for orphan drugs are steadily increasing, and by 2008, 33% of new drug approvals were in this category (Figure 25). Even though approximately 50% of these orphan drug approvals were for oncology therapies, the costs of which can represent a challenge to available healthcare resources, the relative lack of data at the time of expedited approval results in a higher impact on perception and understanding of benefit-risk assessments. According to a publication from the Institute of Medicine Committee onAccelerating Rare Diseases Research and Orphan Product Development, there is a potential lack of robustness in the data available for regulatory review of orphan drugs, and a need for the development of guidelines for that review. In addition to a lack of natural history of disease to characterise the disease processes of conditions treated by orphan drugs, there may be inadequate protocol development in terms of research questions, adequate controls and appropriate and validated biomarkers and an advanced method for the interpretation small sample trial results is required. Because of their potential impact on healthcare system costs, an evidence-based compendium to inform health plan decisions on both orphan and non-orphan drugs would be advantageous. Other solutions proposed by the authors include the harmonisation and sharing of data, resources and research by regulators, government, industry and academia, the collaboration of stakeholders in the evaluation of biomarkers, and the creation of public-private partnerships to develop and manage patient registries.1

**Benefit-risk and patient and physician perceptions**

Important research has been performed on the perception of benefit and risk in patients and physicians, and Professor Perreault presented the results of a preliminary literature search on this topic. According to Nair and colleagues, the evaluation by patients of the potential benefits and harms of medicines is “an ongoing, often unconscious process that required interaction with the health care system,” whilst Ding and associates report that factors such as gender and ethnicity can affect the perception of a medicine by its end users.3 The results of a study of perception of benefit and risk among patients and physicians regarding the use of stents in patients with stable coronary artery disease demonstrated that unlike patients, physicians’ perceptions are primarily influenced by the results of clinical trials.4 However, some physicians may also require assistance in the evaluation of risk probability. In a study of physician perspective on the prognostic benefit of statins in patients with myocardial infarctions, only 50% of general physicians and 68% of cardiologists were able to estimate an absolute risk reduction over 5 years and no physicians in this study felt comfortable using number needed-to-treat or other odds assessments.5 Finally, patients are also essential stakeholders in health technology assessment, and the dearth of patient perspective in this area has not gone unnoticed: Gagnon and co-authors call for the development of organised methods to involve the consumers of medicine in health technology assessment.6

**Canadian benefit-risk initiatives**

Because it is believed that pharmacovigilance in clinical practice with community pharmacists can improve the collection of data regarding patients’ perspective in real clinical practice, the Canadian government will initiate a programme to monitor patients’ clinical signs and symptoms, to determine whether the health outcomes they anticipated are attained, and to capture information regarding positive or negative unanticipated health-related events. This project builds upon multiple existing resources and will be evaluated to determine its efficiency in providing added value in drug surveillance. Data collected will include clinical and laboratory manifestations of adverse events, duration of exposure to the drug, doses used, time to the initiation of the adverse event and the use of concomitant medications, presence of comorbidities and demographic characteristics of affected patients.

Lack of research in benefit-risk understanding and communication has contributed to the underperformance of the healthcare system that is increasingly recognised by multiples stakeholders. Issues surrounding
this underperformance include an imperfect design of individual randomised clinical trials; a lack of evidence of systematic syntheses of all evidence for a particular drug; difficulties in comparative effectiveness analyses among drugs in the same class and between classes; and an imperfect interpretation of individual trials and meta-analyses that focus on statistical inference rather than clinical decision making. In addition, difficulties exist in the extrapolation of study results from clinical trial to uncontrolled real-world clinical practice and there is an incomplete understanding of the predictors of common adverse effects and rare effects for significant morbidity and mortality. Responding to these issues, the Canadian Network meta-analysis of randomised clinical trials and observational studies to support post-marketing research has been proposed.

It is anticipated that these analyses should assist in understanding and communicating the benefit-risk assessment of medicines by using current best methods of systematic review to synthesise the increasing evidence on post-approval drug safety and effectiveness required by patients, clinicians and decision makers; by developing innovative methods of evidence synthesis and by integrating and coordinating research activities from national and international evidence collaborations. Additional methods will consist of inclusion dynamics and integrative knowledge translation, teaching and mentoring to increase Canadian capacities, a general evaluation of systematic reviews and meta-analysis and a systematic review and meta-analysis of observational effectiveness and safety studies. Bayesian analysis will allow the incorporation of many sources of data such as previous experiments, patient values or expert opinion and is ideal when dealing with inadequate or suboptimal data, including missing standard comparative studies. Professor Perreault concluded by remarking that by using this type of analysis, researchers will be able to move towards providing direct probability of the benefit-risk parameter of interest, which is important when communicating results to clinicians and other decision makers.

References
Possible next steps

Professor Stuart Walker
Founder, Center for Innovation in Regulatory Science

In addition to discussing plans for the 2012 CIRS Benefit-Risk Workshop, Professor Walker concluded the 2011 Workshop presentations by reporting that seven pharmaceutical companies and seven regulatory agencies had expressed interest in forming the CIRS Benefit-Risk Taskforce.

The objective of this group will be the facilitation of knowledge exchange in the critical area of the benefit-risk assessment of medicines, thereby enabling productivity and avoiding duplicative efforts. Specifically, the Taskforce will engage in the exchange of information, reports and published papers to relevant parties to ensure the effective knowledge sharing and the exchange of learnings from these various initiatives. Additionally, the group will make recommendations on proposals for workshops, surveys or research that should be undertaken to develop the appropriate toolbox for benefit-risk assessment and to determine how these initiatives might be integrated to ensure their timely development.

At the time of this report, the first meeting of this Taskforce has taken place and Professor Walker is pleased to provide a list of its members herewith.

Chairman: Professor Sir Alasdair Breckenridge, Chairman, Medicines and Healthcare products Regulatory Agency, UK

Dr Xavier Luria, Head of Safety and Efficacy of Medicines, Human Medicines Development and Evaluation, European Medicines Agency

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

Dr Huei-Xin Lou, Director, Pharmaceuticals and Biologics Branch, Pre-marketing Division, Health Sciences Authority, Singapore

Dr Petra Dörr, Head of Management Services and Networking, Swissmedic

Dr Jason Ferla, Director, Prescription Medicines Clinical Unit 3, Therapeutic Goods Administration, Australia

Dr Theresa Mullin, Director, Office of Planning and Informatics, Center for Drug Evaluation and Research, Food & Drug Administration, USA

Dr Mark Walderhaug, Associate Office Director for Risk Assessment, Center for Biologics Evaluation and Research, Food & Drug Association, USA

Dr Richard Hermann, Director, Clinical Research, Epidemiology, AstraZeneca, USA

Dr Ellen Strahlman, Chief Medical Officer, GlaxoSmithKline, USA

Dr Filip Mussen, Vice-President, Psychiatry and EU RED Regulatory Affairs, Johnson & Johnson; Chairman, Benefit-Risk Action Team, Pharmaceutical Research and Manufacturers of America

Dr Bennett Levitan, Director, Epidemiology, Johnson & Johnson, USA

Dr Diana Hughes, Vice President, Safety Strategy, Primary Care Business Unit Lead, Pfizer Inc, USA

Dr Becky Noel, Research Scientist, Eli Lilly and Company, USA

Dr Sinan Bardakci Sarac, Senior Research Fellow, Novo Nordisk A/S, Denmark

Mary Baker, President, European Federation of Neurological Associations

Professor Stuart Walker, Founder, CIRS

Lawrence Liberti, Executive Director, CIRS

Secretary to the Task Force: Dr Neil McAuslane, Scientific Director, CIRS
Introduction to the Scenarios and methodology

Dr Bennett Levitan

Director, Quantitative Safety Research, Department of Epidemiology, Johnson & Johnson PRD, USA

Background

Many benefit-risk decisions can be made qualitatively; that is, by assessing statistical and epidemiologic data without additional modelling. Others, however, are considerably simplified by the use of decision analytic models. Structured framework approaches to pharmaceutical benefit-risk assessment are being developed by several regulatory, industry and academic groups. The primary value of these approaches lies in the framing of the problem, facilitated discussion of viewpoints, and clear understanding of the data – thus communicating a shared understanding of the data and the airing of differing viewpoints.

An efficient way to test the relevance of proposed benefit-risk models is to work through realistic or real-life scenarios in discussion groups with different stakeholders and products, an approach that dovetails with ideas expressed at prior CIRS Workshops. This practical approach was used in the 2010 CIRS Workshop to facilitate the identification of the best practices among each of these methodologies. The scenarios and exercises for both the 2010 and 2011 Workshops were designed and led by Dr Bennett Levitan, who as a member of the Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team (PhRMA BRAT), based the scenarios on the considerable body of original work and research he and the BRAT group conducted while developing the BRAT Framework. The purpose of the 2011 exercise was to engage the Syndicate groups in a structured approach for a benefit-risk assessment. The example was a hypothetical triptan used for the treatment of migraine in patients with cardiovascular (CV) risk factors. By applying structured decision-making approaches, the Syndicate discussion groups could each make a benefit-risk decision and then compare and discuss the results. Before the discussions, Dr Levitan provided background information regarding triptans, orientation to data on the mock triptan and directions for the Syndicate sessions. Three sessions were held in parallel, lasting 4 hours each; followed by reporting of the decisions made and insights gleaned from each group.

Migraines

Migraines are defined as a recurrent headache disorder occurring as rarely as once a year to as frequently as several times a week. Sufferers report attacks lasting from 4 to 72 hours. Although the cause is incompletely understood, it is currently believed to result from a neurogenic process associated with changes in cerebral perfusion. Typical characteristics of migraine attack include unilateral headache with pulsating or throbbing pain of moderate or severe intensity that is aggravated by routine physical activity. Migraines can also be associated with nausea and light and sound sensitivity. Fewer than 20% of migraine sufferers experience an aura; that is, visual displays, smells or other cues before or during attacks. Migraines affect approximately 12% (29.5 million) of Americans and are most prevalent between ages 15 and 55, occurring three times more commonly in women. There is currently no cure, with treatment focusing on the prevention of attacks and the cessation or mitigation of symptoms. First-line therapy for this condition consists of the use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen/paracetamol or caffeine (alone or combinations). These approaches to therapy were demonstrated to be superior over placebo by randomised clinical trials, with headache relief noted at 2 hours after therapy in 46% to 56% of patients.
Triptans

Designated as second-line therapy for migraines, triptans have demonstrated efficacy clearly superior to placebo in many randomised clinical trials, with small tolerability differences compared with placebo that were generally considered to be dose related. First approved in 1991, triptans act on serotonin receptors in nerve endings and blood vessels, resulting in the constriction of cranial blood vessels and the inhibition of pro-inflammatory neuropeptide release. Triptans are approved for the acute treatment of migraine attacks with or without aura in adults. One of the seven marketed triptans is also approved for use in adolescents age 12 to 17.

Because of their vasoconstricting effects, triptans are contraindicated in patients with ischaemic heart disease, coronary artery vasospasm, cerebrovascular syndromes, peripheral vascular disease and uncontrolled hypertension. However, determining the actual triptan-related CV risk is complex. Results of observational studies indicate that baseline CV risk in patients suffering from migraines is greater than that of the general population. Furthermore, no clear relationship between triptans and CV events has been observed, in part because relatively few patients with CV risks have been studied in triptan randomised clinical trials.

Syndicate discussion scenario

Triptan T, the hypothetical example presented by Dr Levitan, was based on a scenario developed by RTI-Health Solutions for PHRMA BRAT using data drawn from references on marketed triptans, NSAIDs (ibuprofen, naproxen, though not COX-2 inhibitors) and meta-analyses. Triptan T was approved for the acute treatment of migraine attacks in adults with a history of migraine with or without aura. There was also a recommendation against its use in patients in whom unrecognised coronary artery disease is predicted by the presence of certain CV risk factors.

In the scenario, a new randomised, active-control study was recently completed comparing two oral dose strengths of Triptan T to a single oral dose of an NSAID for the acute treatment of migraine in adults with one or two CV risk factors. In this one-year hypothetical trial, 1,000 patients aged 18 to 65 were enrolled in each of three treatment arms (2 triptan dose arms, 1 NSAID arm). Patients in the trial were required to have experienced one to six migraine headaches per month with or without aura for at least one year and their migraine history must have begun before age 50. Other study inclusion criteria specified one or two CV risk factors such as hypertension, hypercholesterolemia, smoking, obesity, diabetes, family history of coronary artery disease, being a female with surgical or physiological menopause or being a male older than 40 years. Patients who had ischaemic heart disease, cerebrovascular disease, coronary artery vasospasm or other significant underlying CV diseases were excluded.

Key aspects of the hypothetical product’s benefit-risk profile were provided by Dr Levitan in the form of a value tree.
Benefits were grouped into three categories: the reduction of pain, the reduction of sensitivity to light and sound and the reduction of functional disability or nausea and vomiting. Pain relief was further categorised as rapid relief, headache relief, pain-free response and sustained relief. Risks associated with triptan T were identified as transient triptan sensations, central nervous system adverse events, chest-related adverse events and myocardial infarction. Definitions and measurements for all risks and benefits were supplied for purposes of evaluation (Figures 26 and 27).

Clinical trial data provided to the Syndicate discussion groups included the proportion of acute migraine attacks with the outcome for each treatment arm; that is, the outcome for those receiving 15 mg or 30 mg of Triptan T or the NSAI D, as well as the difference in proportion of acute migraine attacks with the outcome prevented (or caused) for each of the three treatment arms in comparison with other two. All supplied data included confidence intervals and were available both in tabular and forest plot formats (Figures 28-30).

**Data implications**

Operating on the presumption that each treatment arm of 1,000 patients would be expected to experience approximately 24,000 migraines over the course of 1 year, the headache relief experienced by 63.6% of patients in the high-dose triptan treatment arm would mean that 15,264 attacks were relieved. Similarly, a reduction in functional disability for 56% of those patients would mean that 13,440 patients experienced improved functioning. However, 16 of those patients would also suffer myocardial infarctions. Calculating rate differences between the treatment arms in terms of patient-years revealed that in 1,000 patient-years, when compared with the NSAI D treatment group, the group of patients receiving the high-dose triptan could expect to see 4,656 more attacks relieved and 3,888 more patients with reduced functional disability; however they would also experience 6 more myocardial infarctions.

The tables and forest provided to the Syndicate sessions, as well as the software used in Sessions 1 and 2, allowed for representations both per 1,000 migraines and per 1,000 patient-years.

**Discussion session structure**

For the discussion session, each of three Syndicates was tasked with conducting a structured benefit-risk assessment for the hypothetical triptan. Two Syndicates were instructed to use a qualitative approach in which they reviewed the decision context from either a regulatory or an industry perspective and revised the provided value tree. Then, using data tables and visualisations, the groups were to review the data and attempt to choose whether to approve Triptan T at the low dose, the high dose, at both doses or neither dose in this patient population. If a second round of review was required, discussants were to perform a point allocation exercise to obtain weights for outcomes and

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**Figure 29. Comparison of rate differences for favourable and unfavourable events occurring in high-dose triptan and non-steroidal anti-inflammatory drug treatment groups.**

**Figure 30. Forest plot comparison of rate differences for favourable and unfavourable events occurring in high-dose triptan and non-steroidal anti-inflammatory drug treatment groups.**
review data visualisations augmented by these weights to make a decision. These groups were expected to work with the value trees, data tables and forest plots with software developed for the BRAT Framework and customised by Dr. Levitan for this exercise.

The third Syndicate was tasked with using a quantitative approach, which was constructed and run by Dr. Lawrence D. Phillips, Professor, London School of Economics and Political Science, UK, who had collaborated with Dr. Levitan prior to the Workshop. This Syndicate was to review the decision context, and starting with the given value tree, perform a multi-criteria decision analysis exercise. Using a decision conferencing approach and the multi-criteria decision model software Hiview* to model the benefit-risk balance, this group also was expected to choose whether to approve Triptan T at the low dose, the high dose, at both doses or neither.

It was hoped that by using either qualitative or quantitative methodologies, a decision process that was informed by the patient’s perspective, could reach a conclusion whose rationale could be communicated clearly and transparently to other stakeholders.


The author thanks David Biondi for his very helpful commentary in developing the triptans scenario.

References
RESULTS

Syndicate 1: A qualitative approach from the regulators’ perspective

Definition and focus: For the members of Syndicate 1, defining and focusing on the decision context for the assessment exercise was key. That is, it was essential to clearly articulate and agree on the research question and meticulously delineate the target population with appropriate granularity.

Patient input was also determined to be vital. Participants repeatedly turned to “patients” in the group (those who had been treated for migraine) to inform their thinking process. Most importantly, this information altered the group’s decision framing by providing the patient’s perspective on the benefits and harms. Patients in the Syndicate were typically interested in those benefits that were not usually considered to be the primary outcomes by the regulators or sponsors and were consistently more willing to take risks that exceeded those assumed by the developers or regulators.

Visualisation tools, such as value trees, tables of key benefits and forest plots help to structure discussions, by providing a focus on critical issues and identifying knowledge gaps. It was determined by the Syndicate that these tools, which have been used in practice to inform regulatory Advisory Committee decisions, can also help to illustrate overlapping benefits and harms, provide a succinct summary of key information needed to make the benefit-risk assessment decisions and facilitate sensitivity analyses. The value tree, in particular, facilitated comprehension and communication, as it worked within the constraints for the average five-to-seven-item cognitive limit of most reviewers. In addition, the tree-focused questions allowed issues to surface and be discussed, supported the selection of the primary benefit to be evaluated and exposed the need for a clear label lexicon. Syndicate members cautioned, however, that visualisation tools require training for optimal use and interpretation and would benefit from ongoing refinement.

Weighting: Syndicate 1 decided that implicit if not explicit weighting is an inescapable aspect of benefit-risk decision making. Although a simple and accessible approach may suffice, more developmental work is required to construct a widely acceptable benefit-risk weighting approach. Because subjective interpretations of harms and benefits introduce an important variable, it is likely that weighting will remain an elusive component of the equation until a more robust approach is identified.

Conclusion: It was the consensus of this Syndicate that the triptan should be approved at the low dose, with at least one participant feeling that the use of both proposed doses was appropriate. In addition to this conclusion, Syndicate 1 developed a list of recommendations for the conduct of similar benefit-risk assessments.

Observations and Recommendations

• Ask the right question; that is, clearly outline the research question and explicitly define the treatment population to which this question applies
• Regulators should use a value tree to obtain early agreement with sponsors regarding key benefits and risks
• Redouble efforts to get patient input early in the framing process when benefits and harms are subjective and variable
• Support the use of a table of key benefits and risks and forest plots to summarise the benefit-risk assessment in regulatory submissions
• Continue to refine visualisation tools and develop harmonised guidance and look to CIRS for training in their use
Syndicate 2: A qualitative approach from an industry perspective

Chair Dr Filip Mussen, Janssen R&D, Belgium
Rapporteur Dr Richard Hermann, AstraZeneca R&D, USA
Facilitator Dr Bennett Levitan, Johnson & Johnson PRD, USA

Modified value tree: Certain benefits and risks provided in the case study were removed from the value tree by this Syndicate in their evaluation of the triptan (Figure 32). For example, “Pain-Free Response” was removed because participants who were also migraine sufferers in this group noted that the background state of pain in migraine is such that pain-free status might not be expected. “Sustained Response” was retained because of its importance to predict pending disability (as informed from the patient perspective) as was “additional emergency room visits” (a reflection of the physician perspective). “Transient Triptan Sensation” was removed because of its relatively minor nature as well as its similarity to “Central Nervous System Adverse Events.”

Weighting was performed by Syndicate 2 by allocating 100 points amongst the outcomes (Figure 33). Myocardial infarctions were designated as the most serious outcome and therefore, an initial relative weight of 100% was applied to these events. All of the outcomes weighted as 0 were deleted. Of the remaining outcomes, all benefits were evaluated as being more important than non-serious risk outcomes. Using the BRAT software modified by Dr. Levitan, a forest plot ordering outcomes by decreasing weight was created (Figure 34.)

Syndicate members cautioned that significant cardiovascular events (i.e. MI) may be mistaken for chest-related adverse events.

Despite having robust incidence statistics, the group’s ultimate decision was a qualitative one based on valuing and not numerical weighting of the events. The Syndicate indicated that having highly informed, health-literate ‘patients’ in an atmosphere of free discussion, with excellent facilitation greatly optimised the exercise. The weighting exercise went quickly and the group was reasonably comfortable with the methodology. Real-time tabular and graphic feedback was extremely valuable for the assessment. This exercise was representative of a patient group informing the pharmaceutical company about their perceptions of the benefits and harms associated with the medicine.

According to this group, the assessment exercise could be improved with the benefit of having had more background context and discussion regarding the disease state and treatment options. Moreover, the group felt that it would have been optimal to have had a representative from clinical development present and Medical Affairs input would be required to assist with the eventual communication of the
Observations and Recommendations

- Bring in patient experience early in the developmental process
- Patient advocate representation in benefit-risk discussion may be valuable, particularly in the discussion of therapies for rare disease states
- Assumptions are made about data at multiple points in a benefit-risk assessment; awareness of the impact of these assumptions and uncertainties on ultimate decision making is critical
- Methodological issues in weighting must be considered as these can greatly influence the value judgements; for example, small changes in a highly weighted risk need to be offset by a large change in a lower-weighted benefit
Syndicate 3: A quantitative approach

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<td>Facilitator</td>
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Value tree: Syndicate 3 agreed that use of the value tree was the most important part of this quantitative decision-making process. Although there were more favourable than unfavourable effects listed for the exercise, potentially indicating a bias toward benefit, several of the favourable effects were considered by the group to be interrelated; for example, “Pain-free Response” could be considered a subset of “Headache Relief.” It was remarked that although these interrelated effects might be statistically correlated, they might also be “preference independent,” which was taken into consideration in the weighting process.

Three out of four unfavourable effects were tolerability issues while only one, myocardial infarction, was considered to be a serious adverse event. To reflect this fact, myocardial infarction was split out as a separate undesirable event versus the other three events in the value tree.

Weighting and scoring: Unlike the other two Syndicate groups, this group was charged with using a quantitative weighting approach to inform their decision. In the weighting process, the group first identified the range of treatment effects for each of the three treatment options, which ranged from 0% to 70% for favourable effects and 8 to 16 per 1,000 person years for the adverse event myocardial infarction. For each effect, a swing-weight was assigned based on the added preference value, from 0 to 100. These values were based on which attributes were viewed as clinically important, meaningful or valuable, especially from a patient’s perspective, with several syndicate participants who had experienced migraines providing input as “patients.”

The three tolerability adverse effects were assigned very low swing weights whilst the weight for myocardial infarction was designated as 100. This evaluation assumed a linear value function between effect size and weighting for all favourable and unfavourable effects. There was some discussion regarding the non-linearity of myocardial infarction, but consensus was not reached on this point.

As a result of this input, the main benefit-risk trade-off was determined to be that between reduction of functional disability and myocardial infarction. Using the Hiview programme, scores for both the 15- and 30-mg doses were higher than those for NSAIDs and placebo.

Syndicate 3 agreed that there was excellent engagement from all participants in their discussion. The exercise allowed a complex problem to be reduced to a series of smaller more manageable issues that followed a logical progression. The sensitivity analysis provided reassurance regarding the results, with participants recognising that small changes in the weights did not substantially change the outcome; for example, the rate of myocardial infarction associated with the 30-mg triptan dose would have had to increase from 16 per 1,000 person years to 45 per 1,000 person years for the score for NSAIDs to be higher than that for this treatment.

The group felt that there were several areas of the exercise that could be improved. The relatively limited time for the exercise was an issue. Weighting requires considerable effort and determining the methods for this aspect of evaluation involves substantial discussion. In addition, the Syndicate was also faced with the challenge of ensuring that the weighting process was transparent and understandable for all participants.
with several uncertainties such as whether to assume the perspective of regulators, patients or physicians in their decision making; how to incorporate uncertainties in the data; and how to define unmet need for a new therapy. Finally, there was considerable discussion regarding whether the size of a treatment effect should be regarded as linear with respect to the preference value. As there was no clear approach on how to determine this, the group defaulted to linearity.

**Conclusion:** Based on weighting scores, both doses of the triptan were deemed approvable by this Syndicate group.

**Observations and Recommendations**
- The methodology for and results of this benefit-risk evaluation, including the inclusion of weighting based on patients’ feedback, were of the type that could be included in the European Public Assessment Reports (EPARs) although prescribing physicians may require some education for interpretation.
- Results could be simplified for patients by providing a visual quantification of the tradeoff showing the number of migraines improved with the triptan compared with NSAIDs and number of myocardial infarctions that would occur with triptan compared with NSAIDs, based on 100 patients treated for 1 year.

**OVERALL CONCLUSIONS FROM THE SYNDICATES**
- Assessment tools, be they more qualitative or quantitative in their approach, help provide a transparent structure for the discussion of multifactorial elements of the benefit risk assessment of a medicine.
- Visualisation tools help to focus benefit-risk discussions on critical issues, identifying gaps and exposing overlapping benefits and harms and providing a succinct summary of the information needed to make benefit-risk decisions.
- In addition to transparency, consistency and communication, articulating and reaching consensus on research questions and meticulously delineating target populations are essential to benefit-risk evaluation.
- For conditions involving subjective benefits and harms, patient input is invaluable in informing the thinking of decision makers such as regulators and researchers.
- Communicating decision rationales reached through multi-criteria decision analysis to prescribing physicians may require some education on methodology. Results could be simplified for patients by providing a graphically displayed quantification of tradeoffs.
## Appendix: Workshop Attendees

### Regulatory and Government Agencies

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<thead>
<tr>
<th>Name</th>
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<td>Prof Sir Alasdair Brekenridge</td>
<td>Chairman</td>
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<td>Prof Bruno Flamion</td>
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<td>Belgian Committee for Reimbursement of Medicines, Belgian National Institute for Health and Disability Insurance, Belgium</td>
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<td>Dr Torbjörn Callréus</td>
<td>Chief Medical Officer</td>
<td>Danish Medicines Agency</td>
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<tr>
<td>Dr Petra Dörr</td>
<td>Head of Management Services and Networking</td>
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<td>Prof Hans-Georg Eichler</td>
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<td>Dr Jason Ferla</td>
<td>Director, Prescription Medicines Clinical Unit 3</td>
<td>Therapeutic Goods Administration, Australia</td>
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<td>Dr Joyce Korvick</td>
<td>Deputy Director for Safety, Division of Gastroenterology and Inborn Errors Products, CDER</td>
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<td>Dr Huei-Xin Lou</td>
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<td>Health Sciences Authority, Singapore</td>
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<tr>
<td>Dr Theresa Mullin</td>
<td>Associate Director, Office of Planning and Informatics, CDER</td>
<td>Food and Drug Administration, USA</td>
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<td>Dr Supriya Sharma</td>
<td>Director General</td>
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<td>Dr Robert Temple</td>
<td>Deputy Center Director for Clinical Science, CDER</td>
<td>Food and Drug Administration, USAD</td>
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<td>Dr Mark Walderhaug</td>
<td>Associate Office Director for Risk Assessment, CBER</td>
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<td>Dr Sabine Wever</td>
<td>Head of Division Clinical Review</td>
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### Industry

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<td>Robin Keen</td>
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<td>Dr Alain Micaleff</td>
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<td>Dr Timothy Franson</td>
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<td>Professor Stuart Walker</td>
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