# REFINING THE BENEFIT-RISK FRAMEWORK FOR THE ASSESSMENT OF MEDICINES:

## VALUING AND WEIGHTING BENEFIT AND RISK PARAMETERS

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## EXECUTIVE FORUM

CMR International
INSTITUTE FOR REGULATORY SCIENCE

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The Institute has a distinct agenda dealing with regulatory affairs and their scientific basis, which is supported by an independent Advisory Board of regulatory experts.

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# REFINING THE BENEFIT-RISK FRAMEWORK FOR THE ASSESSMENT OF MEDICINES:

## Valuing and weighting benefit and risk parameters



## Section 1: Executive Summary

### Background

Determining the benefit-risk balance of a medicine is one of the most important steps in its development, review and post-approval re-assessment. The need for and establishment of a benefit-risk framework is recognised as critical from both a regulatory agency and pharmaceutical company perspective in order that there is a transparent articulation of the benefits and risks considered in making the final regulatory decision. Moreover, by applying the parameters derived from new assessment models, regulatory agencies and sponsors have a framework that allows a scientific discussion of benefit-risk.

There is a consensus regarding the essential elements that should comprise any framework as well as regarding the five key steps that take data through a systematic process prior to making the final decision. These steps are construction of summary tables; development of a value tree of benefits and risks; assessment of importance and prioritisation of benefits and risks; assignment of value and weightings for the benefits and risks; and finally, benefit-risk assessment through the application of expert judgement.

Although there is agreement concerning the steps that are required for the framework, the assignment of weighting and values to each component parameter is more difficult, owing to different views, methods and stakeholder perspectives, not just on what should be used in weighting, but how it should be used.

In order to address this specific issue and based on the Workshops held by the CMR International Institute for Regulatory Science (the Institute) in 2007 and 2008, the Institute held this Executive Forum facilitated around real case studies and focussed on refining the benefit-risk framework through a discussion of the assignment of value and weightings.

### Objectives

- Present the opportunity to refine the Institute's benefit-risk framework by making it more robust, understandable and practical
- Develop an agreement on the principles that should be used in the weighting and values step of the framework
- Provide a forum for regulatory agencies and industry to review case studies and discuss the utilisation of weighting and values in making a benefit-risk decision
- Discover agency and industry perspectives of which weighting and values can be used and which issues need to be addressed within the benefit-risk framework

### Lessons Learned

- Benefit-risk assessment exercises involving all stakeholders should be conducted throughout a product life cycle with benefits and risks added and subtracted as data become available
- Although there should be some overlap in stakeholder opinion regarding the importance or inclusion of specific benefits and risks in the assessment, significant differences should also be expected based on the difference in stakeholder perspectives and should form the basis of stakeholder discussions
- Tools such as a value tree and supportive data tables are necessary for a structured benefit-risk debate
- The introduction of novel visualisation tools to diverse stakeholders (ie regulators, clinicians, patients) should proceed in a methodical, educational manner, to allow each group to familiarise themselves with the strengths and weaknesses of each proposed approach
- A Forest plot is a simple way to represent and visualise the results of a benefit-risk assessment
- The process for developing a standard, simple (not simplistic) approach to benefit-risk assessment should build on a qualitative approach, eventually developing into a quantitative framework

## Presentations

### Forum introduction

Responses to Project 2020, a survey designed and conducted by the Institute of pharmaceutical companies regarding 39 scenarios that may represent future aspects of the regulatory environment by the year 2020, indicate that the number one scenario of importance is the development of a common framework for benefit-risk assessment for use in dossier reviews and in the communication of the results of those reviews to stakeholders.

In addition to providing the results of the Project 2020 survey, **Professor Stuart Walker**, *Founder, CMR International Institute for Regulatory Science (the Institute)* discussed the history of the Institute's work in benefit-risk and set the objectives for the Workshop. He described the evolution of the Institute's benefit-risk framework over the past 25 years, which has been endorsed by international regulatory agencies and has served as the conceptual underpinning for other sophisticated initiatives in this arena. Professor Walker explained that this framework is well designed to permit the integration of a weighting/valuing system as a critical step to support final expert judgement and decision making. A common approach to assessing benefits and risks allows all stakeholders, regardless of their backgrounds or responsibilities, to verbalise their understanding of the value of a particular parameter, thereby providing the context for a structured discussion about each one's decision-making process.

### Industry perspectives

**Dr David Jefferys**, *Senior Vice President, Global Regulatory, Healthcare Policy Dept, Eisai Europe Ltd, UK*, outlined Eisai's work in benefit-risk, saying that Eisai has recently introduced Global Regulatory Analysis Strategic Plans (GRASP), electronic records of each new medicine's complete global strategy. Available company wide, GRASP has proved a valuable source of cross fertilisation. Eisai has found that benefit-risk assessment also improves internal communications, helping groups to focus on key product attributes.

Benefit Risk Assessment in New and old drugs (BRAIN), a simple and transparent method used by Novo Nordisk to assess and analyse the treatment-related effects of drugs in clinical trials while preserving as much objectivity as possible for decision makers, was detailed by **Dr Sinan Bardakcki Sarac,** *Quantitative Clinical Pharmacology, Novo Nordisk A/S, Denmark and the Technical University of Denmark, Department of Physics* and **Dr Christine Hallgreen**, *IMI PostDoc, Quantitative Clinical Pharmacology, Novo Nordisk A/S, Denmark*.

In his presentation on the visualisation of benefit-risk, **Dr Douglas Manion**, *Vice President, Neuroscience and Virology, Bristol-Myers Squibb, USA*, discussed the March 2010 BMS presentation of belatacept data to the US FDA Advisory Committee. He described how each element of the benefit and risk value tree for belatacept was transparently quantified using simple graphs that included relative point estimates and confidence intervals; this quantitative graphic approach allowed the committee to readily understand belatacept's potentially complicated benefit-risk story.

**Dr Rebecca Noel**, *Research Scientist, Eli Lilly and Company* provided details of the Lilly Benefit-Risk Assessment Model (BRAM), designed to help focus discussion on the primary elements of risk and benefit for a specific treatment and its alternatives. The model uses multiple attributes because it is not only necessary to discuss the relative importance of benefit and risk when assessing the overall utility of a treatment, but also the trade-offs a decision-maker is willing to make between the various aspects of benefit and risk.

GSK has an integrated benefit-risk evaluation team and representatives from different therapy and functional areas within the company provide a broad base and multiple perspectives on benefit-risk assessment. **Dr Marilyn Metcalf**, *Director, Quantitative and Decision Sciences, GlaxoSmithKline, US* explained that this team is building a framework for the evaluation of benefit-risk that will answer the needs of multiple stakeholders at different levels, including colleagues, regulators, payers, healthcare providers and patients.

### Regulatory Agency perspectives

The benefit-risk methodology research project was begun in 2009 with 29 EU countries. **Dr Xavier Luria**, *Head of Safety and Efficacy of Medicines, EMA*, explained that it is the goal of this project to improve the quality, transparency and consistency of benefit-risk assessments, resulting in more auditable and robust evaluations. It is further envisioned that benefit-risk assessment could be harmonised across the European network and that the time to assess a Market Authorisation Application could be reduced.

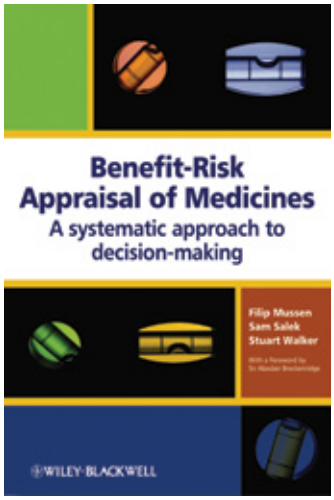
Providing the US regulatory perspective on benefit-risk decision making, **Dr Theresa Mullin**, *Director, Office of Planning and Informatics, CDER, FDA*, said that the US statutory standard does not require that a new therapeutic product be superior to available choices, only that it be safe and effective for the intended use. This standard implicitly values choices and frames regulatory decision making. Dr Mullin stressed that using a process that clearly outlines the available data and documents how judgements were made can improve transparency of the decision-making process.

**Dr Petra Dörr**, *Head of Management Services & Networking, Swissmedic* and **Dr Jason Ferla**, *Director, Clinical Evaluation Section 3, Office of Prescription Medicines, Therapeutic Goods Administration, Australia*, detailed the progress of the Consortium, a group formed through bilateral agreements for information sharing and shared reviews of new medicines among the mid-sized regulatory agencies of Health Canada, Swissmedic in Switzerland, HSA in Singapore, and TGA in Australia. The group intends to discuss the next steps in early 2011.

A benefit-risk framework has value throughout a product's lifecycle. Proposed approaches discussed in this forum will improve the consistency and transparency of communications around a product's benefit and harm profile. A framework serves to align benefit risk discussions across agencies, for example across EU member states, and to foster aligned international conversations about new products. A framework also helps regulators meet statutory requirements for transparency.

The various approaches to benefit-risk assessment such as the Institute's framework, the EMA's reflection Paper, the PhRMA BRAT initiative and the various other techniques being developed by industry described in this report, have a common genesis in decision analysis, and today are converging to draw on each one's strengths as we build toward the common goal of developing a standardised tool for the transparent assessment and discussion of a medicine's benefits and risks.






The CMR International Institute for Regulatory Science announces that its founder, Professor Stuart Walker, in collaboration with Professor Sam Salek, Welsh School of Pharmacy, Cardiff University and Dr Filip Mussen, Johnson & Johnson Pharmaceutical Research and Development, Belgium, has authored a new book - *Benefit Risk Appraisal of Medicines: A Systematic Approach to Decision Making*. The book reflects more than 10 years of research and discussion on the balanced evaluation of the risks and benefits of new medicines among stakeholders at the highest level of the pharmaceutical industry, regulatory agencies and academia.

*Benefit-Risk Appraisal of Medicines*, published by Wiley-Blackwell, establishes the background and criteria required to assess benefit and risk and reviews the current practices by regulatory authorities and the pharmaceutical industry, including currently available models. It outlines the development and evaluation of the authors' pioneering benefit-risk assessment framework, which uses multi-criteria decision analysis, and analyses the implications of its implementation.

For more information or to purchase *Benefit Risk Appraisal of Medicines: A Systematic Approach to Decision Making*, please go to **http://www.wiley.com/WileyCDA/WileyTitle/productCd-0470060859.html**

# Section 2: Presentations

## Chairman's welcome, introduction and setting the scene

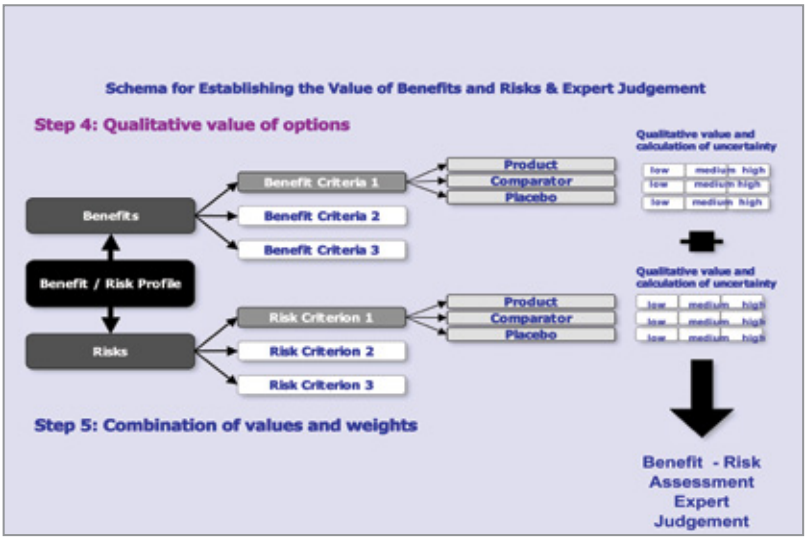
**Professor Stuart Walker**

*Founder CMR International Insitute for Regulatory Science*

### The Institute and benefit-risk assessment

The assessment of the benefits and risks of new medicines continues to be at the top of the agenda of many pharmaceutical companies and regulatory authorities. This topic has long been of interest to the Institute, beginning with the first meeting on the topic convened by Founder Professor Walker in 1985. Dr Filip Mussen performed his doctoral research under the guidance of Professors Walker and Sam Salek, building on the work of Professor Larry Phillips who had used multi-criteria decision analysis in a number of other disciplines and industries. Dr Mussen established a seven-step decision-making process outlined below, that could be used specifically to assess the benefit-risk profile of a medicine.

1. Look at the context of the decision
2. Identify the options, which in the case of a new medicine is the new medicine, the comparator, and the placebo
3. Identify the benefit and risk criteria
4. Organise those into a value tree
5. Assess the performance of each of these options against the criteria and calculate the uncertainty
6. Assign a weight to each criteria
7. Produce a weighted score, and conduct a sensitivity analysis



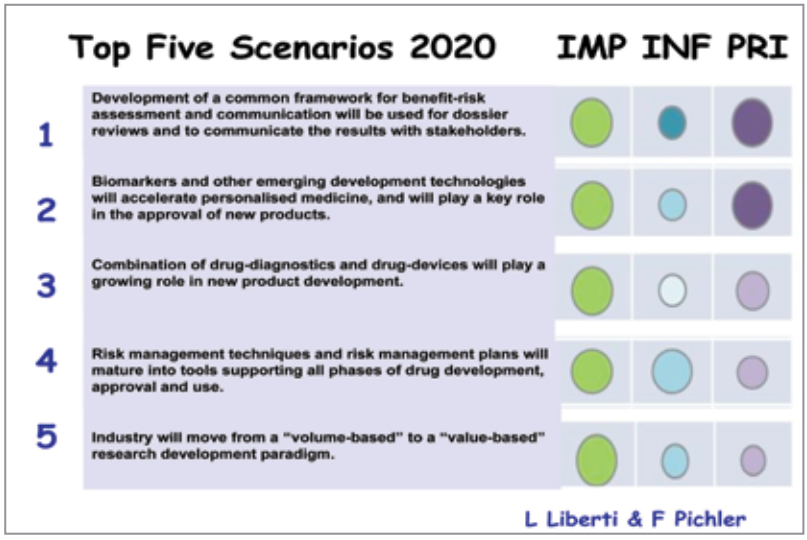

In the most critical step, a valuation is made of the product versus an active comparator or placebo, in some subjective, qualitative, or in some cases, quantitative way, resulting in the expert judgement of benefit-risk assessment. This judgement relies on wisdom and experience as well as the data that have been provided in the submission. Professor Walker explained that this is a somewhat challenging methodology, which whilst it may not be feasible for use by regulatory authorities at this stage of development, would be used during the Syndicate discussions at this Executive Forum for the systematic benefit-risk assessment of a hypothetical statin.

Dr Mussen's seven-step process was also used by the Institute to develop its framework and qualitative approach to benefit-risk assessment and in 2009, Dr Mussen and Professors Walker and Salek published the seminal work: Benefit-Risk Appraisal of Medicines: A Systematic Approach to Decision Making.[1]

### The 2020 Survey

Over the last year, The Institute has been working on Project 2020, a survey of pharmaceutical companies regarding 39 scenarios that may influence future aspects of the regulatory environment by the year 2020. Respondents were asked to provide insight into the impact that these scenarios may have on their companies and the extent to which they believed that their company may be able to influence that impact. They were also asked to specify their company's priorities by indicating what proportion of their budget they would allocate to exert an influence on the scenarios.

It was significant that industry responses indicate that the number one scenario of importance is the development of a common framework for benefit-risk assessment for use in dossier reviews and in the communication of the results of those reviews to stakeholders. Other topics




of interest to the respondents included the use of biomarkers and emerging technologies as part of regulatory strategies, the combination of drug-diagnostics and drug-devices, risk management techniques and plans, and the move within industry from a volume-based to a value-based product development paradigm.

Several others of the 39 scenarios can be regarded as being interconnected and interrelated to the development of the common benefit-risk framework including those surrounding transparency and public disclosure; the impact of safety failures on the development and review processes and the resulting re-examination of data; risk management techniques and post-marketing surveillance; and increasingly, the involvement of patients in the whole area of benefit-risk assessment. Which is why the common framework is important, not only to adequately describe what happens when companies and agencies make benefit-risk assessments, but ultimately, what is meant, understood and recognised as benefit-risk assessment in all stakeholder communication.

### The Benefit-Risk Framework Survey

In a brief, ongoing survey, the Institute's member companies were questioned regarding their use of a formal systematic structured benefit-risk framework, the hurdles to the establishment of the framework and solutions to overcome those hurdles. Although a limited response has been received to date, six basic hurdles have emerged:

1. A lack of an accepted, validated, international model that the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Japanese Pharmaceuticals and Medicines Development Agency (PMDA) would recognise and use in their assessment of a new drug application
2. The absence of an academic, industry or government agreement on methods for the quantitative valuation of benefits and risks
3. Perceived difficulties in making and applying value judgements
4. A reluctance to change from existing assessment methods, tempered by cultural issues
5. An insufficient internal belief at the level of senior R&D staff of the added value of a benefit-risk framework
6. The need to use a thoughtful, cautious approach towards moving to complete decision-making transparency

Despite initiatives to establish agreements among stakeholders such as the one being undertaken for example, by the Next Steps Group, there has yet to be an agreement on methods for quantitative evaluation. In fact, the Institute's own initiative has focused on qualitative approaches, which although the most appropriate way forward at this stage, will hopefully be developed into quantitative methodologies in the future.

An equal number of solutions to these perceived hurdles were also suggested by the survey respondents:

1. The establishment of a collaborative working group of representatives from industry, regulators, patient groups and health care professionals
2. The agreement between industry and regulatory agencies on a common approach, or at least on a common set of principles for a benefit-risk framework
3. Internal education on the value and approach to the quantification of benefits and risks
4. The identification of the characteristics of a benefit-risk model recognised by FDA and other health agencies
5. Benefit-risk methodology taught in medical and pharmacy schools to prepare the next generation of medical reviewers
6. The availability and publication of worked examples using different methodologies of benefit-risk assessment, as the basis for guidance.

While a number of agencies are working

collaboratively at the present time, there are challenges to the agreement of a common approach. In Europe, for example, there are 27 member states, and each of those may have a different perspective, a different approach, and a different way of making benefit-risk decisions. Indeed, they may even have different definitions of what they understand by benefits and harms. Both the Institute and the EMA are addressing the publication of worked examples of different methodologies of benefit-risk assessment. The EMA are additionally looking across different methodologies and approaches and systems in order to make a side-by-side comparison.

Professor Walker concluded by detailing the three important objectives for this meeting:

1. Establish a Forum for regulatory agencies and industry to regularly review case studies and the current status on benefit-risk assessment in the development and during the regulatory review of medicines
2. Provide an opportunity to refine the benefit-risk framework and provide a perspective on which weightings and values might be used in making benefit-risk decisions
3. Review a case study for a hypothetical statin that would enable a discussion on its benefit-risk assessment from the perspective of regulators, sponsors and patients

He expressed the hope that this particular forum, which is now the seventh Workshop convened by the Institute in the area of benefit-risk assessment, would take development of the benefit-risk framework forward to a critical new level.

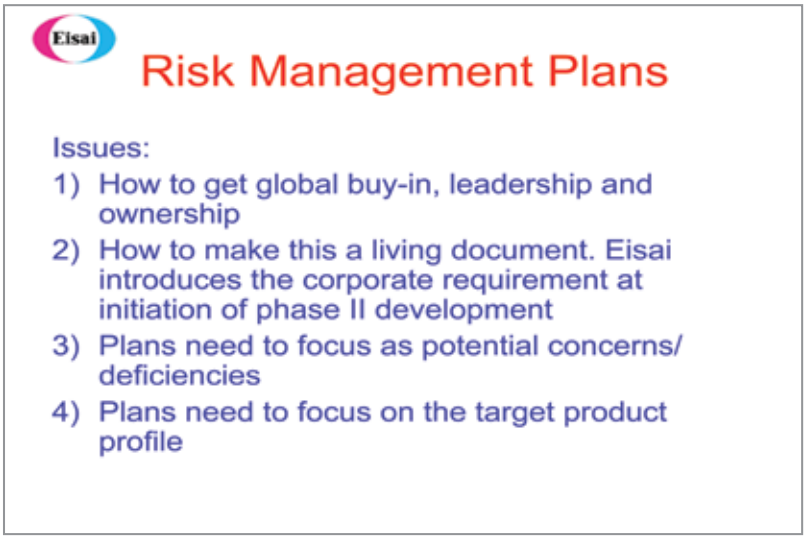
### Reference

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

## Eisai's approach to benefit-risk assessment

**Dr David Jefferys**

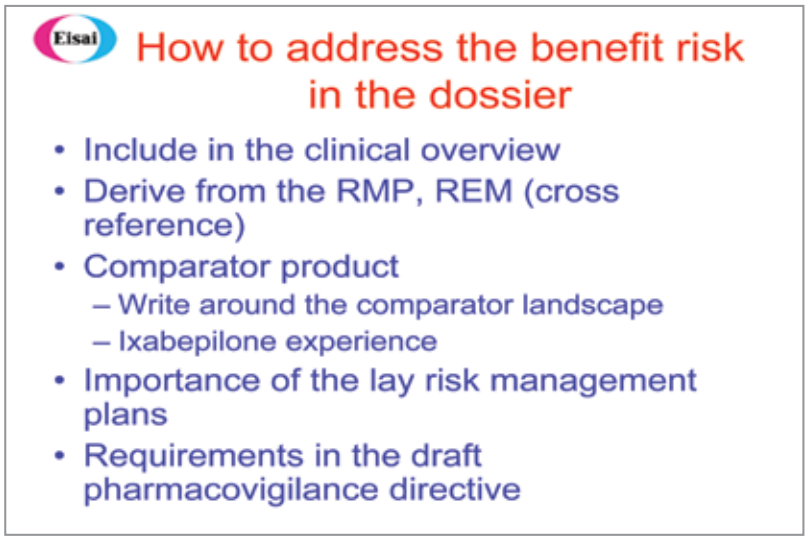
*Senior Vice President, Global Regulatory, Healthcare Policy Dept, Eisai Europe Ltd, UK*




### An industry view

Dr Jefferys began by sharing some of the discussions he has had on the topic of benefit risk with his colleagues in the European pharmaceutical industry and in the Association of the British Pharmaceutical Industry. It was the consensus of those groups that the process of benefit-risk evaluation provided an opportunity for the industry to assess a product in an integrated fashion through its development and commercial life cycle. Although this seems an obvious conclusion, it was nonetheless a product of long discussions and a change in perspective. Benefit-risk evaluation is now regarded as a direct opportunity to communicate the actual balance of benefits and risks to regulatory agencies and beyond that to healthcare professionals and patients. Benefit-risk is also now being reflected in health technology assessments and it is clear that it is also informing pricing and reimbursement decisions.

Although it is widely recognised that benefit-risk evaluation is a work in progress, one of the issues that is emerging is how the evaluation can be incorporated into a dossier, especially into a global regulatory dossier. Related questions include: where the assessment should be placed in the dossier; how the balance should be presented between benefits and risks




in the assessment; and ways to include the different risk management plans. In today's international environment, there is a need for a comprehensive, global approach, but there are different requirements emerging between approaches taken by the EMA and the FDA, and the PMDA is now entering into the discussion. These disparate regional perceptions regarding both risk and benefit need to be addressed when making simultaneous global filings.

### Eisai and benefit-risk

The topic of benefit-risk was introduced to Eisai in 2005 with presentations of the multi-criteria decision analysis (MCDA) model by Larry Phillips and others. That model was in the process of being evaluated when Eisai was required to produce the first corporate standard operating procedure for risk management plans as part of its dossier submissions. After being established, this SOP was updated in 2008 in light of the initial Eisai experience and included an examination of how benefit-risk could be embedded in a more comprehensive way within the structures in the company, with its system of committees, of checks and procedures.

At the same time, all of Eisai's primary discovery, clinical research and some of the manufacturing research were brought together in one company, the Eisai Research and Development Management Company (ERDC), which in turn was overseen by the Research and Development Management Committee (RDMC). The RMDC, which met for two years, put benefit-risk at the heart of its debates, ultimately deciding that it should be a key element of the Eisai global safety board and the global regulatory committee.

In 2009 Eisai introduced the Global Regulatory Analysis Strategic Plans (GRASP), living documents bringing together each new medicine's complete global strategy, from development though filing for regulatory approval. The GRASP are stored in an electronic library available to others across the company and have proved a valuable source of cross fertilisation. Eisai has found that benefit-risk assessment also improves internal communications, helping groups to focus on key product attributes.

The company initiates the development of risk management plans at the beginning of phase 2 development; however, it is important to realise that risk management is not yet a globally accepted nor standardised process. Furthermore, although industry should be focussing on a product's potential concerns and deficiencies, and updating product profiles throughout development, it is not always clear that that happens, often because of concerns regarding ongoing project funding and prioritisation within the company's portfolio.

Eisai places the benefit-risk component of the dossier in the clinical overview, extensively cross referencing it to the risk management plan from which it is derived. Global dossiers, however, present a challenge as international regulatory agencies each view benefits and risks from a different perspective, and Eisai as well as the rest of industry would find a global guideline on benefit-risk expectations to be extremely useful.

## Novo Nordisk A/S development of a benefit-risk assessment method

**Dr Sinan Bardakci Sarac**

*MD, Quantitative Clinical Pharmacology, Novo Nordisk A/S, Denmark and the Technical University of Denmark, Department of Physics*

**Dr Christine Hallgreen**

*IMI PostDoc, Quantitative Clinical Pharmacology, Novo Nordisk A/S, Denmark*

Several years ago, Novo Nordisk recognised, as did many other companies and agencies, that there was a need for a simple and transparent method that could assess and analyse the treatment-related effects of drugs in clinical trials, preserving as much objectivity as possible for decision makers. However, instead of developing a method for data analysis and then inputting the data into that model, the method was developed as an interactive process based on the experience gained from working with several different medicines. This process continued over several years and resulted in a method that can extract information from clinical trials, which are otherwise not captured by statistics. The method, called the Benefit Risk Assessment in New and old drugs (BRAIN), consists of eight steps, some of which are familiar from traditional decision analysis.

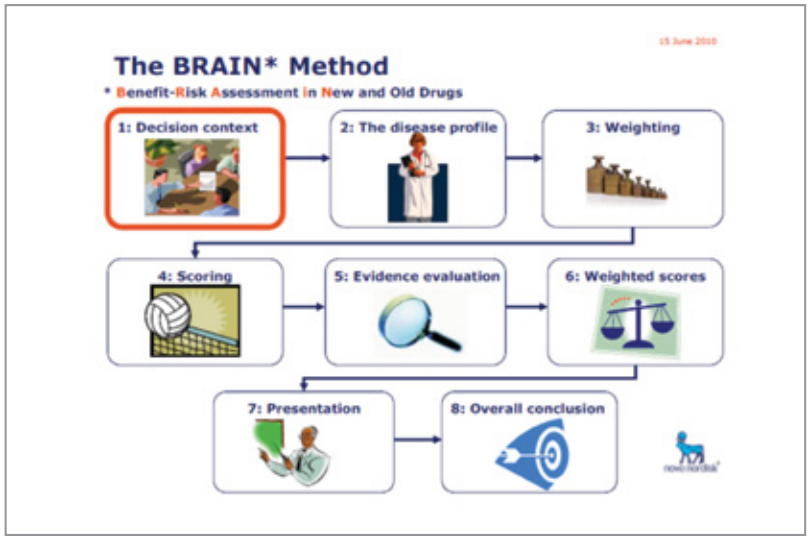



*Figure 1: The BRAIN method consists of eight steps, which are systematically assessed.*

- **Step 1:** Decision context. Here the aims and the goals of the assessment are defined. The expectations of the assessment are described. All relevant information to support the benefit-risk assessment is identified. This can include e.g. clinical trials, high level preclinical information, safety data, information from the public domain, choice of comparator etc. A hypothesis is formulated when relevant. The hypothesis is to be accepted or rejected in the overall conclusion of the assessment.
- **Step 2:** Disease profile. This includes the identification of benefit and risk criteria that characterise the disease. These criteria are either measured objectively, e.g. blood pressure, or subjectively, e.g. quality of life. Once the most important criteria are selected within the given decision context, one has to justify the choice of these criteria, so decisions can be tracked.
- **Step 3:** Weighting. To compare benefits and risks on the same scale, they are weighted on the same value scale. The weights are based on the relative importance of a criterion in the given context and all weights are justified. Weighting is not based on the actual data sets. Each benefit and risk criterion is given a weight of 1 (low), 2 (medium) or 3 (high) importance. The weights are common for all drugs in the given assessment.
- **Step 4:** Scoring. This is the process of assessing the performance of a drug relative to a comparator by assigning a numerical value for each criterion. Scoring is based on available data sets from clinical trials or other information, e.g. preclinical findings. For each criterion, the drug is scored relative to the comparator on a simple scale; -1 (inferior), 0 (non-inferior) and +1 (superior).

Different types of clinical data require different methods for scoring. For continuous variables such as biomarkers (e.g. HbA1c), vital signs (e.g. blood pressure and weight) and frequent events (e.g. minor hypoglycaemia) the scoring method is based on difference distributions. For events (e.g. responder rate, adverse events etc.) the scoring method is based on confidence intervals.

**Difference distribution scoring:** Data-driven scoring methods were introduced based on descriptive statistics. To capture trends, difference distribution scoring is conducted in which end-of trial values for drug and comparator are used to create a difference distribution. The 2:1 principle is then applied

and the difference is considered substantial if at least 2/3 of the subjects experience better performance with either drug or comparator. In crossover trials, the difference distribution varies depending on the correlation of the groups. The size of the trial is incorporated in the scoring by the use of re sampling techniques.

**Confidence interval scoring** can be used, when dealing with sparse events, to find out if the probability of one event per subject is different between the drug and the comparator, two one-sided binomial tests for both the drug and comparator are performed to gain an interval for scoring. If the scoring intervals do not overlap, the probability for an event between drug and comparator is considered different and if the intervals overlap, it is then considered not different.

- **Step 5:** Evidence evaluation. If the evidence is weak an objective score can be changed to an interval.(-1 to 0, 0 to +1 or -1 to +1) A list of elements of evidence evaluation were recommended by the Committee for Medicinal Products for Human Use (CHMP) Working Party in their reflection paper on Benefit-Risk evaluation (adopted March 2008).
- **Step 6:** Weighted scores. Weights and scores are multiplied.
- **Step 7:** Presentation of the results. The weighted scores are visualised through a Tornado-like diagram. Results from multiple trials can be combined to give an overall benefit-risk assessment as seen in Figure 2. Each trial is assigned an impact factor based on its importance, e.g. the power of the trial and a mean score for each criterion is calculated based on the weighted scores and the impact factor of the involved trials.
- **Step 8:** Overall conclusion. The hypothesis formulated in the decision context is either accepted or rejected. Any uncertainty is described, including how that uncertainty impacts the results. Unexpected issues are described, and strategies for further studies are presented. Finally a recommendation and conclusion is given.



### Overall assessment of drug vs comparator

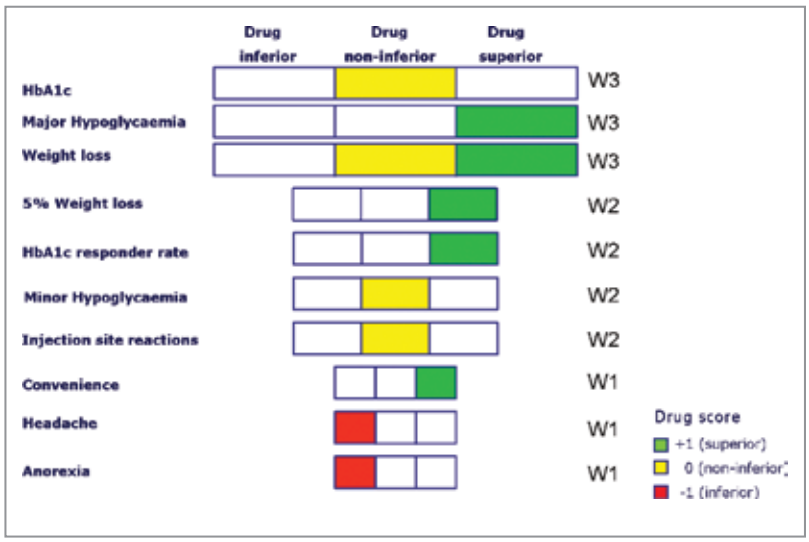



*Figure 2: The width of a box indicates the relative importance of a criterion. The wider the box, the more important is the criterion. The colours indicate the performance of the drug relative to a comparator. The green colour indicates that the drug is superior, the yellow colour indicate non-inferiority and the red colour indicate inferiority.*

## Visualisation of benefits and risks: an innovative approach

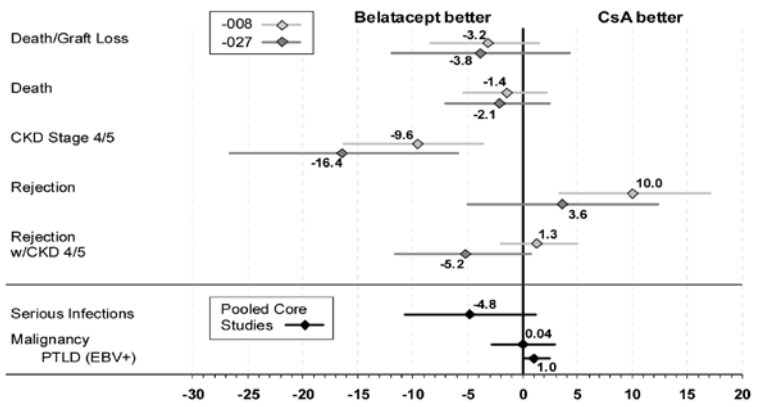
**Dr Douglas Manion**

*Vice President, Neuroscience and Virology, Bristol-Myers Squibb, USA*

### Emotional context of benefit-risk decisions

As human beings, we all deal daily with benefit-risk information and decisions. Which risks get excessive attention, however, and which get overlooked depends on a hierarchy of factors, the most important of which may be "dread." The more pain or suffering something causes, the more humans tend to fear it; for example, more people fear AIDS, which kills slowly, than a heart attack, despite the fact that heart disease claims nearly 50 times as many Americans than AIDS each year. Situations that provoke the most anxiety and dread result in a less precise emotional assessment of the estimation of their risk.

In his presentation *The Emotional Salience of Context* given at the Institute of Medicine meeting in 2006, Dr Peter Ubel explained that the human perception of benefit-risk is based on our emotional state and that this perception can be manipulated positively or negatively by the way in which the data are presented. Furthermore, it is possible to manipulate qualitative data when quantitative data are not available to drive an audience to an a priori conclusion. This possibility for manipulation is the basis for the dichotomy of the paternalistic and benevolent approaches to physician-to-patient education and benefit-risk communication. In the paternalistic approach, the physician presents himself as the learned intermediary who explains that it is in the patient's best interest to take a drug because the benefits outweigh the risks or risks may not be mentioned at all. In the benevolent approach, physicians tell the unlearned patient everything that can be known regarding the benefits and risks, and then leaves the often overwhelming decision to the patient. A classic example of this approach is risk-labelling such as calling bovine spongiform encephalopathy (BSE) "mad cow disease," presenting emotional connotations, which drive patients toward a highly negative risk conclusion.




Comprehensive Benefit-Risk Assessment: Absolute Difference between Belatacept LI and Cyclosporine (%).

### Decision- making theories

- According to *Fuzzy Choice* theory, humans are able to make correct choices based on less information because human judgement and decision making is not fundamentally computational. Instead, humans have a fuzzy processing preference that generally leads to superior decisions based on the use of less information, which is processed more simply. Physicians, who often make such decisions, may feel uncomfortable revealing the thought processes behind their decisions.
- *Game Theory* is a branch of applied mathematics and economics that studies situations in which players choose different actions in an attempt to maximise their returns. The essential feature, however, is that it provides a formal modeling approach to social situations in which decision makers interact with others in a context of uncertainty.
- In *Standard Gamble* decision making, an individual is asked to choose between the certainty of surviving for a fixed period in a particular state of ill health and a gamble between surviving for the same period without disability on the one hand and immediate death on the other. The probability of surviving without disability, as opposed to dying, is then varied until the person shows no preference between the certain option and the gamble. The probability then defines the utility of an individual for the disabled state on a scale between 0 and 1 whose end-points are bracketed by death and perfect health.
- There are several different other heuristics used to quantify benefit-risk such as the *Q-Twist, NNT/NNH, Lynd-O'Brien* and *Sutton*

methods. All of these methods present a thesis for judging benefit-risk, use a scoring or preference system through which the relative impact of any given risk to any given benefit can be gauged, and include processes to take uncertainty in account. The output of all these methods allows the transparent visual presentation of benefit-risk data without bias from emotional context.

## The belatacept FDA Advisory Committee meeting

Success in clinical transplantation is achieved through increasingly powerful, lifelong, multi-drug immunosuppressive regimens that suppress the T-cell-mediated rejection response. Virtually all renal transplant recipients use some variation of regimens, the mainstays of which are the calcineurin-inhibitors (CNI's) tacromilus and cyclosporine and for some, sirolimus. CNI's are potent immunosuppressants, but are nephrotoxic, leading to declining renal function, graft fibrosis and scarring. They also increase cardiovascular risk by contributing to declining renal function, diabetes, hypertension, and hyperlipidaemia, adding to the risk of graft loss and patient death.

Clinical trials for the BMS drug belatacept, a selective T-cell co-stimulation blocker, showed that using this drug compared with cyclosporine improved renal function over time, improved cardiovascular metabolic profiles, and preserved short-term patient and graft survival. It was associated with a higher incidence of pathologic rejection and an incrementally higher rate of serious adverse events, including progressive multifocal leukoencephalopathy, which is fatal, as well as PTLD, which is a peri-transplant-related B-cell lymphoma akin to Hodgkin's Disease.

In March of 2010, BMS presented belatacept data to the US FDA Advisory Committee. Using data display charts and juxtaposing two different doses of belatacept against cyclosporine, in two different patient populations, point estimate differences with confidence intervals were shown, allowing the committee to identify which treatment was associated with superior results and with what level of certainty. Results included those for the primary end point, graft survival over time, renal function based on glomerular filtration rate, and progression to stage 4 or 5 chronic kidney disease, which is itself a precursor to alograft loss. All of these measurements revealed benefits with belatacept use.

In portraying measurement of relative risk from the safety database, the incidence of death was examined first and showed an overall trend toward higher death rates in the cyclosporine compared with the low-dose belatacept arm. Belatacept was also associated with lower rates of infection leading to death, although there were similar incidences of polyoma virus, which causes progressive multifocal leukoencephalopathy in the cyclosporine and high-dose belatacept. When examining incidence of neoplasms, it became evident that there was a higher rate of this Hodgkin's-like lymphoma in people who received belatacept. This lymphoma was caused by Epstein-Barr virus in people who had no antibodies to this virus. Therefore, by excluding people who were Epstein-Barr virus negative in the remainder of the phase 3 programme, the incidence was very low.

All of these graphs detailed, in a very transparent way, how each element of the benefit and risk value tree for belatacept was transparently quantified. The final graph presented to the Advisory Committee was a forest plot showing for each of the primary belatacept trials, the relative point estimate difference for each of the variables comparing belatacept to the cyclosporine control arm, including confidence intervals to allow for a visual ascertainment of uncertainty. For the display of benefit, the individual point estimates from the studies were used, and for risk, data were pooled across the studies. This graphic proved to be an extremely helpful method to allow the Committee to be able to grasp, in a single visual, a densely complicated benefit-risk story[1].

The result was that the renal and cardiovascular Advisory Committee of the US FDA recommended approval of belatacept by a 12-5 vote. Whilst final approval is still pending, BMS received positive feedback from the advisors as well as from the FDA regarding this graphic depiction of the benefits and risks of a new medicine, particularly for its lack of undue abstraction or false precision. This representation, however, is very much targeted toward the physician audience and BMS is now addressing the need to convert it into documentations for patients that will be delivered as part of a risk management programme.

## Reference

1. Belatacept (BMS-224818): FDA's Cardiovascular and Renal Drugs Advisory Committee Briefing Document for March 2010 Meeting BLA 125288, January 25, 2010. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM201859.pdf. Accessed November 2010.

## Benefit-risk assessment: The Lilly Perspective

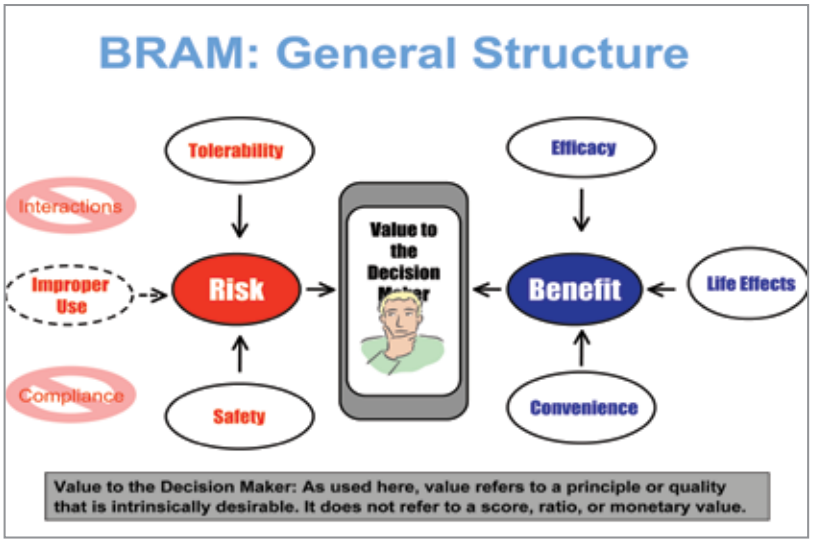
**Dr Rebecca Noel**

*Research Scientist, Eli Lilly and Company*

### BRAM

The Lilly Benefit-Risk Assessment Model (BRAM) was developed over the course of 2005, piloted in 2006, and then selectively implemented across the company in 2007. Because questions of healthcare treatment require regulators and clinicians to balance multiple criteria while making a value or preference-based decision in the face of uncertainty, the BRAM is a multi-attribute model. It was designed to help focus discussion on the primary elements of risk and benefit for a specific treatment and its alternatives. The model uses multiple attributes because it is not only important to discuss the relative importance of benefit and risk when assessing the overall utility of a treatment, but also the trade-offs a decision-maker is willing to make between the various aspects of benefit and risk.

The BRAM consists of a general structure that is tailored to a specific issue or question and is always developed in the context of a frame, which takes into account the disease state, population, and the perspective from which the assessment is made. According to the BRAM, the relevant components of benefit include efficacy, life effects, and convenience. Efficacy attributes are the primary points of disease relief, as determined in clinical trials. Life effects are the non-clinical points of disease relief, such as improved activities of daily living, while convenience is defined by attributes that describe overall ease of use. Risk, on the other hand, is composed of tolerability and safety attributes. Safety attributes encompass both real and perceived threats to health while tolerability is a measure of nuisance events that may negatively impact quality of life, such as nausea or headaches. Drug interactions, lack of compliance, or misuse are not accounted for in this model, because these elements are captured in the frame. The BRAM is designed to provide a transparent framework for informed discussion of the marginal benefits and risks and was not intended as a tool to produce a single, summary "score".




It should also be noted that the BRAM is not a static tool but rather is used as a "snaphot," easily updated to evolve over time. This snapshot can be created through an 8-step process.

1. Declare the perspective for making value judgments (e.g., patient, regulatory, or sponsor viewpoint)
2. Define the appropriate assessment frame
   a.Disease state, (sub)population
3. Develop an initial set of treatment alternatives
4. Identify and group treatment attributes that comprise benefit and risk in the context of the frame and the set of treatment alternatives
5. Refine the set of treatment alternatives
6. Assign values to attribute scores for the treatment alternatives
   a. Protocols have been valuable for consistent valuation of risk attributes
7. Assign weights to treatment attributes
   a. Abstract importance tempered by discriminatory power
8. Calculate marginal contributions of benefit and risk

Ideally, BRAMs would be built from both a company and regulator perspective and differences in those perspectives would provide a structured framework to facilitate and focus discussion to enhance the transparency of the decision-making process and to help communicate how decisions were reached.

### The BRAT framework modified for Lily

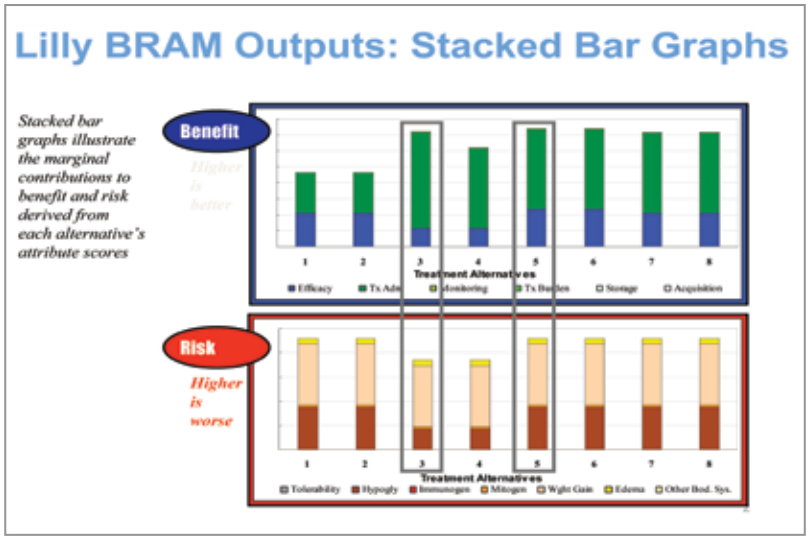
In parallel to the development of the BRAM, the Pharmaceutical Research and Manufacturers of American (PhRMA) formed the Benefit-Risk Action Team (BRAT) to advance a framework for benefit-risk assessment. The goals of BRAT are three-fold: to increase the transparency, predictability and consistency with which regulatory decisions are made; to improve communication of benefit-risk to all stakeholders; and to strengthen the overall drug development and regulatory approval process. The BRAT framework with slight modifications is a set of processes and tools that are used at Lilly to select, organise, interact and summarise data.

**Step 1: Define the assessment frame**

- Ensure reference sources are updated
- Specify disease state and indication
- Specify populations
- Specify perspective from which assessment is being made
- Specify comparators and reasonable and/or relevant alternative therapies within the competitive landscape

**Step 2: Identify outcomes**

- Potential and identified risks may be taken from company documentation, which includes references to plausible comparator set when appropriate
- Benefit attributes can be identified from company documentation




- Team identifies risks and benefits for comparator set, within and outside class
- Team considers available established scales
- Build initial value tree
- External (to team) validation required at this step

**Step 3: Refine measurement scales**

- Determine measurement scales (may be available from existing Company documentation)
- For situations when two or more scales are available, the team determines the appropriate approach
- While likely rare, if no established scale, develop an appropriate scale

**Step 4: Build and modify the data source table**

- Verify complete data package is available
- Identify and organise the data sources for Lilly and external assets
- Create data source table shell
- Validate data source table shell with core team
- Populate data source table shell with data
- Validate data source table with core team

**Step 5: Calculate and evaluate scores and weights**

- Determine weighting method
- Assign weights to attributes
- Define score functions
- Calculate scores

**Step 6: Interpret the assessment**

- Distil list of key benefit and risk attributes from value tree and summary table
- Apply judgment based on weights and scores for list of attributes
- Assess "What does the benefit-risk balance mean?" using summary table and clinical judgment to drive recommendation; understand what can be mitigated and highlight what can drive decision making
- Communicate benefits and risks to groups that will incorporate into phase 3 decision making

Like the BRAM, the BRAT is not a model that is intended to give a score or summary statistic, but is rather a tool designed to facilitate high-quality decision-making. BRAT and BRAM are two primary methods of thinking about decisions that are very much underpinned and informed by scientific discipline drawn from value-focused thinking. As stated by Keeney, "Values are what we care about…(they) should be the driving force for our decision making… (and) the basis for the time and effort we spend thinking about decisions. Alternatives are relevant only because they are the means to achieve your values."[1]

## Reference

1. Keeney RL. *Value-focussed thinking*. Cambridge, MA: Harvard University Press, 1992.

## Q&A

**Question:** How widely accepted and understood is your model in Lilly? And how do you use it to support decision making? Do you use it proactively through drug development, for example, to inform the next stage of trial design and so on?

*Answer: The learning map, the BRAT and the BRAM are all underpinned by the same processes and the same tools, the same principles that come out of value-focused thinking. The techniques that get emphasised at different points along the cycle are different. All of this is accompanied by something that is called a reference package, a compilation and summary of all the data that goes into this decision making: data from clinical trials, observational studies, health-outcomes and preclinical data. This reference source sits alongside with the teams as they are going through this process.*

*So forcing teams to come together to discuss the answers to significant questions is key: What do we believe, based on our medical expertise and our judgement, are the most significant safety issues for this particular drug? What do we see as the most significant tolerability issues? What are the best efficacy attributes? Once you have identified what these attributes are, then that can drive everything that is done downstream in clinical management and risk management plans.*

*I think there is an education and an uptake and adoption hurdle that we clearly still have to get over. But it is my firm belief that we are on the tipping point. I think the BRAT represents an alternative tool that takes a much more qualitative approach and uses the more simplistic approach in terms of mathematical perspective to creating valuing and weighting. But at the end of the day, it allows you to generate similar visual outputs that are very effective and very powerful communication tools.*

*At Lily we now put in the basic elements of a risk management plan from the first human dose onward in the clinical plan document. At the meeting held at the end of phase 2, two things are required: a well-characterised risk management plan and an assessment of the benefit-risk proposition. This assessment could be simplistic, and qualitative or quantitative, but it leads the product team forward into phase 3 development and onward.*

**Question:** One concern from the regulatory perspective is that this would add a layer of opacity to the process, that in each one-off model the drug sponsor will choose the benefit and risk attributes that put the drug in the best light, then we'd still then have to take apart the model and understand it. Our time constraints mean that models must facilitate decision making and be very transparent and data must be in a standardised format.

*Answer: That is a very valid point. What we would envision is that in future data would be available in a reference package in a standard format. When we have tools and processes in place that help facilitate standardisation, any data manipulation becomes immediately transparent.*

## Valuing Benefits and Risks: A GSK Example

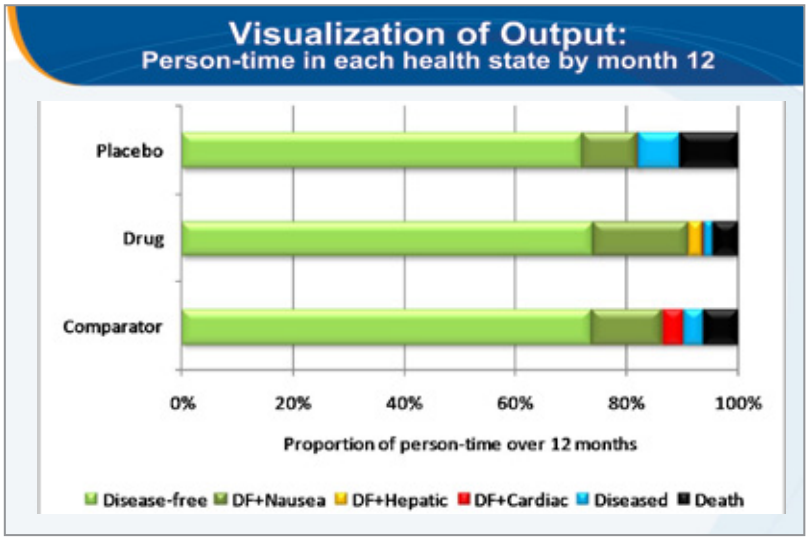
**Dr Marilyn Metcalf**

*Director, Quantitative and Decision Sciences, GlaxoSmithKline, US*

Transparency in the identification, measurement, analysis, and communication of benefits and risks continues to be of vast importance in the development of new medicines. Internally, GSK has an integrated benefit-risk evaluation team and representatives from different therapy and functional areas within the company provide a broad base and multiple perspectives on benefit-risk assessment. This team is building a framework for the evaluation of benefit-risk that will answer the needs of multiple stakeholders at different levels, including internal colleagues, regulators, payers, healthcare providers and patients.

### A BR case study (Analysis by Patrick Ryan and Michael Colopy)

Although a medicine being developed at GSK for prevention of a serious disease showed significant benefits in phase 3, it was also associated with some uncertainties around rare events. Therefore, an external group of stakeholders requested an indirect comparison of its benefits and risks with a marketed therapy. These stakeholders wanted to track only the most serious adverse events in patients, with the understanding that those would overshadow any of the more minor conditions. A Markov model was used for this comparison, which in this case incorporated an implicit valuation of "better" and "worse" health conditions as part of disease progression.




To use this model, efficacy and safety endpoints or outcomes must be pre-specified and defined in the context of health states and rates of transition from one health state to the next must be specified. Health states are then selected that both compare and differentiate therapies in an unbiased manner and the outcomes are then associated with these health states. Two outcomes may reflect the same health state and can be combined, but combining broadly into one health state may make the differentiation of medicines more difficult, so this is an area where evidence for choosing priorities is especially important. A time interval for the transition between health states must also be specified.

When synthesising data, assumptions regarding limitations must be made clear to allow transparency in the analysis. For example

- If data come from different studies, an assumption should be stated about the patient populations being similar
- If safety data are for all doses combined, an assumption should be stated about the safety events not being dose-related
- If events are reported as a cumulative incidence, an assumption should be stated about the event rate being constant over time

Various aspects of the data can be visualised in different ways. In this study, the drug and active comparator were thought to have similar benefits, with regard to median times to event, but with higher uncertainty about harms, thus choosing adverse events became a priority. When survival data became available, the Kaplan-Meier curves for both disease and survival from different studies were indirectly compared. The curves diverged after the median times, showing patients on the GSK drug stayed disease-free longer turning the focus away from harms and toward benefits.

Clinical trial statisticians are accustomed to checking the robustness of the analysis by performing both parametric and nonparametric analyses of both the intent-to-treat and the per-protocol populations, or by performing subgroup analyses. In this case, however, there is slightly more latitude. Robustness might be analysed by sensitivity analysis. The outcomes may also be weighed differently according to stakeholder preferences. The analysis is complete

when there are enough data to support clear and transparent decision making.

### The GSK Benefit-Risk Toolkit

An internal, ad-hoc analysis was requested for a specific reason. The model required special knowledge, technical expertise, and intense effort and answered a set of questions that could be updated if needed. Although this type of an analysis can be replicated as needed, GSK was able to derive significant learning that can be more generalised as well. The GSK Benefit-Risk Toolkit derived from this exercise and others is now under development.

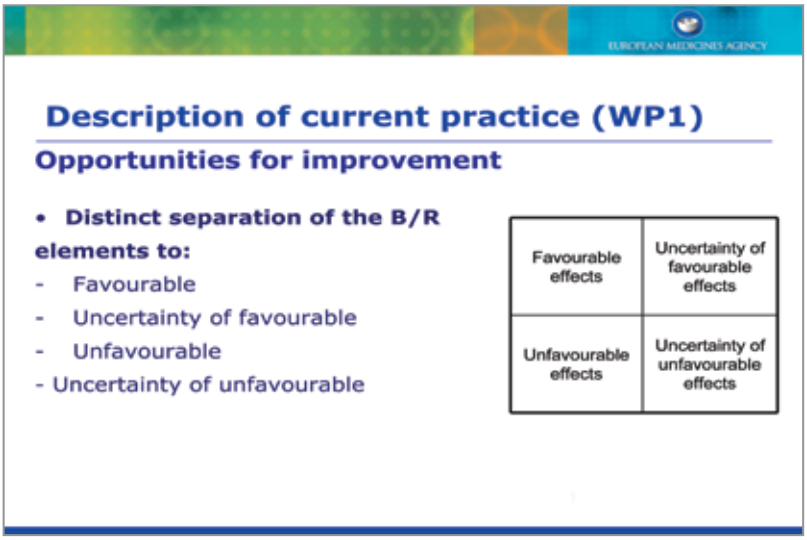
It is envisioned that starting very early with dialogue with internal early development teams, regulators and key opinion leaders, evidence such as candidate selection data, strategies and the benefit-risk management planning would be examined in context. Then as clinical development begins, the preclinical and clinical data are examined and dialogue expanded to include patients and patient advocates. Next, internal teams, supported by analysts and communicators, need to determine the key benefits and risks for the medicine, preparing for health technology and subgroup analyses. Finally, risk management plans will need to be developed as well as benefit-risk management plans. Dialogue must be maintained with the regulators and healthcare practitioners. As healthcare changes continue to advance globally, the information needs of legislators will also be considered and benefit risk extended into life cycle management.

## Update from EMA on benefit-risk assessment

**Dr Xavier Luria**

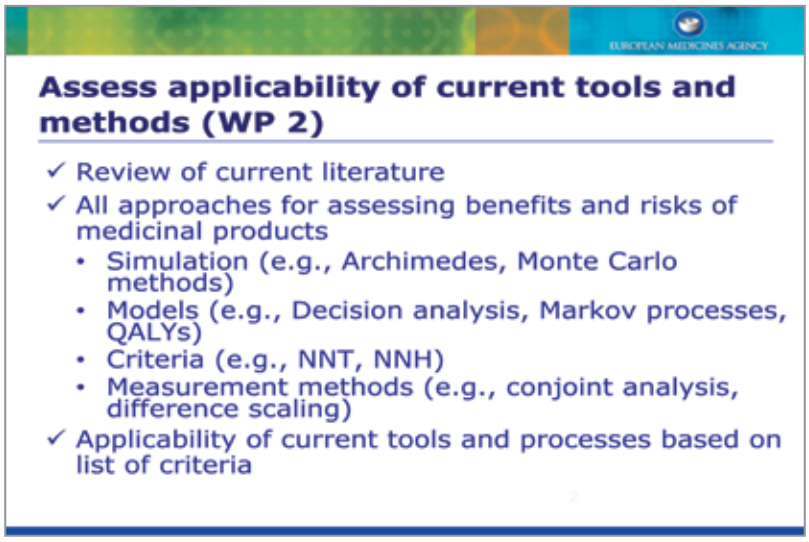
*Head of Safety and Efficacy of Medicines, EMA*

In an EMA audit conducted in November 2004 it was determined that there was a need for a more systematic approach that would improve the consistency of benefit-risk analyses and accordingly, an EMA/CHMP Working Group was set up in May 2006. Subsequently, the March 2008 CHMP Reflection paper on benefit-risk assessment methods outlined two main recommendations: first, that the benefit-risk balance section of the CHMP Assessment Report template be revised to include a structured list of benefit and risk criteria, guidance and improved consistency, transparency and communication. Second, that research methodologies of benefit-risk balance be developed involving experts and assessors, and specialists in Decision Theory. Following a pilot phase and Workshop, a draft template for the CHMP Assessment Report was agreed and draft guidance adopted by the CHMP with implementation of the template into all existing reports. This rollout was initiated in 2009 and its implementation is now being monitored.




### Benefit-risk methodology project

The benefit-risk methodology research project, formally titled *Development and testing of tools and processes for balancing multiple benefits and risks as an aid to informed regulatory decisions about medicinal products* was begun in 2009 with 29 EU countries participating. As a research project, the programme is by its nature exploratory and accordingly, several new elements have been integrated since its inception. It is expected that this project will improve the quality, transparency and consistency of benefit-risk assessments, resulting in more auditable and robust evaluations. It is further envisioned that benefit-risk assessment could be harmonised across the European network and that the time to approval of a Market Authorisation Application could theoretically be reduced.




The benefit-risk project was divided into five work packages: first, a description of the current practices; second, applicability of tools and methods; third, a field test of some of the methods; fourth, the development of tools and methods for benefit-risk assessment and fifth, a training module for benefit-risk assessors. A CHMP Steering group in concert with the London School of Economics and the University of Groningen is managing this programme.

### The Status of Work Package 1

For the first work package, which is now complete, the intention was to describe the current practice of benefit-risk assessment at six regulatory agencies: Spain, France, Germany, Netherlands, Sweden, and the UK. Interviews based on a predefined protocol were conducted with more than 45 assessors and statisticians to develop each agency's profile in relation to eight items:

1. History and purpose
2. Relationships with governmental and non-governmental organisations
3. Organisational structure
4. Information flow
5. Meaning of "benefits" and "risks"
6. Benefit-risk assessment processes
7. Consistency
8. Existence of models

The main findings from these interviews were that there are divergent views on benefits and risks and on weighting these among assessors and agencies. It was additionally observed that benefits and risks are typically balanced intuitively with generally no systematic approach to the assessment, because there is a perceived difficulty of deriving a benefit-risk balance from the data. Finally, the results of the research showed that there are no single, clear definitions of benefits and risks and there are also different views on the relative importance of benefits and risks, depending on the case.

These findings identified opportunities for improving the benefit-risk assessment process at the agencies, including the distinct separation of a medicine's effects as favourable or unfavourable and the categorisation of the certainty of that effect. Favourable effects were defined as any beneficial effects for the target population that are associated with the product. Unfavourable effects were identified as any detrimental effects that can be attributed to the product or that are otherwise of concern for their undesirable effect on patients' health, public health, or the environment. It was noted that uncertainties about both types of effects arise from variation, important sources of bias, methodological flaws or deficiencies, unsettled issues, and limitations of the data set. Dr Luria noted that the benefit-risk section of the assessment report template has integrated precisely this approach.

### Next steps

As a result of Work Package 1, five criteria were defined for assessing the acceptability of benefit-risk methodology and tools: logical soundness, comprehensiveness, acceptability of results, practicality and "generativeness." The EMA is now implementing Work Package 2, reviewing the current literature and applying the five acceptability criteria. The results have been published on the EMA web site and includes the identification of the tools and methods to be tested in Work Package 3.[1]

### Reference

1. European Medicines Agency. Benefit-risk methodology project: Work package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment. August 2010 Available at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500097750.pdf. Accessed November 2010

## US regulator's perspective on risk-benefit considerations

**Dr Theresa Mullin**

*Director, Office of Planning and Informatics, Center for Drug Evaluation and Research, Food and Drug Administration*

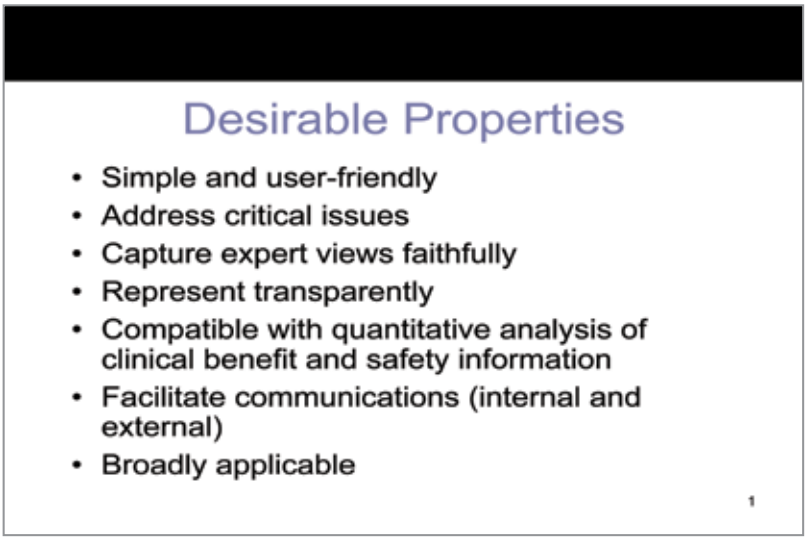
Ensuring the safety and effectiveness of human drugs is the primary regulatory goal of the Food and Drug Administration (FDA). The FDA defines "safe" to mean that a drug product's benefits outweigh its risks. The current benefit-risk assessment process utilises the extensive evidence of safety and effectiveness submitted by a sponsor in the New Drug Application and a complex array of other factors affecting the benefit-risk assessment such as the benefit-risk findings for other drugs approved to treat the same condition. This process involves both quantitative analyses as well as a subjective weighing of evidence that leads to a regulatory decision on a new drug's benefit-risk assessment. Once approved, FDA evaluates post-market safety data to continually ensure that the drug's benefits outweigh its risks as it is prescribed to the broader population.

The FDA's benefit-risk evaluation is a dynamic process. When a regulatory action is taken on a new drug, benefit-risk information is generally available only from controlled clinical trials in the intended patient population. However, knowledge of a particular product's benefits and risks continues to evolve after a drug is marketed. Some risks may not become apparent until after a drug has been approved and becomes available to larger and more diverse populations than the population studied in the pre-market clinical trials. Benefit-risk decisions also require judgement on the part of the regulator, and the perception of tolerable risk and desired level of benefit are influenced by factors that may change over time. For example, a serious risk of a certain drug may be tolerated if the drug offers a unique benefit or fills an unmet medical need. This assessment could change if another product offers similar benefit for the same indication without the particular risk. Statutory and regulatory standards, social expectations, and personal values can also influence the benefit-risk assessment of the data available for a product at a given point in time.

A benefit-risk decision framework that addresses these challenges should have several properties. It should:

- Be simple and user-friendly
- Address critical issues
- Capture expert views faithfully
- Represent the scientific basis for regulatory decisions in a transparent manner
- Be compatible with quantitative analysis of clinical benefits and patient-level safety information
- Facilitate both internal and external communication
- Be broadly applicable to a wide variety of products and product classes.

The FDA has recently discussed its proposed framework in various public forums (see figure below)




The benefit-risk framework was piloted using case studies of four previous regulatory decisions. It encourages regulators to examine the benefit-risk considerations in the following five dimensions:

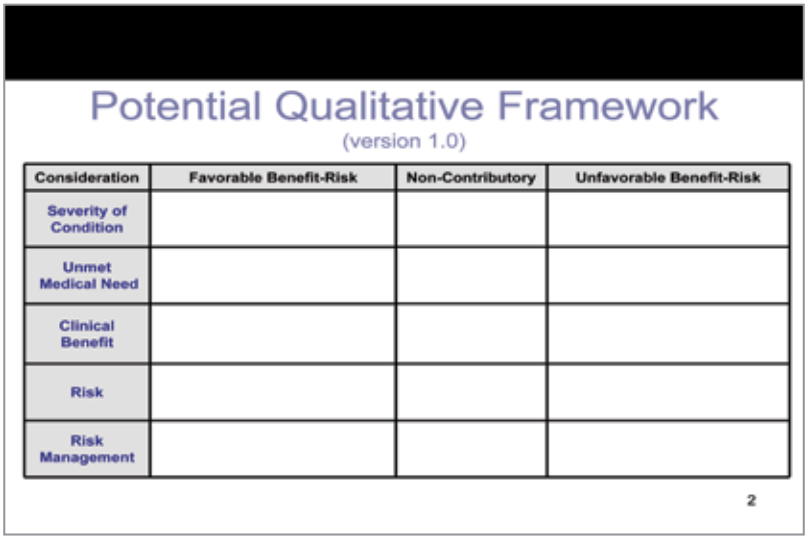
- The severity of the condition assesses whether the condition will be life threatening, rapidly fatal, serious, or non-serious if left untreated
- Unmet medical need establishes the current state of the armamentarium for a given condition. This includes an assessment of the benefits provided by existing treatments and how well they are tolerated by the patient population. Consideration is also given to underserved patient subpopulations

- Clinical benefit addresses efficacy outcome measures, including decreased mortality, and whether the product cures the condition or alleviates symptoms
- Consideration of risk requires a determination of the frequency, severity, time of onset, and reversibility of adverse events. In addition, risk assessment involves considering whether certain subpopulations may be at increased risk for particular adverse events
- Consideration for proposed risk management plans, post-marketing studies, or labeling to mitigate adverse events of concern

During the pilot phase, several attributes have emerged as desirable qualities in future revisions of the benefit-risk grid. The framework must:

- Be "simple" to understand, but avoid "simplistic" judgements.
- Support sound expert judgement, rather than acting as a replacement for it
- Identify and respect areas of expert disagreement
- Support explicit presentation and discussion of the scientific evidence, any uncertainties regarding interpretation of the evidence, implications stemming from analysis of the evidence, and assumptions that are used to aid the process of scientific interpretation or analysis

The value of a standardised framework lies in its ability to capture the relevant issues and lay out the rationale for a particular regulatory decision which could improve the predictability and consistency of regulatory decision making. It also helps to facilitate communication and more structured discussion – both within FDA and with the public – of the various dimensions in which benefit-risk assessments are performed. As a product is used in the broader populations, the framework can serve as a living document, easily updated based on new information and experience. Science provides the data to inform the analyses of benefit-risk, but it does not provide the answers. Judgement is required. Regulators at FDA use the available information on a drug's benefits and risks from controlled clinical studies to extrapolate to how the product will perform in the general population. Doctors and their patients must translate this population-based consideration to make decisions at the individual level.



Potential Qualitative Framework

(version 1.0)

| Consideration | Favorable Benefit-Risk | Non-Contributory | Unfavorable Benefit-Risk |
|---|---|---|---|
| Severity of Condition | | | |
| Unmet Medical Need | | | |
| Clinical Benefit | | | |
| Risk | | | |
| Risk Management | | | |

2

## Q&A

**Question**: Do you see benefit-risk assessment in FDA being different eventually from what is happening in Europe?

*Answer: I do not know whether it will be completely different. I think there may be different approaches to treatment and different factors in health delivery systems that affect some of those details. We are at the beginning of trying to understand the most cost-effective approach to doing risk evaluation and mitigation strategies (REMS). We are concerned about getting the right balance between preventing harm, burdening providers, and providing patient access.*

*As to whether we come out in a different place with respect to benefit-risk goes back again to differences in the statutory parameters and social expectations. I don't know how active other public stakeholders are in your regulatory work, or whether they are as proactive and vocal about what they want and expect as in the United States. I think it is very critical for us to be very good at communication. It is not uncommon for decisions or new information about FDA-approved drugs to make it to the front section of the newspaper. Maybe information from other contexts would be helpful to the public.*

**Question:** At what stage is the qualitative framework? Have you done any case studies? Will it be made publicly available? Would you welcome the opportunity for pharma companies to use your qualitative framework in their submissions in order to describe how they have come to a particular decision with regard to a benefit-risk assessment of a medicine?

*Answer: The framework is still in development. One of the important aspects of using something like this is to facilitate discussion in meetings with stakeholders of different perspectives.*

*I think pharmaceutical companies could try to use the framework, although when that idea was suggested there was still some residual concern. It would be useful to see how the company perceives their product, including what they might think are risks that need to be managed. Coming forward with that information early in the review process probably would help. I know there is some concern from companies that they do not hear from us soon enough about whether a REMS is going to be required.*

**Question**: What flexibility do you think sponsors will have, or perhaps what flexibility will FDA allow? If your phase 3 trial design is one of superiority, or one of non-inferiority or just on safety, or if you are going head to head with a gold-standard drug that has its own profile and you win on your clinical endpoints but perhaps you are not superior on your safety endpoints. Is there room in the modelling? I know it might be a bit early to provide that sort of flexibility and still come up with benefit-risk.

*Answer: Absolutely. I think that is why we are not moving to a more restrictive framework right now because we still think there's a lot of variability in what may be found in the course of trials. We would not want to make it difficult to include that information. That's why we are still at this high-level framing because that seems like the right place to be right now so we do not miss information.*

## Improving the Benefit- Risk Assessment of Medicines: A "Consortium" Initiative

**Dr Petra Dörr**

*Head of Management Services & Networking, Swissmedic*

**Dr Jason Ferla**

*Director, Clinical Evaluation Section 3, Office of Prescription Medicines, Therapeutic Goods Administration, Australia*

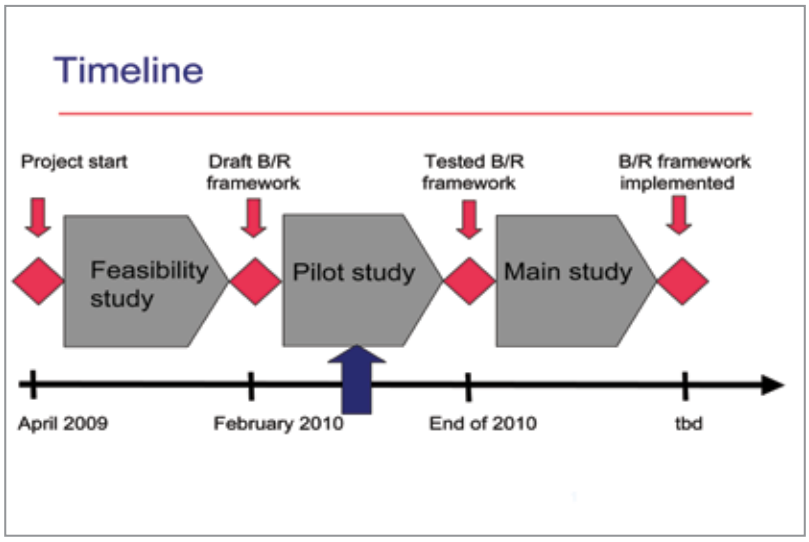
The Consortium, a global initiative begun in 2006, is based on a network of bilateral agreements for information sharing and shared reviews of new medicines among regulatory reviewers in Health Canada, Swissmedic in Switzerland, HSA in Singapore, and TGA in Australia. All of these mid-size agencies share similar regulatory philosophies and face similar challenges regarding resource management that could be positively affected by work sharing and gained efficiencies.

Dr Dörr reported that with the agreement of sponsors, pilot parallel reviews of submissions have been completed, in which there was an exchange of assessment reports, an analysis of findings and the rendering of independent decisions. Work sharing is envisioned in the future through the review of parts of the dossier by one of the agencies, followed by the sharing of assessment reports. Although final approval decisions would still be independent, cross-agency synergies could be achieved.

To achieve the planned work sharing, however, a harmonised benefit-risk assessment template is required. Accordingly, the Consortium together with the Institute has embarked on a project to develop a qualitative framework for the benefit-risk assessment of medicines that would allow a systematic standardised approach to the appraisal of medicines during the regulatory review and post-marketing by the four agencies.

The project was begun in April 2009 with a feasibility study in which a draft benefit-risk template was developed using the value tree developed as detailed in Professor Walker's presentation. The group intends to discuss the next steps in early 2011.

Next, Dr Ferla provided an update on the pilot study, saying that clear benefits to using the template have already emerged:




- Specificity
- Evaluators are required to articulate each benefit and risk clearly
- Serves as a checklist on what to consider, especially for new evaluators
- Potential for standardised approach across agencies
- Potential for comparison with other drugs in the class
- Potential for comparison of risks that lead to regulatory decisions
- Internal consistency for regulatory decision making
- Can aid in communicating benefits and risks consistently and clearly

The group is currently discussing methods for weighting the individual assessed parameters. Other issues being discussed include:

- The role of the template from a regulatory agency perspective. Is it a potential substitute for or an enhancement to an evaluation report or an assessment? How can these two approaches be integrated?
- How should pivotal studies versus non-pivotal studies, or phase 1, phase 2 studies be valued? There is the potential to have a very large number of studies, comparing result of studies with dissimilar methodology
- The Consortium may need to consider adding graphic representation such as Forest plots to the template
- A common set of terminology and definitions is required
- How many secondary endpoints should be considered?

The value of these detailed discussions is evident in the progress that the Consortium has made in the practical application of the Institute's benefit-risk framework. Two recent papers have been published on this initiative.[1,2]

## References

1. Walker S, McAuslane N, Liberti L, Salek S. Measuring benefit and balancing risk: Strategies for the benefit-risk assessment of new medicines in a risk-adverse environment. *Clin Pharmacol Ther.* 2009; 85:241-246.
2. Liberti L, McAuslane N, Walker SR. Progress on the development of a benefit/risk framework for evaluating medicines. *Reg Focus.* 2010;15:32-37.

# Section 3: Syndicate Discussions

## A scenario for discussion: Setting the scene

**Dr Bennett Levitan**

*Director, Quantitative Safety Research, Dept of Epidemiology, Johnson & Johnson PRD, US*

One of the most critical contributors to the success of a benefit-risk assessment is engaging stakeholders in a structured discussion to develop the appropriate set of benefits and risks for the assessment. In fact, this identification of the relevant benefit and risk outcomes is one of the first steps in which decision-maker values come into play – outcomes are weighted as relevant or not-relevant. The Institute asked Dr Levitan to guide Workshop participants in a practical hands-on experience to illustrate how using a simple benefit-risk framework can stimulate dialogue, identify differences in values, and help to structure an analysis of a product's benefit-risk profile. For the purposes of this exercise, Dr Levitan developed a scenario for the evaluation of a hypothetical statin (in comparison with no treatment) for the prevention of atherosclerotic cardiovascular disease in patients with a modest risk for coronary heart disease.

After introducing relevant background on cardiovascular diseases and the role of statins, Dr. Levitan introduced the scenario, a framework approach and the prepared visualisations and tools. Three Syndicate groups asked to represent the views of patients, pharmaceutical sponsors and regulatory agencies were charged with developing a value tree of benefits and risks for this compound, providing a ranking for their weighting and, time permitting, a final overall benefit-risk assessment for the medicine from the viewpoint of the designated stakeholder group. Groups contained about 12 members each.

## Background on statins and cardiovascular disease

### Cardiovascular disease

The clinical and public health consequences of cardiovascular disease (CVD) are very significant. Over 28 million Americans have high blood pressure, coronary heart disease, stroke, or other forms of CVD. Collectively, CVD causes more death than cancer, diabetes, accidents, and chronic lung disease combined. In 2007, the direct medical expenditures and lost productivity due to CVD in the United States was $432 billion.

### Cholesterol

Cholesterol, a precursor to bile acids and steroid hormones, is a fat-like substance found in cell membranes. Accumulation of the low density lipoprotein (LDL) type of cholesterol in arteries (atherosclerosis) leads to coronary artery disease, stroke, coronary heart disease (CHD) and death. A strong causal relationship between LDL and CHD is well established; for example, a 2% drop in LDL leads to an approximate 1% drop in CHD risk. For these reasons, LDL is the primary target for cholesterol-lowering therapy.

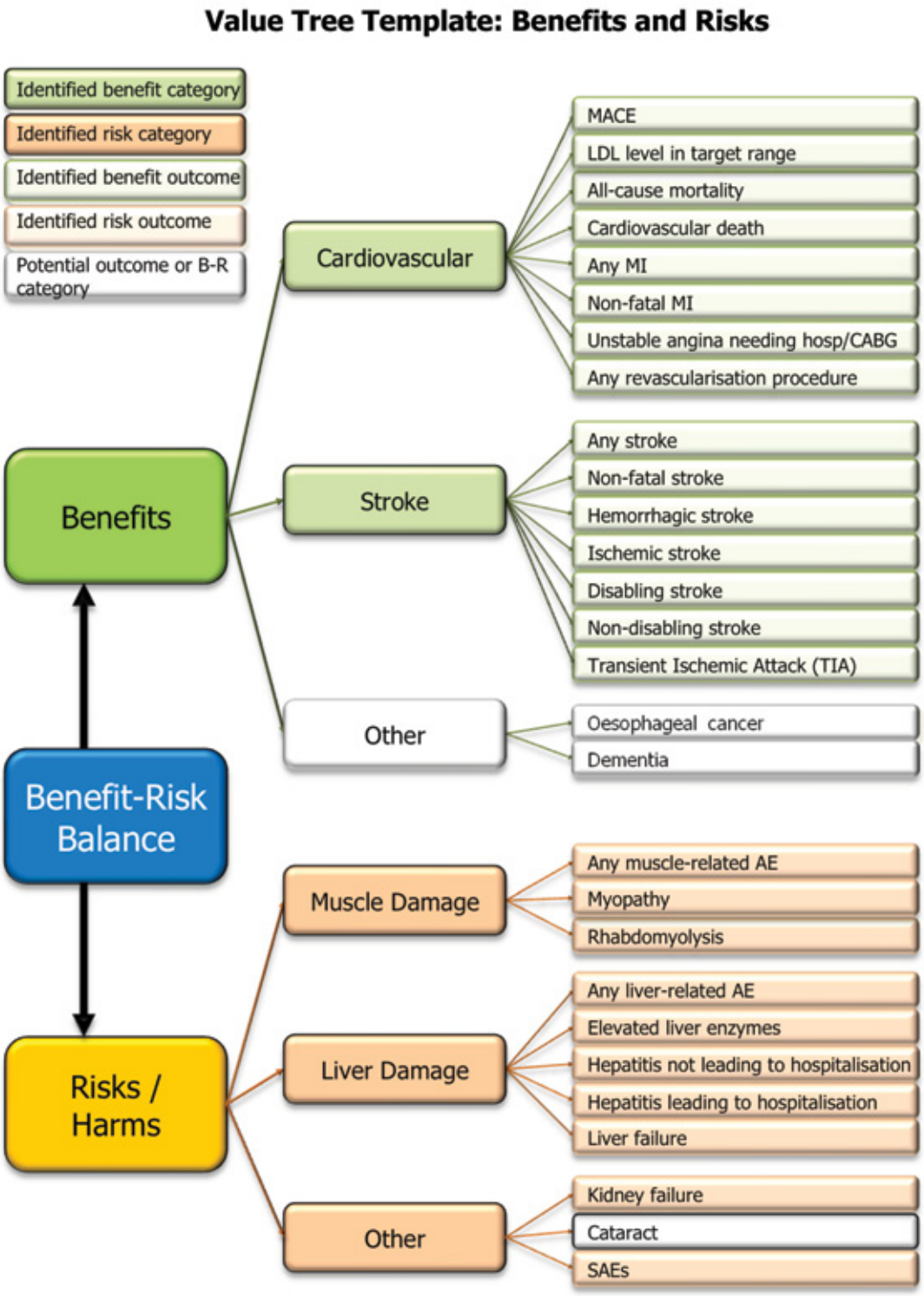
### Statins

The first statin (lovastatin) was approved by the FDA in 1987. Statins work by inhibiting a step in the endogenous synthesis of cholesterol, thereby reducing production of cholesterol in liver. They also increase clearance of LDL from bloodstream. It has been demonstrated in repeated clinical trials and observational studies that statins are very effective in preventing CHD. They are well established and approved for use in patients with CHD (secondary prevention) and patients without CHD but at high risk for it ("high-risk" primary prevention). Their use in patients at low risk for CHD ("low risk" primary prevention) is more uncertain, but there has been recent approval for rosuvastatin in primary prevention in people with no clinically evident heart disease but with all three of the following risk factors: age (older than 50 years in men; older than 60 years in women); elevated high-sensitivity C-reactive protein (>2 mg/L); and presence of at least one additional cardiovascular risk factor such as high blood pressure (BP), low high-density lipoprotein (HDL) levels, a smoking habit, or a family history of premature heart disease.

## Orientation to exercise

### Benefit-risk decision context

The drug to be evaluated in this exercise was a hypothetical statin with the proposed indication of the primary prevention of atherosclerotic cardiovascular disease (prevention of new onset). The intended population was men older than 55 years of age without established CVD, with LDL


Value Tree Template: Benefits and Risks
Identified benefit category
Identified risk category
Identified benefit outcome
Identified risk outcome
Potential outcome or B-R category
Benefits
Benefit-Risk Balance
Risks / Harms
Cardiovascular
Stroke
Other
MACE
LDL level in target range
All-cause mortality
Cardiovascular death
Any MI
Non-fatal MI
Unstable angina needing hosp/CABG
Any revascularisation procedure
Any stroke
Non-fatal stroke
Hemorrhagic stroke
Ischemic stroke
Disabling stroke
Non-disabling stroke
Transient Ischemic Attack (TIA)
Oesophageal cancer
Dementia
Muscle Damage
Liver Damage
Other
Any muscle-related AE
Myopathy
Rhabdomyolysis
Any liver-related AE
Elevated liver enzymes
Hepatitis not leading to hospitalisation
Hepatitis leading to hospitalisation
Liver failure
Kidney failure
Cataract
SAEs

levels of 130 to 160 mg/dL. They must also have one additional CV risk factor (such as high BP, low HDL, smoking, family history of premature heart disease). The comparator was a placebo. This example is based on a scenario developed by RTI-Health Solutions for the PhRMA BRAT with data based on published results from actual statins.

## Outcomes studied

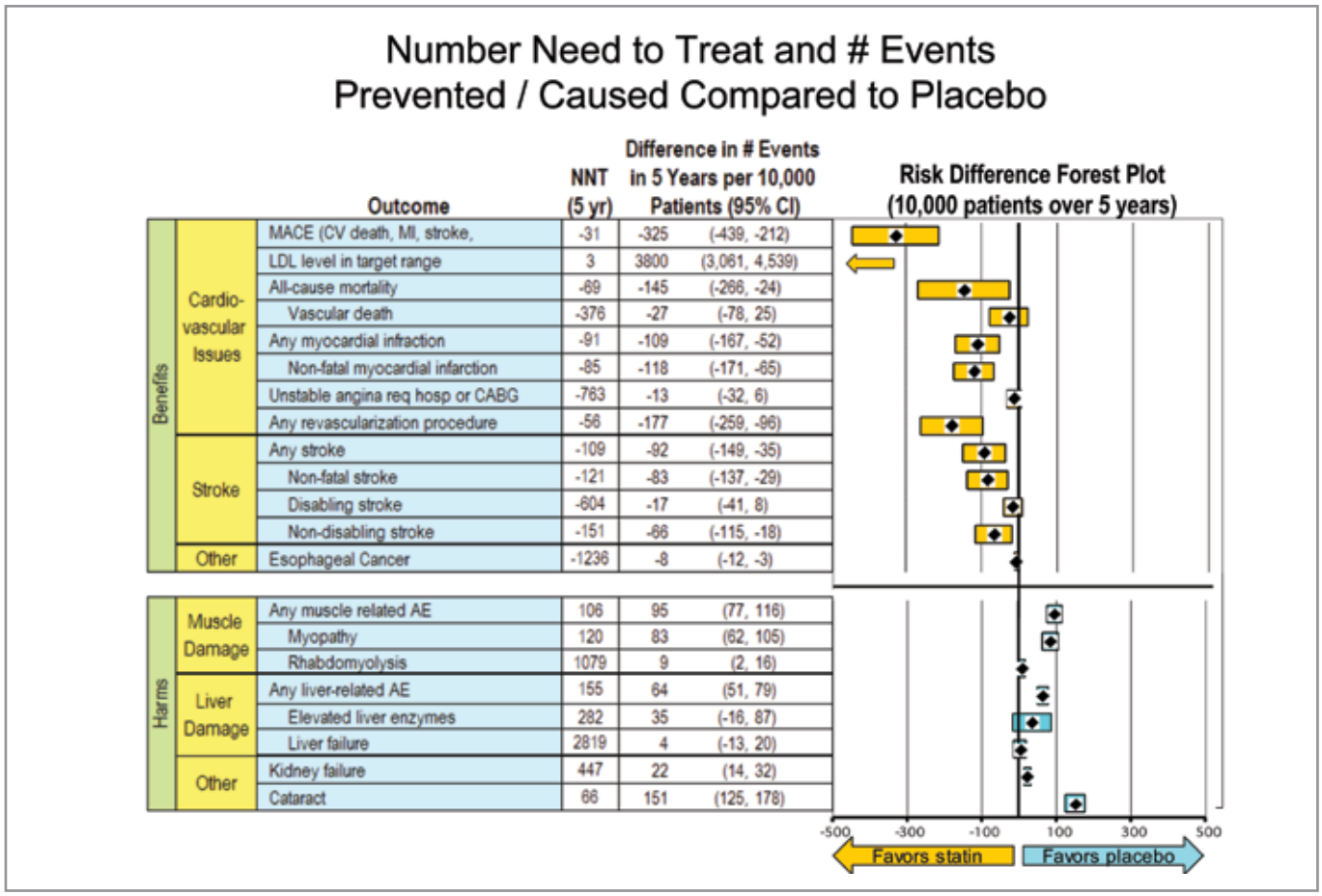
A large set of outcomes were made available for the exercise, shown in both value tree form as an editable template and in tabular form. Effects on major cardiac adverse events (MACE) was the main efficacy endpoint for approval. While its definition is varied, it was defined for this exercise as the composite endpoint of cardiovascular death, myocardial infarction, stroke, or any revascularisation procedure. Other efficacy outcomes included: LDL level being in the target range, all-cause mortality, death due to cardiovascular disease, various definitions for different classes of stroke, esophageal cancer and dementia. These last two outcomes are based on observational studies and reflect a complexity seen in real assessments.

Specific safety risks/harm outcomes included muscle-related outcomes (myopathy and rhabdomyolysis), liver-related outcome (LFT elevation, hepatitis and liver failure) as well as kidney failure, cataracts and other serious adverse events. The inclusion of cataracts was also based on observation studies.

This large number of outcomes was included for two reasons: (i) To ensure the exercise was realistic for those participants experienced in statins research. Omitting an important outcome would have hindered their ability to participate (ii) To provide a sufficiently complex exercise to ensure the participants had to spend considerable thought deliberating which outcomes to include.

## Data overview

Dr Levitan provided the discussion groups with mock data, including the number of events for placebo and the statin per 10,000 patients studied over 5 years. The groups also received information regarding the risk difference and



the number needed to treat/harm (the number of patients who need to be treated to yield one additional favourable/unfavourable event.)

Other information often used in benefit-risk assessments was not provided, including the medicine's effects over time (Kaplan-Meier plots), the size of changes in continuous endpoints, discontinuation rates, drug-drug interactions, preventability, reversibility, manageability, latency, dose-response, subgroup data, off-label use risks, magnitude of treatment effect, study design/robustness of clinical data, and treatment compliance.

## BR assessment exercise

Operating from the perspective of regulators, sponsors or patients, the three groups were instructed to conduct a simplified, structured benefit-risk assessment for the mock statin in primary prevention of CVD. Using the basic approach described earlier in this report, each group was required to first identify what they believed to be the relevant benefit and risk outcomes and represent them in a value tree, and to document the rationale for outcome selection decisions. They next ranked the outcomes (tabulations for each group are presented herein to illustrate the differences in valuations that each group assigned) and, using their collective judgement, choose the intervention (statin or placebo) they considered to have the better benefit-risk profile. A rank of 1 indicates the more important outcomes.

Groups were asked consider whether to include outcomes that overlapped or were similar or outcomes that reflected the causal consequences of another outcome. They were also required to choose how fine-grained the outcomes should be, and how to handle outcomes with no direct visible symptoms such as cholesterol level or liver function test evaluation. Each group presented their findings in a discussion forum with all Workshop participants.

## Results

For each group below, the text summarises the key topics from the discussion, and the table shows the outcomes included by the group and the ranking they applied. The rationales in the table are shown as entered by the rapporteur from each group.

### Sponsors' perspective

This group examined the benefits and risks of the statin from an industry perspective, and appeared to look for benefits methodologically, considering the results of primary clinical trial endpoints first, while also keeping in mind that the composite or secondary endpoints such as cardiovascular effects needed to be evaluated for this medicine. Primarily, however, they focussed on ensuring an evidence base to support specific wording in an indication statement.

The medicine's effect on LDL was considered the most important benefit for primary prevention in the asymptomatic patient specified for this exercise, both because it was the primary trial endpoint and because of its correlation with cardiovascular outcomes. In fact, like effects on LDL and cardiovascular health, many of the benefits were difficult to separate from one another. Accordingly, although all benefits were ranked, after ranking MACE as the most important followed by LDL and cardiovascular outcomes, most other outcomes were ranked as fifth in weight. It was also observed that it is important to examine the data with more granularity than may be possible with this type of evaluation. For example, unlike the broad categories of the exercise, there are clinically different levels of myocardial infarction and stroke, each associated with varying impact on patients that could be assessed within a value tree.

As with benefits, the group regarded many of the risks as difficult to separate from one another. Rhabdomyolysis and liver failure were ranked as the most important risks, while most other outcomes received equal third-tier ranking. Working from the sponsors' perspective, the group did not feel it appropriate to delete any risks from the list.

Overall, it was believed that this kind of qualitative ranking might not be the most appropriate method of benefit-risk evaluation, but if used, requires much more time to implement than could be provided in this exercise. It was agreed that examination of the data in detail is important and may require content experts from different functional areas to contribute to the discussion and understand the implications of the data. Visualisation of the findings was thought to be an important tool to help render a decision.

The group agreed that this method can best be used after phase two of a clinical programme before designing the phase three component. It was also commented that a great advantage of this exercise is that it evaluates the benefits and risks of a new medicine together, as opposed to the post-marketing environment in which people examine risks separately typically without the balance of benefits.

### Sponsors' outcome ranking

| System | Outcome | Included | Rank | Rationale for inclusion/exclusion |
|---|---|---|---|---|
| CV | MACE (CV death, MI, stroke, revascularisation) | Yes | 1 | Primary endpoint |
| CV | LDL above target range | Yes | 2 | Relevant for primary prevention; helps establishing the causal basis; LDL-C effect of treatment to be monitored |
| CV | All-cause mortality | Yes | 4 | Also a risk component involvement |
| CV | Vascular death | Yes | 3 | Secondary endpoint |
| CV | Any myocardial infraction | Yes | 5 | Secondary endpoint |
| CV | Non-fatal myocardial infarction | Yes | 5 | Secondary endpoint |
| CV | Unstable angina req hosp or CABG | Yes | 5 | Secondary endpoint |
| CV | Any revascularisation procedure | Yes | 5 | Secondary endpoint |
| Stroke | Any stroke | Yes | 5 | |
| Stroke | Hemorrhagic stroke | No | | Not relevant for a statin |
| Stroke | Ischemic stroke | Yes | 5 | Secondary endpoint |
| Stroke | Non-fatal stroke | No | | |
| Stroke | Disabling stroke | No | | |
| Stroke | Non-disabling stroke | No | | |
| Stroke | Transient ischemic attack (TIA) | Yes | 5 | Risk factor for stroke |
| Other | Oesophageal cancer | No | | Not relevant for the indication |
| Other | Dementia | No | | Not relevant for the indication |
| Muscle | Any muscle-related AE | Yes | 7 | |
| Muscle | Myopathy | Yes | 6 | |
| Muscle | Rhabdomyolysis | Yes | 1 | Should it be no.1? |
| Liver | Any liver-related AE | Yes | | |
| Liver | Elevated liver enzymes | Yes | 5 | Important but threshold? Hy's Law? |
| Liver | Hepatitis not leading to hospitalisation | Yes | 7 | |
| Liver | Hepatitis leading to hospitalisation | Yes | 4 | |
| Liver | Liver failure | Yes | 2 | Should it be no. 1? |
| Other | Kidney failure | Yes | 3 | |
| Other | Cataract | Yes | 7 | |
| Other | SAEs | Yes | 7 | Discontinuation due to AEs is also relevant |

### Regulators' perspective

The group charged with providing the regulators' perspective felt challenged with respect to dealing with aggregate data rather than individual outcomes; although it was acknowledged that aggregate data may provide a broader approach to a specific experience. Another point of discussion was whether an early emergent adverse event should be rated as more important than an adverse event that would occur later during the course of the disease. For instance, although rhabdomylosis was obviously a concern, the importance of the resulting kidney failure could not be discounted. Regulators also felt it important to supplement the outcomes of hepatitis leading to and not leading to hospitalization with a new outcome of hepatitis overall.

Although the group initially thought that regulators would not consider the impact of surrogate measures, they were ultimately included in the evaluation, not because of their clinical relevance but because of their ease of measurement and potential for providing insight into the activity of the intervention. Although it was difficult for the group to reach consensus as to the use of the proposed methodology, there was consensus on the outcome. Overall, the judgement was positive for the new medicine, although a liver monitoring test would be part of a required risk management plan. There was disagreement within the group about using ranking as a means of weighting risks and benefits. While not the intent for this exercise, it was perceived that the ranks were serving essentially as linear weights, which was difficult for the group since the difference between, say, ranks 1 and 2 was not considered of the same significance as the difference between other adjacent ranks, say ranks 3 and 4.

Of interest, the group moved in the direction of calculating an incremental net clinical benefit measure; and expressed a wish to apply a weight to the risk differences and calculate a weighted net clinical benefit sum. The group also noted that the processes of determining which outcomes belonged in the value tree could have been combined with the ranking of the outcomes.

### Regulators' outcome ranking

| System | Outcome | Included | Rank | Rationale for inclusion/exclusion |
|---|---|---|---|---|
| CV | cardiovascular death | Yes | 1 | Excluding CHF not secondary to MI |
| Muscle | Rhabdomyolysis | Yes | 1 | Known side effect of statins |
| Liver | Liver failure | Yes | 1 | Serious outcome |
| Other | SAEs | Yes | 1 | Standard inclusion |
| CV | MACE (CV death, MI, stroke, revascularisation) | Yes | 2 | Hodge podge? Narrows uncertainty? Important for licensing. |
| CV | Any myocardial infraction | Yes | 2 | Serious outcome |
| Stroke | Any stroke | Yes | 2 | Serious outcome |
| Liver | Any hepatitis | Yes | 2 | Catch all |
| Other | Kidney failure | Yes | 2 | Serious outcome of muscle pathology |
| Stroke | Hemorrhagic stroke | Yes | 3 | Related to claim for statins unsure of potential risk |
| Stroke | Ischemic stroke | Yes | 3 | Related to claim for statins |
| Liver | Hepatitis leading to hospitalisation | Yes | 3 | Serious |
| CV | LDL above target range | Yes | 4 | Informs clinical practice |
| Muscle | Myopathy | Yes | 4 | Known side effect of statins |
| Liver | Elevated liver enzymes | Yes | 4 | Sensitive measure but not specific |
| Other | Cataract | Yes | 5 | Observational data indicates potential |

### Patients' perspective

The group performing the exercise from the perspective of patients agreed that these stakeholders represent a varied population, and therefore, reaching a consensus may require more time to make benefit-risk evaluations than was provided for this exercise.

Furthermore, a wide range of background knowledge and experience would need to be accommodated, which might require the provision of supplementary information and education to enable the understanding of the relative importance and ratings of some of the outcomes by patients of different experience and educational levels.

### Patients' outcome ranking

| System | Outcome | Included | Rank | Rationale for inclusion/exclusion |
|---|---|---|---|---|
| CV | MACE (CV death, MI, stroke, revascularization) | No | | Patients probably wouldn't understand this composite measure |
| CV | LDL above target range | Yes | 4 | Whilst LDL may not be fully understood, it is the reason for prescribing and a link to health outcomes is clear. |
| CV | All-cause mortality | Yes | 1 | Beyond question |
| CV | Vascular death | Yes | 1 | Beyond question |
| CV | Any myocardial infraction | Yes | 3 | |
| CV | Non-fatal myocardial infarction | No | | Considered that this is covered by the "Any MI" outcome |
| CV | Unstable angina req hosp or CABG | Undecided | | Not fully understood by patients who may not see themselves as affected by this risk |
| CV | Any revascularisation procedure | No | | Not fully understood by patients who may not see themselves as affected by this risk |
| Stroke | Any stroke | Yes | 2 | Fully understood as an overall risk that warranted avoidance, differentiating between sub-categories was not considered necessary |
| Stroke | Hemorrhagic stroke | No | | |
| Stroke | Ischemic stroke | No | | |
| Stroke | Non-fatal stroke | No | | |
| Stroke | Disabling stroke | No | | |
| Stroke | Non-disabling stroke | No | | |
| Other | Dementia | Yes | 5 | Anything that comes as a benefit is a good thing - isn't it? |
| Other | Oesophageal Cancer | Undecided | | |
| Muscle | Any muscle related AE | No | | Non-specific |
| Muscle | Myopathy | Yes | 6 | Impacts ability to lead a normal lifestyle |
| Muscle | Rhabdomyolysis | Yes | 3 | A potentially serious event |
| Liver | Any liver-related AE | No | | Unclear significance |
| Liver | Elevated liver enzymes | No | | Unsure what this means |
| Liver | Hepatitis without hospitalisation | Yes | 5 | Understood and perceived to be undesirable |
| Liver | Hepatitis with hospitalisation | Yes | 4 | Understood and perceived to be undesirable |
| Liver | Liver failure | Yes | 1 | Understood and perceived to be undesirable |
| Other | Kidney failure | Yes | 2 | Seems obvious - well understood not to be a good thing |
| Other | Cataract | Yes | | Seems obvious - well understood not to be a good thing |
| Other | SAEs | Yes | 7 | Seems obvious - well understood not to be a good thing |

The MACE composite outcomes measure was viewed as too abstract and difficult to conceptualise, particularly as all of the constituent elements were present within other outcomes. There was a tendency to focus on broad categories of events rather more granular descriptions, for example, the medicine's effect on strokes in general was rated as important, but stroke subcategories were not. The concept of the relative value of one therapy over another (comparative effectiveness) is one that is of growing importance to patients, and a framework should be able to address this discussion.

It was noted that US patients may be better informed about the benefits of impacting LDL than their European counterparts as a result of continual exposure to direct-to-consumer advertising and information in the general press. Despite the fact that the group as a whole did not understand the relevance of including oesophageal cancer and dementia on the list of benefits (Note: they were included due to their appearance in observational studies for statins), they ultimately included dementia, because it ranks high on a list of patient fears. To make a better informed decision, the participants suggested that it may also have been helpful to have more information to better understand the relative risks for each outcome.

### Composite of Perspectives

This exercise clearly used only a single convenience sample of participants with highly varied backgrounds in statins. The regulator group was composed of all regulators participating in the syndicate plus two industry members who are former regulators; however, the patient group was composed of industry representatives trying to emulate patients. Despite the fact that this ranking approach was not ideal for obtaining weight information, and properly performing this type of exercise requires significantly more time than provided, some preliminary observations can be made. Interpreting an "undecided" for an outcome as not excluding it from the assessment, the composite table shows:

- Patients included 14 outcomes, regulators included 16, and sponsors included 22
- Regulators and sponsors agreed on 14 outcomes, sponsors and patients agreed on 13 outcomes, and regulators and patients agreed on 11 outcomes
- No group included the different degrees of stroke severity, though the sponsor group indicated a need to have greater granularity on the clinical impact of the stroke and myocardial infarction outcomes
- Comparing ranks between the groups is of limited utility, but upon visual inspection, the regulator and patients groups differ less in their ranking than do the regulators versus sponsors and patients versus sponsors

Several of these observations suggest that the regulator and patient groups made inclusion/exclusion and ranking decisions that aligned more than those between the sponsor and other two groups; however, the limitations of the exercise make this no more than a hypothesis-generating suggestion. An example where this suggestion is not met occurs with the difference in ranking of severe adverse events (SAEs). Regulators ranked SAEs with a 1 while both sponsors and patients ranked SAEs with a 7.

### Learnings from the exercise

By verbal report, participants found that the practical application of even a simple benefit-risk framework helped bring to light important differences within a stakeholder group with regards to identifying and valuing specific benefits and harms. This is an observation often seen in formal approaches to Decision Analysis, in the decision conferencing component of multi-criteria decision analysis in particular. The positive outcome of this approach is that the framework gives each participant a tool to verbalise and otherwise explain their rationale for choosing a specific set of criteria and making their overall assessment decision. This facilitated discussion within the group ultimately helped explain their assessment rationale and positioning to other stakeholders (in this case represented by the other Forum participants). While at times frustrated by the difficulty of the ranking component of the exercise, participants were highly engaged in the process and felt it valuable. They also found the risk difference forest plot type visualisations quite valuable in understanding the data.

An important observation was that the ranking exercise gave the impression that the difference in importance between ranks was constant, and this assumption of a linear weighting as a function of rank proved uncomfortable for some participants – regulators in particular. A ranking exercise might have been better served by predefined importance categories (eg, critical, important, significant, unimportant)

### Composite outcome ranking

| System | Outcome | Regulators | Sponsors | Patients | Rank - Reg | Rank - Spon | Rank - Pat |
|---|---|---|---|---|---|---|---|
| CV | LDL above target range | Yes | Yes | Yes | 4 | 2 | 4 |
| CV | Vascular death | Yes | Yes | Yes | 1 | 4 | 1 |
| CV | Any myocardial infraction | Yes | Yes | Yes | 2 | 5 | 3 |
| Stroke | Any stroke | Yes | Yes | Yes | 2 | 5 | 3 |
| Muscle | Myopathy | Yes | Yes | Yes | 4 | 6 | 6 |
| Muscle | Rhabdomyolysis | Yes | Yes | Yes | 1 | 1 | 3 |
| Liver | Hepatitis leading to hospitalisation | Yes | Yes | Yes | 3 | 4 | 4 |
| Liver | Liver failure | Yes | Yes | Yes | 1 | 2 | 1 |
| Other | Kidney failure | Yes | Yes | Yes | 2 | 3 | 2 |
| Other | Cataract | Yes | Yes | Yes | 5 | 7 | 7 |
| Other | SAEs | Yes | Yes | Yes | 1 | 7 | 7 |
| CV | MACE (CV death, MI, stroke, revascularisation) | Yes | Yes | No | 2 | 1 | |
| Stroke | Ischemic stroke | Yes | Yes | No | 3 | 5 | |
| Liver | Elevated liver enzymes | Yes | Yes | No | 4 | 5 | |
| CV | All-cause mortality | | Yes | Yes | | 3 | 1 |
| Liver | Hepatitis not leading to hospitalisation | | Yes | Yes | | 7 | 5 |
| CV | Unstable angina req hosp or CABG | | Yes | Undecided | | 5 | |
| Stroke | Hemorrhagic stroke | Yes | No | No | 3 | | |
| Liver | Any hepatitis | Yes | | | 2 | | |
| CV | Nonfatal myocardial infarction | | Yes | No | | 5 | |
| CV | Any revascularisation procedure | | Yes | No | | 5 | |
| Stroke | TIA | | Yes | | | 5 | |
| Muscle | Any muscle-related AE | | Yes | No | | 7 | |
| Liver | Any liver-related AE | | Yes | No | | | |
| Other | Dementia | | No | | | | |
| Other | Oesophageal Cancer | | No | Undecided | | | |
| Stroke | Disabling stroke | | No | No | | | |
| Stroke | Non-disabling stroke | | No | No | | | |

with detailed definitions to which the outcomes could have been assigned. One participant suggested an "allocation of points" approach, in which a fixed number of points, for example 100, would be distributed amongst the included outcomes in proportion to their importance. Stated more openly, the use of numeric ranking exercise was too simplistic and confusing for the exercise, and the exercise would have benefited from a more structured approach.

Key findings from this exercise included:

- Limited as the simplified framework used in this exercise was, it appeared to help decision-makers structure their thoughts and deliberations for benefit-risk assessment
- Having facilitators to guide the qualitative deliberations in a framework is very helpful
- Content experts within each stakeholder group were helpful to interpret the relevant data and guide the conversation; were the exercise to be repeated with a true group of patients, considerable time and pre-reading would be needed to orient them to the outcomes and data
- The process is detailed and therefore, cannot be rushed. Ample time must be given to delve into each outcome being considered and how they work together for a composite picture of the assessment
- Tabulating the supportive data provides a clear way for each group member to monitor the progress of the discussions
- Visualisation tools such as the risk difference forest plots can simplify the assessment process
- Regulators are open to discussions about the use of a Framework to facilitate shared discussions

# Appendix: Workshop Programme

| | |
|---|---|
| **Session 1: Benefit-risk assessments: company submissions - mow is benefit-risk assessment being framed** | |
| **Chairman's welcome, introduction and setting the scene** | **Professor Stuart Walker**, *Founder CMR International Insitute for Regulatory Science* |
| **Presentation of approaches / case studies from pharmaceutical companies using their own benefit-risk framework** | |
| **Eisai's approach to benefit-risk assessment** | **Dr David Jefferys**, *Senior Vice President, Global Regulatory, Healthcare Policy Dept, Eisai Europe Ltd, UK* |
| **Novo Nordisk's development of a benefit-risk assessment model** | **Dr Sinan Bardakcki Sarac**, *Industrial PhD Student and* **Dr Christine Hallgreen**, *IMI PostDoc, Clinical Pharmacology - Biosimulation Novo Nordisk A/S, Denmark* |
| **Visualisation of benefits and risks – an innovative approach?** | **Dr Douglas Manion**, *Vice President, Neuroscience and Virology, Bristol-Myers Squibb, USA* |
| **Conclusions** | **Professor Stuart Walker**, *Founder CMR International Insitute for Regulatory Science* |
| **Session 2: Benefit-risk assessments: company submissions how is benefit risk assessment being framed** | |
| **Chairman Introduction and recap of first day** | **Professor Stuart Walker**, *Founder, Institute for Regulatory Science* |
| **Focus on weighting and valuing in a benefit-risk framework** | |
| **A case study from Eli Lilly** | **Dr Rebecca Noel**, *Research Scientist, Eli Lilly and Company, USA* |
| **Valuing benefits and risks: A GSK example** | **Dr Marilyn Metcalf**, *Director, Quantitative and Decision Sciences, GlaxoSmithKline, USA* |
| **Agency views** | |
| **Update from EMA on benefit-risk assessment**<br><br>**US Regulator's perspective on risk-benefit considerations** | **Dr Xavier Luria**, *Head of Safety and Efficacy of Medicines, EMA*<br><br>**Dr Theresa Mullin**, *Director, Office of Planning and Informatics, CDER, FDA* |
| **Improving the benefit-risk assessment of medicines: A "Consortium" initiative** | **Dr Petra Dörr**, *Head of Management Services & Networking, Swissmedic*<br><br>**Dr Jason Ferla**, *Director, Clinical Evaluation Section 3, Office of Prescription Medicines, Therapeutic Goods Administration, Australia* |
| **A Scenario for discussion: Setting the scene**<br>A scenario has been developed for the evaluation of a hypothetical statin in comparison with no treatment. This will be presented from the viewpoint of how a benefit-risk assessment might be evaluated. Then during the syndicate sessions after lunch, there will be the opportunity for three individual groups representing patients, sponsors and the regulatory authorities to develop a value tree of benefits and risks, to provide a ranking for weighting and then to make final benefit-risk assessment from the viewpoint of the relevant stakeholders | **Dr Bennett Levitan**, *Director, Quantitative Safety Research, Johnson & Johnson PRD, USA* |
| **Syndicate session for the statin scenario exercise** | |
| **Feedback from the syndicate sessions and summary of key points and recommendations with regard to the appropriate methodology for valuing and weighting of benefit and risk parameters** | |

# Appendix

| Workshop Attendees | | |
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| **Regulatory agencies** | | |
| **Prof Sir Alasdair Breckenridge** | Chairman | Medicines and Healthcare products Regulatory Agency, UK |
| **Dr Petra Doerr** | Head of Management Services and Networking | Swissmedic |
| **Dr Jason Ferla** | Director, | Therapeutic Goods Administration, Australia |
| **Dr Joyce Korvick** | Deputy Director for Safety | Center for Drug Evalua tion and Research, Food and Drug Administration, US |
| **Dr Huei-Xin Lou** | Acting Director, Pharmaceuticals and Biologics Branch | Health Sciences Agency, Singapore |
| **Dr Xavier Luria** | Head of Safety and Efficacy of Medicines | European Medicines Agency, EU |
| **Dr Theresa Mullin** | Director, Office of Planning and Informatics | Center for Drug Evaluation, Food and Drug Administration, US |
| **Dr Supriya Sharma** | Director General, Therapeutic Products Directorate | Health Canada |
| **Dr Mark Walderhaug** | Associate Director for Risk Assessment | Food and Drug Administration, USA |
| **Industry** | | |
| **Dr Nayan Acharya** | Senior Director, Risk Management and Pharmcoepidemiology | Eli Lilly and Company, USA |
| **Dr Sagar Adusumalli** | Director, Global Regulatory Affairs | Eli Lilly and Company, USA |
| **Dr Graham Burton** | Senior Vice President, Regulatory Affairs Pharmacovigilance and Corporate QA Compliance | Celgene Corporation, USA |
| **Dr Paul Coplan** | Executive Director, Risk Management and Epidemiology | Purdue Pharma LP, USA |
| **Peter DiRoma** | Vice President, Global Regulatory AIID and ET | EMD Serono Inc, USA |
| **Dr Allen Feldman** | Vice President, Risk Management | Daiichi Sankyo Pharma Development, USA |
| **Dr John Ferguson** | Vice President and Global Head of Pharmacovigilance and Medical Safety | Novartis Vaccines and Diagnostics, USA |
| **Dr John Freeman** | Corporate Vice President, Global Drug Safety & Risk Management | Celgene Corporation, USA |
| **Dr Christine Erikstrup Hallgreen** | IMI PostDoc, Clinical Pharmacology – Biosimulation | IMI PostDoc, Quantitative Clinical Pharmacology, Novo Nordisk A/S, Denmark |
| **Dr Diana Hughes** | VP Worldwide Safety Strategy | Pfizer Medical, Pfizer Inc, USA |
| **Sanjay Jalota** | Senior Director, Global Regulatory Affairs | Johnson & Johnson PRD, USA |
| **Dr David Jefferys** | Senior Vice President, Global Regulatory and Healthcare Policy | Eisai Europe Ltd, UK |
| **Mark Jungemann** | Executive Director | Eli Lilly and Company, USA |
| **Dr Stephen Kanes** | Medical Science Director | AstraZeneca, USA |
| **Dr Bennett Levitan** | Director, Quantitative Safety Research | Johnson & Johnson PRD, USA |
| **Dr Filip Mussen** | Senior Director, Global Regulatory Affairs Neurosciences | Johnson & Johnson PRD, Belgium |
| **Dr Karen Naim** | Global Medical Safety Senior Scientist | Johnson & Johnson, USA |

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| **Dr Rebecca Noel** | Research Scientist | Eli Lilly and Company, USA |
| **Kenneth Palmer** | Director, Commercial Regulatory Affairs | Daiichi Sankyo Inc, USA |
| **Dr George Quartey** | Safety Statistical Expert | Hoffmann-La Roche, UK |
| **Dr Ron Robison** | Head of Global Regulatory Affairs | Abbott (formerly Solvay Pharmaceuticals), USA |
| **Dr Colette Saccomanno** | Integrated Safety Risk Manager | Hoffman-La Roche, USA |
| **Dr Sinan Bardakci Sarac** | Industrial PhD Student | Novo Nordisk A/S, Demark |
| **Dr Joseph Scheeren** | Senior Vice President, Head of Global Regulatory Affairs | Bayer Healthcare Pharmaceuticals Inc, USA |
| **Sarah Sellers** | Director of Epidemiology and Safety Surveillance | Baxter Healthcare, USA |
| **Dr Mel Walker** | Director, Integrated Payer Strategy | GlaxoSmithKline, UK |
| **Steven Wojtanowski** | Vice President, Global Regulatory Affairs | Abbott Products Inc, USA |
| **Attendees from the Institute** | | |
| **Lawrence Liberti** | Executive Director | CMR International Institute for Regulatory Science |
| **Dr Neil McAuslane** | Director | CMR International Institute for Regulatory Science |
| **Dr Franz Pichler** | Manager, HTA Programmes | CMR International Institute for Regulatory Science |
| **Prisha Patel** | Portfolio, Manager, Emerging Market Programme | CMR International Institute for Regulatory Science |
| **Gill Hepton** | Administrator | CMR International Institute for Regulatory Science |
| **Patricia Connelly** | Manager, Communications | CMR International Institute for Regulatory Science |
| **Prof Stuart Walker** | Founder | CMR International Institute for Regulatory Science |