

Measuring Benefit and Balancing Risk:

*Strategies for the benefit-risk assessment
of new medicines
in a risk-averse environment*

CMR International Institute for Regulatory Science
Workshop, 19-20 June 2008, Washington, D.C., USA

Workshop Report:

Overview and Outcome

(Section 3: Summary of Presentations included in pre-final draft)



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CMR INTERNATIONAL INSTITUTE FOR REGULATORY SCIENCE

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Workshop on Measuring Benefit and Balancing Risk

Strategies for the benefit-risk assessment of new medicines in a risk-averse environment

19-20 June 2008

Sofitel Lafayette Square

Washington, D.C.

Workshop Organisation

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WORKSHOP ON MEASURING BENEFIT AND BALANCING RISK: Strategies for the benefit-risk assessment of new medicines in a risk-averse environment

Section 1: Overview

Background to the Workshop

Measuring the benefits and risks of medicines is the underlying theme whenever the development, review and regulation of new medicines are discussed. The CMR International *Institute for Regulatory Science* first looked specifically at methodology for Benefit-Risk (BR) assessment and at the communication of risk at two Workshops in 2002 and the current Workshop revisited both these themes. In the intervening years, the Institute has initiated a specific study and held special focus workshops to look at multi-criteria decision analysis (MCDA) as one of the models that can be applied to BR assessment.

A primary objective of the current Workshop was to 'discuss whether a global framework for benefit-risk assessment is achievable and examine the opportunities and barriers that might be involved.'

Syndicate discussions

The *Syndicate groups* (breakout sessions) at this Workshop were asked to take the first steps towards defining a 'Framework for Benefit-Risk Assessment'. This would identify the essential elements that both regulators and companies should take into account throughout the development, review and post-marketing experience of new medicines in order to determine the BR balance. The Syndicates then went on to discuss three related aspects: How the *Framework* should be taken forward; The management of benefit and risk throughout the product lifecycle and; The communication of benefit and risk to stakeholders.

OUTCOME

A Framework for Benefit-Risk Assessment

The background to the Syndicate discussions was feedback from previous and current Institute surveys on the elements considered by companies and agencies when assessing benefit and risk. This took account of the recent reflection paper on BR assessment from the EMEA¹

A preliminary listing of the core elements for a BR framework has been drawn up on the basis of the Syndicate discussions and is divided into the safety, efficacy and BR balancing parameters that are needed routinely (or only on a case-by-case basis) for making an evaluation.

There was general agreement on the value of a universal BR framework that would help determine the research priorities for the development of new medicines and their review for marketing.

It was, however, recognised that a great deal of further work would be required to achieve a universal BR framework. An important starting point is the need to agree on a common *lexicon* to set the **terminology and definitions** for the Framework.

It was felt that the process for developing a BR framework would need to depart from the established pattern of acceptance by the ICH-affiliated regions and subsequent adoption elsewhere. Since all agencies are at a relatively early stage of developing BR strategies, agencies in '**emerging market**' countries should be included in the discussions, from the outset.

Taking the Benefit-Risk Framework Forward

Recommendations were made to the CMR International *Institute for Regulatory Science* proposing two studies that would help take the Framework Project forward:

A pilot project including case studies to test the Framework among different stakeholders (patients, physicians, companies and regulators)

A comparative study of current regulatory review templates relating to BR analysis, with a view to improving the consistency and value of the assessment.

It was also recommended that the Institute should include discussions of the BR framework when convening future Workshops with **health technology assessment** (HTA) experts.

Managing Benefit and Risk throughout the Product Lifecycle

It was agreed that the work programme for the CMR institute should include a future Workshop that looks at the way in which the Benefit-Risk framework could be applied at different stages in the lifecycle of a new medicine and integrated into its risk management plans.

Communicating Benefit and Risk to Stakeholders

It was similarly agreed that the Institute should convene a Workshop that would address the difficult issues that are constantly faced by both agencies and companies in trying to explain the methodology and outcomes of BR assessments for new medicines in era of transparency.

¹ Reflection Paper on Benefit-Risk Assessment Methods in the Context of the Evaluation of Marketing Authorisation Applications of Medicinal Products for Human Use, www.emea.europa.eu

WORKSHOP HIGHLIGHTS

Dr Theresa Mullin, *Associate Director for Planning and Business Informatics, CDER, FDA, USA* chaired the first Session of the Workshop that addressed the development of a benefit-risk framework for regulatory review of new medicines. Dr Mullin opened the meeting with an overview of FDA initiatives to establish a more formalised approach to benefit-risk analysis including a detailed review and testing of current methodology.

Dr Victor Raczowski, *US Vice President, Regulatory Affairs, Solvay Pharmaceuticals Inc, USA*, expressed his belief that agreed benefit-risk (BR) frameworks would improve the underlying science of drug development as well as improving the decision-making process, and creating a greater alignment and clearer communication among stakeholders. Agreed frameworks will enhance the quality, effectiveness, and efficiency by which patients have access to therapies with favourable BR profiles.

Dr Joyce Korvick, *Deputy Director, Division of Gastroenterology Products, FDA, USA*, gave an FDA perspective on the evolving approaches to BR assessments and the need to build a 'bridge' between efficacy and safety assessments, in terms of a BR framework that moves from the current qualitative approach to a more quantitative one. The goal is to improve transparency of decision-making throughout the lifecycle of medicines for the benefit of regulators, healthcare providers, and patients.

Prof Bruno Flamion, *Chair, Scientific Advice Working Party EMEA*, described the development of the CHMP Reflection paper on BR assessment¹ and the different models that had been reviewed. He discussed the way the conclusions will be taken forward by EMEA in a methodology project that aims to develop and test tools and processes for balancing multiple benefits and risks as an aid to informed regulatory decisions.

Dr Robyn Lim, *Scientific Advisor, Progressive Licensing Project, Health Canada*, described how improved BR assessment is one of the components being integrated into Health Canada's drug regulatory modernisation efforts and the Progressive Licensing Framework. She discussed the philosophy behind, and the regulatory tools for, taking assessments beyond 'safety, efficacy and quality' to encompass the benefit and risk equation.

Dr John Ferguson, *Vice President and Global Head, Pharmacovigilance and Medical Safety, Novartis, USA*, gave an industry viewpoint on the potential value of frameworks and models for evaluating benefits and risks in the decision-making processes for new medicines. He reported the outcome of a survey carried out predominantly among companies and looked, in particular, at the prerequisites of a structured benefit-risk framework. Dr Ferguson stressed the importance of capturing and evaluating patient preferences.

Dr Filip Mussen, *VP, Psychiatry and EU Psychiatry and EU Research & Early Development Regulatory Affairs, Regulatory Affairs, Johnson & Johnson PRD, Belgium*, gave an overview of the multi-criteria decision analysis (MCDA) approach to BR decisions for medicines. He emphasised the importance of assigning weightings to the different criteria and the possibilities for sensitivity analysis. The use of MCDA is particularly appropriate for complex and difficult BR evaluations.

Dr Robert O'Neill, *Director Office of Biostatistics, CDER, FDA, USA*, presented a perspective on quantitative BR assessment at FDA. He saw an asymmetry between the ability to evaluate efficacy from clinical trials ('the metrics of benefit') and the lack of similar data on safety ('the metrics of harm') at the pre-marketing stage. Dr O'Neill discussed approaches to analysing the massive volumes of safety data that are required but concluded that the asymmetry between efficacy and safety metrics must be addressed before a scientifically-based balance between benefit and risk can be made.

Prof Robert Peterson, *Clinical Professor of Paediatrics, University of British Columbia Faculty of Medicine, Canada*, chaired Session on the wider benefits of a developing a benefit-risk framework and the Syndicate discussions.

Dr Neil McAuslane, *Director, Institute for Regulatory Science, CMR International*, presented the results from the CMR survey on current practices and perceptions of companies and agencies in measuring benefit and balancing risk. The study and its outcome provided material for the Syndicate discussions.

Dr Janice Bush, *VP, Translational Pharmacovigilance BR Management, J&J Pharma R&D, USA*, reviewed the development of risk management plans (RMPs) by companies and discussed the ways in which a more structured BR framework could help inform these and shift the emphasis from the risks to benefits of a medicine throughout its life cycle.

Prof Hans-Georg Eichler, *Senior Medical Officer, EMEA* asked whether the public and patients are really becoming more 'risk averse' or whether the change results from a much greater 'risk awareness'. He suggested that the regulator's response to the latter must be to reassess communication strategies and discussed the goals and pitfalls of enhanced BR communication to stakeholders.

Dr John Lim, *Chief Executive Officer, Health Sciences Authority, Singapore*, gave a viewpoint from a relatively small agency but one that faces all the issues of its larger partners. He confirmed the value of international BR frameworks but these must maintain the flexibility to accommodate national and regional differences in risk thresholds, culture and values. Global partnership will be a key success factor in developing such frameworks.



**WORKSHOP ON MEASURING BENEFIT AND BALANCING RISK:
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Section 2: Outcome

Syndicate Discussions

Sessions 2 and 3 of the Workshop, during which the Syndicate discussions took place, were chaired by **Professor Robert Peterson**, *Clinical Professor of Paediatrics, University of British Columbia Faculty of Medicine, Canada*.

The Workshop participants formed three Syndicate groups. The Chairpersons and Rapporteurs were:

Syndicate 1	<i>Chair:</i> Prof Hans-Georg Eichler , <i>Senior Medical Officer, EMEA</i> <i>Rapporteur:</i> Dr Filip Mussen , <i>VP, Psychiatry and EU RED Regulatory Affairs, Johnson & Johnson PRD, Belgium</i>
Syndicate 2	<i>Chair:</i> Dr Mark Walderhaug , <i>Associate Office Director for Risk Assessment, CBER, FDA, USA</i> <i>Rapporteur:</i> Dr Paul Coplan , <i>Senior Director, Risk Management, Wyeth Research, USA</i>
Syndicate 3	<i>Chair:</i> Dr John Lim , <i>Chief Executive Officer, Health Sciences Authority, Singapore</i> <i>Rapporteur:</i> Dr Jeff Kirsch , <i>Director, Global Health Outcomes, GlaxoSmithKline, UK</i>

SUMMARY OF THE OUTCOME

The Syndicate discussions were held in two Sessions:

SYNDICATE SESSION 1: Essential Elements for a Benefit-Risk Framework

This was addressed by all three Syndicate Groups who agreed on the feasibility of establishing the basis for a universally applicable *Benefit-Risk framework* that would be of value to both regulatory agencies and companies. The first step towards this goal was established by reviewing and proposing a list of parameters to be included in the benefit-risk assessment of a new medicine (*Annex 1*) but more work is needed to develop this further. Specific recommendations included:

- Agreement on a common terminology or 'lexicon' to avoid ambiguity in discussions
- The need to include regulatory agencies from the 'emerging nations' early in the further development of the Framework.

SYNDICATE SESSION 2

The three groups were assigned to three different topics for this Session.

TAKING FORWARD the Benefit-Risk Framework

Recommendations were made to the CMR International Institute for Regulatory Science for two specific studies to be undertaken to take the Framework Project forward:

- A pilot project including case studies to test the Framework among different stakeholders (patients, physicians, companies and regulators)
- A comparative study of current regulatory review templates relating to BR analysis, with a view to improving the consistency and value of the assessment.

It was also recommended that the further development of the Framework should include considerations that might also be applicable to the Health Technology Assessment (HTA) of the product for reimbursement.

MANAGING BENEFIT and RISK throughout the Product Lifecycle

It was agreed that the work programme for the CMR International Institute should include a future Workshop that looks at the way in which the BR framework could be applied at different stages in the lifecycle of new medicine and integrated into risk management plans (RMPs).

Specific points to be included when designing the Workshop included:

- Ensuring that the patient perspective was taken into account in the discussions
- Examining the challenges of using electronic databases vs. other methods for obtaining follow-up information on the safety and use of approved products;
- Using case studies to illustrate benefit-risk profiling throughout a product's life cycle.

COMMUNICATING BENEFIT and RISK to Stakeholders

It was similarly agreed that the Institute should convene a Workshop that would address the difficult issues that are constantly faced by both agencies and companies in trying to explain to key stakeholder the methodology and outcomes of BR assessments that may affect the availability and use of new medicines.

Recommendations included:

- A survey to be carried out by the Institute among companies and regulatory agencies on current communication practices.
- Ensuring that issues were discussed with all relevant stakeholders: patients, physicians, pharmacists and the media.

Other items included methods to develop and assess **communication strategies** and the need for **general education** on the meaning of, and methodologies for, BR assessments

1. ESSENTIAL ELEMENTS FOR A BENEFIT-RISK FRAMEWORK

Background

Syndicate participants were presented with a draft schedule of parameters that could be taken into consideration in trying to formulate a *Benefit-Risk framework*, which would be applicable across different companies and different regulatory bodies. The Syndicates were asked to discuss these parameters and 'rank' them according to whether they are essential for all BR assessments, important on a case-by-case basis or of little relevance to the Framework. The outcome, which is discussed further below, is given in *Annex 1*.

CMR International Institute Survey

The draft parameters were based on the outcome of an Institute survey that was carried out in preparation for the workshop and the results of which were presented to the Workshop by **Dr Neil McAuslane**, *Director, Institute for Regulatory Science* and summarised in *Annex 2*.

The objective of the survey was to identify the current company or Agency approach to Benefit-Risk and to investigate current perceptions of the parameters that should be considered when looking at current practices and models for BR assessment.

The parameters included in the survey and in the Syndicate notes are the data points that might be covered in a BR assessment and are divided into *Safety*, *Efficacy* and those needed to determine the *Benefit-Risk Balance*. The list was derived from work carried out under the auspices of the Institute in 2002/2003 (see *Annex 2*), input from expert advisors to

the Institute, with additions from regulatory agency publications, especially the recent *Reflection Paper* on BR assessment, issued by the EMEA¹

1.2. Benefit-Risk Framework: Outcome

In order to collect and collate the views of the whole Workshop participation, the three Syndicate Groups were given the same list of parameters for a BR framework. The amalgamated results, taking account of ranking and priorities, are given in *Annex 1*.

Notes on the outcome

- The parameters presented in *Annex 1* remain in the order in which the Syndicates discussed the points and no attempt has yet been made to sort the items according to priority.
- It was acknowledged by Syndicate participants, that the priorities, rankings and weightings assigned within the limited time for discussion should be regarded as indicative rather than definitive, at this stage.

1.3 Benefit-Risk Framework: Recommendations and Observations

A universal framework

There was agreement that it was feasible to define a common foundation for BR assessment that would be applicable across different company and agency platforms and different geographical regions. The work carried out at this meeting should be regarded as a first step that would require further study and refinement.

A common framework of the elements to be considered routinely would benefit both regulators and sponsors. Companies would be able to design their R&D programmes to ensure that the relevant data items are covered in the regulatory dossier.

The target for the BR assessment needs to be clear. The 'default' primary audience is the labeled population for the medicine but there will be cases where public health issues need to be taken into account, i.e., the assessment should extend beyond the patient level to the population level. Also, the BR assessment might differ if looked at from the patient/physician perspective (as the ultimate users) rather than a regulatory perspective based on efficacy and primary endpoints (see also 1.4 below).

A quantitative BR model was seen as the ultimate goal in that it would force discipline and accountability and would assist communication of risk. Practical problems in achieving this were, however recognised especially in terms of agreeing on the basis for **weighting** the relative importance of different criteria, in the context of a product's use.

It was agreed that the quantitative metrics that might derive from a standardised BR framework is **not a substitute for decision-making**. The outcome such a framework would help **inform** the assessment as judgement aid.

A common terminology

It was apparent from the Syndicate discussions that different interpretations were being placed on different terms used to discuss benefit-risk even at the level of defining a 'BR framework' vs. a 'BR model'.

It was recommended that work to take the Framework forward should start with the development of a **lexicon** to ensure common, defined use of terms.

¹ Reflection Paper on Benefit-Risk Assessment Methods in the Context of the Evaluation of Marketing Authorisation Applications of Medicinal Products for Human Use, Reference: EMEA/CHMP/15404/2007, London, 19 March 2008, available via www.emea.europa.eu

Accommodating changes in the benefit-risk balance

A universal framework for BR assessment must not focus only on the data that is applicable at the pre-approval and post-launch stages. BR assessment must be seen as a **continuum** that needs to be revisited throughout the product life-cycle, taking account of post-marketing surveillance and epidemiological data.

Surrogate endpoints should be confirmed in the post-marketing phase and will have an impact on the BR assessment.

The therapeutic environment will change and it may be necessary to re-evaluate the benefits and risks between products including older, well-established products that may need to be re-assessed in the light of therapeutic advances.

A global approach

The adoption of a universal BR framework should not follow the 'traditional' pattern of development and acceptance by the established agencies (ICH regions, Canada, Australia) before being discussed with agencies in other regions.

It was recommended that agencies representing the 'emerging' nations in the field of drug regulation should be included, from the start, in formal moves towards the development of a basic framework for BR assessment.

Once further development work has been carried out by the Institute the question will need to be addressed of a mechanism to drive the development of a BR framework. Suggestions included the International Institute of Medicines (IOM) and ICH but, as noted, the 'classic' ICH approach was considered too restrictive and may also be too lengthy.

It was proposed that a less formal collaboration of regulators, industry, academic experts and patient representatives might be formed to take the topic forward.

1.4 Other points from the Syndicate discussions

The preliminary listing of BR parameters given in *Annex 1* includes brief notes on the discussions, including priorities. The following summarises some of the specific discussion points that arose from the Syndicate discussions.

Benefit-Risk ratio: It was agreed that this terminology, as 'traditionally' applied to BR evaluations, should be avoided as it implies that a definitive metric can be calculated for comparing benefit and risk. The terms *Benefit Risk Balance* or 'Profile' were preferred.

Value of secondary endpoints: There was discussion of whether secondary endpoints should be a factor in BR assessment. The regulatory review normally focuses on the primary use of the product in the target labeling, but it was pointed out that secondary outcomes, especially where these have quality-of-life benefits, might have much greater weight if the BR assessment is made from the patient perspective. It was felt that **both secondary endpoints and non-pivotal trials** should be accommodated within in the Framework.

Patient compliance: The item in the BR framework relating to 'patient compliance' requires further discussion and clarification. It was apparent that this could be (and was) interpreted in different ways: as a measure of patients 'lost to follow up' as they fail to complete the trials or as a projected measure of whether patients will take the medicine, once authorised, in accordance with the labelled instructions.

Best practices: Although the Syndicates were asked to comment on establishing 'best practice' this was felt to be premature, since actual practice of BR assessments is at a relatively early stage. In addition to the 'building blocks' of the Framework (data definitions, ranges of 'acceptability', *a priori* specifications etc) consideration might be given to drawing up 'Guiding principles'.

Work in progress: The outcome of this Workshop should be seen as an important 'first step' towards developing an internationally acceptable BR framework, but further development must take account of other initiatives, such as those being taken by FDA and the CHMP/EMA in order to avoid duplication and redundancy of effort.

2 TAKING FORWARD THE BENEFIT-RISK FRAMEWORK

This was considered as part of the Second Syndicate Session when three specific recommendations for follow-up action were made:

2.1 Pilot Project and Case Study

It was recommended that the CMR International Institute should undertake further development of the Framework by setting up a *Pilot Project* that would test the model using one or more case studies

Special focus Workshops: The framework could be tested at one or more study sessions using the interactive format that the Institute used successfully when helping to evaluate the multi-criteria decision analysis (MCDA) model in 2004/2006:

- **Weightings:** The workshops would look, in particular, at the way in which weightings should be applied to the parameters within the Framework;
- **Case study:** The same or a similar 'dummy' product could be used from the earlier workshops to test the Framework. This product has some basis in fact, but has been 'anonymised' and the data changed to avoid identification with an actual case.

Stakeholders: A wider range of stakeholders should be involved than on the previous occasions and these should carry out the same exercise in parallel to compare, in particular, the weightings assigned to different assessment parameters. Two groups were envisaged:

- **Patients and physicians**
- **Regulators and industry**

The media: There was discussion of ways in which journalists could be involved in order to see the values that the media place on different BR parameters. It was felt, however, that this should be deferred to a later stage.

End of Phase 2: There was discussion of extending the pilot project to see whether the Framework was applicable to the decision-making process at the end-of-phase 2 or proof of concept stage. The objective would be to define the boundaries of acceptable safety and help inform the patient exposure required in Phase 3.

It was noted that, whilst standards are set for demonstrating efficacy, there are no parallel guidelines for determining acceptable safety, in relation to efficacy. It might be possible, for a given effect size, to specify the acceptable risk level and hence calculate a realistic trial size. Patients would accept a higher possibility of risk for a product with major symptomatic or therapeutic benefits, when the condition is serious and/or debilitating.

2.2 Enhancement of Regulatory Review Templates

It was recommended that the CMR International Institute should carry out a comparative study of current regulatory review templates with a view to improving the consistency and value of benefit-risk analyses

The objectives of the study would be to:

- Compare the review templates currently being used by regulatory agencies and evaluate whether an overarching BR framework could enhance criteria for BR review, within the template;
- Increase the awareness of reviewers of the current discussions on BR models for evaluating value and risk;
- Encourage the application of a more consistent framework for BR review among different agencies.

Methodology:

The proposed methodology is to work initially with the smaller agencies (e.g., Swissmedic, Therapeutic Goods Administration (TGA), Singapore's Health Sciences Authority (HSA), and Health Canada) rather than EMEA and FDA.

- The agencies would be asked to share their review templates, which would be compared with the overarching features of the general BR framework;
- When the outcome of the study is shared, FDA and EMEA would be included in the review of the outcome;
- Agencies in the 'emerging markets' would also be involved and kept informed of the study.

2.3 Incorporation of Health Technology Assessment (HTA) values

It was recommended that the CMR International Institute work with HTA agencies should be extended to include discussions incorporating HTA values into a BR framework

It was noted that the CMR International Institute has held one Workshop on *Regulation and Reimbursement*² and a further meeting is planned in 2009. It was also noted that a recent Institute Workshop had recommended that the Institute should develop a white paper to address the implications of an increased alignment between regulatory and HTA processes³.

- Future Workshops should look at the similarities and differences in the way HTA and regulatory agencies address benefit-risk assessments for new products with a view to narrowing the gap and improving uniformity;
- The white paper should include the topic of BR assessment for regulatory and reimbursement purposes.

3. APPLYING AND COMMUNICATING BENEFIT-RISK ASSESSMENTS

The Syndicates in the Second Session were asked to look at applying BR assessments throughout the life cycle of a product and at ways to communicate essential information on BR assessment methodology and outcomes. In addition to general observations and recommendations, the groups were asked to advise on the elements that might be included in future Institute Workshops on these topics.

3.1 Managing Benefit and Risk throughout the Product Lifecycle

The BR framework was seen as a positive advance for tracking the evolution of benefit and risk information throughout the lifecycle of a product.

It was recommended that the concept of managing the BR profile up to and beyond product approval should be incorporated in a future CMR International Institute workshop with the focus on **integrating benefit-risk assessment into risk management plans**

The Workshop should be structured to ensure that the **patient perspective** is included.

There was discussion of whether the Workshop should focus specifically on continuing BR assessments into the post-approval phase, but it was felt that the programme should preferably try to cover the way the BR profile impacts **all stages of development**. A diagrammatic representation of the ways in which BR considerations are embedded in the different stages of development is given in *Figure 1*.

² Workshop on Regulation and Reimbursement: *Two sides of the same coin?*, January 2007, Woodlands Park, Surrey, UK. Report available from institute@cmr.org

³ Recommendation from the Workshop on Knowledge Sharing and Communication, April 2007, Nutfield Priory, Surrey, UK. Report available from institute@cmr.org

It was noted that the correct application of BR analyses at the critical decision stages (e.g., discovery to development and End of Phase 2) could inform the scale and direction of the subsequent development programme in a way that would soon justify the additional investment (time and additional statistical/epidemiological resources).

Figure 1

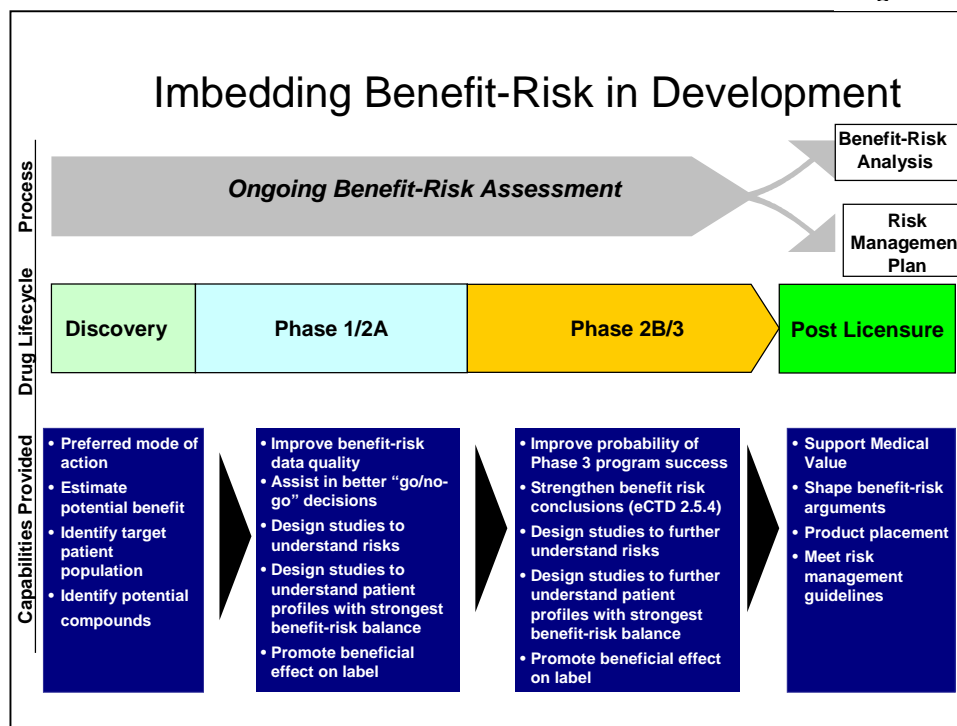


Chart provided by Dr Paul Coplan

3.1.1 Points from the discussion

The following points from the Syndicate discussions could be incorporated in the topics to be addressed at an Institute Workshop:

Background and 'scene-setting' issues

Presentation of benefit-risk arguments: The way in which companies present comparative efficacy and safety data in submission dossiers is often deficient. *Would the BR framework improve this?*

Risks are not well identified in randomised clinical trials: *Could trial design be improved through early BR analysis?*

Benefits are often overlooked in the post-approval phase when the emphasis is on risk detection. *Would the balance be redressed by on-going BR evaluations?*

The 'geography' of risk detection has changed over the last ten years. Although new medicines are often filed almost simultaneously in the EU and US there is a 'reimbursement lag' before marketing in Europe with the result that post-approval detection of novel safety issues now occurs earlier in the US. *How does this impact the ongoing BR assessment?*

The addition of new indications later in the lifecycle provides an opportunity for extending the BR profile to a new patient population. *Can the BR framework accommodate such changes?*

Challenges in assessing benefit and risks in the post-approval phase

Data from electronic databases of patient records are advocated as a means of tracking usage and adverse events for marketed products but the quality varies considerably between medical record databases, insurance claims databases, and registries of patients and prescriptions.

There are also issues of confidentiality and a lack of information on 'channelling bias' i.e., the criteria that influence the selection of particular treatments for (or by) different patients.

Spontaneous reporting of adverse events is notoriously incomplete and reporting rates change with time over the product's lifecycle, with a drop-off in reporting rates after 10 years.

Head-to-head trials may be advocated as the 'gold standard' for obtaining comparative post-marketing data but these are extremely expensive and often very lengthy.

Meta-analyses often use non-adjudicated endpoints, which confound results (e.g., Avandia and myocardial infarcts).

The 'hierarchy' of data quality needs to be taken into account and integrated into a BR assessment: Data from spontaneous reporting and epidemiological studies have less credibility than the results of randomised clinical trials, but need to be addressed, especially during the post-approval period.

Patient and physician preferences are not currently captured other than through *ad hoc* assessments by patient representatives at expert committees or through small panels of expert physicians. A mechanism is needed for a more systematic collection of data on preferences and perceived problems and therapeutic benefits.

Options for taking post-approval BR assessment forward

The Workshop programme might include a discussion of:

Good Practices: The development of standardised procedures or *Good analysis Practices* for post-approval BR assessment;

Off-label usage: A separate analysis might be carried out for the benefits and risks associated with off-label use;

Comparison with older drugs whose safety profile may not be well characterized may require new data generation on the comparator in the post-approval situation;

Concomitant medication might need to be included as a variable in the BR profile and methods for dealing with this will need to be developed;

New biological entities (NBEs) typically require longer-term follow-up than other products and may be dependent on data from registries.

- It was noted that, for vaccines, the **Vaccine Safety Datalink** has been an excellent database for assessing benefits and risks in disease reduction through immunisation. There is currently no similar resource for drugs but FDA's *Sentinel Initiative* (on medical product safety) and the *European Network of Epidemiology* are working in similar areas.

Possible case studies

The workshop could look at specific cases where there have been discrepant decisions on marketing approval by, for example, FDA and EMEA and/or cases where other, smaller agencies have reached different conclusions from the lead agencies.

- **Tysabri** (natalizumab) was proposed as an example: The product is authorised for multiple sclerosis by FDA and EMEA but an extension to Crohn's disease was accepted by FDA but refused by the CHMP.

3.2. Communicating Benefit and Risk to Stakeholders

This was recognised as a complex and multi-layered issue that could be approached from many angles according to the perceived purpose of communication, that is, whether it is an **educational** exercise to inform patients, physicians and the public of the way in which BR decisions are made or a **product specific** exercise to provide information on a particular medicine, including crisis management when potential problems arise.

It was recommended that the CMR International Institute should convene a Workshop that would take forward discussions on ways to both educate and inform key stakeholders on the assessment of the benefits and risks of medicines with particular reference to the development of the Benefit-Risk framework,

Preparatory work

It would be necessary to set a **Research Agenda** to assemble information on the current situation in preparation for the Workshop. A literature review that went beyond communication on healthcare issues and included a broader review of social science would be useful. An objective of this review would be to gain a better understanding of perceptions of benefit and risk by different stakeholders.

In addition, a specific study by the Institute was proposed:

It was recommended that the CMR International Institute should conduct a survey of the current communication practices that are in place, or have been used by companies and regulatory agencies for educational purposes or to communicate product-specific issues.

Such a study would be useful in identifying, for example, whether there are communication practices that are targeted differently to different patient groups and/or stakeholders. Additionally, the value of patient information leaflets could be assessed.

Gap analysis

The study could incorporate a *gap analysis* between patients' needs for benefit-risk information and the approach being taken by industry and authorities. This would, however, require sources of information on perceived patients'/carers' feedback on timing, format and content of such information.

Stakeholders

The Workshop would need to include participants (speakers and/or observers) representing stakeholders other than industry and agencies: patients, physicians, pharmacists and the media.

Discussions involving these stakeholders could include:

- **The effectiveness** of communication strategies and different forms of communication practices;
- **Identification of target audiences** (e.g. sufferers from chronic diseases vs. acute illness, experienced patient groups vs. newcomers);
- **Support for physicians and pharmacists** in their communication with their patients to ensure consistency in the messages given;
- **Case studies** that illustrate the way sensitive issues have been addressed, including those where there have been conflicting views between regulators and sponsors.

3.2.1 Points from the discussion

The following points from the Syndicate discussions could be incorporated in the topics to be addressed at an Institute Workshop on communication:

Product-specific information

Regulatory decisions and conditions: The role and usefulness of current information from regulatory agencies, e.g., the EU 'triumvirate' of EPAR, Product information (label) and Patient Information leaflet (PIL).

Crisis communications: The effectiveness of different approaches when urgent issues arise and the need to look beyond the 'reactive' response to possibilities for proactive communication strategies.

Patient compliance: The role of communication in improving the way in which patients take medicines and adhere to instructions should be covered. It should also be remembered that with increased patient empowerment individuals can influence the **choice of medicines**. Input might also be sought from the Medicines Use Review (MUR) among pharmacists in the UK.

Communications Strategy

Strategies adopted by agencies and pharmaceutical companies might include the establishment of communications divisions, procedures for press briefings and cooperation with patient support groups.

Internal communication: It is equally important to ensure good communications within companies/agencies to ensure a consistent and credible approach.

Educational role: Communications can have an educational role in preparing stakeholders to receive and understand BR messages in addition to making them receptive to product-specific information.

Handling the media: Strategies for countering the 'negative' messages and images about medicines often portrayed in the press.

Measuring effectiveness: Determining whether agencies and companies are taking steps to measure the impact of communication strategies or carrying out benchmarking exercises.

Mechanisms for communication

The workshop should invite experts to review the effectiveness of different types of communication practices and discuss ways that these could be improved. Topics could include:

- The role and best use of websites and podcasts and other electronic media;
- Improved patient information: How to communicate changes and make these 'living documents';
- The role of effective communication through 'dear doctor' letters in an electronic age;
- How to ensure consistency and measure the impact of communications;

3.2.2 The Proposed Benefit-Risk Framework

This should be pivotal to the programme for, and discussions at, the proposed Workshop.

The Workshop would provide an opportunity to explain the work on developing the Framework and its purpose. The role of the Framework in encouraging transparency and balanced direct-to-consumer communications should be discussed together with the roles of regulators, industry, physicians, other health professionals and patients in taking forward the work of education and communication on benefit-risk issues.

Annex 1

CONSTRUCTING A BENEFIT-RISK FRAMEWORK

Preliminary results from the Syndicate discussions

Notes:

The three Syndicate groups were asked to review and comment on the same draft list of parameters for assessing benefit and risk. Time did not allow the preliminary views from the Syndicates to be consolidated and confirmed in plenary session.

The results given below, therefore, indicate where there was clear consensus that an item should be considered '**high priority**'. Where opinions were divided, but the item was accepted for routine inclusion in the Framework, it is designated as '**important**'. Some parameters were felt by all (or a majority) of groups to be relevant only on a **case-by-case** basis and not as a routine requirement.

Safety parameters

Parameter	Notes
Overall incidence of serious adverse effects	High priority for inclusion
Discontinuation rate due to adverse effects	High priority for inclusion but discontinuation due to other parameters, e.g., lack of efficacy also needs to be taken into account
Incidence, seriousness and duration of specific adverse effects, also characterised according to reversibility, latency, preventability and manageability. AEs recorded from trials and marketed use, under labelled conditions.	High priority for inclusion
Extrapolation of the safety profile to the target population for the labelled indication (e.g., long-term safety, potential for rare adverse effects and steepness of the dose-response curve)	High priority for inclusion The size of the safety population, potential risks and long-term safety for chronic use products are important to consider
Adverse effects of the pharmacological class and of other classes for this indication	High priority for inclusion
Safety in subgroups , e.g., age, race, sex, polymorphic metabolism, patients with renal insufficiency, patients with hepatic insufficiency	Important for inclusion even if data is only available on a case-by-case basis.
Issues raised by nonclinical data	Important for inclusion but with the caveat that animal model findings may not be predictive or relevant.
Overall incidence of adverse effects (broken down into categories)	Not a high priority for all products but appropriate on a case-by-case basis. Less important than serious and specific adverse events.
Demonstrated interactions with other drugs and with food	Not a high priority for all products but appropriate on a case-by-case basis in the context of the significance of the interaction for the target patient population.
Potential safety risks with off-label use (including overdose)	Not a high priority for all products but appropriate on a case-by-case basis when there is a specific likelihood of off-label use. This may be a life cycle rather than a registration issue.
Safety elements that can be prevented by specific measures e.g., screening, risk evaluation and mitigation strategies (REMS), vaccination, pregnancy testing etc.	Addition to the original list (opinion of one Syndicate group). Appropriate on a case-by-case basis
Transmission of AEs to close contacts in the case of vaccines and immunologicals	Addition to the original list (opinion of one Syndicate group). Appropriate on a case-by-case basis

Efficacy parameters

Note: One group felt that, when taking the Framework forward, the efficacy parameters should be arranged in parallel with the safety parameters such that they characterise the specific benefits of the product in relation to incidence, clinical relevance and duration of the condition being treated.

Parameter	Notes
Magnitude of the treatment effect as obtained from the results of the (primary) endpoint(s) of the pivotal clinical trials	High priority for inclusion
Clinical relevance of the magnitude of the treatment effect	High priority for inclusion (but it should relate to the threshold effect).
Statistical significance (p-values, confidence intervals) for the treatment effect	High priority for inclusion (<i>Exceptions:</i> No p-values for adaptive trials with Bayesian stats or bioterrorism products).
Relevance of the (primary) endpoint(s) of the pivotal clinical trials	High priority for inclusion
Relevance of the studied population of the pivotal clinical trials	High priority for inclusion
Discussions on dose (e.g., dose-response, minimally effective dose, etc.)	High priority for inclusion
Methodology issues beyond statistical p values, e.g., multiplicity issues and post-hoc analyses	Essential for inclusion but opinions were divided on whether it should be included on parameters on trial design and not as a separate point
Statistical/design robustness of the pivotal clinical trials (e.g., absence of bias, results replicated in second trial)	Important for inclusion but may perhaps be incorporated in an uncertainty measure
Discussions on the comparator	Important for inclusion but must be distinct from the parameter on trial design (above)
Validation of scales and outcome measures	Important for inclusion but opinions were divided on whether this should be a separate item or included in other parameters (e.g. patient outcomes). Validation of biomarkers is important.
Evidence for the efficacy in relevant subgroups in the pivotal clinical trials according to baseline characteristics	Not a high priority for all products but appropriate on a case-by-case basis
Confirmation of treatment effect by results of secondary endpoints and the results of non-pivotal trials	Not a high priority for all products but appropriate on a case-by-case basis, especially where the secondary endpoint gives a major patient benefit (see report section 1.4). One group suggested that this parameter should be split (secondary endpoints and non-pivotal results).
Patient reported outcomes whenever available	Not a high priority at registration but would have a role in life-cycle BR assessment.
Anticipated compliance of patients	Opinions were divided on the importance of this item, possibly due to different interpretations of 'compliance' (adherence to the trial protocol or adherence to the approved labeling -see report item 1.4).
Patient convenience of dosage form	Addition to the original list: appropriate on a case-by-case basis
Special conditions of use (pandemic, terrorist attack)	Addition to the original list: (opinion of one Syndicate group) Appropriate on a case-by-case basis
Maintenance of effect for some diseases e.g., schizophrenia, depression	Addition to the original list: (opinion of one Syndicate group) Appropriate on a case-by-case basis

Constructing Benefit Risk Balance

Parameter	Notes
Description of the alternative therapies or interventions (where relevant), i.e., clear description of the medical need	High priority for inclusion
Calculation of the uncertainties on benefit and risk , i.e., the amount and precision of available data	High priority for inclusion
Direct comparison (within product) of the absolute gains (efficacy) vs. harms (safety) in terms of lives saved or lost, or in terms of specific clinical events;	High priority for inclusion.
Evaluation of the level of risk that would be acceptable with regards to the level of clinical benefit in the specific context	High priority for inclusion Must take account of existing products and also whether an acceptable level of risk relates to a patient or a regulatory perspective
Evolution of the BR balance over time and its sensitivity to various assumptions. To be assessed: - As observations increase - As the prescribed population changes - As the environment changes	High priority for inclusion
Evaluation of a BR balance in each major patient subpopulation, including pharmacogenomic subgroups	Not a high priority for all products but appropriate on a case-by-case basis (although there was split view on this). Studies may not be powered to achieve this evaluation at registration but it might be applicable in lifecycle management.
Identification of any outstanding issues and potential post-marketing commitments in this regard	Not a priority. Not necessary if potential risks are in the model. Should be an offshoot of earlier parameters.
Consideration of the different regulatory options for approval (e.g., standard marketing authorisation, conditional/priority marketing authorisation).	Not a priority. This relates more to the outcome of the model.
Model should include <i>a priori</i> weightings of benefits and risks that evolve over time	Addition to the original list (opinion of one Syndicate group)

Annex 2

Institute Study on the Current Status of Benefit-Risk Assessment among Companies and Agencies

Dr Neil McAuslane, *Director of the Institute for Regulatory Science*
CMR International

In preparation for this Workshop on *Measuring Benefit and Balancing Risk*, and particularly as preparation for the Syndicate discussions on a 'Framework' for benefit-risk assessment, a brief survey was carried out among pharmaceutical companies and regulatory agencies. The objectives were:

- To identify companies' and agencies' current approaches to benefit-risk (BR) assessment and investigate current perceptions of the models/frameworks available or being developed;
- To identify the parameters that need to be included in a framework for measuring BR in order to make the Framework fit for purpose.

Methodology

The survey questionnaire was sent to the 23 member companies of the Institute and to 13 regulatory agencies: EMEA and 6 EU national agencies; US FDA (CDER and CBER); Health Canada; TGA, Australia; Swissmedic, Switzerland; and HSA, Singapore). The Workshop received a summary of the responses from 9 companies (all represented at the meeting) and 10 agencies (8 attending the meeting).

The topics covered in the questionnaire included:

- Types and timing of the BR assessment currently used by the agency/company;
- Parameters taken into account to assess BR;
- Perception of the need for an appropriate BR framework;
- Views on the value of published models/frameworks for BR assessment;
- The major hurdles and possible solutions when looking at a possible BR framework.

Summary of the outcome

Quantitative and qualitative methods

Asked whether their system for BR assessment system for pre-submission was quantitative vs. qualitative, the response to the pre-set statements was as shown:

<i>Statement</i>	<i>Companies</i>	<i>Agencies</i>
Qualitative: Our internal system is a purely qualitative system based on internal experts or management making a "gut decision" on the BR profile of each product	4/9	6/10 ^a
Semi-quantitative: Our internal system is semi quantitative in that it has a structured (written) framework or standard operating procedure for data collection and analysis but also incorporates expert judgment into the final decision	4/9	4/10 ^a
Quantitative: Our internal system is a fully quantitative model, which gives a BR ratio for a new medicine. Experts and management simply oversee and approve the results	1/9 ^b	0/10

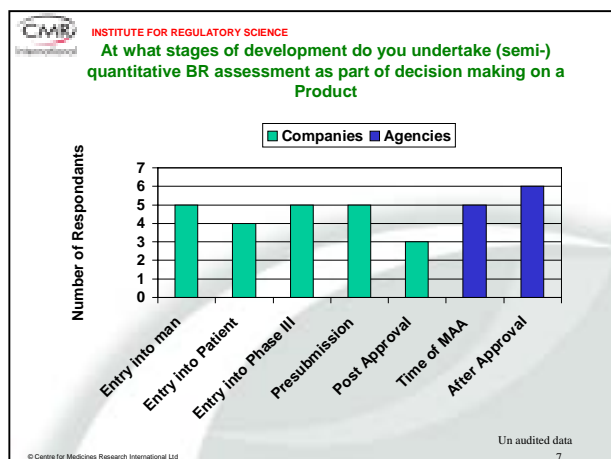
^a One agency answered positively for both qualitative and semi-quantitative.

^b The company indicating that its assessment was fully quantitative puts a value on each of the benefit and risk parameters and these are weighted.

Stage of BR Assessment

Respondents were asked about the stage at which they use a BR assessment as part of the decision-making process and the responses are shown in *Figure 1*

Figure 1



The results indicated that companies are using BR assessments throughout the pre-submission development stage but, as might be expected, only 3/5 reported that they used the same assessment system at all stages.

Agencies reported using BR assessment both before and after approval and 3/6 use the same system at both stages.

A simple question asked whether a 'model' was used for BR assessment. Five of the 9 companies and 4 of the 10 agencies reported that they used a model.

Parameters for assessing Benefit-Risk

The questionnaire included a list of safety and efficacy parameters that might be used to evaluate benefit and risk and a list of parameters relevant to assessing the BR ratio or balance when making the assessment. Companies and agencies were not only asked which they used for their own procedures but also to give a view on whether they should be included in a formal BR framework with wider applicability.

The parameters identified for a formal BR framework were carried forward to the Syndicate discussions that are itemised in **Annex 1** (10 Safety parameters, 14 Efficacy parameters and 8 parameters for a BR balance).

Other parameters that were reported as being used in current systems are shown in *Table 1*

Table 1: Additional BR parameters reported on questionnaires

Safety	Efficacy
Adverse effects of other therapies for the indication	Validation of outcome measure
Manageability/practicality of options	Minimally effective dose
Dose-response effects	Comparison with other therapies
AE impact on disease context	Standard of care
Possible linkage between AE	Relevance to domestic population (local practice issues & disease epidemiology)
Anticipated population AEs	Long-term effect
Relevance to domestic population	Waning of effect
Dependence	Availability of alternatives
Reversibility	Relative efficacy
Transmission of AE to close contacts (live vaccine virus)	Dosing duration needed
Relative safety with other products with same indication	Advantages with dosage forms
Vulnerability of the population (infants vs. adults)	Population benefiting
Preventability of AE	Conditions of use (pandemic, terrorist attack)
Risk period (risk only when being administered or does risk persist beyond administration)	* Convenience factor (e.g. storage, acquisition, monitoring etc)
* Safety profile compared to Standard Treatment and medical need	* Importance of considering lowest effective dose
* Robustness of safety results	Benefit-Risk balance
* Laboratory data (particularly liver, renal and muscle enzymes)	Risk management programs beneficial
	* Seriousness of the medical condition
	* Availability of other proven therapies (or lack thereof)

* Company responses

Note: The parameters in the questionnaire (carried forward to the Syndicate discussions) were based on work carried out in 2002/2003 by the (then) Institute Fellow Filip Mussen as part of his PhD thesis and in preparation for the first Institute Workshop on Risk Management (April 2003). In addition, items were included, at the suggestion of Professor Bruno Flamion, from the EMEA *Reflection Paper* on BR Assessment¹.

The Need for a Benefit-Risk Framework

The questionnaire included 15 statements relating to the need for, and usefulness of, developing a formal BR framework that might have a wider use outside individual companies and agencies. Respondents were asked to rate the statements from 'Strongly agree' to 'Strongly disagree'. The results, showing the percentage of agencies and companies that responded 'strongly agree' or 'agree' are summarised in Table 2.

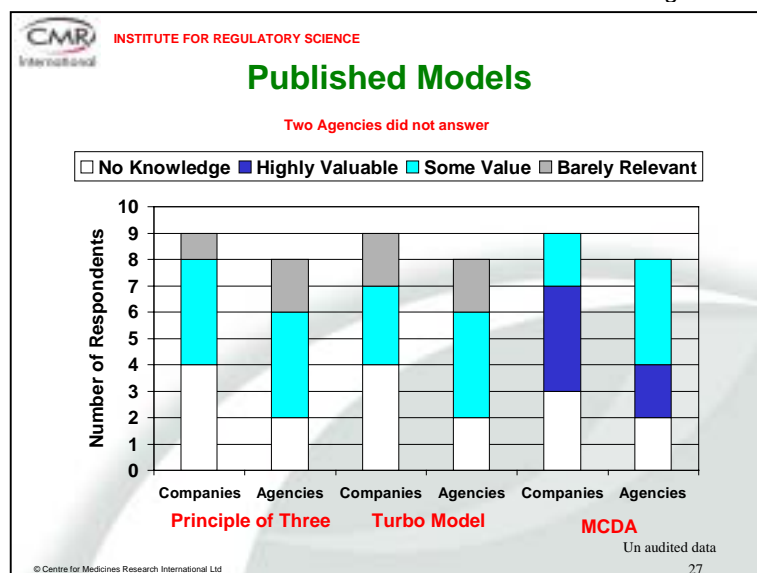
Table 2: the need for a BR framework			
Statement	A %	Diff	C %
Key: A=Agency: C=Company: Diff=A%-C%			
The purpose of establishing an appropriate BR framework is to improve:			
A) The consistency of decision making	100	0	100
B) The transparency of decision making	100	0	100
C) Communication of the decision	100	0	100
There is a need for a BR framework to be developed that can be used by both agencies and companies	90	10	100
It is important that any BR framework, if developed for registration purposes, is utilized across regulatory divisions within an agency and across agencies worldwide	89	22	67
This BR framework should also be applicable to health technology assessment groups	75	-14	89
An appropriate BR framework for registration should also enable assessment of risk management plans.	70	-19	89
It is important that all stakeholders (agencies, companies, doctors and patients) are part of the development and validation of an appropriate BR framework	70	-19	89
For the registration of new medicinal products it will be possible to develop an overarching BR framework	67	-33	100
An appropriate BR framework for registration should also apply to all stages of drug development from cradle to grave	60	-7	67
Our company/agency preference would be a quantitative approach to BR assessment rather than a purely qualitative approach	56	-7	63
For the registration of new medicinal products it will be necessary to develop therapeutic area specific BR frameworks	50	-17	67
The best framework for BR assessment would be a decision tree approach	25	-38	63
The purpose of an appropriate BR framework is to define a number that translates the BR ratio in absolute terms and can be used to measure its sensitivity to various parameters	22	-16	38

¹ Reflection Paper on Benefit-Risk Assessment Methods in the Context of the Evaluation of Marketing Authorisation Applications of Medicinal Products for Human Use, www.emea.europa.eu

Use of Published Models

The questionnaire identified three specific, established models for assessing benefits and risk: The *Principle of Three*, The *Turbo Model* and *Multi Criteria Decision Analysis* (MCDA). Respondents were asked for their knowledge and opinion of these rated from *Highly Valuable* to *Barely Relevant*. Respondents also indicated where they had no knowledge of the system. The results are shown in *Figure 2*.

Figure 2



As shown, only the MCDA model scored as a 'highly valuable' model among both companies and agencies.

Three agencies and 4 companies referred to other published frameworks or models currently available. These included: Benefit-risk profiling; Patient preferences; Quality of life (QALY); Incremental net benefit and; Number needed to treat/number needed to harm (NNT/NNH). Reference was also made to the EMEA/CHMP Reflection paper mentioned above.

Barriers and Solutions

The survey asked participants to give views on the barriers to achieving a BR framework that could have 'universal' application and possible solutions to overcome these hurdles. Responses generally fell into three categories:

- Issues relating to stakeholders, particularly patients
- Quantifying benefit and risk
- Models and acceptance

Highlights from the responses were presented to the Workshop but these were also provided to the Syndicates as verbatim listings, which are reproduced as the *Attachment* to this report.

And finally ...

The survey asked both agencies and companies the question; *If a validated framework was developed, would you be interested in using it?*

Dr McAuslane was pleased to report that the respondents from both companies and agencies had unanimously replied that they would.

Survey Attachment 1

Barriers and Solutions to achieving a Benefit-Risk Framework

The CMR survey included a question: *‘What are the top three major hurdles today for achieving an appropriate Benefit Risk framework? What is your opinion on how these can be overcome?’*

The following is a (verbatim) compilation of the responses received from companies and regulators

Major hurdles	Possible Solutions
Issues relating to Stakeholders, particularly the Patient	
Patients differ in how they value specific benefits and value specific risks	Allow for flexibility in pharmaceutical development plans and in regulatory decision making to avoid a “one size fits all” approach.
Patients differ in how they perceive specific benefits and perceive specific risks.	Allow for flexibility in pharmaceutical development plans and in regulatory decision making to avoid a “one size fits all” approach.
Communicating and defining value judgements and risks	More education of patients and patient groups
Communication tools to explain to researchers, regulators, prescribers and patients how a benefit-risk assessment is done and how to interpret it	Multi-stakeholder working groups to develop appropriate, state-of-the-art tools
In the context of achieving an appropriate Benefit Risk framework that is universally usable by all stakeholders, one of the major difficulties would be the inherent differences in the systems and risks among the stakeholders; unless the Framework is otherwise sufficiently generic such that it can be adopted and developed further according to the needs of the individual agency/company.	
Quantifying benefit and risk	
Benefits and risks are measured in clinical studies in ways than are difficult to compare directly (i.e., ‘apples and pears’)	When applicable and feasible, measure benefits and risks with measures that can be compared with one another
How to quantify risks and benefits on some common scale. What that common scale should be is controversial.	Assessments need to be made consistently. One would want to know if the decision is sensitive to the choice of scale (e.g., NNT versus NNH; QALYs, etc.). The point is that the relative values are important when making therapeutic choices, even if the absolute values are not easily interpretable.
Uncertainty in data from random variation, unclear causality, or	Better data collection instruments, larger studies, more targeted

Major hurdles	Possible Solutions
subgroup heterogeneity	patient pools. Multi-stakeholder working groups to develop appropriate, state-of-the-art approaches.
Quantifying benefit and risk (cont.)	
General agreement on specific values for each criterion	Agreement could be reached through meetings but this is highly time-consuming
A point that bothers people is the “tyranny of the average”, that is, the benefit: risk discussion, they argue, should be made on an individual patient basis. This does NOT reduce the value of quantification, but does argue in favour of providing a RANGE of benefit: risk values for various assumptions about the importance placed on specific items, whether benefits or risks, by individual patients.	We may never agree on a single value of NNT/NNH or any other measure that can serve as a universal threshold, but a threshold might be defined for an individual patient or a homogeneous group of patients. We will certainly never agree on specific “weights” (utilities, etc.) to assign that would apply to all patients.
What “benefits” should be counted? Should “convenience” factors matter, for example? PRO’s should certainly matter, but it’s hard to meet FDA standards for how to study those.	Broader inclusion of a range of “benefits”, with varying weights or importance assigned to those benefits. Convenience (or some other attribute) may not matter to the agency, but may matter a LOT to patients.
Comparative efficacy and safety data against Standard of Care, especially where head-to-head trials would require enormous size to achieve adequate statistical power	Not sure
Models and acceptance	
Concern that these frameworks minimize the importance of clinical judgement and decision making	Identify methods that have their foundation in clinical judgement while offering transparency and consistency in application of such judgement
Entrenched views tend to ‘bang the drum’ for a particular framework	Industry/academia/agencies partnership to review and validate methodologies
Lack of pragmatism – <i>the perfect is the enemy of the good</i>	Continue to highlight how many criticisms being raised re: possible solutions in this area actually already exist today...one of the biggest gains is transparency and consistency in decision making
Lack of institutional experience, expertise, and resources to implement	More public discussions like this one; Development of training

Major hurdles	Possible Solutions
use of new frameworks	programs in the field
Preparation of disease models or indications models	Test different systems – methods on real life data
Models and acceptance (cont.)	
Validation and consistency	Test and prepare a system which can be used to select criteria and evaluate correlations between the individual criteria
Flexibility and simplicity of the method	Ensure tested software is available
The MCDA model is too time consuming the others are too simplistic	Improved software may reduce resource requirements
Gaining global acceptance	Improve understanding
Lack of globally harmonised regulatory approach	ICH like harmonisation
Lack of common inter-company approach	Regulatory Harmonisation
No single commonly accepted methodology	None at this time.
Lack of understanding of health economics	As above
Complexity of the decision process	The model needs sophistication yet should be easily comprehensible
Identify appropriate model, understanding its advantages and disadvantages	More research
Validating it	More research and piloting
Gaining global acceptance	Improve understanding
Gaining acceptance universally	
Practical implementation	

WORKSHOP PROGRAMME

SESSION 1: DEVELOPMENT OF A BENEFIT-RISK FRAMEWORK FOR REGULATORY REVIEW OF NEW MEDICINES	
Chairperson's introduction	Dr Theresa Mullin , Associate Director for Planning and Business Informatics, CDER, FDA, USA
Keynote Presentation - The need for agreed Frameworks	Dr Victor Raczowski , Vice President, US Regulatory Affairs, Solvay Pharmaceuticals Inc, USA
Current and future approaches to benefit-risk assessment for regulatory agencies	
• A perspective from the US FDA	Dr Joyce Korvick , Deputy Director, Division of Gastroenterology Products, FDA, USA
• A perspective from the EMEA/CHMP	Professor Bruno Flamion , Chair, Scientific Advice Working Party EMEA
• A perspective from Health Canada	Dr Robyn Lim , Scientific Advisor, Progressive Licensing Project, Health Canada
What are the current approaches and future views to benefit-risk assessment?	
Prerequisites of a benefit-risk framework for the registration of a new medicine	Dr John Ferguson , Vice President and Global Head, Pharmacovigilance and Medical Safety, Novartis Vaccines and Diagnostics, USA
Multi Criteria Decision Analysis (MCDA) approach to benefit-risk decisions for registration of new medicines	Dr Filip Mussen , VP, Psychiatry and EU Research & Early Development Regulatory Affairs, Johnson & Johnson PRD, Belgium
A Perspective on Quantitative Assessment of Clinical Benefit Risk at FDA: What Needs to Change and How to Move Forward	Dr Robert O'Neill , Director Office of Biostatistics, Office of Translational Sciences, CDER, FDA, USA
SESSION 2: SYNDICATE DISCUSSION 1	
Chairman's introduction	Professor Robert Peterson , Clinical Professor of Paediatrics, University of British Columbia Faculty of Medicine, Canada
Institute Study on the Current Status of Benefit-Risk Assessment among Companies and Agencies	Dr Neil McAuslane , Director, Institute for Regulatory Science, CMR International
Syndicate Discussion Session 1	Reported in Section 2 of this Report
SESSION 3: DEVELOPMENT OF A BENEFIT- RISK FRAMEWORK: IS THERE A WIDER BENEFIT?	
Global Risk Management Informed by Benefit Risk Assessments in a Framework	Dr Janice Bush , VP, Translational Pharmacovigilance Benefit Risk Management, Johnson & Johnson Pharma R&D, USA
Ability to enhance benefit-risk communication to stakeholders: A critical factor for any accepted benefit-risk framework?	Prof Hans-Georg Eichler , Senior Medical Officer, EMEA
Benefit-Risk Assessment: A Singapore perspective	Dr John Lim , Chief Executive Officer, Health Sciences Authority, Singapore
Syndicate Discussion Session 2	Reported in Section 2 of this Report



**WORKSHOP ON MEASURING BENEFIT AND BALANCING RISK:
Strategies for the benefit-risk assessment of new medicines in a risk-averse environment**

Section 3: Summary of Presentations

**SESSION 1: DEVELOPMENT OF A BENEFIT-RISK FRAMEWORK FOR REGULATORY
REVIEW OF NEW MEDICINES**

CHAIRPERSON'S INTRODUCTION

Dr Theresa Mullin

Associate Director for Planning and Business Informatics, CDER, FDA, USA

Introducing the meeting, Dr Mullins explained that FDA had established a new function entitled *Planning and Business Informatics* concerned with long-term planning, modernisation of the way FDA functions. A more systematic approach to the way FDA addresses Benefit-Risk assessment is part of this. A key meeting on Benefit-Risk (BR), in November 2007, and subsequent interviews with review staff in both CBER and CDER had provided an opportunity to examine the *state of the art* tools currently available and their applicability to the agency's work. Many agreed that a more formal template was needed for BR analysis but not one that tries to be so elaborate and comprehensive that it obscures the obvious, dominant benefits and risks that are often apparent with some new drugs. It was felt that BR models have a role in the less clear-cut cases but that the methodology needs further study through actual case studies. Suitable subjects for such a study by outside experts have been identified.

Among the other concerns expressed by staff was that a single formalised way of expressing the BR balance could lose much of the valuable information that is currently provided for clinicians and patients in the labeling. It was also felt that better measures are needed for measuring 'benefit' as opposed to 'efficacy' and that improved, standardised tools are needed for the evaluation of *quality of life* benefits.

THE NEED FOR AGREED FRAMEWORKS

Dr Victor Raczowski,

Vice President, US Regulatory Affairs, Solvay Pharmaceuticals Inc, USA

In his presentation, Dr Raczowski provided an overview of the issues surrounding the need for a more formal approach to benefit-risk frameworks and set the scene for the following Workshop discussions. He provided arguments and illustrations that led to his overall conclusion that:

Agreed frameworks will enhance the quality, effectiveness, and efficiency by which patients have access to high-quality therapies with favourable benefit-risk profiles and that affect patients' lives in meaningful and positive ways

A common goal in a changing environment

Not only has the environment for research and development of new medicines changed but the perception of risks has also changed. The thresholds for approval and market access are perceived as becoming higher and more difficult to overcome and there is a renewed and heightened focus on safety, with less willingness to accept uncertainty.

Increased requirements and the challenging practicalities of product development have led to the well-documented increasing timelines and escalating costs, with fewer new chemical entities being approved for marketing. Meanwhile, despite greater transparency and publication of data in the public domain (e.g., ct.gov) the public perception of the pharmaceutical industry and its regulators remains negative. Product withdrawals are met with a public outcry, questions of assigning blame and suspicions that data has been concealed.

Dr Raczkowski put forward the thesis that the lack of an agreed framework for evaluating benefit-risk and explaining decisions has, in the past, contributed to the poor development environment and that the way forward is through establishing such frameworks. Both regulators and the pharmaceutical industry share a common focus to improve and advance patient care.

This is reflected in the mission statements of both agencies and companies that emphasise the importance of providing patients with access to high-quality therapies with favourable BR profiles. The shared responsibility for achieving these goals, however, goes beyond companies and regulators and extends to healthcare providers, professional societies, patients and their support networks and society as a whole.

Cascade of events.

The adoption of BR Frameworks should stimulate a 'cascade' of improvements in the development and review process leading to better informed, higher quality, and more consistent benefit-risk decision-making:

- **Data:** Improved knowledge of the underlying science and increased availability of high-quality data upon which well-informed benefit-risk decisions are based;
- **Analysis and interpretation:** Increased use of suitable metrics and greater consistency in the analyses from which valid benefit-risk inferences can be made;
- **Communication on how decisions are made:** Greater alignment, confidence and understanding among all stakeholders.

Good practices

Increased clarity and transparency in the process of decision-making is essential to the acceptance of the underlying assumptions, values, perceptions, and judgments that are used in BR assessments.

A case can be made for proposing that there should be a code or codes 'good decision-making practices analogous to other GxPs.

The need for flexibility

In establishing good practices and a BR Framework there is a need for flexibility. A single 'one-size-fits all' Framework is not a realistic option.

Frameworks might differ by therapeutic area and because of regional differences such as patient characteristics and standards of care. The benefit-risk threshold can be affected by the seriousness of the condition being treated and the availability of other proven treatments.

Flexibility is also needed because individuals differ from one another in how they perceive and value of specific benefits and specific risks, for example the value of improved symptoms or the impact on survival. Account must also be taken of the fact that benefits and risks are not always measured by variables of comparable clinical significance thus limiting the ability to make direct comparisons without the use of appropriate weightings

Figure 1

Good Decision-Making Practices

- A product's benefit-risk profile evolves through its life-cycle
- Benefit-Risk decision-making is one of the most critical activities in which all stakeholders engage
- Benefit-Risk decisions have a significant impact on the products to which patients will have access and on how such products will be used
- Critical activities are addressed by GxPs
- Are GxPs on making decisions needed (e.g. GDPs)?

BENEFIT-RISK FRAMEWORKS A US FDA Perspective

Dr Joyce Korvick

Deputy Director Division of Gastroenterology Products.
Center for Drug Evaluation and Research, FDA, USA

Dr Korvick referred to the revised FDA mission statement that now speaks in terms of 'protecting' and 'advancing' public health by helping to speed innovations and helping ensure that 'accurate, science-based information' is available not only to experts but to the people.

The assessment of benefit and risk for medicines, through a sound framework is integral to this mission and Dr Korvick used the analogy of the framework for a bridge that links the 'benefit' data of the *integrated summary of efficacy* (ISE) to the 'risk' data in the *integrated safety summary* (ISS) – see Figure 2.

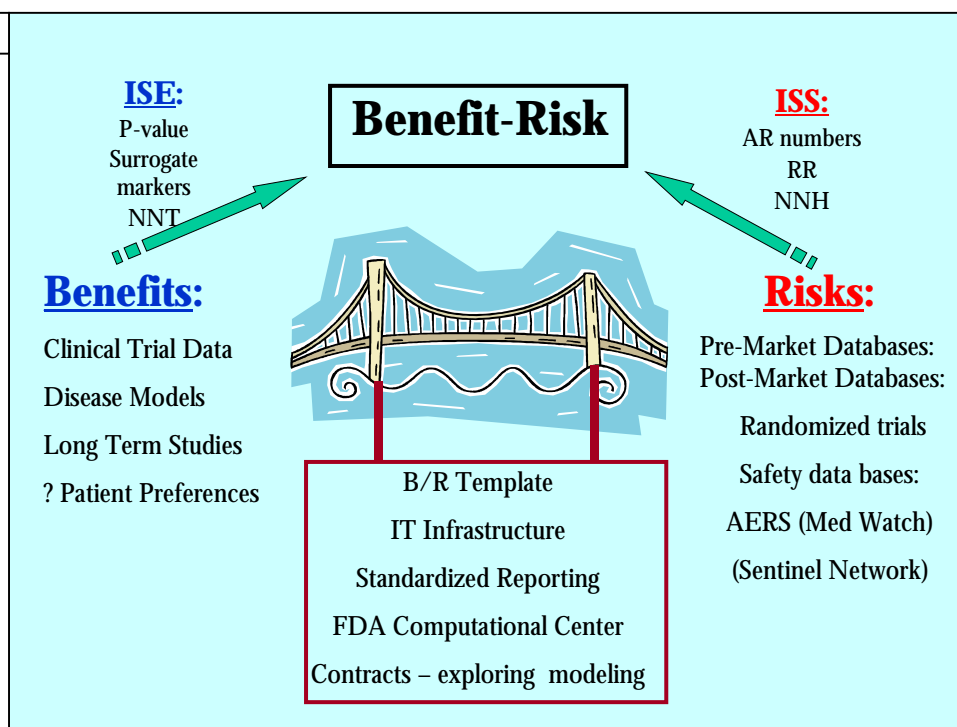
One weakness is that there is not currently a formal part of the regulatory submission for a discussion of the benefit-risk balance. There are possibilities for such discussion at the PSUR (Periodic Safety Update Report) stage but a framework is needed that applies to both the application and the review. This needs to be applicable throughout the product lifecycle, pre- and post-marketing as benefits and risks are dynamic and change with use and patient exposure to the product.

FDA Mission Statement, (2008)

The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and

Figure 2



Factors in the discussion of such a framework include risk management plans, the availability of therapeutic options, and the ability to communicate the facts and uncertainties to populations and individual patients. Historically, the focus of clinical development has been on establishing efficacy and clinical end points but there is not the same certainty, at the marketing stage in respect of safety and rare adverse events.

This was addressed by Dr Janet Woodcock, *Director, CDER, FDA*, at a meeting convened by FDA in November 2007 when she noted that ‘Benefit-risk assessment has been largely limited to the presentation of the trial results without a summary of composite effect of both benefit and risk’ and that the agency relies on ‘enumerating the number and kinds of harms observed in trials’. In discussing the techniques and methodologies for evaluating benefit-risk there was a need to strike the right balance between over-complicated modelling and over simplicity, as well as concerns that models may give a ‘false sense of precision’. A second issue was the communication of information in a transparent manner to a public that does not generally understand the BR ‘tradeoffs’ that need to be adopted when a medicine is approved.

FDA response to the benefit-risk challenge

Two major stimuli for FDA to review the way it addresses BR assessments have been the publication of the Institute of Medicine (IOM) report on Drug Safety in September 2006 and the FDA Amendments Act September 2007 which calls on the FDA to collaborate with public and private entities to provide for advanced analysis of drug safety to improve the quality of post-marketing benefit-risk analysis.

Safety First Initiative

The IOM’s recommendations on strengthening the science base that supports the medical product safety system and on improving operations and management to strengthen drug safety system have led to the launch of FDA’s *Safety First Initiative* in February 2008. This is a team-based approach with new posts of *Deputy Division Directors for Safety* and *Safety Project Managers* being established within the Office of New Drugs to bring the process and project management for safety issues in line with those for efficacy. An *Office of Epidemiology* was also established in February 2008 with Divisions of Risk Management, Medication Error Prevention, Epidemiology and Adverse Event Analysis.

Closely related is the *Safe Use Initiative* with the focus on collaboration among stakeholders in the healthcare system to devise effective, efficient steps to ensure drugs are used as appropriately as possible, in ways that minimise medical errors and manage risks aggressively. This includes developing a cutting-edge pharmacovigilance system for evaluating drug performance using electronic health data (The Sentinel Network)

Challenges and conclusions

Today’s challenge is to move from a predominantly qualitative approach to BR assessment to a more quantitative approach, recognising that the elements of benefits (efficacy) and risks (harms) are ‘asymmetric’: Benefits are ascertained and reported differently from harms in randomised clinical trials (RCTs). Such trials are sized to detect differences in defined efficacy endpoints but analytical approaches to safety are relatively unsophisticated.

In summary

The current integration of benefit and risk evaluation is qualitative and ways to move forward include improving the transparency of the decision making process throughout the life cycle of drugs and biologic products. This includes communication of benefits and risks to healthcare providers and patients based upon timely assessments.

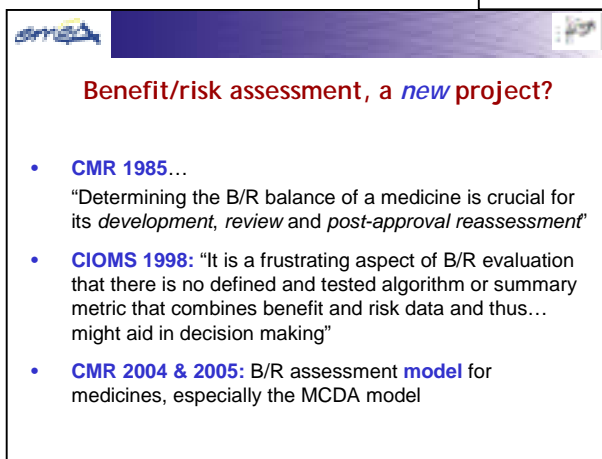
Framework development is necessary to the evolving approaches to BR assessment and the move towards a more quantitative model for decision-making and analysis. .

BENEFIT/RISK ASSESSMENT METHODS: A new project at the CHMP

Prof Bruno Flamion
Chair, Scientific Advice Working Party EMEA

Figure 3

Professor Flamion described the recent developments at EMEA that had led to the publication of the EMEA reflection paper on benefit-risk assessment¹ but he recognised that the discussions were not 'new' and that EU regulators had been involved in discussions on the topic for many years. He cited, in particular, CMR International and CIOMS meetings that had called for the development of methodology and models for BR assessments (Figure 3).



Benefit/risk assessment, a new project?

- **CMR 1985...**
"Determining the B/R balance of a medicine is crucial for its development, review and post-approval reassessment"
- **CIOMS 1998:** "It is a frustrating aspect of B/R evaluation that there is no defined and tested algorithm or summary metric that combines benefit and risk data and thus... might aid in decision making"
- **CMR 2004 & 2005:** B/R assessment model for medicines, especially the MCDA model

CHMP activities

In February 2006 the CHMP Efficacy Working Party (EWP) held an information session on methodology for BR assessment that was linked to a training session on how to improve the quality of clinical assessment reports. The Multi-Criteria Decision Analysis (MCDA) model that had been demonstrated at previous CMR International Institute meetings was one of the items discussed.

The EWP concluded that the benefits of a BR model were that it would:

- Enhance consistency and comprehensiveness in the process of expressing the B/R balance (shared understanding of issues among assessors)
- Enhance transparency of regulatory decisions
- Force assessors to focus on BR
- Provide a tool to compare products In relation to the MCDA model, the usefulness of the sensitivity analysis was particularly recognised.

There was, however no agreement on the potential improvement in accountability of decisions using a model.

The group felt that the shortcomings of using a model were that:

- It does not enhance objectivity of BR decision-making (the numerical outcome of the analysis from the model may give a false reassurance)
- Deviation between the outcome from the model and the regulators' final decision would be difficult to explain
- Building a model for every situation and factor, with discussions on values and weightings is time-consuming and may require more time/resources than are available
- There are potential conflicts between industry and regulators in the way in which a product is scored

¹ Reflection Paper on Benefit-Risk Assessment Methods in the Context of the Evaluation of Marketing Authorisation Applications of Medicinal Products for Human Use, www.emea.europa.eu

As a result of the EWP meeting, a formal CHMP Working Group on BR Assessment was set up and, in May 2006, this group met FDA and PhRMA to discuss the topic. The conclusions were very similar but, on this occasion, the discussions extended to the importance of including the impact of BR assessment on reimbursement decisions and need for involvement and communication with physicians and patients.

The scope of the CHMP Working Group discussions is outlined in *Box 1*. The Group reported its conclusions in December 2006, which led to the publication of the 'Reflections' paper, referenced earlier.

An overall conclusion of the group was that *expert judgment* is expected to remain the cornerstone of BR evaluations for the authorisation of new medicinal products, as it has in the past. Nonetheless, the value of models was recognised for the more difficult cases and, in particular, the value of: Clear identification of the most important benefits and risks that drive the assessment;

- Explicit weights assigned to individual benefits and risks;
- Quantification of the strengths of evidence and of the uncertainties. These were already part of the review process but needed to be included in the BR template or framework.

Box 1

CHMP Working Group on BR Assessment December 2006 report

Preamble

- The focus was on new drug application
- BR assessment must reach a certain level of confidence that a set level of Q,S&E of the new product has been demonstrated
- All relevant data have to be analysed and judged but EC 726/2004 requires that "authorisation decisions should be taken on the basis of objective scientific criteria of Q,S&E of the new product to the exclusion of economic and other considerations such as cost-effectiveness"

Models

The group reviewed several existing models:

- *Principle of Three*, TURBO, etc: more general models, mostly for reassessment of marketed medicines in case of new safety issues
- *Simple models* based on Number needed to treat (NNT)/Number needed to harm (NNH) or Incremental net benefit (INB) which can incorporate utility functions, including patients preferences
- *MCDA*: the most sophisticated model
- *An 'HTA-like' model* based on quality of life measures (QALYs), etc.

Recommendations

The recommendations from the Working Group, which are carried over into the 'Reflections' paper were twofold:

- *Firstly* there should be a revision of the current BR assessment section of the final CHMP Assessment Report template, incorporating a structured list of BR criteria with appropriate guidance.
- *Secondly* the CHMP should conduct further research into the methodology of BR assessment, involving further experts and assessors.

Revision of the BR Assessment Template

The recommendations in relation to the BR assessment template were that it should:

- Use a structured and mainly qualitative approach
- Be explicit about the importance of benefits and risks in the specific therapeutic context
- Describe sources of uncertainty and variability and their impact on the BR assessment. Indicate the amount and accuracy of available evidence
- Be explicit about the perspectives of the various stakeholders, in particular patients and treating physicians
- Define the level of risk acceptability corresponding to the perceived degree of clinical benefit (in the specific context)
- State the benefits in a way that is comparable to risks (e.g. NNT/NNH) – avoid relative expressions of benefit and risk

- Describe how the BR balance may vary across different factors (e.g. patient characteristics)
- Discuss the sensitivity of the BR balance assessment to different assumptions (e.g. the 'worst case scenario')

It was felt that, before implementation, the modified template should be tested in a pilot phase and revised as necessary. Regular training and monitoring should also be put in place.

Further research

An EMEA Methodology Project is proposed under the title: Development and testing of tools and processes for balancing multiple benefits and risks as an aid to informed regulatory decisions about medicinal products. The objective would be to:

- Describe the current practice of BR assessment in the EU regulatory network
 - Examine the applicability of current models, tools and processes, assessed against criteria relevant for BR assessment at different stages of drug development/approval
 - Field test selected models/tools (in one or more domains)
 - Develop a new method to be used as a decision-aid for BR assessment by regulators
 - Develop a training package for assessors
- In addition to the EMEA, potential participants are the London School of Economics (Prof. Larry Phillips), the University of Bordeaux, Department of Clinical Pharmacology and contributing EU regulatory agencies on a voluntary basis.

Box 2

IMI_Call_2008_1_06

Key points:

A thorough *post-marketing* surveillance system is essential to ensure a positive B/R balance of medicines.

Pharmacovigilance has shifted to a more proactive approach but new expertise, resources and methodologies are needed, especially:

- New methods of data collection and signal detection and evaluation,
- Less biased observational research based on healthcare/claims databases (pharmacoepidemiology),
- Data mining of large, pan-European safety databases

Another project in which EMEA will be participating, but one which will take a broader view of the topic, is the Innovative Medicines Initiative (IMI) call No 6 on *Improving and strengthening the monitoring of the B/R of medicines marketed in the EU* (see Box 2).

An EMEA-led *Application Consortium* has been proposed which would participate in the IMI project and interested parties have been invited to join.

Concluding, Professor Flamion suggested, however, that this research project was missing:

- Links with patients, physicians, industry, HTA units
- Links with regulatory agencies outside the EU
- BR assessment at different steps in the regulatory pathway

CURRENT AND FUTURE APPROACHES TO BENEFIT-RISK ASSESSMENT: A Health Canada Perspective

Robyn R. Lim, Ph.D.

Scientific Advisor, Progressive Licensing Project,
Health Canada

Box 3

Dr Lim outlined Health Canada's drug regulatory modernisation activities and the *Progressive Licensing Framework* as they relate to benefit-risk assessment. Health Canada initiated, in the fourth quarter of 2006, a third major evolution of its regulatory framework through amendments to the Food and Drugs Act and its Regulations, processes and practices. The principles of the Progressive Licensing Project (PLP) can be summarised as an evidence-based and life-cycle approach backed by good planning and accountability. In the context of benefit-risk, PLP provides an opportunity to ensure that appropriate BR assessment considerations are included in the drug regulatory framework through best practices.

The latest Bill C-51² includes the specific requirement for evidence standards that 'Market authorizations may be issued if a person has established that the benefits associated with the product outweigh the risks' [18.7 (1)]

Progressive Licensing Framework

The Progressive Licensing Framework is guided by two objectives:

- to protect the public from the marketing of unsafe therapeutic products; and
- to support the safest use of therapeutic products. With three supporting objectives:
 - To align the Progressive Licensing Framework with the system of health care in Canada to achieve positive health outcomes;
 - To ensure that the new regulatory structure enables Health Canada to implement best international regulatory practices and maintain appropriate oversight without unduly increasing regulatory burden; and,
 - To encourage and make best use of evolutions in the science of product development and regulation.

The regulatory perspective

The regulator can be seen as a 'catalyst' to direct, support, encourage best evidence, methodologies and practices in benefit-risk consideration. Although the primary, visible, role of regulators is at the review and decision-making stage, they can also form a link throughout the evidence chain from development by industry and its partners to the 'real world' decisions made by patients, health care professionals and payers (see Figure 4)

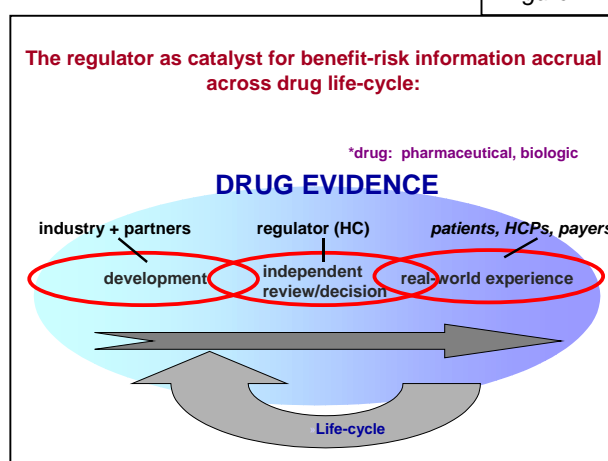
BR evidence

Whilst the core, primary data for a BR assessment are safety, efficacy and quality (SEQ), the concept is much broader. 'Secondary' and 'tertiary' layers of evidence can be identified that are implicit but are important drivers for regulatory decisions.

Secondary levels of evidence can be considered as 'performance framing' and reflect the conditions of use, impact and utility of the product and include:

- The nature of disease/condition (e.g. life-threatening vs. non-debilitating);
- The nature of the drug's effect on the disease/condition (e.g. disease modifying vs. symptomatic management);

Figure 4



² Web reference:

http://www2.parl.gc.ca/HousePublications/Publication.aspx?Language=E&Parl=39&Ses=2&Mode=1&Pub=Bill&Doc=C-51_1

- The nature of the target population (e.g. vulnerable populations, level of overall health, degree of heterogeneity);
- The nature of the treatment environment (e.g. availability, performance, uncertainties of other therapies) and the degree of unmet medical need;
- Clinical practice environments (domestic, international) and the clinical expectations for the product;
- Practicality issues, including anticipated compliance, convenience of use, anticipated risk manageability;
- Anticipated use patterns once on market, which may lie outside the conditions of use studied and approved.

Tertiary levels of evidence are considerations that go beyond specific drug performance and include such issues as:

- Population vs. more individualised health considerations
- Access issues ('choice' and 'hope')
- The risk tolerance and uncertainty tolerance of decision-makers
- The ability to accrue further SEQ evidence after approval and marketing, e.g., the ethical and logistical challenges of enrolling patients into further trials.

Benefit Risk Assessment

Regulatory benefit-risk assessment can be viewed as a context analysis, a gap analysis and an options analysis.

As a *context analysis* BR assessment can be seen as adding layers upon the SEQ evidence, allowing for considerations of conditions of use that are necessary for decisions to be realistic and relevant in the 'real-world'. It has a broader scope than the SEQ analysis and is often less systematic and more qualitative as it incorporates values and ethics as well as the perspectives and perceived roles of industry, payers, healthcare practitioners and patients.

BR assessment is a *gap analysis* in that it needs to bridge the 'uncertainty gap' between the pre-market review and the 'real world' conditions of use: Do the conditions studied reflect those recommended in the proposed label and the anticipated/actual real-world conditions?

The regulatory approval spectrum ranges from an outright rejection to an outright approval of an application. Where the outcome falls between these two extremes, the BR assessment as an *options analysis* can provide a management strategy for optimising benefits and minimising risks through the conditions of licensing, risk management plans and appropriate labelling.

New assessment tools

Visual benefit-risk assessment tools, including graphical and pictorial representations of benefit-risk balance, are currently under development at Health Canada to support reviewers' best practices and regulatory decision-making transparency.

Precautionary principle

The BR assessment of medicines aligns with Canada's federal framework for science-based decision-making about risk which is based on the application of precaution but recognises the necessity for decision-making in the face of a lack of full scientific certainty about risks. The range of tools for precautionary measures include measures to manage and/or reduce drug uncertainties and it is recognised that a simple accept/reject decisions can stall evidence development and identification of risks and benefits.

Judgement

The overarching element of BR assessment, however, is judgement and comprehensive benefit-risk assessment reveals the necessity for judgement calls more explicitly than SEQ assessment. Judgment is required regarding the interpretation of the extent and meaning of the evidence available and the uncertainties in the SEQ and BR evidence that will always exist.

BALANCING BENEFITS AND RISK

Prerequisites of a benefit-risk framework for the registration of a new medicine

Dr John Ferguson

Vice President and Global Head, Pharmacovigilance and Medical Safety,
Novartis Vaccines and Diagnostics, USA

Dr Ferguson presented arguments to support the value of a *framework* approach to benefit-risk assessment and outlined the ways in which progress towards this goal was being achieved.

It is generally acknowledged that there are no 'safe' medicines and the possibility of harms are accepted in return for possible benefits that outweigh them. There appears, however, to be a greater emphasis on risk, for example in risk management plans, than on benefits.

The state of the art

Whilst a formal framework for risk management has been in existence for several years (with a cursory mention of benefit the context of balancing benefit-risk) there are no regulatory standards for BR evaluation or guidance on how to carry it out. The current approach can appear to be a 'black box' within which decisions are made using a 'heuristic' approach of learning by experience.

Whilst a heuristic approach continues to have its place, without transparency and structure the benefits of such learnings are lost, especially as complexity increases. Furthermore, without a standardised framework for integrating and weighting the evidence, the process becomes inscrutable, subjective and piecemeal. The regulatory implications of subjectiveness and reliance on individual judgement can be that different decisions are made and different actions taken within and between agencies.

'State of the art' BR Survey

A survey, which included US, European and Japanese pharma/biotech companies and two European regulatory agencies, was carried out and reported to the DIA Annual Conference, Boston, 2008³. The results indicated a high level of interest in a structured framework for balancing benefit and risk but indicated that the current emphasis is on risk management plans with the emphasis on risk. A small proportion of companies are actively investigating or using structured BR approaches and a still smaller number investigating the use of quantitative measures. The survey indicated some scepticism about the validity as well as the widespread need and applicability of currently available quantitative approaches, until further information is available on performance characteristics.

Pre-requisites for a framework

In accepting the value of a framework or other models it must be acknowledged that these are decision aids and not statements of scientific fact. *Figure 5* sets out the benefits of a BR framework and the by-products that can be expected to accrue.

The pre-requisites for a workable framework include the need to:

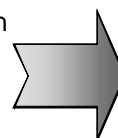
- adapt to any indication;
- capture and address perceptions of multiple stakeholders;

Figure 5

Value of a BR Framework

Attribute:

- structure
- standardization
- simplification
- flexibility
- accessibility
- recording
- iteration



By-product:

- transparency
- reproducibility
- feasibility
- utility
- understanding
- learning
- refinement

³ Whitebrook J, Markey J. for the IntraspHERE Corporation. DIA Boston 2008

(See also the outcome of the CMR International Institute Survey reported in Section 2, Annex 2 of this report (page 15))

- be accessible to all stakeholders;
- weigh/prioritise all available data (values/level-of-evidence);
- capture variability and uncertainty;
- allow for time-dependence;
- support balancing on a common scale;
- support cross-product comparisons;
- have acceptable operating characteristics;
- support registration and labelling.

Decision Framework

A working Definition

A system used to coordinate a collective thought process, carefully managed to clearly delineate a meaningful and tractable problem, in unambiguous and actionable terms, leading to explicit decisions that can be measured, revisited and revised.

Work in progress

The pharmaceutical industry is working on a structured BR framework that has as its two main components: a *value tree* and *data tables*. The framework defines the way in which the elements from the data tables are to be associated with the value tree and the weightings that should be assigned to these elements.

Further work is required on the development of such a framework but the basic design has been informed by consultation with academics and regulators as well as modelling and risk management experts. A test bed has been developed and funding has been secured to start testing this using actual but 'anonymised' products and by adding simulated data to extend the framework or model as far as possible.

Frameworks and quantitative models

As indicated in *Figure 6*, decision frameworks have a role in all types of decision-making but quantitative models are likely to become increasingly important as the complexity increases. Quantitative models should therefore be incorporated in frameworks that are specifically designed to accommodate them.

A framework can therefore be seen as the basis for specifying desirable, context-specific model characteristics and setting performance requirements (validation) for quantitative (mathematical) models.

Validation

Remembering that decision models are *aids* to decision-making and not statements of scientific fact, and conclusions derived from them will be conditional on the assumptions that are made. Structural assumptions must, therefore, be explicitly reported and these assumptions along with parameter estimates must be assessed against the data. The dependency of the output upon input data should be tested using sensitivity analysis.

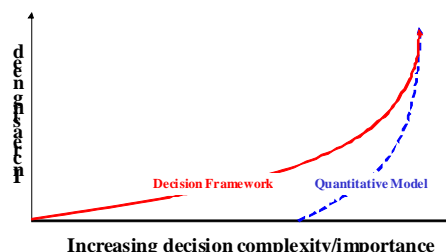
Patient preferences are an important factor that requires further evaluation in relation to the ways they can be used as an adjunct to frameworks and quantitative models in order to inform thinking.

Ultimately, benefit risk assessment is about the patient and the prescriber. There must be a shared understanding of decision-making and decisions through a structured framework and no 'black box' decision aids.

Figure 6

Need for Structure in Decision-Making

Framework vs. Quantitative Model



Quotable quotes

"Only decision-making processes based on the pursuit of negotiated outcomes, conducted in an open and transparent manner and inclusive of all legitimate actors involved in the issue are likely to resolve the complex issues surrounding the ... [balancing of benefits & risks for pharmaceuticals, biologics and vaccines]"

(From the World Commission on Dams modified for Benefit-Risk models)

Beyond complexity lies simplicity. In the words of *Albert Einstein*: "... as simple as possible and no simpler"

MULTI CRITERIA DECISION ANALYSIS (MCDA) as an approach to benefit-risk decisions for registration of new medicines

Dr Filip Mussen

VP, Psychiatry and EU Research and Early Development Regulatory Affairs,
Johnson & Johnson PRD, Belgium

Dr Mussen provided an overview of the ways in which a Multi-Criteria Decision Analysis (MCDA) model can be applied during the assessment of new medicines. MCDA allows the use of decision analysis techniques to be applied to benefit-risk decision making during the development and regulatory review of a product.

The essence of MCDA is that it:

- Disaggregates a problem into pieces;
- Examines data and allows judgements on those pieces;
- Reassembles the pieces to present a coherent overall picture.

As with other models, MCDA is a tool to assist decision-makers and does not substitute for the routine assessment of safety, quality and efficacy data or the expert judgement required for its evaluation.

Elements of the MCDA Model

The six steps for creating and using the model are set out in *Box 4*.

Value tree

The cornerstone of the model is the value tree (Step 2) that maps the way in which the data will be considered in terms of benefits (e.g. primary and secondary efficacy endpoints from pivotal trials) and risks (e.g., adverse effects). The 'leaves' of the value tree identify the different criteria to be evaluated and analysed.

Scales are then developed for scoring and weighting each of these criteria.

Box 4

MCDA-Based Model: Critical Steps

Step 1: identification of the options to be appraised:

The subject medicine, the comparators (usually active and/or placebo) used in the pivotal clinical trials

Step 2: identification of the relevant benefit and risk criteria and organisation in a value tree

Includes identification of the relevant efficacy and safety data set (for the subject indication)

Step 3: assessment of the performance of each option against the criteria

Construction of a value scale for each criterion (using partial value functions, qualitative value scales and/or direct rating)

Scoring of each option on each criterion

Step 4: assignment of a weight to each criterion (using for example a specific technique called 'swing-weighting')

Step 5: calculation of the weighted scores at each level and calculation of the overall weighted scores

Step 6: sensitivity analysis

The benefit and risk criteria that should typically be considered and included in the analysis were defined in a recent publication (Mussen, Salek and Walker, 2007)⁴ and are summarised in Table 1.

Scoring and sensitivity analysis

The system of scoring and weighting the scores for each criterion (Steps 3-5) allows the calculation of a total benefit score, a total risk score and a benefit-risk score. These, however, can only be interpreted when compared with similar analyses of the other options (i.e., use of a comparator product or placebo).

A major strength of the MCDA technique is that the modelling software allows sensitivity analyses (Step 6) to be carried out on the data in order to see the impact of varying the weight and/or score of any criterion, e.g., to look at 'worst case' and 'best case' scenarios and investigate uncertainties.

⁴ The development of a new model using multi-criteria decision analysis, Pharmacoeconomics and Drug Safety, Vol.16, S2-S15

Table 1: Key benefit and risk criteria for inclusion in the analysis

<p>Suggested Benefit Criteria</p> <p>For each pivotal trial:</p> <ul style="list-style-type: none"> • Efficacy versus comparator (primary endpoint(s)) • Evidence for the efficacy in relevant subgroups • Efficacy as per the results of the non-primary endpoint(s) <p>Other benefit criteria:</p> <ul style="list-style-type: none"> • Efficacy as per the results of relevant non-pivotal trials • Anticipated patient compliance in clinical practice <p>Benefit criteria to be taken into account in the weighting process (but not in value tree):</p> <ul style="list-style-type: none"> • Design, conduct and statistical adequacy of each pivotal trial • Clinical relevance of the primary endpoint(s) • Representativeness of the studied population 	<p>Suggested Risk Criteria</p> <p>Adverse effects:</p> <ul style="list-style-type: none"> • Overall incidence of adverse effects • Overall incidence of serious adverse effects • Discontinuation rate due to adverse effects • Incidence, seriousness, duration and reversibility of specific adverse effects <p>Other risk criteria:</p> <ul style="list-style-type: none"> • Safety in subgroups • Interactions with other drugs and food • Potential for off-label use leading to safety hazards <p>Potential for non-demonstrated additional risk:</p> <ul style="list-style-type: none"> • Due to limitations of clinical trials and/or length of patient exposure (to be taken into account in the weighting process but not in the value tree) • Safety issues observed in preclinical safety studies • Safety issues observed with other drugs of the same class
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Why and when the MCDA model should be used

The particular attributes of an MCDA model lie in its ability to encompass all relevant efficacy and safety data and to incorporate and balance multiple benefit-risk criteria.

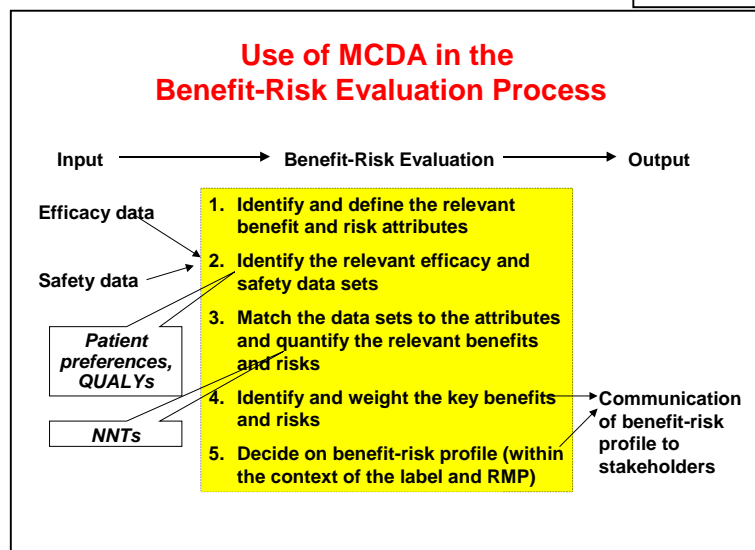
By superimposing evaluative judgements on the scientific data (by assigning weights) MCDA can, in effect give a systematic and explicit picture of the way in which people make intuitive benefit-risk decisions.

Whilst the use of an MCDA model does not substitute for capturing and analysing the relevant efficacy and safety data, it fits within the BR evaluation process, particularly at stages 4 and 5 of the schematic shown in *Figure 7*.

Whilst the quality of the results from MCDA techniques, when compared with other models, can be very high, it is acknowledged that the method is resource intensive and can lack transparency to stakeholders. Its primary use is for complex and difficult benefit-risk evaluations.

Furthermore, the best use of MCDA is to develop the model *a priori*, preferably through joint discussions between the sponsor and agency, and certainly in advance of the decision-making process or advisory committees, which are not the appropriate forums for the development of a model.

Figure 7



The next steps

- In order to extend the value from the assessment of individual products to a broader usage, MCDA models should be developed for specific therapeutic classes with appropriate content validation.
- The scales should be developed further, particularly to fill the gaps in quantification of the different attributes of specific adverse effects, in terms of incidence, severity, duration and reversibility.
- Further testing of MCDA models should be undertaken in group settings to evaluate the extent to which they can add value to the decision-making process.

A PERSPECTIVE ON QUANTITATIVE ASSESSMENT OF CLINICAL BENEFIT RISK AT FDA:

What needs to change and how to move forward

Dr Robert O'Neill

Director Office of Biostatistics, Office of Translational Sciences, CDER, FDA, USA

Dr O'Neil addressed the asymmetry that currently exists between the knowledge of the benefits and risks of new medicines, particularly at the pre-marketing assessment. He argued that randomised clinical trials (RCTs) are primarily designed to demonstrate efficacy and that the science of quantifying risk and the harms is lagging behind. This imbalance needs to be addressed and new assessment tools need to be developed if a workable BR Framework is to be achieved.

Framing quantitative BR assessment

There are differences in the way safety data are approached from a quantitative aspect and different approaches to adverse events are needed when considering, for example, treatment vs. prevention, acute vs. chronic exposure/usage and severity and frequency/rarity of the condition.

Data on risks can derive from RCTs but can be external to these, often from spontaneous reporting and observational databases within health care plans, Medicare and Medicaid. The benefit-risk balance is a function of time that will change over the life-cycle of the product in the market place where one is dealing with a multiplicity of benefits, risks and competing events.

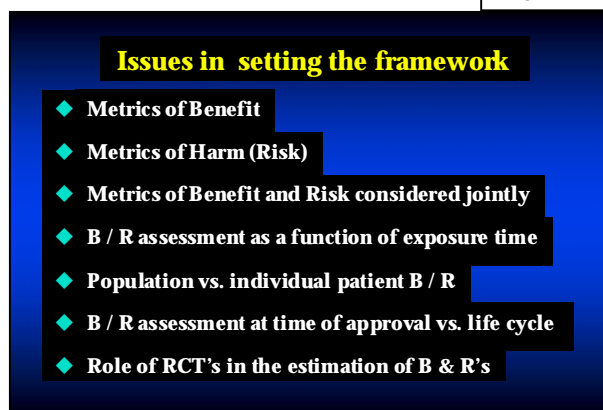
Three situations exist: Firstly where benefits and risks of a new molecular entity are observed only in RCTs and evaluations are based primarily on these; Secondly where the Benefits are observed in clinical trials but potential risks are observed outside of the trials and are not quantifiable and; Thirdly where benefits and risk change over time, with multiple usage, and emerging information.

Complicating factors in collecting safety data

As noted, RCTs are primarily designed to evaluate efficacy rather than safety as a result of which:

- Safety endpoints may not be as precisely measured or adjudicated as in efficacy trials where there are a few pre-specified endpoints

Figure 8



- Exposure time may be critical to onset of events (dose, cumulative dose, mechanism of action - liver damage);
- Safety events can occur after withdrawal from exposure – lack of follow-up in a study can lead to loss of this information;
- There may be recurrent events and multiple different events per subject;
- The way in which events are counted and coded, even under the agreed MeDDRA terminology, might not be consistent and uniformly applied.

The consequences are that safety endpoints are measured, collected, or followed with less accuracy than for efficacy and 'after the fact' the endpoints may get adjudicated, when it is too late to obtain other patient information that may be pertinent to the adjudication.

This asymmetry needs to be addressed if the net benefits are to be better quantified, in particular, the detection of delayed and late onset side effects that will be missed through inadequate follow-up, especially of patients that withdraw from trials.

Flaws in safety reporting

Medical Journals

The CONSORT (Consolidated Standards of Reporting Trials) checklist for reporting clinical trials was drawn up by a group of journal editors and scientists and first published in 1996. Although subsequently modified, the 22-item list, in 2003, included only one point that was specifically addressed to safety. In response to concerns about the reporting of harms in RCTs, the CONSORT Statement was revised to include 10 new items about reporting harms-related issues.

Dr O'Neil cited examples of misleading and flawed reporting in relation to the reporting of statistical data on the reduced GI affects of the COX2 inhibitor rofecoxib (Vioxx) and the subsequent reports of increased cardiovascular events over time. Other examples related to the meta-analyses of RCTs to evaluate low-incidence events with serotonin re-uptake inhibitors, the antidiabetic rosiglitazone (Avandia) and IBS medication alosetron (Lotronex).

The Regulatory Review Infrastructure

Dr O'Neil heads the FDA Office of Biostatistics which provides back-up to the 15-16 medical review divisions and has oversight of all the safety data that comes to FDA. There are some 100 statisticians on the FDA staff and about 20% of these are assigned to quantitative safety assessment.

Although there is an internationally agreed ICH guideline on *The Structure and Content of Clinical Study Reports* (ICH E3), the FDA clinical reviewers look at the raw data beneath these summary reports and study the line-listings for individual patients. FDA publishes an 102-page internal *Reviewer Guidance* for 'Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review'. It is an intricate and complicated process currently requiring physical cross-checking of line-listings in printouts and there is scope for a fundamental overhaul of the way the large volumes of data are submitted electronically for review. Analytical tools are needed that will display the data visually at patient level as well as conceptualising time dependencies (cumulative exposure, interaction with other medications, covariates).

The FDA Computational Centre is exploring the use of available electronic tools and possibilities for developing new ones. Potential approaches include:

- Visual graphics and informative displays giving individual subject case report profiles;
- Summarizing patient outcomes by treatment group;
- Comparisons of treatment groups with respect to patterns and event rates (Event history charts);
- New measures of cumulative events - counting events and adjusting for duration of exposure.

Coding control

Strategies for exploring associations, multiplicities, time dependencies, syndromes, event combinations, etc depend heavily on the integrity of the coding of adverse events using MeDDRA. Companies using several CROs for clinical trials often overlook the importance of coordinating and monitoring a uniform coding strategy.

It is essential that companies allocate time in planning their IND/NDA process to discuss with FDA prospective plans for the collection and analysis of safety outcomes.

In conclusion

Appropriate quantification of benefit and risk is just beginning to be understood and addressed. There is a need to borrow from other epidemiological fields and understand better the limits and practicalities of quantifying efficacy and harms. Quantification of efficacy is more refined with 30 years of development and guidelines but the quantification of safety (risk, harm) is far behind. Hence the thesis that there is currently an asymmetry in BR quantification

A prerequisite of a Framework for BR assessment is that the scientific level for both safety and efficacy must be comparable and this will require work on standards for clinical trials, data formats and tools for access, storage and retrieval.

Finally, a culture change is needed to recognise that new tools and new approaches must be adopted, for example to recognise that epidemiologic observational studies are no substitute for large trials from which low-level signals can be quantified. Furthermore, the talent base and training are not currently in place that would allow a true understanding of the science of safety assessment and the science of evaluating benefit and risk.

SESSION 3: DEVELOPMENT OF A BENEFIT- RISK FRAMEWORK: IS THERE A WIDER BENEFIT?

GLOBAL RISK MANAGEMENT INFORMED BY BENEFIT RISK ASSESSMENTS IN A FRAMEWORK

Dr Janice Bush,

*VP, Translational Pharmacovigilance Benefit Risk Management,
Johnson & Johnson Pharma R&D, USA*

Dr Bush discussed the value of a BR framework in relation to developing sound Risk Management Plans (RMPs) and stressed the importance of keeping 'benefit' clearly in the equation that is often dominated by considerations of safety and risk.

Definitions

Definitions are important and those shown in *Box 5* have withstood the test of time and still appear to be current. It is important to emphasise that these refer to life cycle management and that the risk management plan is a strategic approach.

Evolution of risk management in the US

In the early 1990s, before PDUFA, companies had RM Programs albeit under different terminology, but PDUFA 3 in 2002, gave a specific focus to safety and risk management, giving rise to the three final FDA guidance documents on risk management (March 2005). RiskMAPs were also introduced for the first time although FDA was not given the legal authority to impose RiskMAPs (except in the case of subpart H – 'conditional' approvals).

Nonetheless sponsors are often compelled to utilise RiskMAPs in order to achieve a BR balance that allows FDA to approve the product.

In contrast, PDUFA 4 and the FDA Amendments Act (FDAAA) of 2007 introduced Risk

Box 5

DEFINITIONS

Risk Management: The comprehensive and proactive application of scientifically-based methodologies to identify, assess, communicate, and minimize risk throughout a drug's life cycle so as to establish and maintain a favorable benefit-risk balance in patients.

Risk Management Plan: A strategic approach which encompasses all planned efforts to increase knowledge about a drug, including additional data on risks and benefits, as well as all efforts to minimize or mitigate the risk from the use of the drug. The plan may be quite extensive and include epidemiological studies, clinical trials, as well as a number of interventions to minimize risk, or may be as simple as professional product labeling and good routing post-marketing surveillance. The detail needed in the actual plan will be driven by the specific risks of the particular drug.

Box 6

RiskMAPS

A RiskMAP (*Risk Minimization Action Plan*) is a strategic safety program designed to meet specific goals and objectives to minimise the known risks of a product while preserving its benefits.

Goals are the nucleus of a RiskMAP and address the key product risks and should be stated in absolute terms (e.g., 'there should be no foetal exposure with patients on X drug').

Objectives are intermediate steps to achieve the goal and should be pragmatic, specific, and measurable (e.g., pregnancy test given before each administration).

Tools help achieve objective (e.g., reminder stickers).

RiskMAPs should also include an **evaluation component** although this is less well defined.

Evaluation and Mitigation Strategies (REMS) and gave these the force of law by codifying them in the statutes.

REMS under FDAAA

A proposed Risk Evaluation and Mitigation Strategy (REMS) will be required **preapproval** as part of an NDA or BLA if FDA determines that one is necessary to ensure that the benefits of the product outweigh the risks. FDA may also require a REMS **postapproval** as new safety information becomes known.

There are ten elements (see *Box 7*) that can be included in a REMS although, in practice, only a selection will be appropriate:

Benefits as part of BR assessment

Discussions of including benefit data in a BR framework are often sidetracked by concerns about the quality of the data that is available. With risks, however, this does not seem to arise and all safety data, regardless of quality is considered important. A transparent framework that brings together both benefits and risk elements would be of great value in providing a platform for similar discussions on both benefit and risk

Benefits have multiple facets and different measurements The assessment of the collective benefit may drown out a specific benefit. A framework is needed that will help capture, assess and articulate benefit.

A framework to inform a RMP

A BR Framework is a tool to identify factors contributing to benefit and risk and to define those that are important. It is also a strategy to help identify gaps in the information. If agreement is reached on the gaps it provides the context to develop a plan to deal with those gaps and a RMP is the ultimate outcome.

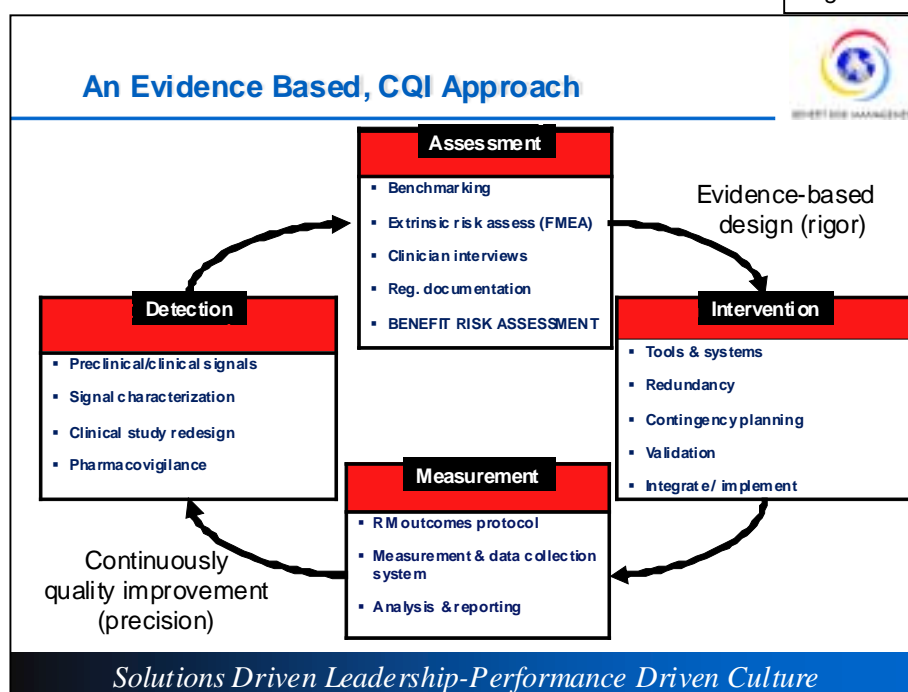
The elements chosen for a particular RMP will depend on how well the gaps and areas of risk are identified and on agreements between the Health Authorities and Sponsor on how these are to be mitigated. The BR Framework that informs the RMP needs flexibility in order to be applicable at multiple levels (patient, regional, societal). *Uncertainty* naturally occurs in any BR assessment and there is the question of how this can be incorporated in a BR Framework and the resulting RMP.

Box 7

Possible elements in a REMS

- A timetable for assessment (in all cases);
- Patient information as a MedGuide or PPI;
- A communication plan to health care physicians (HCPs);
- Information about the REMS to encourage compliance or explain safety protocols;
- Dissemination through professional societies;
- Particular training or experience for, or certification of HCPs;
- Certification of pharmacies, practitioners, or health care settings that dispense the drug
- Dispensed to patients only in certain health care settings
- Dispensed to patients with evidence or documentation of safe use conditions (e.g., lab test results)
- Patients subject to certain monitoring
- Patient using drug is enrolled in a registry
- Company system for monitoring implementation of the system

Figure 9



Continuous quality improvement (CQI)

Risk management plans evolve and are updated through continuous quality improvement (see Figure 9). BR assessments also change over time as the data increases and the updated BRA should be a key component in the evolving RMP. This will, however, only succeed if there is shared understanding and agreement which requires the process to be comprehensive and, above all, transparent, taking into consideration the needs and perspectives of multiple stakeholders.

To date, however, few RM programs have been reviewed retrospectively and metrics have not been a major component. The 'science' of risk management is not well advanced. BR assessments can identify gaps but how to 'treat' them remains uncertain. It is hoped that this will change under the new legislation on REMS and with new FDA priorities and resources.

Conclusions

Neither RMPs nor REMS alone provide a complete solution and over-restrictive risk management can provide barriers to access for patients needing care. Better tools are needed to evaluate new medicines in the first place and, to this end BR Frameworks will have an important role.

A BR Framework can be used to inform RMPs and help re-examine decisions as they are updated.

A shared understanding and agreement of the BR Framework, between Health Authority and Sponsor, is critical to achieving an appropriate RMP and the framework will provide a platform for greater transparency and better communication.

ABILITY TO ENHANCE BENEFIT-RISK COMMUNICATION TO STAKEHOLDERS: A critical factor for any accepted benefit-risk framework?

Prof Hans-Georg Eichler
Senior Medical Officer, EMEA Eichler

Professor Eichler challenged the concept that the public and the regulators were becoming more **risk averse** and argued that the impression lay in people becoming more **risk aware**.

He cited an excerpt from the Dutch Medicines Evaluation Board (see Box 8) that suggested a trend towards 'zero tolerance', but questioned whether the willingness to accept the risks associated with medicines has actually changed. Being 'risk averse' would imply accepting a lower level of risk for a given benefit, i.e. a lower 'willingness to trade' but social scientists have little evidence that this is happening. The perception of lower risk tolerance is more probably linked to the greater public awareness of the risks associated with medicines leading to an increased awareness of potential problems.

Box 8

Zero tolerance?

Excerpt from: Strategic Business Plan 2005-2009, Dutch Medicines Evaluation Board "Refusal to accept risks.

The ... trend concerns the refusal to accept risks. Consumers are less prepared to take risks; 'zero-tolerance' rules.

The government is expected to preferably eliminate all risks for the population. The refusal to accept risks also extends to medicines; side effects are becoming increasingly unacceptable."

Professor Baruch Fischhoff was quoted as saying⁵, on refusal to accept risks, that 'Calls for 'safe' products can be unfairly ridiculed, by treating them as demanding zero-risk [but] ...people assess an event's probability by how easily instances come to mind'. Media coverage (among other things) can make events disproportionately available, inducing biased judgement.

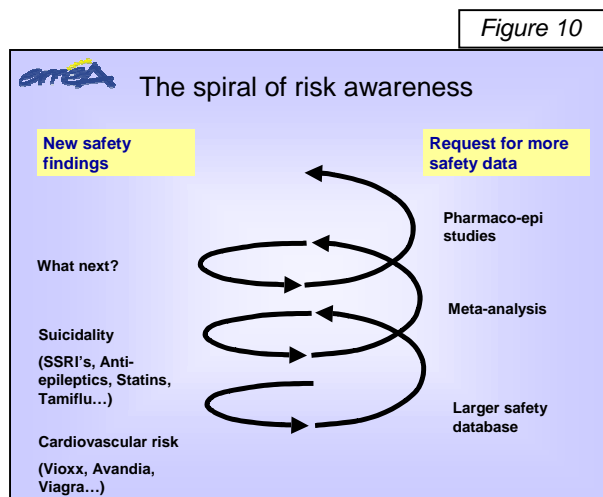
⁵ Fischhoff, B. (2008 in press). Risk perception and communication Oxford University Press

The spiral of risk awareness

In relation to medicines, if society was actually becoming more risk averse, regulators should be raising the 'entrance barriers' and refusing a greater proportion of applications. Figures on the frequency of applications rejected by EMEA over the last 10 years do not, however, show this trend.

The analogy was made with using a more powerful telescope to look at the stars. A greater number will be seen but this does not mean that the actual number of stars has increased.

Nonetheless changes in risk perception are having an impact on data requirements to achieve authorisation. The spiral of risk awareness (see Figure 10) means that the public outcry over safety issues is leading to demands for larger trials, meta analyses and ever more advanced systems for collecting and analysing pharmaco-epidemiological data.



Responses to the spiral

A two-fold response to address the consequences of spiralling risk-awareness was suggested: Enhanced methodology for BR assessment and a revised communication strategy.

Methodology

The goals for enhanced BR methodology should include a transition from a qualitative to a quantitative basis for assessment and a progression from implicit to explicit criteria. These must incorporate patients' valuations of beneficial and/or adverse outcomes.

The EMEA response to this challenge has been set out in the CHMP reflection paper on benefit-risk assessment⁶, discussed at the Workshop by Professor Flamion (see page 29). The actions to be taken include revising the structure of the current benefit-risk assessment section of the CHMP assessment report and undertaking further research into the methodology of benefit risk assessment.

Communication

Revisiting and revising communication strategies means addressing both content and communication skills.

On the **content of communications** about medicines it has been said that 'Companies tout the *benefits*, regulators do the *risks*, and consumers are left in the middle' (Press statement).

EMA information releases on the authorisation of new medicines have, historically remained 'silent' on the benefits of a product and have given somewhat 'standardised' benefit-risk statements: e.g., 'Having assessed all available data, the CHMP concluded that the benefits of ... continue to outweigh their risks'.

When the marketing authorisation of thalidomide needed to be announced recently, however, there were fears of a public outcry and the wording of the press release was modified to emphasise the benefits (see Box 9).

Box 9

PRESS RELEASE

[EMA] recommends the approval of thalidomide for [...]

CHMP concluded that the benefits of Thalidomide [...] outweigh its risks for [...] treatment of multiple myeloma [...]. Clinical studies have shown that adding Thalidomide Pharmion to [...] can prolong survival time by about 18 months in newly-diagnosed multiple myeloma patients over 65 years of age, as compared to patients...

⁶ Reflection Paper on Benefit-Risk Assessment Methods in the Context of the Evaluation of Marketing Authorisation Applications of Medicinal Products for Human Use, www.emea.europa.eu

Avoiding mention of specific 'benefits' in EMEA communications stems from concerns that the agency might be seen to be 'promoting' the product. Action is needed, however, to migrate from *Risk communication* to *Benefit-Risk communication*

On the issue of agencies' **communication abilities** Professor Eicler again quoted Professor B. Fischhoff: *'One should no more expose individuals to an untested risk communication than to an untested drug'*

Regulatory agencies are not experts in communicating and agencies need to address this lack of appropriate skills. One project that the EMEA is supporting, under the IMI Call on Strengthening the Monitoring of Benefit/Risk, is the 'Establishment of methods for graphical expression of the benefit and risk of medicinal products...'

In conclusion

There are potential stumbling blocks in the path to improved communications. Many agencies lack experience and will need to learn from scratch. There is the fear of being seen to be 'advertising' products if the benefits are highlighted and there may be transparency: concerns about being explicit about the process between reviewing data and making decisions on products.

However, the ability to enhance benefit-risk communication to stakeholders is not merely important, it is vital.

BENEFIT-RISK ASSESSMENT: A Singapore perspective

Dr John Lim

Chief Executive Officer, Health Sciences Authority, Singapore

Dr John Lim looked at the developments in benefit-risk assessment from the point of view of a regulatory agency in a relatively developed Asian country but one that is often consigned to the 'rest of the world' in regulatory discussions, that is, outside the ICH. Discussions of a framework for benefit-risk assessment, which has not been specifically addressed by ICH, however, provides an opportunity to involve a wider range of regulatory agencies from the start and not leave such involvement to the stage when guidance has been agreed.

Singapore, sandwiched between the two major countries of India and China is not necessarily representative of Asian-Pacific countries but is at the centre of the global and national regulatory issues that affect the region. All agencies are affected by the increasing pressure on regulators and industry, in today's environment and by the shifting 'appetite' for risk, whether this is a true 'risk-aversion' or the result of greater awareness. Regulators in the Asia-Pacific region also have the increasing burden of dealing with counterfeit and illegal drugs.

The Health Sciences Authority (HSA)

HSA is a small agency but relatively well resourced for the region, in relation to the size of the country. Nonetheless, with limited resources, it has to deal with the same number of products as the major agencies since almost all will sooner or later be submitted in Singapore. This means that there is a need to apply innovative approaches to making the review of medicines both economical and effective.

HSA also faces the challenge of being an 'enabling' agency that supports rather than obstructs Singapore's politically and economically important *Biomedical Sciences Initiative*. Attracting and retaining talent is an important factor and, fortunately, opportunities for this are provided by HSA's unique structure which is suited to research and collaborative development.

The regulatory paradigm

The regulatory philosophy adopted by HSA is the judicious adoption of good international regulatory principles and practices to meet Singapore's unique situation, without:

- Over-regulating
- Simplistically adopting systems of reference agencies
- Blindly approving products already approved elsewhere

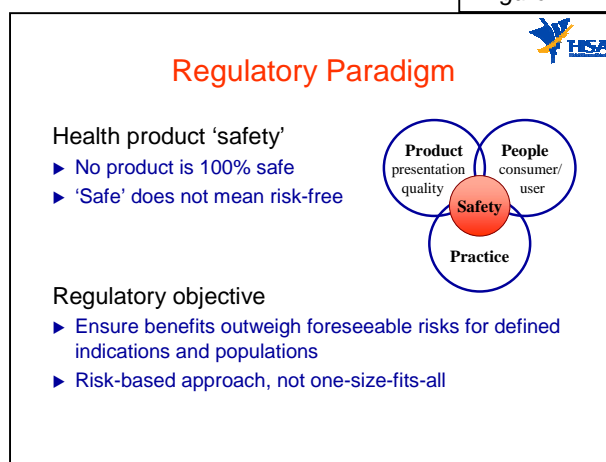
This involves tapping into the expertise of external experts and researchers and fostering strategic partnerships both internationally and regionally. Of particular importance is information sharing and collaboration through memoranda of understanding (MOUs) and mutual recognition agreements (MRAs). These enable the agency to leverage the expertise and work of more advanced agencies and provide opportunities for work sharing with like-minded agencies

The concept of benefit and risk is not widely understood by policy-makers and there is a need to educate the public with simple messages that a 'safe' medicine is not entirely risk free.

On-going communication is of the essence as it is too late, once an urgent problem has arisen, to start introducing the agency and explaining the basis of its benefit-risk decisions.

The regulatory paradigm for HSA therefore includes a proactive communications strategy aimed at inspiring trust

Figure 11



Risk Management

Singapore has developed a 'risk-based' approach to the regulation of medicines with an emphasis on risk management throughout a product's life cycle.

Product review and authorisation

Without being able to handle the volume of data seen by FDA, the HSA must, nonetheless, apply the same standards of safety, efficacy and quality. This is achieved by triaging applications to different evaluation routes according to the inherent risk of the product and its regulatory status elsewhere. HSA has the capability to carry out a **complete review** of products that have not been previously approved but less resource-intensive routes are followed when reliance can be placed on prior assessments by reference agencies.

An **abridged application** process is available for applications approved in one reference agency (FDA, EMEA, PMDA, Swissmedic TGA) where HSA relies on summaries of the basic safety and efficacy data, and its prior assessment, but carries out a full review of the quality and clinical data from Phase II and Phase III trials. For products that have been approved by two or more reference agencies and where the *identical* product is proposed for the Singapore market, there is a **verification** route, which relies on full assessment reports from the other agencies.

Coordinated Risk Management Planning

Risk management plans are developed through a teamed assessment by pre- and post-market HSA personnel, and active discussions with the applicant. Examples of risk mitigation plans include:

- Physician's education materials (including pertinent monitoring parameters);
- Patient's education materials;
- A drug-specific patient registry with regular reports to HSA;
- Reporting of local and overseas serious adverse events (SAEs).

Post-market Risk Management

Risk management after marketing is a continuum to monitor the on-going benefit-risk profile of the product and consists of surveillance and communication elements:

- **Risk detection** through an electronic ADR reporting system but also using forensic pathologists and the HSA toxicology laboratory:
 - Cases were cited of the detection of dangerous adulterants in imported herbal medicines;
- **Risk Assessment:** Seeking the Pharmacovigilance Advisory Committee's advice on major safety concerns with high clinical impact;
- **Risk communication:** Ensuring rapid outreach to doctors through emails, faxes, etc;
- **Corporate communication strategy:** Educating the public on risks in order to influence and manage the 'risk appetite':
 - With an emphasis on the importance of good spokespersons and the need to build long-term trust.

In conclusion

- Benefit-Risk frameworks need to account for variable risk thresholds, cultures and values in different jurisdictions.
 - It is important to develop robust benefit-risk assessment frameworks with universal application and relevance to different global settings
 - There is also a need to enhance communication strategies and skills
 - **Global partnership is a key success factor**
-