STRATEGIES FOR COMMUNICATING BENEFITS AND RISKS TO DECISION-MAKERS:

EXPLAINING METHODS, FINDINGS AND CONCLUSIONS THROUGH A COMMON LANGUAGE APPROACH

WORKSHOP
17- 19 June 2009
Washington, DC, USA

WORKSHOP REPORT

CMR International
INSTITUTE FOR REGULATORY SCIENCE

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The CMR International Institute for Regulatory Science (the Institute) is a not-for-profit division of the Healthcare and Science business of Thomson Reuters. It works in the regulatory and policy arena and in close association with the research-based pharmaceutical industry and regulatory authorities around the world. The Institute operates autonomously with its own dedicated management and funding that is provided by income from a membership scheme.

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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Section 1: Overview and Executive Summary

Background to the Workshop

Determining the benefit-risk (BR) balance of a medicine is one of the most important steps in its development, review and post-approval re-assessment. This Workshop was convened by the CMR International Institute for Regulatory Science (the Institute) to allow regulatory Agencies and industry to share progress updates on their initiatives to develop and implement a BR assessment framework and to investigate the characteristics of effective BR communication between Sponsors and regulators.

Workshop Highlights

Professor Stuart Walker, Founder of the CMR International Institute for Regulatory Science opened this, the sixth Workshop convened on the topic of benefit risk since the first was held in 1985, discussing the past, present and future of BR assessment and providing an update on the development of a proposed five-step BR framework.

The European Medicines Agency (EMEA) has initiated an ambitious programme to further enhance the BR assessment of medicines. **Professor Hans-Georg Eichler, Senior Medical Officer, EMEA,** provided a summary of these initiatives set in the context of the BR tasks of data generation, analysis, synthesis and communication along the pharmaceutical development time points of premarketing, post-marketing and ongoing relative safety and effectiveness assessment.

In May 2006, PhRMA (the Pharmaceutical Research and Manufacturers Association of America), which represents the leading pharmaceutical research and biotechnology companies in the United States, announced that it would develop a semi-quantitative model for BR assessment. As one of the members of the Benefit-Risk Action Team (BRAT), **Dr Filip Mussen, Vice-President, Psychiatry and EU RED Regulatory Affairs, Johnson & Johnson Pharmaceutical Research and Development** detailed the progress in the development of this model.

Daniel E. Everitt, MD, Chief Safety Officer, Pharmaceuticals, Johnson & Johnson, presented a clear and graphic approach used by Johnson & Johnson to understand and explicitly communicate key BR to regulatory authorities.

The presentation thesis of **Paul Coplan, ScD, MBA, Senior Director, Risk Management Global Safety Surveillance and Epidemiology, Wyeth** was that BR assessment can be an excellent metric to use when designing development programmes for medicinal products and evaluating when to allocate scarce resources to develop or in-license a product. If medicinal products will be judged on BR criteria, it is vital to ensure that the development programme is designed to generate the necessary data.

Dr Brian Daniels, Senior VP Global Development & Medical Affairs, Bristol-Myers Squibb discussed BR communication as a seamless continuum throughout the product life cycle, which is becoming more standardised, personalised, transparent and informed by payor and patient viewpoints.

In 2007, the US Congress passed the Food and Drug Administration Amendments Act (FDAAA), which mandated post-approval studies and risk evaluation mitigation strategy (REMS) for certain medicines and to facilitate more effective communication with the public about issues of drug safety. **Dr Gerald Dal Pan, Director, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US FDA**, discussed the significance of three of the sections of the FDAAA as they apply to safety surveillance and BR communication to patients.

In his examination of the relationship of a BR framework with REMS, **Dr John Ferguson, Vice President, Global Head, Pharmacovigilance & Medical Safety, Novartis Vaccines & Diagnostics**, provided the positive example of the effective REMS for Tysabri (natalizumab; Biogen Idec). REMS, while not warranted for most medicines, can and should be regarded an opportunity for BR optimisation for some compounds.

Using the example of two websites developed by Pfizer, **Dr Ramzi Dagher VP WRAQA, Regulatory Head, Oncology and EM Business Units, Pfizer, Inc.** discussed the challenges and opportunities to healthcare practitioner BR communication. The future of these communications will centre on the definition of goals, enlargement of audience and development of methods to address state, country and regional guidelines whilst maintaining broad appeal in an evolving regulatory and practice environment.

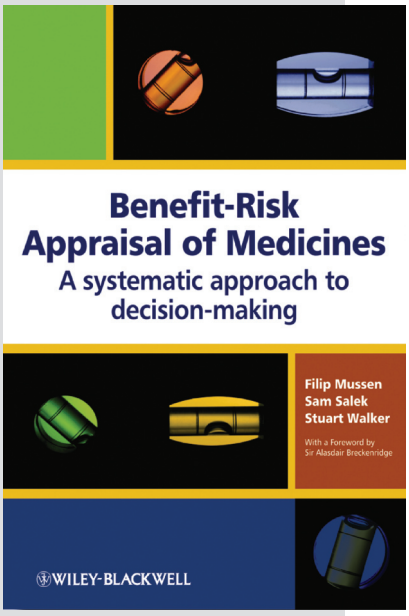
Dr R. William Soller, Professor, UCSF School of Pharmacy; Executive Director, Center for Self Care provided several important recommendations to improve BR communication to patients, including labelling comprehension studies for high-risk medicines; specific education on BR counselling for practitioners; and defining validated ways to get practical comparative drug efficacy and safety information to the consumers.

Because decisions are driven as much by behaviour as by information, **John I Howell III, President, Portfolio Decisions International, LP** informed the Workshop that it is imperative to understand the decision-maker's perspective and to be rigorous, transparent and trustworthy, customising communications to the situation without compromising the content.

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: Syndicate Discussions

Workshop participants formed three syndicate groups to discuss the following topics:

Topic A: Optimising strategies for communication between Sponsors and Agencies- Industry viewpoint

Topic B: Optimising strategies for communication between Sponsors and Agencies- Agency viewpoint

Topic C: Using benefit-risk discussion outcomes to optimise drug development

The Chairpersons and Rapporteurs for the groups follow:

Syndicate 1	Chair:	**Dr Supriya Sharma**, *Director General, Therapeutics Product Directorate, Health Canada*
	Rapporteur:	**Dr Steven Miller**, *Vice President, Regulatory Affairs, Johnson & Johnson, USA*
Syndicate 2	Chair:	**Dr Leonie Hunt**, *Head, Office of Prescription Medicines TGA, Australia*
	Rapporteur:	**Dr Steve Caffe**, *Global Regulatory Affairs and Pharmacovigilance, Baxter Healthcare Corporation, USA*
Syndicate 3	Chair	**Dr Joyce Korvick**, *Deputy Director for Safety, CDER, Food and Drug Administration, USA*
	Rapporteur:	**Alan Sbi**, *Director, Global Regulatory Autoimmune and Inflammatory Diseases and Emerging Therapies EMD Serono Inc, USA*

Background

Two of the Syndicates were asked to consider which communication strategies and tools are being used by pharmaceutical companies to communicate findings of benefit and risk within their organisations and to Agencies and how these could be improved. Their objectives were to identify the main factors that are barriers to achieving the common goal of reaching agreement on the benefits and risks of a new medicine, or those that impede a common understanding of divergences. It was further hoped that strategies, solutions and tools to avoid these communication barriers could be proposed both from the point of view of the industry Sponsor and the regulatory Agency.

The third Syndicate was asked to consider how ongoing evaluative discussions of a product's benefits and risks can be used to develop, modify and guide the overall development plan for a new medicine. The anticipated outcome for this group was the articulation of the way in which a decision process is developed, including how it would inform decisions-making at each development milestone/hurdle and how it should be embedded into the development strategy and core research principles.

One of the key points from this Workshop, which underpinned the Syndicate discussions was that all Agencies and companies are faced with the difficult issue of explaining (communicating) the methodology and outcome of their BR assessment in a transparent manner. In this context *transparency* means lack of ambiguity between participants.

Outcome of Discussions

Barriers to BR communication

Fundamental barriers to BR communication that were identified in syndicate discussions included a lack of common definitions and of agreement on standards of evidence. In fact, the framework for the regulatory evaluation of medicines itself is based on safety and efficacy rather than benefit and risk, which although a seemingly small distinction, may in fact be a significant impediment to the exchange of information.

Multiple constituencies in Agencies and industry emerged as another important barrier to BR communication. Within Agencies, there is difficulty in accessing all relevant parties, and their varying levels of interest and experience may require individualised communication.

Whilst within industry, it may be difficult to achieve consensus on BR messages and on the strategy for their communication.

Assessment of BR communication

Syndicates indicated that an effective BRF should be able to be used to define the scope of a Sponsor's risk evaluation and mitigation strategy (REMS). The success of BR communications could also be measured by the easier acceptance of BR decisions. Finally, as a result of effective BR communications, Agency satisfaction with Sponsor presentations and Sponsor satisfaction with quality and predictability of Agency decisions should be increased, as assessed through the Institute Scorecard Project

Recommendations

1. **Support the Institute's continued development of the framework for BR assessment.**

   Participants agreed that it would be ideal to separate qualitative from quantitative BR assessment. Agencies and Sponsors should continue to engage in discussions to explore common approaches to a BRF, and the role that payors should have in the development and validation of a BRF needs to be considered.

   A dataset from volunteer Sponsors could be used to test the practical application of the framework. A scorecard with industry/Agency feedback would be useful to evaluate the BRF, and one of the case studies prepared by BRAT (page14) could also be used to evaluate other frameworks for BR assessment by various Agencies and also to obtain the perspectives of different stakeholders.

Simple BR presentation tools, potentially using visualisation, should be developed and used, as more transparent communication results in more informed patient/prescriber decisions. Furthermore, if different conclusions are reached by several Agencies, these tools would help make explicit the previously implicit factors in the decision.

2. **Ensure BRFs have certain key features.**

   BRFs should be formally created within a pharmaceutical company, approved by relevant company committees and informed with considerations for new mechanisms of action and precedents set in the class; they may also be informed by precedent within the therapy class through interaction with an Agency without disclosing other proprietary information.

   The target product profile may serve as the basis for development of the product's BRF and for discussion with Agencies. The framework should evolve from being predominantly qualitative with minimal data in early stages to being increasingly quantitative and detailed. It should concentrate on safety and efficacy with a focus on the "low- hanging fruit" of pivotal efficacy and pivotal safety parameters.

   The BRF should incorporate clear data collection methodology and can be developed through input from additional stakeholders such as patients if those data are also collected within a sound scientific methodology. It may also include competitive information and goals for improved safety profile advantages.

   The portfolio risk approach will be strengthened by the consistent application of a BRF, using a more broadly based disease-management method. BRFs must be seen by the Sponsor as adding value while minimising the influence of economic assumptions that may be underlying BR evaluation.

3. **Encourage development of a common lexicon.**

   That is, define what is meant, for example, by benefit and risk, specifying whether these would be benefits and risks to the individual or to a population and establishing the magnitude of those effects and the probability of their occurrence.

4. **Transparency in BR assessment is key.**

   Simplifying the complexity of ambiguous factors in BR assessment is essential but not to the extent that essential information is lost. The use of a BRF similar to those proposed by Professor Walker (page 10) and Dr Mussen (page 14) will be helpful because it will provide for a structured discussion between Agencies and Sponsors, leading to greater transparency in decision-making.

Simple BR presentation tools, potentially using visualisation, should be developed and used, as more transparent communication results in more informed patient/prescriber decisions. Furthermore, if different conclusions are reached by several Agencies, these tools would help make explicit the previously implicit factors in the decision. Interagency standardisation of such a tool would be preferred. It would be particularly useful if the FDA/EMEA would prepare publicly available case studies and lessons learned from BR assessment.

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5. **Section 2.5.4 of the Common Technical Document (clinical overview of the application) and European Public Assessment Reports could be improved with a better guidance for the BR assessment.**

   Sponsors should be encouraged to use the proposed BRF to construct the BR summary in their applications and would like guidance on how to incorporate a BRF in the BR section of a CTD; but regulatory Agencies must be willing to comment on whether this improves the presentation of the BR information.

6. **Optimise timing and characteristics of BR communication.**

   Whilst a BRF cannot be used as the sole criterion for approvability, it can help guide the pharmaceutical development process. Early interaction between Sponsors and Agencies is key. Using disease knowledge to define the BR parameters, Sponsors should set internal focus on these parameters early in a product's development cycle and seek agreement on the framework with Agencies.

   Earlier communication by the Sponsor of BR expectations for a new medicine can be hindered by the lack of complete safety data. Class effects known by an Agency, however, can trigger requests for rigorous examination of specific safety data that may not be anticipated by the Sponsor in early-stage development.

   Although most advisors agree that the best time for an informed BR discussion is at the end of phase 2, most still occur at the time of the New Drug Application submission; there is also potential value of BR discussion at the end of phase 3 to help guide the expectations of regulatory reviewers.

   BR discussions between Agencies and Sponsors should include a level of efficacy that is clinically relevant and proposals should be made for acceptable risk thresholds based on up-to-date aggregate data. Full transparency and clear risk thresholds will help Sponsors make go/no go decisions and facilitate early discussion with Agencies. Finally, a clear deductive audit trail is needed to improve BR communications.

7. **Ensure risk management plans have certain key features.**

   Risk management plans include proposed strategies to manage various safety issues for Agency feedback. They should also incorporate discussion, as appropriate, on how to compare health outcomes, including a value placed on each parameter assessed.

   Although risk management programmes are designed to gather post-marketing safety data surrounding signals of major concern, there is the possibility that the application of BRFs may reduce the significance of some safety signals and the consequent need for risk management. Systematic identification of gaps identified by a BRF will aid in the development of a risk management strategy.

   Systematic retrospective analyses of safety issues either identified early or appearing late in development should be part of the risk management plan. This includes weak signals that did not eventually materialise, new signals that were not identified previously, and early signals that remained significant.

General Workshop Discussion

Patient communication

The translation of benefit and risk from a population to an individual level is one of most difficult challenges in patient communication faced by health care practitioners. The fact that benefit and risk may not remain as constant values over time further complicates this communication. In order to be able to provide quantifiable information to their patients about their medications, healthcare practitioners should receive specific education on BR counselling in professional schools and as a part of annual continuing education requirements.

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Assigning values to BR

Development of a BRF continues to focus on overcoming the fourth step, the assignment of weights to BR criteria. Although both Agencies and Sponsors currently apply weights to BR parameters, the rationale behind the weighting is not explicit. In addition, although patient preference surveys have been used to determine the level of risk that is acceptable for potential treatment benefit, these surveys are confounded by intrinsic differences such as age and geography and the application of patient values in regulatory decisions are not yet part of the process.

It was agreed that this complex topic will require specific structured discussion. It was proposed that a special Workshop be convened around this issue, possibly following the suggested application of a BRF to a BRAT case study.

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Communicating Benefits

Unopposed communication of risk without the communication of benefit may serve to undermine public discourse. There is a global need for increased, ongoing post-marketing surveillance and communication regarding a medicine's benefits.

It should be possible to look at effectiveness of a medicine with the same methodologies and databases used to monitor safety signals. A future focus for public post-marketing communications should be on bringing the wealth of information contained in the integrated summaries of safety and efficacy to a practical level, helpful to healthcare professionals and patients alike.

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The Anti Rheumatic Therapy in Sweden (ARTIS) database was cited as an example of a successful programme of post-marketing efficacy and safety data collection. A collaboration of the Medical Products Agency and the Swedish Society for Rheumatology started in 1999, ARTIS combines patient information from regional and national clinics, registries, and centres for pharmacovigilance, resulting in data useful for clinical epidemiology, health economy and medical management. In addition to data for anti-rheumatic therapy, ARTIS is expected to expand to include registry data for therapies in neurology, dermatology and gastroenterology.

WORKSHOP PROGRAMME

Session 1: Benefit-risk assessments: How decision-making frames communication	
Chairman's welcome and introduction	**Professor Sir Alasdair Breckenridge**, *Chairman, MHRA, UK*
Development of a benefit-risk framework: past, present and future	**Professor Stuart Walker**, *CMR International Institute for Regulatory Science, UK*
Benefit-risk assessments of marketing authorisations: an EMEA reflection	**Professor Hans-Georg Eichler**, *Senior Medical Officer, EMEA, UK*
The PhRMA Benefit Risk Assessment Team (BRAT) initiative: a status update	**Dr Filip Mussen**, *VP, Psychiatry and EU RED Regulatory Affairs, Johnson & Johnson PRD, Belgium*
Communicating benefit and risk to a regulatory agency: endpoints and other metrics - one company's experience	**Dr Daniel Everitt**, *Chief Safety Officer - Pharmaceuticals, J&J Pharmaceutical R&D,USA*
Using qualitative and quantitative benefit-risk management assessments to inform stage-gate decisions during the drug development process	**Paul Coplan**, *Senior Director, Wyeth Research, USA*
Session 2: Facilitating the benefit-risk communication process using a common framework	
Chairman's introduction	**Dr David Jefferys**, *Senior Vice President, Eisai Europe Ltd, UK*
How should Benefit and Risk be communicated within the CTD: promise and pitfalls in practice	**Dr Brian Daniels**, *Senior VP Global Development & Medical Affairs, Bristol-Myers Squibb, USA*
REMS, RiskMAPs, PSURs, Labels and the Benefit-Risk Framework: communicating risk to prescribers and patients **Regulatory agency perspective** **Industry perspective**	**Dr Gerald Dal Pan**, *Director of the US FDA Office of Surveillance and Epidemiology, FDA,USA* **Dr John Ferguson**, , *VP and Global Head, Pharmacovigilance and Medical Safety, Novartis Vaccines and Diagnostics, USA*
Communicating Benefit and Risk to end-user stakeholders **Meeting the needs of the clinician** **Meeting the needs of the patient**	**Dr Ramzi Dagher**, , *VP, WRAQA Regulatory Head Oncology and Emerging Markets, Pfizer Inc, USA* **Dr William Soller**, *Professor and Executive Director, Center for Self Care, University of California San Francisco School of Pharmacy, USA*
The psychology of decision making: a quantifiable metric?	**John Howell III**, *President, Portfolio Decisions Inc, USA*

SECTION 3: WORKSHOP PRESENTATIONS

Session 1: Benefit-risk assessments: How decision making frames communication

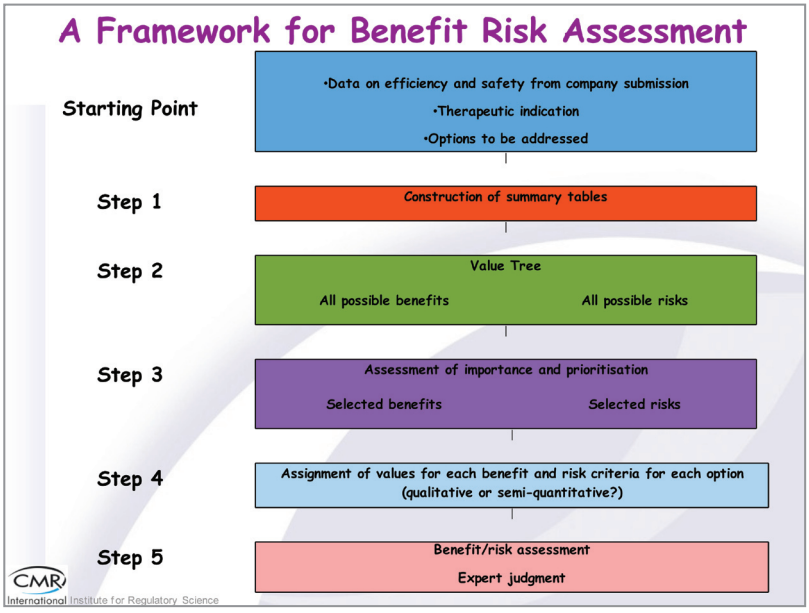
Chairman: Professor Sir Alasdair Breckenridge, Chairman, MHRA

Development of a benefit-risk framework: past, present and future

Professor Stuart R Walker

Founder, CMR International Institute for Regulatory Science

Professor Stuart Walker, Founder of the CMR International Institute for Regulatory Science (the Institute), discussed the past, present and future of benefit-risk (BR) assessment, explaining that the current Workshop represented the sixth one convened on this topic by the Institute since the first, held in conjunction at the Ciba Foundation in 1985.



Past

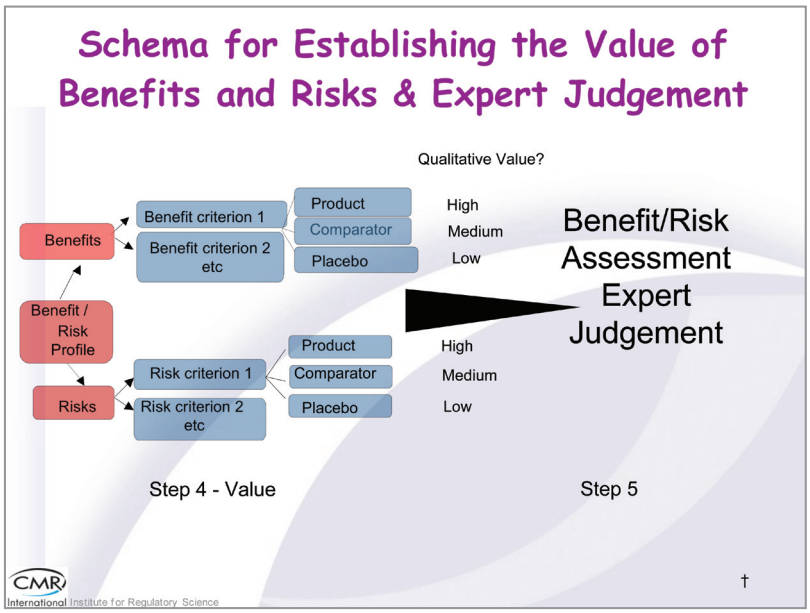
Results of a 2008 survey conducted by the Institute revealed that companies, in general, use either a qualitative model in which internal experts or management make a subjective assessment of the BR profile of each product or a semi-quantitative model in which a structured framework or standard operating procedure for data collection and analysis is employed, but which also incorporates expert judgment into the final decision. Only one company surveyed used a fully quantitative model, which experts oversaw and approved. Regulatory Agencies surveyed were evenly divided between those using the qualitative and semi-quantitative models for their dossier assessments.

Professor Walker noted that current models can result in inconsistency from both industry and regulators; that is, benefits and risks are not always presented in a coherent and well-structured manner and when different Agencies come to different conclusions when faced with essentially the same application data, it is difficult to explain the discrepancies. A BR framework (BRF) that includes the views of a wider range of stakeholders including regulatory reviewers, pharmaceutical industry, physicians, payors and patients could be an important advance in this effort. Furthermore, there has been increasing pressure on Agencies to increase transparency and accountability and to establish a paper trail to explain how their decisions are reached.

Present

At a 2008 Institute Workshop, several BR assessment issues were identified. First, it must be established which benefits should be considered and which risks should be measured during a development programme. In addition, because benefit and risks are measured in clinical studies in different ways, they may require the use of a common scale for comparison. It should be recognised that patients differ in how they value and perceive specific benefits and risks compared with regulators and physicians, and that they require more education with regard to BR assessment. Finally, communication tools must be developed to explain to all stakeholders how a BR assessment is carried out and how to interpret it.

Separate concerns were identified for the acceptance of any BRF by regulators and industry, first of which is the recognition that such frameworks should be regarded as supportive tools that do not minimise the importance of clinical judgment. It was further agreed that the complexity of the decision-making process requires specific methodology to enhance transparency, and that new methods must be validated, flexible and simple to implement. Lack of experience in the use of these frameworks, however, may mean that a cultural change from current methodology and views is required.



Future

A proposed framework

A five-step process for BR assessment has been proposed by Professor Walker in which after data on product safety and efficacy are identified, summary tables are constructed, a value tree is developed, a prioritisation of the those values is made, a weight is assigned to the prioritised values and the BR evaluation is finalised using expert judgment.

Recommendations for the development of a BRF have emerged from previous Institute Workshops and other thought leader meetings. These recommendations include

- the development of a common lexicon;
- a list of benefit and risk parameters;
- case study comparisons of the different frameworks
- and an analysis the values assigned to parameters by all stakeholders, including Health Technology Assessment (HTA) Agencies.

An evaluation of how a common BRF might be of value in developing a standardised, reproducible transparent system and the formation of an organisation or a Next Steps Group to monitor and report on the various initiatives were also recommended.

CASS Initiative

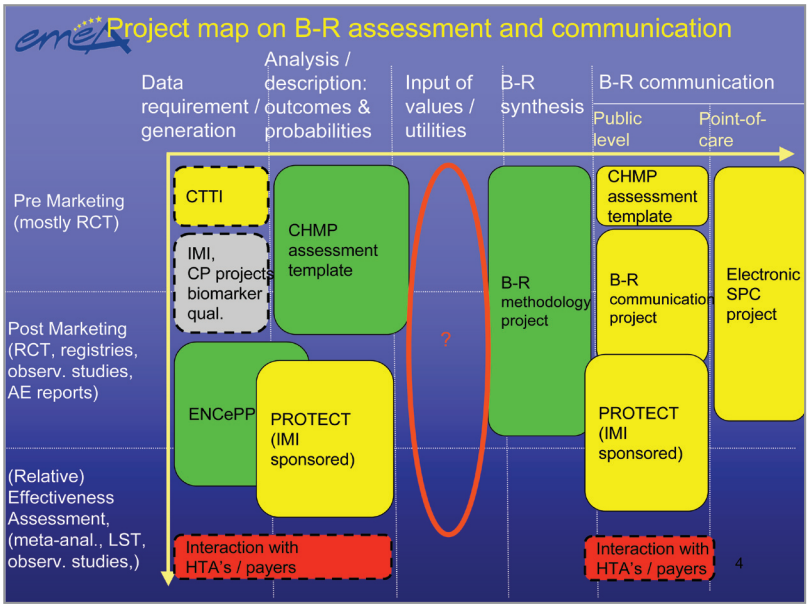
A group of representatives from Health Canada, the Therapeutic Goods Administration of Australia, Swissmedic and the Singapore Health Science Authority has been formed by the Institute (the CASS Group) to study the practical application of a formal BRF. Thus far the group has developed a draft list of efficacy and safety parameters and decided on the use of a modified version of the CHMP template, which draws from work pioneered by Dr Fillip Mussen under the direction of Professor Walker. The group will initiate a pilot study in the fall of 2009 of the BR assessment of two or three products for which a final regulatory decision is about to be made. The main study, which will be a prospective study for new active substances and major line extensions, is planned for 2010.

EMEA initiatives to strengthen the assessment and communication of benefits and risks of medicines

Professor Hans-Georg Eichler

Senior Medical Officer, European Medicines Agency (EMEA), UK

The EMEA has initiated an ambitious programme to further enhance their core deliverable, which is the benefit-risk assessment of medicines. Professor Eichler provided a summary of these initiatives set in the context of the benefit-risk tasks of data generation, analysis, synthesis and communication along the pharmaceutical development time points of premarketing, postmarketing and relative effectiveness assessment.



BR data generation

In the premarketing stage of BR data generation, the EMEA recognises the important work of the European Innovative Medicines Initiative (IMI) and the US Critical Path Initiatives (CPI) in the improvement in clinical trial development and conduct and contributes to these programmes based on available resources.

Within the postmarketing phase of BR data generation, the EMEA is the driver for the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The goal of ENCePP is to establish an infrastructure of database owners and academic pharmacoepidemiology centres that will enable retrospective and prospective safety studies of consolidated healthcare databases. Currently, research standards, independence and transparency rules and quality criteria for centres are being developed.

BR analysis

The EMEA has completed the first phase of modifying the current BR assessment section of the CHMP assessment report template, which is being used in both the pre and postmarketing stage of BR analysis. The modification will include the incorporation of a structured list of BR criteria and guidance to their use. A structured and mainly qualitative approach will be used, which will be explicit regarding the importance of benefits and risks in the specific therapeutic context; and describe sources of uncertainty and variability and their impact on the BR assessment.

PROTECT (Pharmacoepidemiologic Research on Outcomes of Therapeutics by a European ConsorTium) is a methodologic framework for pharmacoepidemiology studies that will enhance early detection and assessment of adverse drug reactions from different data sources and enable the integration and presentation of data on BR. PROTECT, which is being developed by the IMI and supported by EMEA, will enable data mining, signal detection and evaluation in various types of datasets including data of spontaneous reports, registries and other electronic databases. Means of combining results from randomised clinical trials, spontaneous reporting and observational data will be developed, comparing Bayesian modelling, multi-criteria decision analysis and other analytical methods.

BR synthesis

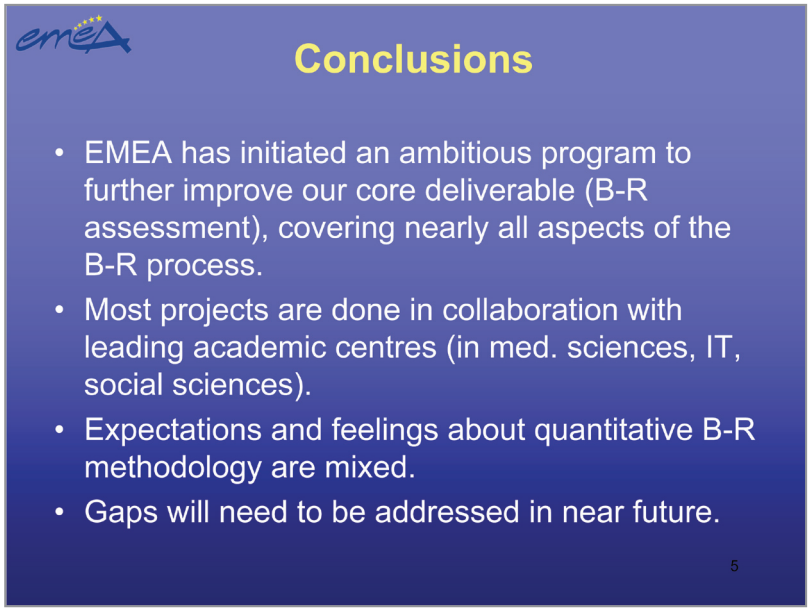
The EMEA has begun the Benefit-Risk Methodology Project, which aims to adapt or develop tools and processes to conceptualise and make explicit BR trade-offs, thereby providing an aid for regulatory decision-making, training of assessors and communicating BR decisions to stakeholders.

This project will be divided into five "work packages," the first of which is currently in progress: 1) describe current practice of B-R assessment in the EU; 2) evaluate the applicability of current tools and processes for regulatory BR assessment; 3) for one or more domains, develop and field test tools and

processes to demonstrate their usefulness; 4) synthesise information from the field test and develop a BR tool and process that can add value in other domains (alternatively, if research establishes that different levels of complexity in balancing benefits against risks require different approaches, then this work package will outline how the tools and processes are contingent on the level of complexity); and finally, 5) develop a training package for regulatory assessors.

BR communication

To support the two-way communication of pharmaceutical benefits and risks to influential stakeholders such as academics, regulators, manufacturers, patients' organisations and journalists, the EMEA has initiated a project to analyse perceptions of the EMEA communications issued for three products with recent high-profile safety issues : Viracept, Acomplia and Gardasil. It is hoped that the results of this research, which are expected by March 2010, will guide the development of future EMEA public BR communications.



In another aspect of the current IMI PROTECT project, methods for the graphic communication of BR to different stakeholders will be developed and tested. This part of the project represents a means of combining results from clinical trials, spontaneous reporting and observational data, comparing Bayesian modelling, multi-criteria decision analysis and other analytical methods.

In an effort to improve BR communication at the point of patient care, the EMEA has embarked on the Electronic Summary of Product Characteristics (e-SPC) Project, which will structure the BR information of the SPC so that it can be linked to electronic health records and prescribing systems to support prescribing decisions, and to improve the quality of pharmacotherapy . The pilot phase will encompass either a specific therapeutic area or specific part of the SPC.

Gaps

The EMEA recognises that its BR assessment process and procedures have not yet been informed by the input of the patient experience or Health Technology Assessment Agency requirements and hopes to address both of these gaps in the near future.

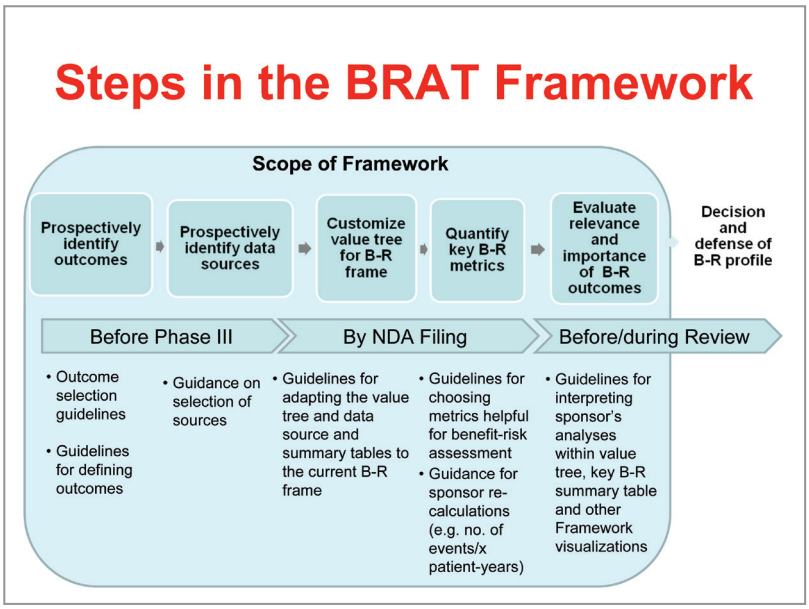
The PhRMA Benefit-Risk Action Team (BRAT) Initiative: a Status Update

Filip Mussen, PhD

Vice-President, Psychiatry and EU RED Regulatory Affairs, Johnson & Johnson Pharmaceutical Research and Development

Within the past several years, many organisations such as the US Food and Drug Administration (FDA) and the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) have issued statements regarding needed revisions to the methods applied to the BR assessment of medicines. These statements emphasised in particular the need to improve methodology, transparency, consistency and communication, to take a systematic approach and to develop and to incorporate new quantitative tools.

In May 2006, PhRMA (the Pharmaceutical Research and Manufacturers Association of America), which represents the leading pharmaceutical research and biotechnology companies in the United States, announced that it would develop a semi-quantitative model for BR assessment. As one of the members of the Benefit-Risk Action Team (BRAT), Dr Filip Mussen detailed the progress in the development of this model.



PhRMA hopes to establish a structured, transparent framework for BR evaluation that will increase the transparency, predictability and consistency with which BR assessments are conducted and to facilitate the framework's integration into the regulatory decision-making process both at the time of medicine approval and postapproval. The goals of the project are to improve the communication of BR information to Agencies, patients and healthcare professionals by ensuring that there is a better focus on both the benefits and risks of medicines and to strengthen the pharmaceutical development and regulatory approval process. It is envisioned that the framework, which will serve to enrich rather than substitute for expert judgment, will employ a primarily qualitative approach, but one that has the flexibility to incorporate quantitative elements as needed.

Concepts and context of the BRAT framework

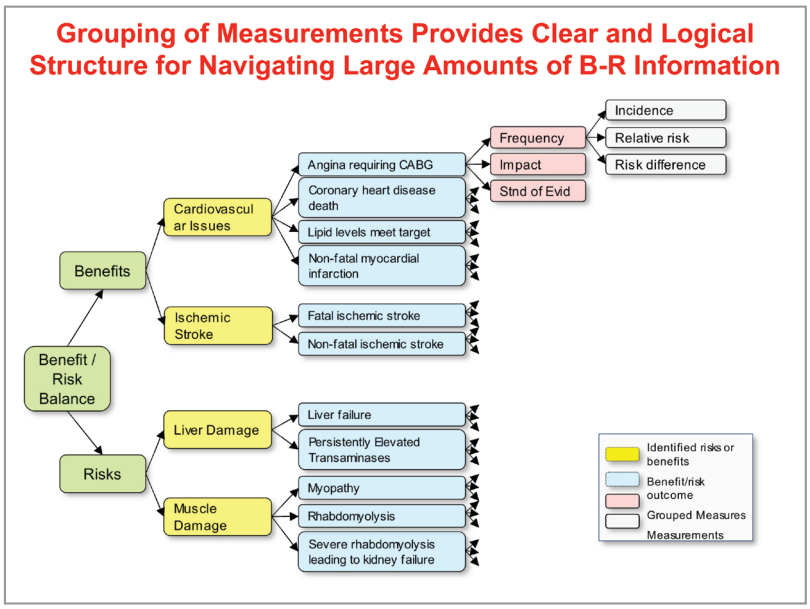
In the construction of the BR framework, it has been agreed that the nature of the disease should be taken into account, all relevant data sets should be considered, made explicit and where possible, weighted, and the existence of missing or inconclusive data should be recognised. It has been further determined that BR cannot be captured by a single attribute and should be evaluated with the context of the product label, new emerging efficacy and safety information, postapproval commitments, and risk management and minimisation plans. Although BR evaluation is a comparative process, noncomparative data (eg, spontaneous safety data reports) should be equally captured when appropriate. To aid in the development of a framework that will yield a high-quality, transparent BR assessment, a "weighting" decision approach will be used.

Steps in the BRAT framework

The BRAT framework employs a 6-step approach similar to that detailed in Professor Walker's presentation in which outcomes are prospectively ascertained; data sources identified; a customised value tree is created; key BR metrics are quantified; and the importance of the BR outcomes are evaluated. The ultimate decision, however, is not considered to be in the scope of this framework but is rather left to the expert judgement of the regulators.

BRAT has developed an example of the use of this framework, focussing on data collection, organisation, reduction and visualisation. A table was presented based on a fictional compound

with data fabricated for illustrative purposes only. A value tree was constructed that reflected outcomes relevant to the assessment. A key summary table allowed utilisation of graphic or tabular displays to support rapid interpretation of information on multiple outcomes. The use of Forest plots with confidence intervals has emerged as a particularly useful graphic tool to facilitate BR comparison. Source details are readily available in the sample framework.



Through use of the framework, BR analysis and weighting will be possible from the perspective of multiple stakeholders. It is recognised that the perspective of Sponsors and regulators may best be incorporated through this weighting process rather than through standard utilities. Patient BR perspectives may be elicited through a tool such as the Stated Choice Patient Survey, which is also be Sponsored by PhRMA, but which is currently outside of scope of BRAT. A method for incorporating the perspective of prescribers into the framework has yet to be developed.

Lessons learned to date

A BR framework should put equal emphasis on all steps in the BR evaluation, be based on the current informal process and require sufficient level of sophistication and detail with specific rather than abstract outcomes. The need is for a flexible, interactive framework that can be fine-tuned for specific therapeutic classes

BRAT has embarked on the second phase of development and testing of the framework. They are committed to work with stakeholders and other interested parties to determine the extent of the framework's utility in the BR evaluation process and encourage Sponsors to start applying the basic concepts of the framework as it is still being developed. BRAT strongly believes that this BR framework will improve the quality of the BR decision making for new drug applications; permit a focus on both benefits and risks; allow a more systematic rather than ad hoc discussion during regulatory deliberations; and increase the transparency of the discussions and outcome of regulatory evaluations to all stakeholders.

Communicating Benefit and Risk to a Regulatory Authority

Daniel E. Everitt, MD

Chief Safety Officer, Pharmaceuticals, Johnson & Johnson

Dr Everitt presented a clear and graphic approach that has been used by Johnson & Johnson to understand and explicitly communicate key benefits and risks to regulatory authorities. He introduced a hypothetical example of this approach by explaining that although the benefits for a new medicine usually extend from efficacy endpoints and may be anticipated, risks emerge from an assessment of all trial data and are not usually fully known until later in the life cycle. Both attributes, however, should be quantified in a clear and understandable manner.

He further explained that in presenting benefits and risks to the regulatory authorities it is important to use a format that allows key benefits and risks to be evaluated side by side, on the same page. Terms not understood by a broad audience and concepts and methodology that are open to controversy or that may distract should be avoided.

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The hypothetical example given by Dr Everitt was for the communication to the US FDA and its Advisory Committee of the BR profile for a novel fictitious protein biologic for the prevention of serious lower respiratory tract disease caused by severe respiratory syncytial virus (RSV) disease in at-risk infants. The pivotal clinical development consisted of blinded trials of the new medicine against a standard-of-care (SOC) comparator therapy.

Key identified benefits would be derived from the primary outcome measure, the incidence of hospitalisation due to RSV and from the secondary outcome measure, the incidence of death due to severe RSV disease. Key risks were hypothesised to be severe allergic reactions leading to hospitalisation and anaphylaxis leading to death. In this example, these events were extrapolated to a hypothetical population of 10,000 treated patients and a number was calculated that represented the difference between incidences of hospitalisation for RSV that were prevented by use of the new drug (330) and hospitalisations from allergic reaction that occurred as a result of the new drug over that seen with SOC (90). Overall, therefore, treatment with the new drug resulted in a decrease in 240 hospitalisation events per 10,000 patients, which could be clearly visualised using this approach.

In addition, a summary table was constructed of hypothetical serious adverse events that would occur in 10,000 patients; in this example, the graphic representation of these data clearly showed that the excess numbers of events overall favoured the use of the new drug.

Dr Everitt concluded his presentation by stating that the appropriate use of a product in clinical practice requires that benefit and risk have been characterised accurately and communicated in a way that optimises prescribing behaviour and understanding by both the healthcare professional and the patient. The challenges in understanding and communicating benefits and risks start with understanding the data, and require that the benefits and key risks are conceptualised in a clear, understandable manner that allows direct comparisons. The data should be presented in a way that is conceptually clear, avoiding confusing terms and concepts. Novel graphic representations such as these proposed can advance the understanding and communication of BR among all stakeholders.

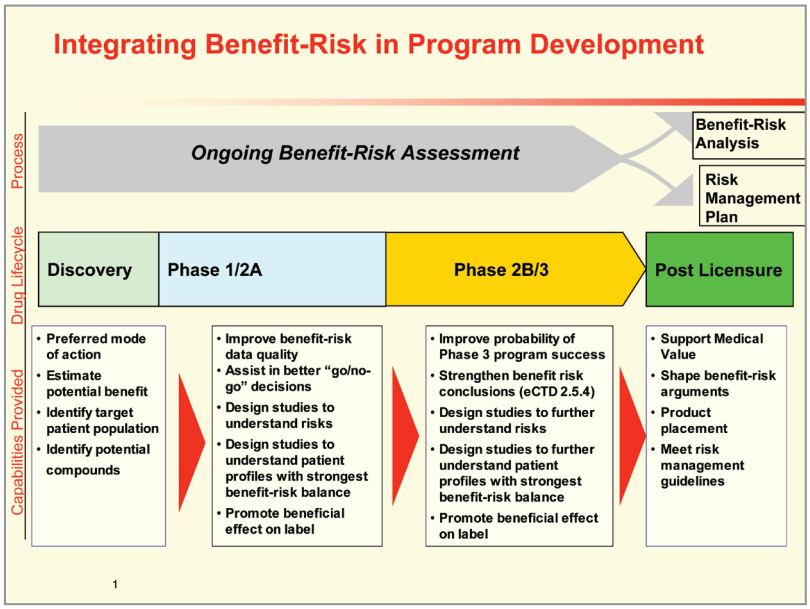
Using Qualitative and Quantitative Benefit-risk Management Assessments to Inform Stage-gate Decisions During the Drug Development Process

Paul Coplan, ScD, MBA

Senior Director, Risk Management Global Safety Surveillance and Epidemiology, Wyeth

The thesis of Dr Coplan's presentation was that a) benefit-risk assessment can be an excellent metric to use when designing development programmes for medicinal products and evaluating when to allocate scarce resources to develop or in-license a product, and b) using the principle of "begin with the end in mind", [1] if medicinal products will be judged on benefit-risk criteria, it is important to ensure that the development programme is designed to generate the necessary data to meet benefit-risk criteria.

Dr Coplan began his presentation by defining BR assessment as the measure of the medical value of a treatment from the multiple perspectives of the patient, provider, regulator, and payor. This assessment does not displace any safety, efficacy, and quality requirements for a standard development programme and is a "second-order" function of strength of evidence.



The goals of BR assessment depend on the perspective from which it is viewed. From a societal perspective, the goal of the assessment is to enhance the BR balance of available medicines by minimising instances of providing licensure of medicines with a net harmful effect (ie, false positive approvals) and minimising instances of rejecting medicines with a net beneficial effect (ie, false negative approvals), even if only in a subset of patients. The goal of BR assessment from the perspective of regulators is to improve decision-making for market access approvals and to help communicate and document the basis for regulatory decisions, even several years after the decision is made. The goal of BR assessment from the perspective of sponsors is to establish objective methods to support regulatory decisions and tailor their data collection to better address decision-making needs.

BR components and tools

In identifying how to incorporate BR assessment into the lifecycle of development of new medicinal products, it is important to establish the important elements or steps to include in BR assessment, as well as to define the available tools for assessing whether benefits outweigh risks. The components of BR assessment are outlined well in the EMEA template for BR assessment. BR assessment begins with the identification of relevant comparison treatments such as a placebo or standard of care and the benefits and risks of those treatments against the background of unmet therapeutic needs. Next, the benefits and risks of the new medicine must be identified, quantified, and compared in terms of preferences or values. Finally, uncertainties must be clarified.

The tools for evaluating whether the benefits outweigh the risks include the following: a) ensuring that the benefits and risks are presented using a common denominator that incorporates time of the product's use and the length of studies (eg, person-time denominators or time-to-event analyses); b) using a simple numerical comparison of the event rates of benefits and risks that does not account for different value weightings of benefit and risk outcomes; c) incorporating value weights for benefit and risk outcomes derived from preference weightings, utilities or quality-adjusted life year approaches. These are most helpful when they consider the multiple perspectives of relevant stakeholders; d) using decision-analytic approaches that

facilitate decision-making by groups and make transparent group valuations, such as the multi-criteria decision model; and e) visual display of BR data to simplify the interpretation of complex data, such as value trees.

Dr Coplan presented a number of examples of the use of tools in the communication of benefit-risk. One example of the number-needed to treat/number needed to harm approach was used by Pfizer at the FDA Advisory Committee meeting for lasofoxifene, using the approach to demonstrate numerically that the new SERM for the prevention of osteoporosis has a favourable BR balance compared with placebo.

Another BR assessment tool, showing benefits and risks as comparable rates over time was used in a published BR assessment for celecoxib for the indication of prevention of colorectal cancer.[2] In this comparison, in which colorectal cancer and cardiovascular events were assumed to be equal in severity as a simplifying assumption, it was possible to identify that although celecoxib may decrease colorectal cancer (using colon polyps as a proxy marker of colorectal cancer) based on a large phase 3 trial, it also would increase cardiovascular serious adverse events (SAEs) leading to an overall increase in the rate of colorectal cancer and cardiovascular SAEs combined. In contrast, low-dose aspirin trials have shown that aspirin would be associated with a weaker protective effect against colorectal cancer than celecoxib but a protective effect against cardiovascular SAEs. In conclusion, the analysis clearly identified that celecoxib clearly does not have a role in the protection against colorectal cancer when compared to aspirin.

Patient preferences for risk compared with the value placed on potential benefits of treatment were used to develop BR assessments for an Alzheimer's treatment3 and a therapy for irritable bowel syndrome using preference weights derived from conjoint analysis surveys (Unpublished data from Professor Larry Lynd, University of British Columbia).

BR assessment throughout the product development continuum

BR criteria can be applied in all stage-gate decisions in the pharmaceutical development life cycle to enhance the quality of the benefit-risk assessment when needed. It can start as early as when selecting disease areas for R&D prioritisation even before a specific compound is identified. At the beginning of phase 1, specific therapeutic context and the unmet medical need can be developed as a foundation of the BR assessment. Prior to the start of phase 3 trials, a BR assessment can be conducted based on what has been identified about the product in phase 1 and 2 trials, the pharmacologic class, and the unmet medical need in the specific therapeutic context. This preparation aids the development of a well-constructed BR assessment to support marketing approval/licensure that can be submitted at the time of filing of the dossier as part of the Conclusion of the Clinical Overview of the eCTD (Section 2.5.4 Benefits and Risks Conclusions).

Selecting disease areas for prioritisation

At the time of selecting disease areas for prioritisation of a company's R&D resources, Sponsors can use BR criteria to define the specific therapeutic context, the comparison treatments of relevance, the benefits and risks of existing therapies, and hence unmet medical needs in the specific therapeutic context. At this stage, it is also appropriate to identify the minimally acceptable thresholds for benefits and risks that a new product would require in order to meet the unmet medical need and to determine whether it is feasible for the product to achieve the thresholds. It is also important to identify the feasibility of generating data to demonstrate that the product meets the thresholds required to meet the unmet medical need. In some situations it may be unclear what would be a minimally acceptable level of benefits or a maximally acceptable level of risks in the specific therapeutic context. Generating data to assess stakeholder values of minimally acceptable benefits and maximally acceptable risks can help to prospectively define target levels of benefits and risks that developmental products need to achieve to be viable. Preference data can also be used to aid in selecting priority disease areas in a portfolio.

Phase 1

At the time of the phase 1 go/no go decision for a new medicine, it is possible to build on the disease area BR assessment that has already been performed by assessing whether the product is likely to meet the minimally acceptable thresholds for benefits and risks based on preclinical data and mechanism of action.

Next, it is necessary to identify the important areas in which to collect information to close the gaps in knowledge about the BR profile of the product and to ensure that this information will

be prospectively collected during the clinical development programme, and also to make certain that BR criteria are incorporated into phase 1 and 2 dose-selection criteria.

Phase 3

Incorporating BR criteria is particularly important to inform phase 3 go/no go decisions when the stakes for failure are increasingly higher. Continuing to build on the BR assessments made at the disease prioritisation and phase 1 stages, it is now possible to identify the important areas to collect information to close the gaps in knowledge about the BR profile of the product and to ensure that this information is collected robustly. Presently, risk data are generally collected on an adverse event report form that relies on the study site investigator's diagnosis and reporting of information. As a result, diagnoses can vary by investigator and the completeness of data collected on an AE case can vary from case to case. Pre-specification of safety endpoints based on the BR assessment and hence prospective, systematic data collection on risks can improve the quality of data on risks and hence the quality of the BR analysis.

Marketing approval application

BR criteria are used at the time of the regulatory application to present data on the benefits and risks of the new product using a common denominator for benefit and risk outcomes to demonstrate that the benefits of the product outweigh the risks. This is also the time to ensure that information to close gaps in knowledge around the BR profile are communicated and that efforts to mitigate identified risks and enhance benefits of treatment are addressed in risk management plans, pharmacovigilance plans or REMS.

In conclusion, starting in early development with structured BR assessments is imperative for a quality BR assessment at approval submission and post-approval. BR assessment can be an excellent metric to use when designing development programs for medicinal products and evaluating when to allocate scarce resources to develop or in-license a product.

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Session 2: Facilitating the benefit-risk communication process using a common framework

Chairman: Dr David Jefferys, Senior Vice President, Eisai Europe Ltd

Benefit and risk communication: A patient-focussed discussion

Brian Daniels, MD

Senior VP Global Development & Medical Affairs, Bristol-Myers Squibb

In addition to becoming more standardised and transparent, BR assessments are increasingly being made with a focus on the patient viewpoint. Dr Brian Daniels used the published analysis of the results of the PROactive study to illustrate the role perspective can play in BR analysis of medicines.[1] In this publication, the author concluded as a physician that the benefits of pioglitazone in preventing diabetic sequelae were outweighed by the risk of oedema diagnosed as heart failure, giving the medicine an overall negative risk profile. Dr Daniels contended, however, that when the BR for this medicine is evaluated from a patient perspective, it might follow that patients with diabetes are willing to risk an incidence of less serious heart failure that did not require hospitalisation to avoid the possibility for example, of diabetes- associated amputation.

Standard gamble and time trade-off are BR decision tools that can be applied to elicit the perspective of patients and the general public. In one of the best examples of the abstract trade-off of standard gamble analysis, polled patients preferred the risk of a major bleeding event requiring transfusion to the risk of a disabling stroke by a factor of 4 or 5.[2] Similarly in another patient preference analysis, 55% of people with relapsing/remitting multiple sclerosis valued the benefit of avoiding a certain number of disease relapses more highly than the risk of a catastrophic, often fatal infection.[3]

In an historical example of the evolving nature of BR evaluation, Dr Daniels recounted how the first statin received regulatory approval on the basis of a surrogate marker, the lowering of low-density lipoprotein in patients with elevated LDL cholesterol. Although this class of medicines was associated with several known or potential risks including carcinogenicity, cataracts, suicidal ideation and muscle toxicity, it was hypothesised that the benefit of lowering of LDL cholesterol would result in a reduced incidence of heart disease and stroke that outweighed the potential risks. In the intervening decades, the incidences of heart disease and stroke as a cause of death have in fact been reduced by approximately half, with this reduction due, in some part, to the use of statins. Stakeholder recognition of the benefits and acceptance of the risks contributed to this overall societal benefit.

Innovations in the pharmaceutical development paradigm are also creating an impact on BR assessment. In addition to incorporating payor input in development designs, patient selection through pharmacogenomics is helping to target the patient who will derive the greatest benefit from a medicine with the least potential risk. In the case of patients with colorectal cancer for example, it emerged in phase 3 trials for cetuximab that patients with the wild-type K-Ras gene marker rather than those with the mutant type would derive greatest benefit from this compound; these patients became the focus of a successful pharmaceutical development programme.

Dr Daniels concluded by emphasising the need for early decisive action following BR analysis and improved, transparent and rapid communication of those decisions to healthcare providers and patients.

BR analysis should be seen as a series of decisions informed by all stakeholders throughout the life-span of a product. This is particularly important today when there is an increased emphasis on post-marketing BR studies in which the effect of a medicine in a real-world population can be more completely characterised.

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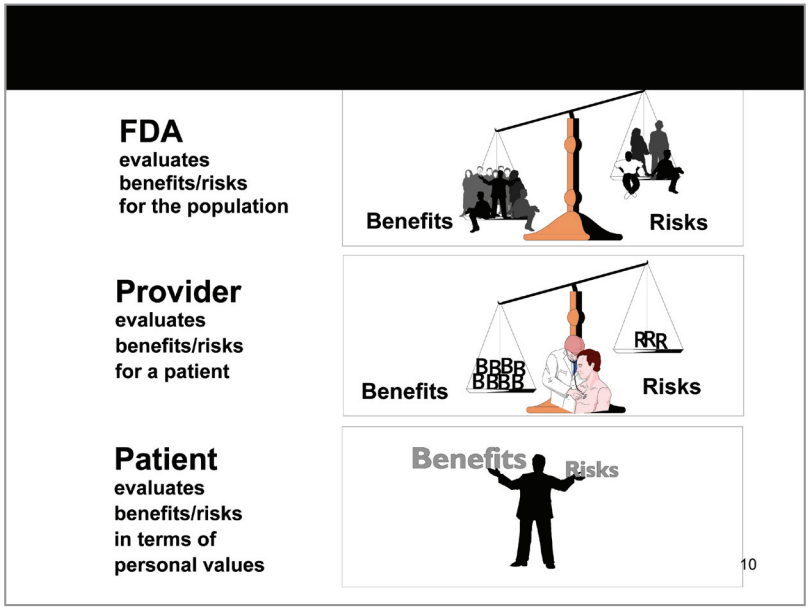
Communicating Risks to Prescribers and Patients

Gerald J. Dal Pan, MD, MHS

Director, Office of Surveillance and Epidemiology Center for Drug Evaluation and Research, US Food and Drug Administration

Today, despite an increasing number of people receiving an increasing number of medicines and a more broad awareness concerning their use and safety, there is a growing societal expectation that the risks surrounding these medicines be well evaluated and communicated to all stakeholders.

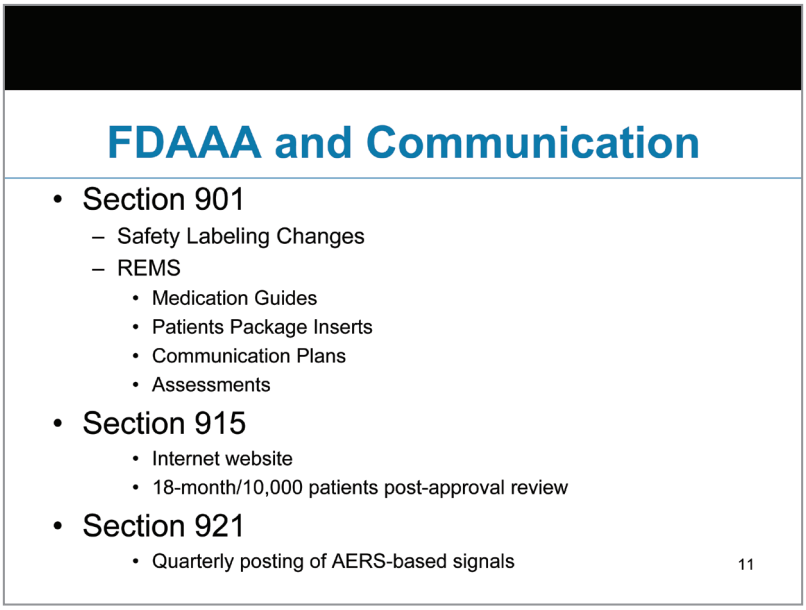
Dr Dal Pan outlined the complex system for the management of the risk of pharmaceuticals in the United States, in which the FDA regulates the pharmaceutical industry by controlling the market access, label content and promotion of medicines. In this trickle-down system of BR assessment, the FDA evaluates BR for the overall population, healthcare professionals (HCPs) evaluate BR for the patients in their own practice, and the patient receives information from companies and regulators that has been distilled through HCPs, and evaluates BR in terms of their own personal values.



Patients in the United States often receive medication information produced by third-party pharmacy vendors that is not regulated by the FDA, can be inconsistent, and that in approximately half of the samples researched by the FDA, has been found to be of little or no practical educational utility. The FDA is working to improve this situation.

In 2007, the US Congress passed the Food and Drug Administration Amendments Act (FDAAA), through which the FDA may require post-approval studies and REMS for certain medicines when certain conditions are met. In addition, FDAAA laid the groundwork for processes through which the FDA could communicate more effectively with the public about issues of drug safety. According to Section 901 of the Act, Medication Guides or Patient Package Inserts can now be required by the FDA as part of a REMS for certain medicines deemed to represent a significant risk. Of over 100 approvals of applications and supplements from March 25, 2008 to June 1, 2009, 52 included approved REMS. For 43 of these, the REMS consisted of a Medication Guide only, whilst 9 of the REMS contained Elements to Assure Safe Use and/or a Communication Plan to professionals. During that same time frame, the FDA sent 58 letters requiring post-market studies or clinical trials: 44 with the initial new drug application or biologics license application approval and 14 post- approvals based on new safety information. Eighteen safety labelling notification letters were also issued. This reflects the FDA's active role in ongoing BR assessment.

FDAAA also required the FDA to develop a website that provides links to drug safety information for the general public. This web site, which was launched in October 2008 http://www.fda.gov/cder/drugSafety.htm, is a comprehensive resource regarding post-market drug safety information for patients and providers.



FDAAA calls for the quarterly posting on the Adverse Event Reporting System (AERS) website "of any new safety information of potential signal of a serious risk identified by AERS within the last quarter." This information is available at http://www.fda.gov/cder/aers/potential_signals/default.htm

All signals are posted, even those eventually found not to be clinically significant. Other initiatives being undertaken by the FDA to fulfil its BR assessment mission include Early Communications, a Drug Safety Newsletter and the Risk Communications Advisory Committee

The safe use of medicines is the responsibility of all stakeholders; much of the harm from approved drugs comes from their misuse, inappropriate use, abuse, and medical mistakes. In recognition of the importance of patient and HCP education as a key factor in fostering the safe use of medicines, in 2009 the FDA initiated the Safe Use programme. This programme plans to use a public/private partnership to informally share best practices that will ultimately encourage safe medicinal use.

REMS, Risk Maps, PSURS, labels and the benefit-risk framework: communicating risk to prescribers and patients: industry perspective

John Ferguson, MD

Vice President, Global Head, Pharmacovigilance & Medical Safety, Novartis Vaccines & Diagnostics

Based on its immediate and increasing impact on BR management, Dr Ferguson focussed his presentation on the relationship of BR frameworks with Risk Evaluation and Mitigation Strategies (REMS).

As a formal risk management framework needs to be supported by a formal approach for assessing benefit and risk, the two concepts are inextricably linked. All stakeholders are challenged, however, by the current asymmetry of risk management systems that emphasise the monitoring and communication of risk at the expense of capturing dynamic information about benefit.

In evaluating whether to require a REMS, the US FDA must consider the nature of the disease or condition that is to be treated with the medicine and the expected benefit of the medicine with respect to such disease or condition. Once the need for REMS is determined, the FDA reviews/approves the REMS, the manufacturer implements the REMS, the FDA periodically assesses REMS effectiveness and if they identify risk, evaluates the product to be sure the benefits continue to outweigh risks. The Agency works with the manufacturer to implement FDA-approved risk mitigation approaches (in effect benefit-risk optimisation) including communication of new findings through labelling updates.

REMS, while not warranted for most medicines, can and should be regarded as an opportunity for BR optimisation for some compounds, motivated by the regulatory mandate to ensure that the benefits of the medicine outweigh

"REMS, while perhaps not warranted for most medicines, can and should be regarded as an opportunity for BR optimisation for some compounds."

the risks, in both the premarketing and post-approval stages of pharmaceutical development.

In order to ensure an ongoing positive BR balance, a REMS programme also comprises effective communication strategies, for example, the use of a Medication Guide, Patient Package Insert, or a formal communication plan. The success or failure of a REMS programme is largely determined by patients, their healthcare providers and their caregivers. Greater understanding of the positive (benefits) and negative (risks) aspects of a therapy should provide a stronger incentive for compliance.

Tysabri: a REMS example

Natalizumab (Tysabri; Biogen Idec) is approved for the treatment of relapsing multiple sclerosis (MS). After numerous patients receiving natalizumab were diagnosed with a serious adverse event known as progressive multifocal leukoencephalopathy (PML), the product was voluntarily withdrawn from the market in 2005. Biogen Idec subsequently developed a restricted distribution and risk management plan, and the medicine was returned to the market. This action was based on the observation that for a certain group of patients, when the medicine was used under careful supervision, the potential benefits of the medicine outweighed the potential risks and benefited patients, their caregivers, prescribers, regulators, and the corporation.

Consistency across REMS is likely to increase their acceptance by clinicians and patients.

The Biogen Idec REMS played a positive role in these events in multiple ways. The company created and maintained a robust network of trained neurologist experts in the use of this therapy. Close links and rapid effective communication to the patient population substantially reduced time to diagnosis and treatment, made early detection and treatment feasible, and resulted in a lower-than-expected mortality rate among those who developed PML

The REMS for natalizumab was instrumental in ensuring that those who can benefit most from this treatment for MS continue to have the opportunity to receive treatment while mitigating the consequences of PML in the few who develop it and progressively increasing the precision of the estimated impact of the disease by making well-controlled therapy available to all potential patients.

There are many benefits to establishing a framework for BR assessment to support a REMS including obtaining and incorporating key stakeholder input and consolidating lessons learned (eg, natalizumab). Consistency across REMS is likely to increase their acceptance by clinicians and patients. Better REMS communications will be balanced in reference to benefits and lead to more targeted efficient communication with regulators in a time-constrained environment.

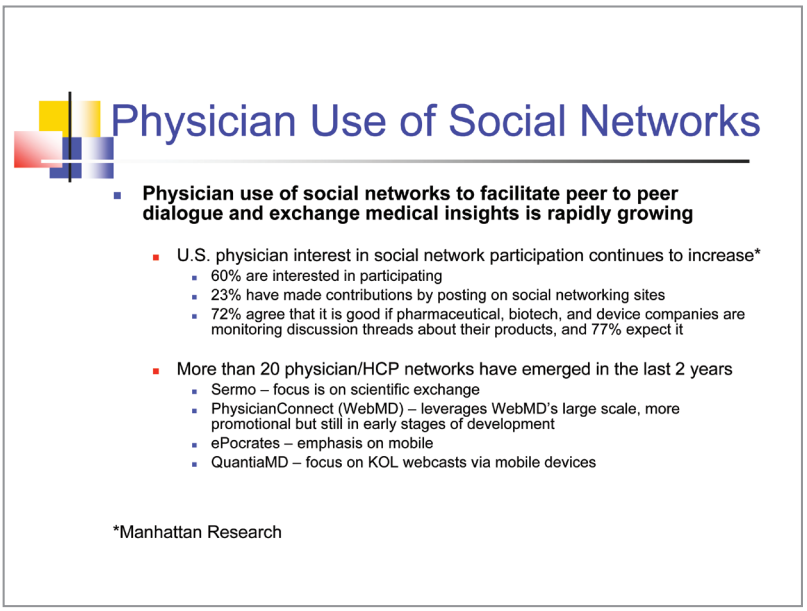
Communicating Benefit and Risk: Meeting the Needs of the Clinician

Ramzi Dagher, MD

VP WRAQA, Regulatory Head, Oncology and EM Business Units, Pfizer, Inc.

Dr Dagher discussed approaches to communicating BR evaluation of medicines to the healthcare practitioner (HCP) throughout the continuum of development, beginning with the classic approaches such as the Dear Investigator letters and journal articles written for generalist and specialist physicians and Dear Health Care Provider communications.

Although these traditional methods of communication provide good "snapshots" of Sponsor and Agency stance in their review of a product and are reflective of approval and some post-approval milestones, they are somewhat static and may not ideally reflect the wide variety of use of medicines in the post-approval environment. In addition, these vehicles may not address the wider audience of HCPs such as nurses and pharmacists. Some improvements to these classic communications have been made recently, including the expansion of publication of Agency approval summaries. In another example of communication enhancement, changes to the www.clinicalstudyresults.org database (Sponsored by PhRMA) have made it more navigable and amenable to interpretation. Furthermore, as more labels are converted to a consistent electronic-friendly format, it may facilitate the dissemination of data for class or therapeutic area effects.



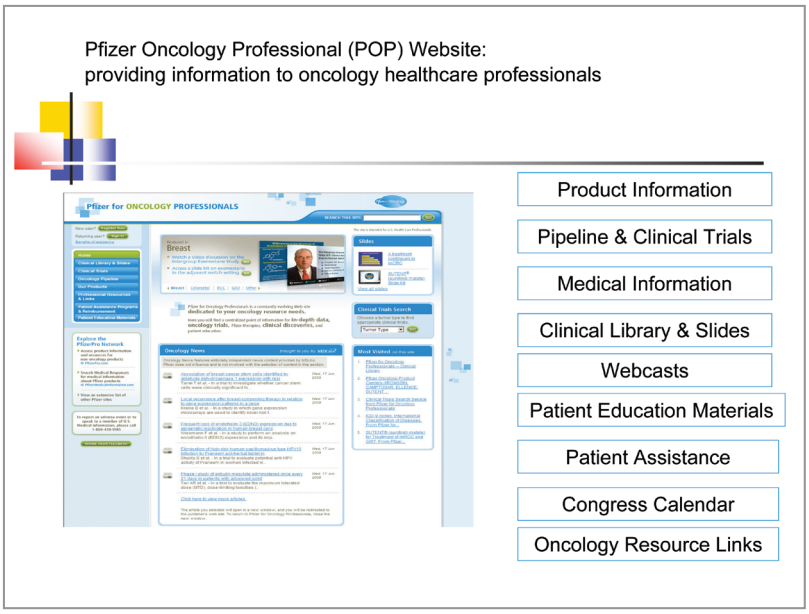
Social Networking

The physician use of social networks to facilitate peer-to-peer dialogue and exchange of medical insights is rapidly growing: in one study conducted by Manhattan Research, 60% of polled HCPs expressed an interest in participating in and 23% have made contributions by posting on a social networking site. More than 20 HCP networks have emerged in just the last 2 years. For some networks, such as Sermo, the focus is on scientific exchange, whilst others such as PhysicianConnect are more large scale and promotional or like ePocrates and QuantiaMD, place a focus on mobile devices. Links to industry and Agencies for these sites could be improved: 72% of HCPs regard industry monitoring of HCP dialogue as a positive development.

Pfizer HCP communication

The Pfizer website www.Pfizer.com/medicinesafety has been developed as an educational resource for HCPs and patients. The goal of the site, which was launched as a public service in the interest of patient safety, was to help bridge the gap in knowledge about how medicine safety is determined, monitored and communicated. The site is experiencing a steady increase in the number of visitors from academia, regulatory Agencies, and patient advocacy groups, medical associations and industry. The website sections "Understanding Risk" and "Medicine Safety for Patients" see the highest traffic volume.

The Pfizer Oncology Professional (POP) website is dedicated to providing information to oncology healthcare professionals, including information regarding products, pipeline, and the practice of medicine. It also includes slide libraries and webcasts and patient education and assistance materials. Plans have been made for site enhancement including surveys, live webcasts, interactive case studies, and a market research function.



Dr Dagher concluded his presentation by outlining the challenges and opportunities to HCP BR communication; these include the definition of the Sponsor's goals with respect to communication, consideration of ways to enlarge the audience to include the broader HCP community and methods to address state, country and regional guidelines whilst maintaining broad appeal in an evolving regulatory and practice environment.

Communicating Benefits and Risks of Medicines – Meeting the Needs of Patients

R. William Soller, PhD

Professor, UCSF School of Pharmacy; Executive Director, Center for Self Care

There is currently a gap in the provision of information about drug and device benefit-risk in the United States, and efforts to better design communication between the regulators and the regulated are vital to fill this void.

Dr Soller began by characterising the gap, explaining that although patients want – and should get – respect, autonomy, beneficence, non-malfeasance and equity in the context of health communications, these are not always the hallmarks of current communication strategies. Practitioners also desire an understanding of those same factors affecting the balance in health communication. Generally speaking, when considering the amount and type of information to communicate, the balance tilts in favour of disclosing all relevant information in a form that assumes "the reasonable consumer" will be able to read and comprehend the information and thus make an informed judgement and take appropriate action.

Relative risk: In the study, there were 34% fewer heart attacks in the treated group than the non-treated group

Decisions of the Study Participants (n=100) Regarding Starting New Medications and Degrees of Certainty (Hux et al., 1995)

Format	Yes		No	
	%	Mean Certainty Rating	%	Mean certainty Rating
Cholesterol Lowering Data				
• Relative risk *34% fewer MI in treated group*	88	8.2	12	7.5
• Absolute risk reduction	42*	6.7	58	7.5
• Number needed to treat	31*	6.4	69	8.1
• Average gain in disease free survival	40*	7.1	60	8.0
• Stratified gain in disease free survival	56*^	6.9	44	8.3
Hypertension Data				
• Relative risk	89	8.0	11	8.0
• Absolute risk reduction	46	7.1	54	7.9

* Compared with relative risk reduction p<0.0001
^ Compared with average gain in disease free years p<0.01

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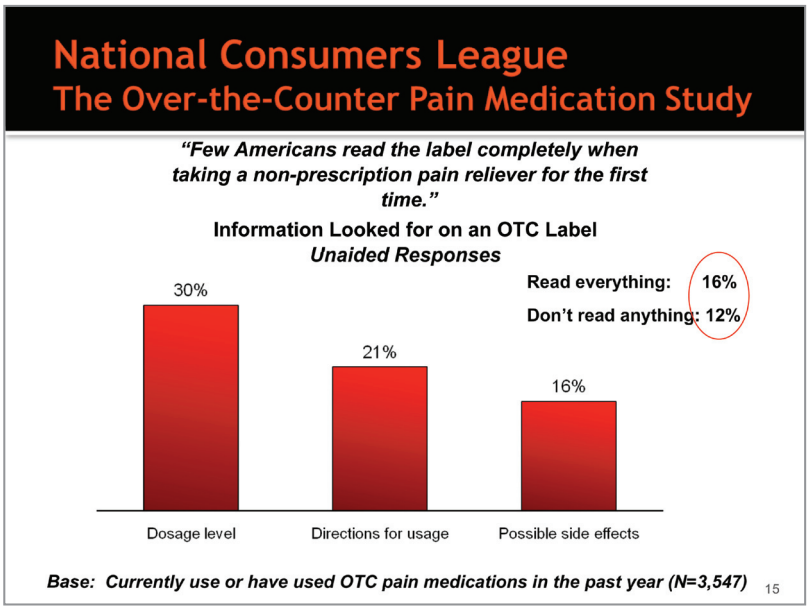
Draft FDA guidance

In May 2009, the FDA issued its Draft Guidance for Industry Presenting Risk Information in Prescription Drug and Medical Device Promotion. Although this document represents the distillation of a very large literature base into a comprehensive resource, offered with the flexibility of guidance rather than requirements, it may leave the guidance for consumers for in the hands of HCPs, the label, the Internet and other media.



The effect of format

In 1999, CH Braddock and associates wrote "More conceptual, qualitative, and quantitative studies are needed to explore fundamental questions about how people process, interpret, and respond to various types of uncertainty inherent in clinical decisions."[1] In support of this need, Dr Soller presented the results of a study conducted by Hux and colleagues[2] in which the likelihood of 100 cardiovascular outpatients using a cholesterol-lowering medication was assessed. Patient interest in taking the medicine varied greatly according to the format in which the medicine's benefits were presented to them. For example, when told of the relative risk reduction associated with the treatment, that is, that there were 34% fewer heart attacks in the treated group than the non-treated group, 88% of the patients said they would be likely use the medicine. However, when the same benefit was expressed as the "number needed to treat," that is, when they were told that if 71 people took the medicine for an average of just over 5 years, the medicine would prevent one of the 71 from having a heart attack, only 31% of those same patients would have been willing to take the medication.

Best case scenario

In the best case scenario of BR communication, all the information necessary for safe and effective use of each prescribed and OTC medicine and device would be given to all patients and consumers for whom each of those products are intended. All stakeholders would be aligned in what, and how, drug/device information is conveyed to patients and consumers.

The Psychology of Decision Making: Lessons from Applying a Benefit-Risk Model

John I Howell III

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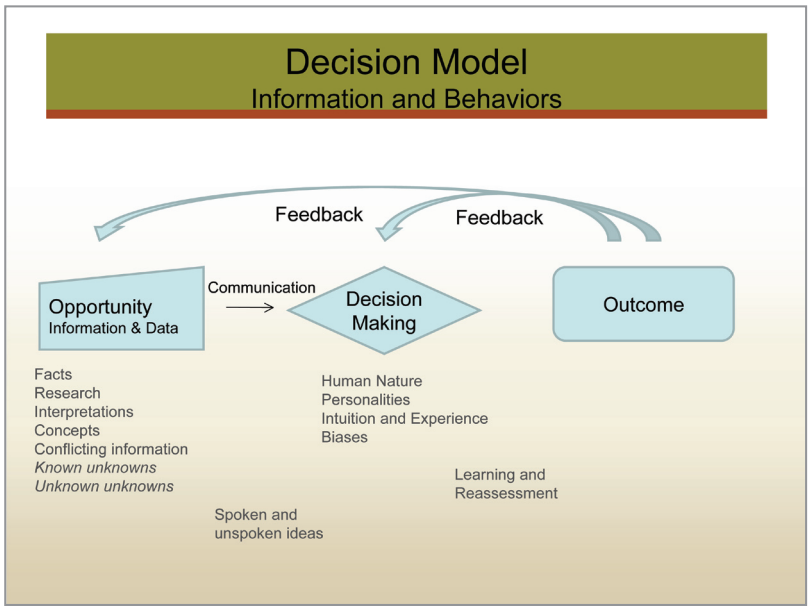
Although the communication of information is a key aspect of the decision-making process, it is important to recognise that decisions are driven as much by behaviour as by information. That is, the human nature, personality, biases, intuition and experience of the decider is an inescapable factor in any decision. When applied to BR assessment, it is, therefore, important to understand the decision-maker's process and perspective; this is often best accomplished through direct questioning of the decision-maker.



Other factors that influence a decision spring from the optimisation of the quality of the information and in the communication of that information. The issues and metrics of the decision must be defined in advance. Communications should be prepared that fully and honestly, reflect the science accurately, make the information readily assimilated by decision-makers, stimulate conversation about critical issues and lead to informed decisions.

It is imperative to be rigorous, transparent and trustworthy with decision-makers, customising communications to the situation without compromising the content and challenging assumptions by requesting that the decision-maker consider different perspectives and options.

Real dialogue can be facilitated by listening and leveraging the thoughts of others, soliciting dissenting opinion and ensuring that all voices are heard. Through the decision-making process, options should be developed to augment knowledge, address scientific and business issues, enhance the conversation with decision-makers and increase credibility of those presenting the information. When the discussion is focussed on critical issues, it will be easier to guide stakeholders towards an evolving decision.

Mr Howell concluded by affirming the ongoing efforts by industry and regulatory Agencies to develop common decision-making frameworks based on best practices, stating that good decision processes can lead to informed outcomes