



UTILISATION OF A COMMON BENEFIT-RISK FRAMEWORK:

CAN IT FACILITATE DECISION
MAKING AND IMPROVE
COMMUNICATION WITHIN AND
ACROSS AGENCIES?

2-3 FEBRUARY 2015
TAIPEI, CHINESE TAIPEI

WORKSHOP REPORT

Workshop report authors

Prisha Patel, MSc

Neil McAuslane, PhD

Lawrence Liberti, MSc, RPh, RAC

Patricia Connelly, BA, ELS

CIRS - The Centre for Innovation in Regulatory Science - is a neutral, independent UK-based subsidiary company, forming part of the Intellectual Property and Science business of Thomson Reuters. The mission of CIRS is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards and its funding is derived from membership dues, related activities and grants.

Centre for Innovation in Regulatory Science (CIRS)

The Johnson Building, 77 Hatton Garden, London, EC1N8JS, UK

Email: cirs@cirsci.org

Website: www.cirsci.org

UTILISATION OF A COMMON BENEFIT-RISK FRAMEWORK

Section 1: Executive Summary

Background to the Workshop

The benefit-risk decision is the cornerstone of regulatory decision making. Indeed, this applies irrespective if an agency is the first to review a medicine or one that relies on the approval of a reference agency, as it is critical that agencies evaluate the information on new medicines in relation to the local population.

Over the last five years work has been conducted by agencies, companies and CIRS in the construction of a benefit-risk framework for use in the approval and ongoing review of medicines. The diverse methodologies employed by these groups all map to the overarching framework, UMBRA (Universal Methodology for Benefit Risk Assessment).^{*} The UMBRA approach has eight key steps that can be used by agencies and companies to structure their benefit-risk evaluations in a systematic way, which enables both the logic and documentation of what was considered and the evidence included in the decision. This systematic, structured approach to the assessment of benefits and risks is becoming one of the key review tools and an essential component of good review practices.

Although regulators in Europe, USA, Heath Canada, Australia, Switzerland and Singapore have experience in assessing the use of framework structured approach, it has not been widely implemented outside of these countries. In 2013 and 2014 CIRS organised pilot studies in Asia to evaluate a methodology based on the UMBRA framework across countries with different regulatory models and assessed the advantages, challenges and opportunities that agencies perceive in using this approach.

The aim of this Workshop was to discuss the utility of a systematic structured approach to benefit-risk assessment and agencies' experience with its use and how the framework might aid a better understanding both within and across regulatory agencies of how benefit-risk decisions are made as well as how this can facilitate communication with companies and other stakeholders.

Workshop Objectives

- **Identify** the processes, procedures and considerations that agencies undertake to make benefit-risk decisions for their jurisdiction and how these processes are documented
- **Discuss** how utilisation of a structured, systematic benefit-risk framework and its documentation within Asian regulatory agencies can aid both the process and communication within and across agencies
- **Recommend** how a benefit-risk framework can be best used to optimise internal decision making and external communication of the decision

^{*} Walker S, McAuslane N, Liberti L, Leong J, Salek S. A universal framework for the benefit-risk assessment of medicines: Is this the way forward? *Ther Innovation Reg Sci*. published online 1 September 2014.

Introduction

Dr Yu-Mei Chiang, Acting Director General, Taiwan Food and Drug Administration, welcomed Workshop participants to Taipei, saying that the utilisation of a systematic and structured framework for benefit-risk assessment should enhance understanding of decision making among all healthcare stakeholders and has been recognised as an important topic among reviewers at the TFDA. She expressed certainty that the Workshop would serve as an excellent platform for regulatory authorities to discuss, learn and share with each other ideas for building better regulatory frameworks to ensure the safety of public health.

Key points from presentations

Years after the introduction of benefit-risk assessments in Europe, a number of challenges remain including an over-reliance on primary endpoints as parameters for evaluation, often to the exclusion of other important clinical findings. Additionally, some experts may be still uncomfortable in explicitly providing the rationale for their benefit-risk evaluations. Other

key issues include the potential for excessive repetition of information within the supportive documentation, the need to explicitly state uncertainties, to avoid prolonged discussions and to clearly identify value judgements. Despite these issues, **Dr Thomas Salmonson**, *Chair, Committee for Medicinal Products for Human Use, European Medicines Agency, UK* maintained that structured benefit-risk assessment is important to regulators for its ability to facilitate discussions within and between regulatory agencies, enable interactions with applicants, to expedite decision making and to effectively transfer knowledge to non-EU regulatory stakeholders and to downstream healthcare participants within the EU. Ultimately, it is an important tool that allows regulators to transparently build trust.

The Australian Therapeutic Goods Administration routinely applies detailed benefit-risk assessment in reaching regulatory decisions but the agency does not utilise a single template for these evaluations. **Dr John Skerrett**, *Deputy Secretary for Regulatory Services, Department of Health, Canberra, Australia* called international collaboration on benefit-risk assessment “critical” and stated that it will be increasingly important to both understand and explain when different decisions are reached by different regulators using the same data. Notwithstanding the current efforts of stakeholders, media reports on medicines often continue to report either risks or benefits but not both and rarely assess causality. Changes in the nature of drugs and clinical trials, progress in regulatory science and demands by patients for a voice in regulatory decision making all mean that benefit-risk assessment must continue to evolve.

In his provision of the industry perspective on the advantages and challenges of benefit-risk frameworks, **Dr Thomas Kühler**, *Regulatory Policies & Intelligence, Novo Nordisk A/S, Denmark* suggested that these frameworks should be explored as tools for planning the drug development process. They could also be used as systematic means to build regulatory memory and seem amenable to soliciting and incorporating patients' views and accommodating patient-reported outcomes. Tools for benefit-risk assessment are already integral parts of life cycle management activities in some companies; however, industry needs clear guidance and predictability in their use. Although complete harmonisation is probably not a realistic expectation, a convergence of approaches may be both desired and achievable.

As of July 2012, Taiwan has required adherence to the International Conference on Harmonisation (ICH) Common Technical Document (CTD) format, Module 2.5.6, which requires benefit and risk conclusions in dossier submissions. **Li-Ling Liu**, *Director, Division of Medicinal Products, Taiwan Food and Drug Administration, Ministry of Health and Welfare, Taiwan* observed that there has been variability in the approaches taken by applicants in presenting benefit-risk assessment. The ICH M4E(R2), regarding standardising the content and presentation of benefit-risk information in regulatory submissions is under development and it is envisioned that such standardisation will increase efficiency in communication of benefit-risk assessments between industry and regulators. Convergence and harmonisation are needed for benefit-risk structures and processes and for standard data exchange models that will streamline the transfer of data between different stakeholders using the electronic CTD.

A documentation system was developed in support of the CIRS Universal Methodology for Benefit-Risk Assessment (UMBRA), an overarching framework that provides a platform for the coordinated development of benefit-risk assessment methodologies. **Dr Neil McAuslane**, *Director, Centre for Innovation in Regulatory Science, UK* reported that the Summary portion of this system, which consists of the Benefit-Risk Template and User Manual, has recently been evaluated in the CIRS international Summary Approach to Benefit-Risk Evaluation (iSABRE) feasibility and pilot studies by regulatory agencies in China, Indonesia, Malaysia, Philippines and Chinese Taipei. Participants rated the Benefit-Risk Summary Template as good to excellent in navigation, clarity of instructions and applicability and comprehensiveness of guidance. They additionally indicated that the template has the advantages of the systems currently in use in their organisation, contributes to achieving consistency of decisions between regulatory agencies and promotes effective communication to stakeholders. For regulatory agencies in maturing markets, the use of the CIRS Benefit-Risk Summary Template may afford an understanding of the reference agency benefit-risk evaluation and the ways in which it maps to the overarching framework, while providing a structured approach for reaching a local decision regarding the benefit-risk profile of new medicines.

As cited by Dr McAuslane, the Philippine FDA was a participant in the CIRS iSABRE feasibility

and pilot studies, in which regulatory agencies in China, Indonesia, Malaysia, Philippines and Chinese Taipei assessed the potential of the Summary portion of the CIRS Benefit-Risk Template for use in their agencies' evaluations of new medicines. **Pia Angelique Priagola**, *Food-Drug Regulation Officer III, Food and Drug Administration, Philippines* informed the Workshop that the Philippine FDA experienced several challenges in the deployment of this evaluation tool, including a lack of experience in its use and the subjective nature of assignment of values and weights to benefit and risk parameters. In addition, it was felt that decisions may be influenced by unmet medical needs for specific diseases in different parts of the country, as well as the various modalities available for healthcare. Despite these challenges, the Philippine FDA is investigating incorporation of the use of the CIRS Benefit-Risk Summary Template into its current review framework. The Philippine FDA currently collaborates with regulatory agencies in ten other countries in the Association of South East Asian Nations (ASEAN). The CIRS Benefit-Risk Summary Template should facilitate this and other collaborative efforts. Furthermore, it will allow enhanced coordination and communication among regulators, academia and other stakeholders.

Azura Abdullah, *Head of Unit/Section for New Drug Products, Centre for Product Registration, National Pharmaceutical Control Bureau, Ministry of Health, Malaysia* reported that the regulators in Malaysia found that elements of the Benefit-Risk Summary Template are already included in their current review processes, although not as part of a specific template or format. Evaluators concluded that a benefit-risk framework acts as a method for communication between industries, agencies and other stakeholders and facilitates the development of better risk communication and risk management strategies. An appropriate, reliable, structured approach to assessment will help to improve the consistency of assessments and provide for reproducible outcomes, which will help to facilitate and improve the regulatory decision-making process.

Dr I-Chun Lai, *Team Leader/Medical Reviewer, Division of New Drugs, Center for Drug Evaluation, Ministry of Health, Taiwan* said that the CDE evaluation showed the CIRS Benefit-Risk Summary Template to be practical in assisting logical thinking and in conducting a benefit-risk assessment. Specific recommendations for enhancement include reconsideration of Section 3.1, which although it was regarded as useful

for reviewers, may become too complex if many pivotal studies needed to be presented, making it more challenging to see key benefits and risks at a glance. Additionally, repetition between sections should be evaluated and guidance provided in weighting benefits and risks, particularly for the results of clinical trials with multiple treatment options, potentially through more information and guidance in the CIRS Benefit-Risk Summary Template User Manual.

Dr Yee Hoo Looi, *Regulatory Consultant, Therapeutic Products Branch, Health Sciences Authority (HSA), Singapore* detailed the results of a retrospective study of the use of the CIRS Benefit-Risk template by HSA reviewers. Although the overall findings were very positive, reviewers expressed concern about duplication of work required to use the template in addition to current systems and training in the understanding and application of relative importance weights. Nevertheless, the study concluded that the Summary Template was fit for purpose in documenting relevant information supporting the study outcomes, regulatory decision and the benefits and risks under consideration and could be useful in comparing the basis for regulatory decisions between jurisdictions.

Good regulatory decision making is the key to achieving a high-quality system for the regulation of medicines. A structured and systematic approach to benefit-risk assessment, based on knowledge and experience as well as on scientific justification, will produce consistent, clear and predictable decision making. Such a framework has been incorporated by the National Committee on Drug Evaluation to generate recommendations for its decision making according to **Dra Nurma Hidayati**, *Director of Drug and Biological Products Evaluation, National Agency of Drug and Food Control, Indonesia*. Benefit-risk evaluations are conducted by both the NADFC review centres and the National Committee on Drug Evaluation as part of their assessments and decisions are based on an evaluation of the clinical, non-clinical and quality data contained within a product dossier as well as an assessment of other relevant data such as input from related ad-hoc experts, national public health needs, medical literature and other agencies' published public assessment reports.

Dr Joey Gouws, *Registrar of Medicines, Medicines Regulatory Authority, Department of Health, South Africa* detailed the challenges faced

by regulators in countries with emerging pharmaceutical markets. Each agency has to determine the public health priority represented by potential new medicines, given the policies of its government. These regulators need to understand the intrinsic and extrinsic factors that are relevant to their population, such as genotypes and phenotypes, disease manifestation and study populations, identifying major scientific questions and possible resolutions to those questions, using the information necessary for marketing authorisation versus the information that must be collected in the post-marketing period. Finally, the benefit-risk profiles of these medicines must be understood, particularly as they relate to patient safety and the actions of other regulatory agencies on the same application appreciated. Consideration of these factors and the implementation of good regulatory review practices including decision-making frameworks will allow the optimisation of available regulatory resources in even the smallest of emerging markets.

Benefit-risk determinations for new medicines are made from early phase development through post-authorisation from the perspectives of stakeholders that include industry, regulators, clinicians and patients. These evaluations are influenced by differences in regulatory policies, procedures and requirements, by local medical practices and guidelines and disease prevalence and by the amount and quality of patient input. **Dr Susan Forda**, *Vice President, Global Regulatory Affairs, Eli Lilly, UK*, provided examples of these influences including the ways in which distinctive local benefit-risk elements affect an approach to global development. The monoclonal antibody ramucirumab was approved in the United States and EU for treatment of gastric cancer, using an orphan drug registration pathway. However in Japan, which has the third highest incidence of stomach cancer in the world at 29.9 per 100,000, the drug could not be granted orphan status, which resulted in a different, tailored submission strategy for that country. Being able to present the benefits and risks of the product in a way that met each agency's expectations has facilitated communication with these agencies.

Health Canada experience with international regulatory collaboration has demonstrated that significant planning and investment are required to build relationships and confidence. Key collaborative tasks include identifying

priority areas, developing work plans with clear deliverables and timelines, convening regular meetings and conducting staff exchanges. Collaboration also requires a forum with a specific mandate and leadership to promote collaboration and link strategically with other international initiatives.

Barbara J Sabourin, *Director General, Therapeutic Products Directorate, Health Products and Food Branch, Health Canada* added that a number of factors are needed to enable collaboration such as a common glossary or lexicon, industry support and engagement, cooperation and buy-in at both the reviewer and senior executive levels within an agency, mechanisms to share confidential information, secure information technology systems, staff training and development and a common framework. In its efforts to utilise a common framework for benefit-risk assessment, the Health Canada Pharmaceutical Safety Efficacy Assessment Template (PSEAT) has been recently modified to incorporate the steps in the CIRS Universal Methodologies for Benefit-Risk Assessment (UMBRA) framework and a new version will be implemented in 2015.

Referencing or leveraging of the work of established regulatory agencies by local authorities can maximise the use of the resources and expertise of these agencies to relieve the work burden and complement ongoing efforts to enhance regulatory capabilities and build confidence for regulatory authorities in emerging markets. Part of a recent study performed by **Dr James Leong**, *Head of Education, Centre of Regulatory Excellence, Duke-NUS Graduate Medical School, Singapore* and colleagues involved the evaluation of a potential decision-making tool by transferring information from publicly available reports from four jurisdictions into the CIRS Summary Template previously detailed by Dr McAuslane. The study found that given the minimal differences among the existing report formats of reference agencies, it may be timely to consider the use of a universal benefit-risk template. If used as a universal template, the CIRS Summary Template could trace and document the evolution of the benefit-risk balance of a product, using data from various jurisdictions and allowing meaningful comparisons, which would lead to increases in consistency, transparency and quality in decision making. It should be recognised; however, that even with a standard assessment template, to develop an appropriate decision for its jurisdiction, each agency still must make its own

critical evaluation, thereby also developing and enhancing its competency.

Beginning in 2010, the CIRS has enlarged and built on its two decades of work in the area of the benefit-risk evaluation of medicines by applying its experiences to the science of decision making as it relates to medicine development. CIRS activities in this regard include Workshops, doctoral research and the global monitoring and evaluation of good review and submission practices. *CIRS Founder, Professor Stuart Walker* remarked that stakeholders in medicines development have indicated to CIRS that decision making is a topic of importance. Accordingly, the CIRS project plan for 2015 to 2017 includes the development of a programme that will identify the general principles of a good decision framework and the processes and practices that build quality into decision making within drug development, regulatory review and health technology assessment. The objectives of this programme include the development and validation of a framework and documentation system for a structured, systematic, transparent and logical approach to decision making and the recommendation and advocacy for the use of good decision-making practices within companies and

Speaking on the role of good review practices in good-quality regulatory decisions, **Dr Justina A. Molzon**, *Former Associate Director for International Programs, Food and Drug Administration, USA* explained that because of the complexity of disciplines and specialties involved in the drug review process, a consistent approach to evaluating submissions and expressing conclusions is needed and guidelines such as those for good review practices have emerged from the need for transparency and consistency. In addition, regulatory processes should incorporate agreed-upon best practices and a common style and review format will help regulators, industry and the public understand the review process from data to interpretation to recommendations and decisions and subsequent regulatory actions. The World Health Organization (WHO) has developed a GRevP document that specifies in part that a good review practice should ultimately enable a reviewer or review team to understand the benefit-risk profile of a medical product, given the indication and context of use. The WHO GRevP guideline further states that adoption of a benefit-risk framework is critical to promote interactions between drug regulatory authorities.

Considering whether structured frameworks can ensure the quality of regulatory decisions, **Professor Hans-Georg Eichler**, *Senior Medical Officer, European Medicines Agency* opined that these frameworks will likely add transparency and relevance to decision making by making the value judgements of regulators explicit. The frameworks may also help to improve the 'light to heat ratio', by shifting the focus of public discourse from questioning the competence or motives of regulators to discussing differences in opinions and perspectives on the basis of the rationales presented by the use of the framework. With all of the available frameworks; however, addressing uncertainty will likely remain the most significant challenge. Use of the frameworks may or may not affect the outcomes of regulatory decisions, which are most influenced by decision makers' attitudes toward risk and ultimately, these tools will likely enhance—but probably not ensure—the quality of regulatory decisions.

Workshop Programme

DAY 1: 2 FEBRUARY 2015	
SESSION: UTILISATION OF A BENEFIT-RISK FRAMEWORK - AN ESSENTIAL COMPONENT OF GOOD REVIEW PRACTICES AND OF REGULATORY DECISION MAKING	
Chairman's welcome and introduction	Barbara Sabourin , <i>Director General, Therapeutic Products Directorate, Health Canada</i>
Country welcome and introduction by TFDA	Dr Yu-Mei Chiang , <i>Acting Director General, TFDA</i>
Development of frameworks for benefit-risk assessment: What is their role and why is it important for agencies, companies, healthcare providers and patients?	
EMA perspective	Dr Tomas Salmonson , <i>Chair CHMP, European Medicines Agency</i>
TGA perspective	Dr John Skeritt , <i>Deputy Secretary for Regulatory Services, Department of Health, Canberra, Australia</i>
Industry perspective	Prof Thomas Kühler , <i>Senior Director, Novo Nordisk A/S, Denmark</i>
Development of UMBRA and its utilisation as an overarching template for a systematic structured approach to benefit-risk assessment of medicines	Dr Neil McAuslane , <i>Scientific Director Centre for Innovation in Regulatory Science, UK</i>
Assessment of benefits and risks in agencies across Asia: Utilisation of a framework approach – challenges, opportunities and future perspectives	
Chinese Taipei	Li-Ling Liu , <i>Director, Division of Medicinal Products, Taiwan Food and Drug Administration, Ministry of Health and Welfare, Taiwan</i>
How do other decision makers collect information from patients and how does this influence decision making? HTA agency viewpoint	
Philippines	Pia Angelique Priagola , <i>Food-Drug Regulation Officer III, Food and Drug Administration, Philippines</i>
Malaysia	Ms Azura Abdullah , <i>Head of Unit/Section for New Drug Products, Centre for Product Registration, National Pharmaceutical Control Bureau</i>
SESSION: PRACTICAL APPLICATIONS AND UTILISATION OF A STRUCTURED APPROACH TO BENEFIT-RISK ASSESSMENT	
How the framework can be used: Potential and practical applications	
Singapore experience from the assessment of abridged applications	Dr Yee Hoo Looi , <i>Regulatory Consultant, Therapeutic Products Branch, Health Products Regulation Group, Health Sciences Authority, Singapore</i>
Use of the framework to communicate and facilitate discussion by the committee	Dra Nurma Hidayati , <i>Director of Drug and Biological Products Evaluation, National Agency of Drug and Food Control (NADFC), Indonesia</i>
Use of the framework to facilitate internal decision making	Dr I-Chun Lai , <i>Team Leader/Medical Reviewer, Division of New Drugs, Center for Drug Evaluation, Taipei</i>

A company assessment of local benefit and risks prior to submission	Dr Susan Forda , Vice President, Global Regulatory Affairs, Eli Lilly, UK
SESSION: ROUNDTABLE DISCUSSIONS	
Roundtable A: Improving local submissions by the use of a structured benefit-risk approach	Chair: Dr John Lim , Deputy Director of Medical Services, Ministry of Health, Singapore; Executive Director, Centre of Regulatory Excellence at the Duke-NUS Graduate Medical School, Singapore Rapporteur: Dr Eyal Schwartzberg , Head of Pharmaceutical Division, Ministry of Health, Israel
Roundtable B: How could a structured decision-making framework assist in enabling patient input into the benefit-risk assessment of medicines?	Chair: Prof Hans-Georg Eichler , Senior Medical Officer, European Medicines Agency Rapporteur: Dr Michael Rozycki , Vice President, Regulatory Affairs Asia Pacific, Allergan Inc, Singapore
Roundtable C: Maximising the value and utility of public summary basis of decision documentation	Chair: Dr Tomas Salmonson , Chair, CHMP, European Medicines Agency Rapporteur: Dr Harindra Abeyasinghe , Vice President, Head of Asia Pacific Regulatory Affairs, Johnson & Johnson Pte Ltd, Singapore
Roundtable D: What are the key elements of different review models that can be used for risk-based approaches to decision making?	Chair: Dr Justina Molzon , Former Associate Director for International Programs, FDA, USA Rapporteur: Prof Bruno Flamion , Professor of Physiology and Pharmacology University of Namur, Belgium
Roundtable E: Monitoring post-authorisation benefits and risks: What are the common elements of a realistic approach for a developing economy?	Chair: Prof Sir Alasdair Breckenridge , Former Chairman, MHRA, UK Rapporteur: Assoc Prof Silke Vogel , Associate Professor / Deputy Director, Centre of Regulatory Excellence, Duke-NUS Graduate Medical School, Singapore
DAY 2: 24 JANUARY 2014	
SESSION: ROUNDTABLE FEEDBACK	
Chairman's introduction	Dr John Lim , Deputy Director of Medical Services, Ministry of Health, Singapore; Executive Director, Centre of Regulatory Excellence at the Duke-NUS Graduate Medical School, Singapore
Feedback by roundtable rapporteurs	
Panel reflection from roundtable session – What are the next steps and opportunities for the utilisation of a systematic structured benefit-risk framework as standard practice in the review of new medicines?	Dr Petra Dörr , Head of Communication and Networking, Deputy Director, Swissmedic Luiza Novaes Borges , Health Surveillance and Regulation Specialist, Brazilian Health Surveillance Agency Gloria Hung , Asia Regional Director, Regulatory, Pfizer, Hong Kong Lawrence Liberti , Executive Director, Centre for Innovation in Regulatory Science

SESSION: BENEFIT-RISK FRAMEWORKS – CRITICAL ELEMENTS TO FACILITATING TRUST AND UNDERSTANDING BETWEEN AGENCIES AND OTHER STAKEHOLDERS.

Chairman's introduction	Dr David Jefferys , <i>Global Regulatory, Government Relations, Public Affairs and European Product Safety, Eisai Europe Ltd, UK</i>
The utilisation of a common benefit-risk framework across countries – How could this underpin trust and understanding between agencies?	
A critical component for regions interested in undertaking shared assessments	Barbara Sabourin , <i>Director General, Therapeutic Products Directorate, Health Canada</i>
Enabling the translation of reference agency decisions to the local jurisdiction for benefit-risk assessment	Dr James Leong , <i>Head of Education, Centre of Regulatory Excellence, Duke-NUS Graduate Medical School, Singapore</i>
A cornerstone of good review practice and an enabler of convergence across regional alignment	Dr Justina Molzon , <i>Former Associate Director for International Programs, Food and Drug Administration, USA</i>
Building quality into the decision-making process: What role do frameworks have in ensuring a quality of decision and what aspects need to be considered?	
CIRS perspective	Prof Stuart Walker , <i>Founder</i>
Mature agency perspective	Prof Hans-Georg Eichler , <i>Senior Medical Officer, European Medicines Agency</i>
Emerging markets agency perspective	Dr Joey Gouws , <i>Registrar of Medicines, Medicines Regulatory Authority, Department of Health, South Africa</i>
Company perspective	Tracy Baskerville , <i>Vice President, Regulatory Affairs, Area and Affiliate, AbbVie, USA</i>

Recommendations from across the Roundtable Discussions

1. Companies and agencies should consider developing local/regional boards of experts to advise on the regional aspects of benefits and risks.
2. Agencies and companies should develop a section of the benefit-risk framework that incorporates local context.
3. Using the industry group TRANSCCELERATE (<http://www.transceleratebiopharmainc.com/>) as a model, an industry-agency group should form to advance the development and use of a globally and locally useful benefit-risk framework.
4. CIRS or other third parties could spearhead efforts to offer training on guidelines for benefit-risk evaluation; potentially at the regional or emerging national level.
5. Commission a study by CIRS to identify and develop case studies of instances in which patient input on benefit-risk was instrumental in bringing a product to market; analyse the case studies to develop an understanding of how to maximise the benefits of patient input and overcome potential barriers; publish and otherwise use the results of the study to develop recommendations for regulators and industry.
6. Initiate discussions with regulatory authorities to develop a plan to formally incorporate patient input into the creation of new therapeutic guidelines.
7. Industry should take the lead on developing and including end-of study benefit-risk feedback methodologies as a formal element of their clinical trials.

8. Regulators should begin to actively request patient input on benefit-risk in certain prioritised marketing authorisations and clinical trial applications. Regulators and industry should work together to identify the best means to incorporate these data into their review process, potentially by adding a new section of the Common Technical Document.
9. Regulators and industry should become more aware of patient input via social media and consider ways to incorporate this input into their benefit-risk assessments.
10. Regulatory agencies that do not have a public assessment report system in place should adopt a format for benefit-risk assessment reports that can also be used as a public assessment report; the current CIRS UMBRA Summary Template is a good framework with some modifications.
11. Regulatory agencies that already have a public assessment report system in place should ensure that these discuss the scientific rationale for why a particular indication was approved; a high-level description of context and medical need; uncertainties regarding benefits and risk especially for conditional approvals and a description of post-marketing commitments.
12. All stakeholders should work through ICH to drive toward a common framework for the convergence of benefit-risk and public assessment reports across all regions.
13. Consider regional agreements on regulatory work sharing.
14. Take advantage of the additional layer of knowledge and level of confidence deriving from previous benefit-risk assessments in mature regions including the direct acceptance of EMA, FDA or neighbouring country decisions, the acceptance of stability data and the review of real world exposure data through periodic safety update reports and updated benefit-risk assessments.
15. Use structured benefit-risk frameworks to develop institutional memory; consider the significant benefits afforded by transparency in benefit-risk evaluation.
16. CIRS could interview regulators from individual countries regarding what information is available to them and how this could be shared to the benefit of multiple jurisdictions.
17. CIRS could provide recommendations on when and how to use facilitated regulatory pathways to expedite the reviews.
18. Stakeholders must recognise the effect of global diversity on post-authorisation issues including cultural differences, variability in healthcare systems, internet technology infrastructure, data collection capabilities and diversity of healthcare professionals involved in data collection and information dissemination.
19. A mutual reliance among stakeholders across and within countries is required, including a commitment to greater and timely information sharing and support for data collection.
20. There is a need for a unified approach to post-authorisation commitments, which currently differ among organisations.

Section 2: Roundtable Discussions

Roundtable Discussion A

Improving local submissions by the use of a structured benefit-risk approach	
Chair	Dr John Lim , <i>Deputy Director of Medical Services, Ministry of Health, Singapore; Executive Director, Centre of Regulatory Excellence at the Duke-NUS Graduate Medical School, Singapore</i>
Rapporteur	Dr Eyal Schwartzberg , <i>Head of Pharmaceutical Division, Ministry of Health, Israel</i>

Background

The overarching elements of a framework for the assessment of the benefit-risk profile of a new medicine have been well articulated over the last five years, resulting in commonality in the steps taken by both agencies and companies in the assessment of a medicine's benefit-risk profile. Indeed, many companies are now internally using a structured framework to assess benefit-risk in order to better articulate the benefit-risk profile of a new medicine. In addition, EMA and US FDA have both committed to using a benefit-risk framework within their evaluation to better document and articulate the considerations and clinical judgements made in benefit-risk decisions.

As companies and agencies move toward agreeing on and using a structured, systematic framework in the research and development and review of new medicines, a standardised presentation of benefit-risk assessment information in regulatory submissions with specific focus on the ICH CTD section 2.5.6 should be considered. A potential revision to ICH Guideline M4E (R1) has now been adopted as a topic for ICH review but it remains to be determined if having a structured systematic framework for benefit-risk assessment would aid in facilitating good submissions and also improve the quality of decision making by both companies and agencies. The focus of this group is not to duplicate the discussions that are occurring through the ICH process but to discuss how having a structured benefit-risk CTD section could facilitate the quality of the local submission and quality and timeliness of the review as well as the decision-making process itself.

Questions for consideration

- Would a structured benefit-risk section in

local submissions contribute to the quality of the submission? – if so how?

- What does the group believe are the main challenges and opportunities for companies to providing a structured benefit-risk section within their local submission?
- What would be seen as the key elements that should be included in a submission to aid agencies as they consider the local benefit-risk decision?
- Would a structured benefit-risk section in local submissions facilitate the quality and timeliness of the review? – if so how?
- What are the challenges for agencies in using a structured framework and how should this be incorporated into the broader key decision-making processes within agencies?
- If a framework for benefit-risk is adopted how can agencies and companies ensure that the framework is actively used as part of the decision process for both the submission and review?
- What recommendations would the group give to inform the ICH discussions on the inclusion of a structured benefit-risk approach within the CTD section 2.5.6?
- In relation to this Roundtable, are there other topics that should be discussed here or aspects that you might suggest that CIRS research or further investigate?

The Roundtable Group was advised that recommendations might arise from the above topics and/or could relate to:

- How the structured approaches to evaluating the evidence in balancing benefit-risk would improve the quality of the submission and review

- The potential influences on good decision making within agencies and companies both at the levels of reviewer/project team and senior management
- Develop considerations of which companies and agencies need to be aware when applying or imbedding the benefit-risk framework within their decision-making processes

Critical issues

This group agreed that benefit-risk evaluation is integral to medicine development. Furthermore, a framework for this evaluation provides structure and transparency and its use should enhance the quality of regulatory submissions. Although both regulators and companies may find the use of a benefit-risk framework to be useful, these groups typically employ different approaches.

From an industry perspective, the multiplicity of models represents a potential complexity and companies would appreciate the development of a globally acceptable structured benefit-risk framework. Failing the existence of this model, a commonality of language for benefit-risk evaluation is vital. It should be recognised, however, that even when a standard approach to benefit-risk evaluation is employed, it is possible to arrive at different decisions in the evaluation of a single medicine; this will occur regardless of the format that companies use to provide benefit-risk data, agencies can deconstruct the presentation according to their needs.

Both regulators and companies agree that dossiers are developed for a global submission plan but each submission may need to be slightly revised to consider local factors. The benefit of this local benefit-risk assessment is that the evaluation is conducted in the context of local standard of care and even though the data are the same as for the global submission, local analyses may change the appropriate indication for a new medicine from being a second-line to a first-line treatment. Despite this important aspect of local evaluation, the need to provide local data in dossiers, such as that from ethnic bridging studies, can represent an extreme logistical challenge for industry.

There are major differences in the capacities and resources of individual countries and agencies and companies' strategic approaches should address not only the market potential but also accommodate the realities of the regulatory environment.

Although companies would be interested in learning what factors lead to specific approvals though public assessment reports, they are frequently not informative due to the fact that sensitive information is often redacted.

Strategies

- Although submission decisions reside with industry and regulatory decisions reside with agencies, other stakeholders act as advisors for those decisions. Patients, healthcare professionals and other experts may provide input that may be very disease, jurisdiction or technology specific.
- Industry has great resources and may be able to lead efforts with some regulatory agencies to build their capabilities.
- Healthcare professionals should be introduced to and trained in the concept of benefit-risk evaluation.
- Regional-level issues such as the need for confidence building or the lack of formal consultation mechanism or opportunity for pre-submission advice should be addressed throughout the benefit-risk process, keeping resource limitations both on the parts of the companies and agencies in mind.
- Global industry executives should be regularly informed about local regulatory considerations and the concerns of their affiliates.
- Agencies should be careful not to oversimplify their interpretation of mature agencies' benefit-risk evaluations.
- Companies should begin to use a benefit-risk template early in product development rather than have to shoehorn data into a format for a specific submission.
- Regulatory transparency should not only centre on the decision outcome but also on the rationale for the decision.
- In order to embed consideration of capacity and resource issues into the development of global benefit-risk guidelines, regional regulators should collaborate and provide their input at the international level through such bodies as ICH.

Recommendations

- Companies and agencies should consider developing local/regional boards of experts to advise on the regional aspects of benefits and risks.
- Agencies and companies should develop a section of the benefit-risk framework that incorporates local context.
- Using the industry group TRANSCCELERATE (<http://www.transceleratebiopharmainc.com/>) as a model, an industry-agency group should form to advance the development and use of a globally and locally useful benefit-risk framework.
- CIRS or other third parties could spearhead efforts to offer training on guidelines for benefit-risk evaluation; potentially at the regional or emerging national level.

Roundtable Discussion B

How could a structured decision-making framework assist in enabling patient input into the benefit-risk assessment of medicines?

Chair	Prof Hans-Georg Eichler , <i>Senior Medical Officer, European Medicines Agency</i>
Rapporteur	Dr Michael Rozycki , <i>Vice President, Regulatory Affairs Asia Pacific, Allergan Inc, Singapore</i>

Background

As companies and agencies develop and review new medicines, there has been a growing awareness that the patient's voice is a critical component in the decision process. Moreover, the patient's role is central throughout a medicine's life cycle. In the development phase, patient input allows companies to ensure that they are developing medicines of value to their primary stakeholder, whilst during the regulatory review of new medicines patients can provide a perspective on the maximum acceptable risk and minimum acceptable efficacy; these may differ from the assessments made by regulators. Therefore, patients' perspectives on benefits and harms and their relative importance are critical to the development and review of new medicines. This is both at the disease level and the therapy level.

Current methodologies for incorporating patient perspectives are criticised as either being too complex and expensive or having issues related to scientific reliability or regulatory acceptance. In addition, regulatory agencies have the challenge of extrapolating individual patient viewpoints on benefit and harms to the general patient population. However, there is agreement from all stakeholders - patients, industry and agencies - that patients need to be engaged in a discussion of benefits and harms and how these can be considered in regard to the relative importance in the benefit of patients.

The focus of this Roundtable was to discuss how and when patient involvement would be of value in providing perspectives on benefit-risk/harms/tradeoffs to both companies and agencies as a new medicine is being developed and approved and if a structured decision-making framework would assist in these efforts.

Questions for consideration

- What do you think is the importance for patients to inform the benefit-risk decision?
- What is the current situation in your country

for companies and agencies in obtaining benefits and harms information directly from patients as part of the development and review process?

- How and when can/should patients contribute to the benefit-risk decision – at a product level, the disease level, or both?
- What are the main areas for which patients can provide information of value to regulatory agencies and companies – would a structured decision-making framework assist?
- Who should be responsible for the collection of patient input and how could this be best achieved?
- If patient information is solicited, should there be feedback on how this information was used in the decision-making process?
- Should submissions have a specific patient perspective section, giving their perspectives on benefits, risks and tradeoffs?
- How should the patient perspective be communicated to external reviewers or expert committees?
- What are the challenges and opportunities for regulatory agencies and companies in soliciting patient input?
- What does the group think is the future landscape for patient involvement in the review process in Asia?
- In relation to this Roundtable, are there other topics that should be discussed here or aspects that you might suggest that CIRS research or further investigate?

Critical issues

The members of the Roundtable Group agreed that patient input into benefit-risk decision making is critical but that patient input via patient-related outcomes has been slow to progress to input into other avenues of benefit-risk assessment. In the past, factors that limited the acquisition of this input included

the perception that because patients were not scientifically trained their input did not add value and the fact that agencies and industry did not want to relinquish control.

However, there has been a recent upward trajectory of patient involvement driven by an information “explosion” and by patients being proactive in their own interest. Trajectory for this trend varies by region, therapeutic area and culture and depends on available opportunities for patient involvement.

It may be necessary to convince regulators and industry to solicit input on a systematic basis as many agencies currently have little contact with these stakeholders and most companies fail to follow up on patients’ experience once the clinical trials have been completed.

Whilst methodologies for soliciting input must be considered, this consideration must be tempered by the need to prioritise finite resources. Other issues to be considered include how much weight to give to patient input and when and the identification of the touch-points in the development and approval process where patient input is most meaningful.

Strategies

Companies and agencies can build a better understanding of the potential benefit of patient input into benefit-risk assessment by developing case studies around previous instances in which patient input on benefit-risk was instrumental in bringing a product to market; for example in HIV. The case studies can then be analysed to develop an understanding of how to maximise the benefits of patient input and overcome potential barriers.

Examining the product development pathway can help to identify potential times where patient input can be encouraged and used to maximum effect. In early or pre-development,

patient input can be utilised in the development of therapeutic guidelines for new products. Patients can be queried to determine what symptoms and other aspects of a disease are most important to them; which known risks they would be willing to accept in a new treatment or how likely their compliance would be with certain courses of treatment.

During clinical development, the experience of enrolled patients can be reviewed at the end of clinical trials to obtain their input on how the treatment benefited or harmed them based on information beyond the data collected for the clinical trial. Although a specific methodology to obtain this patient input must be developed, patients are already providing benefit-risk input in the form of quality of life assessments. These could be expanded to include assessment questions such as “on the whole, was this treatment worthwhile?” potentially augmented by randomised patient interviews. Industry can also include the development of methodologies to elicit patient benefit-risk input on the agendas of things to be discussed during their meetings with regulators.

At the time of regulatory review, patient input on benefit-risk assessment should be included prior to a review decision and more can be done to elicit patient preference as a factor to be weighed by agencies in making approval decisions. Including a patient-input component directly into a benefit-risk framework would certainly facilitate the use of patient preferences in the overall assessment; however, the source and nature of the information must be determined. It may be possible to add a specific, potentially mandatory section to the benefit-risk section of the common technical document, either to discuss the patient benefit-risk data or else to justify why it was not possible to obtain it.

Recommendations

- Commission a study by CIRS to identify and develop case studies of instances in which patient input on benefit-risk was instrumental in bringing a product to market; analyse the case studies to develop an understanding of how to maximise the benefits of patient input and overcome potential barriers; publish and otherwise use the results of the study to develop recommendations for regulators and industry.
- Initiate discussions with regulatory authorities to develop a plan to formally incorporate patient input into the creation of new therapeutic guidelines.
- Industry should take the lead on developing and including end-of study benefit-risk feedback methodologies as a formal element of their clinical trials.
- Regulators should begin to actively request patient input on benefit-risk in certain prioritised marketing authorisations and clinical trial applications. Regulators and industry should work together to identify the best means to incorporate these data into their review process, potentially by adding a new section of the Common Technical Document.
- Regulators and industry should become more aware of patient input via social media and consider ways to incorporate this input into their benefit-risk assessments.

Roundtable Discussion C

Maximising the value and utility of public summary basis of decision documentation

Chair	Dr Tomas Salmonson , <i>Chair, CHMP, European Medicines Agency</i>
Rapporteur	Dr Harindra Abeysinghe Vice President , <i>Head of Asia Pacific Regulatory Affairs, Johnson & Johnson Pte Ltd, Singapore</i>

Background

Communication of and transparency around the benefit-risk decision are key components of any summary basis of approval or public assessment report that is created by the regulatory agency upon licensing a new medicine. This information is critical for both patients and physicians to aid them in understanding the benefits, harms and uncertainty of a medicine and how the agency viewed these to come to the benefit risk decision.

As agencies move toward agreeing on and using a structured systematic framework in the review of new medicines that requires a more explicit evaluation and documentation of the benefits, harms and uncertainties of medicines, should this change the way the decision is communicated in the summary basis of approval or public assessment reports?

The Roundtable was provided with a list of the possible components of benefit-risk assessment tools that might be communicated in the public summary basis of decision document (Figure 1). They were additionally queried as to whether

restructuring the benefit-risk section of the public assessment report or summary basis of approval would improve clarity on the benefits, harms and uncertainties and enable sharing of information across agencies, companies and patients, allowing all stakeholders to understand what the regulatory agency has evaluated and to reach their own benefit-risk decision based on the same information.

Questions for consideration

- Should the benefit-risk section of public assessment reports be structured in the future so that it mirrors the benefit-risk decision framework used by the agency?
- What does the group believe are the main challenges and opportunities for aligning the public assessment reports to the benefit-risk framework?
- Which components of the benefit-risk assessment does the group think will be of most value to share in a public-facing document? (please see table below of possible components)
- What are the key challenges and potential opportunities for improved transparency, decision making and communication by using the structure of the overarching benefit-risk framework in public assessment reports and summary basis of approvals
- Does the group think this could increase the utility of public-facing documents and be of benefit to other agencies as they make their own decision?
- In what ways does the group think this could be of benefit to other stakeholders: companies, patients, doctors, etc?
- What is the value to having a public summary basis of decision for a negative decision?
- In relation to this Roundtable, are there other topics that should be discussed here or aspects that you might suggest that CIRS research or further investigate?

Figure 1. Which of these components should be included in public assessment reports for new medicines?

Possible components of a benefit-risk assessment to share in public-facing documents	
Background (Decision context)	• Specify proposed therapeutic indication • Treatment modalities evaluated • Medical need
Overall summaries	• Quality conclusions • Non-clinical conclusions • Human pharmacology conclusions • Clinical conclusions
Identified benefits and risks	• Listing of all benefits and justification for inclusion and exclusion • Listing of all risks and justification for inclusion and exclusion • Clinical study summary • Risks: Overall summary • Weighting and valuing of benefits and risks
Conclusion	• Discussion on evolution of the benefit-risk balance • Discussion on outstanding issues and other significant information (hearings, advisories, patients, consumers, stakeholder inputs) • Discussion on pharmacovigilance plans and risk mitigation plans • Discussion on need for further studies • Any other information relevant to the benefit-risk decision • Conclusion on the benefit-risk balance for proposed indication • Recommendation indication

Critical issues

Most Asia Pacific regulatory agencies review public assessment reports or summary bases of approval from major health authorities such as the Health Canada, the EU EMA, US FDA or Australian TGA to aid in their local assessment of a regulatory dossier. These major agencies may employ different formats and while all include some description of a benefit-risk assessment in their evaluations, key aspects of these assessments, which may be of public value, can be difficult to locate within the document. Additionally, the context around specific analyses for decision making are often lacking in these reports. Because of resource issues, local acceptance and current legal frameworks, most regulatory agencies in the Asia Pacific do not publicly post their assessment reports. Members of this Roundtable agreed, however, that Asia Pacific agencies use these reports for local assessment and the posting of public assessment reports helps to establish transparency and serves a public need. There was further agreement that benefit-risk assessments should reflect findings from other agencies' assessment reports but should be customized for local utility.

Strategy considerations

The level of technical description employed in assessment reports depends on the target audience, whether that audience is a) healthcare professionals, health technology assessment agencies, industry and patient organisations or b) the media and the general public. Both of these stakeholder groups are important but current assessment reports are targeted to the first group. However, documents for

the general public could be derived from these current reports, while exercising care to avoid duplication of work and overburdening regulators.

There should be limited disclosure of information for negative decisions, including a short summary of benefit and risks; currently only the EMA and TGA post these reports. Additionally, the scope of benefit-risk contained within public assessment reports must be defined for new chemical entities, biosimilars and generics, as each will have unique criteria for benefit-risk assessment.

Recommendations

- Regulatory agencies that do not have a public assessment report system in place should adopt a format for benefit-risk assessment reports that can also be used as a public assessment report; the current CIRS UMBRA Summary Template is a good framework with some modifications.
- Regulatory agencies that already have a public assessment report system in place should ensure that these discuss the scientific rationale for why a particular indication was approved; a high-level description of context and medical need; uncertainties regarding benefits and risk especially for conditional approvals and a description of post-marketing commitments.
- All stakeholders should work through ICH to drive toward a common framework for the convergence of benefit-risk and public assessment reports across all regions.

Roundtable Discussion D

What are the key elements of different review models that can be used for risk-based approaches to decision making?	
Chair	Dr Justina Molzon, <i>Former Associate Director for International Programs, FDA, USA</i>
Rapporteur	Prof Bruno Flamion, <i>Professor of Physiology and Pharmacology University of Namur, Belgium</i>

Background

All regulatory agencies are challenged by an increasing review workload and manpower capacity that rarely keeps pace with that workload. Despite this challenge, agencies remain charged with assuring quality decisions about the benefits and risks of the medicines they review. In order to focus attention on those new medicine assessments that may require the contribution from a diverse mix of staff and outside experts, a risk-based approach to triaging new medicine dossiers could be used. Products that pose less risk or that meet other criteria could be candidates for a more abbreviated, expedited, yet thoughtful review pathway.

Models for this risk-based process are now being considered or implemented in some form by numerous growing agencies. This process allocates a product to a verification, abridged or full review. Some agencies use an ad hoc approach to determining whether a product can be reviewed through an expedited or abbreviated route; however, many agencies are striving to codify a process that will allow a risk-based approach to review such that all

stakeholders, most importantly the dossier holders, will have clarity around the expectations for the submission package and the review process.

A Roundtable Discussion Group addressed the issues of “What are the pathways that can expedite the regulatory review process?” at the January 2014 CIRS Workshop held in Lima Peru and identified elements of a common process and presented these graphically to the Workshop (Figure 2).

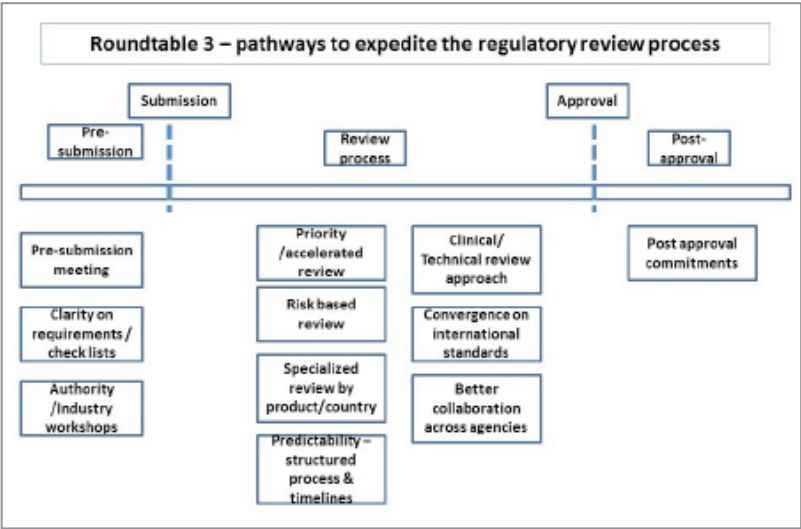
To further this discussion, this Roundtable was charged to explore how agencies are using various review routes and the criteria for and practical aspects of using those diverse routes. They were additionally requested to

- Develop elements of an ideal stratified approach acceptable to sponsors, regulators, legislators and patients while discussing the diversity of approaches agencies use to review new medicine dossiers;
- Identify key elements of risk-based review models that can stratify the approach to reviews and allow an agency to concentrate its efforts on products that have the potential for the most significant risk-based issues and
- Build on the Lima Peru Roundtable’s approach to addressing expedited regulatory approaches.

Questions for consideration

- What criteria should be used to determine which new medicines require a more in-depth review of the dossier versus those that could be assessed by an abbreviated review process/route? (eg, unmet medical need, first in class, prior reviews by mature agencies)
- How do the risks posed by a new product form the basis for determining what type of review a product should undergo?
- What role can a structured benefit-risk assessment tool play in assessing new

Figure 2. Pathways to expedite the review process, presented by Roundtable 3 at the CIRS Lima Peru Workshop, January 2014.



products, irrespective of the approval route? How would the tool need to be modified for each route?

- For products that will undergo some form of abbreviated review, what are the critical elements of the dossier that should be assessed? (eg, number of patients studied, duration of therapy, end point change magnitude, statistical changes, clinical relevance)
- What is the role of external experts in a risk-based review process?
- How do reviews conducted by other agencies inform which pathway a review could follow?
- What options could be developed for different review pathways? How can an agency determine which of these pathways are relevant to its structure/legal mandate?
- How can the elements of a stratified risk-based review model be applied to critical new medicines for unmet medical need?
- What post-approval controls would need to be in place to accommodate the needs of the various risk-based approaches?
- In relation to this Roundtable, are there other topics that should be discussed here or aspects that you might suggest that CIRS research or further investigate?

The Discussion Group was told that recommendations might arise from the above topics and/or could relate to:

- Developing a list/graphic of key elements that underpin a risk-based approach to medicine assessment
- Assessing how this process can help expedite the review process
- Determining ways to maximise the use of existing risk-based assessment platforms

Critical issues

This Discussion Group provided two caveats for consideration surrounding risk-based approaches to regulatory review. First, there are huge global differences in review models based on available resources. The FDA model seems to imply the highest level of flexibility, direct interactions and agreements derived from face-to-face meetings. The EMA model is based on group (committee) decisions, which imply some formalism but results in good reliability and balanced views from twenty-eight member

states and associated experts. Second, review models in emerging countries are particularly resource dependent and sometimes more legally constrained.

Although the value of a risk-based approach to regulatory review is understood and generally acknowledged, in practice this type of review remains uncommon because of a lack of resources, training and expertise; difficulty in ascertaining which products do not raise safety issues before actually assessing them; limited information posted in the public domain by mature agencies who are first to review products and a lack of formal information sharing agreements between countries. Other critical issues in countries with emerging pharmaceutical markets include non-essential, resource-consuming priority tracks sometimes embedded in local regulations such as the use of the Certificate of Pharmaceutical Product (CPP) compliant with World Health Organization format despite the fact that this documentation is often not helpful in assessing quality and the priority placed on items on the countries' essential drug lists such as paracetamol, which gives rise to delays for other, more innovative products.

Beyond risk-based approaches, expedited reviews may be limited by the rarity of pre-submission scientific meetings because of agencies' limitations and the reliance of industry on previous approvals in other regions. In fact, companies' market-driven policies may specify submissions to emerging countries after FDA or EMA submissions except for treatment of local medical needs such as malaria or HIV. In addition, industry representatives may not have appropriate expertise for interaction with local authorities and some countries may require local clinical trials or additional preclinical toxicology studies that are not always readily scientifically justified.

Using "rolling submissions", such as the submission of chemistry, manufacturing, controls (CMC) data first to countries with the capacity for evaluation and the later submission of preclinical and clinical studies to other regional countries with other expertise (e.g, non-clinical, clinical) later, is rarely used. In some countries, sponsors of generics submit dossiers for many products, overburdening the system.

Strategies for emerging markets

The Roundtable Group advocated the broader use by regulatory agencies in emerging markets of pre-qualification programmes established by mature agencies such as Article 58 by EMA. The use of national external experts, with due consideration to the availability of these experts, to the need for training and the advisability of imposing timelines, represents another strategy to improve regulatory review efficiency.

Recommendations

- Consider regional agreements on regulatory work sharing.
- Take advantage of the additional layer of knowledge and level of confidence deriving from previous benefit-risk assessments in mature regions including the direct acceptance of EMA, FDA or neighbouring country decisions, the acceptance of stability data and the review of real world exposure data through periodic safety update reports and updated benefit-risk assessments.
- Use structured benefit-risk frameworks to develop institutional memory; consider the significant benefits afforded by transparency in benefit-risk evaluation.
- CIRS could interview regulators from individual countries regarding what information is available to them and how this could be shared to the benefit of multiple jurisdictions.
- CIRS could provide recommendations on when and how to use facilitated regulatory pathways to expedite the reviews.

Roundtable Discussion E

Monitoring post-authorisation benefits and risks: What are the common elements of a realistic approach for a developing economy?

Chair	Prof Sir Alasdair Breckenridge , <i>Former Chairman, MHRA, UK</i>
Rapporteur	Assoc Prof Silke Vogel <i>Associate Professor / Deputy Director, Centre of Regulatory Excellence, Duke-NUS Graduate Medical School, Singapore</i>

Background

The granting of a new medicine's market authorisation is just the first step in an ongoing process to ensure the availability of safe and effective treatments in a country. The experiences presented in the controlled clinical settings described in the marketing authorisation dossier may not adequately reflect what will occur in the real world and what occurs in the post-approval period may be key to understanding the real benefits and harms of a product as it is being used in real-world settings.

Every agency works to understand the real-world experience of a newly approved medicine, not only in the initial post-authorisation phase but even many years after the first approval. However, not all jurisdictions have the technical infrastructure to enact detailed pharmacovigilance across their constituents and skilled personnel may be at a premium. In the face of these considerations, how can a growing agency work with sponsors, other agencies and other stakeholders to best develop and manage a pharmacovigilance strategy tailored for its country's capabilities and needs?

This Roundtable Discussion Group was requested to discuss the diversity of approaches agencies use to monitor the post-authorisation experience with a new medicine and to identify key elements of pharmacovigilance processes that can form the basis of a common approach.

Questions for consideration

- How can an agency best use information issued by or submitted to other agencies such as safety alerts and periodic benefit-risk assessment reports
- What are the key elements required for a basic yet insightful post-authorisation pharmacovigilance system?
- How and when does the label get changed? What is the most expeditious and practical manner to update product package inserts

and labelling that protects public safety but is not a burden to the company and agency?

- What role can the internet, social media, phone applications and other common technologies play in helping a specific agency understand the benefits and risk of medicines in its country?
- How can internal country-specific controls be used to control and understand post-approval benefits and risks such as limiting prescribing to selected clinics, hospitals and physicians?
- What interactions should the agency expect with the sponsor to understand the evolving benefit-risk profile of an approved product such as periodic summary reports or special alerts?

The Discussion Group was told that recommendations might arise from the above topics and/or could relate to:

- Developing a list of key elements that underpin a basic workable pharmacovigilance programme
- Determining ways to maximise the use of existing pharmacovigilance platforms within each country
- Assessing ways to effectively draw on experiences in other regions to inform local decisions

Critical issues

The four primary stakeholder groups - patients, healthcare professionals, industry and regulators - each have responsibilities in the post-authorisation process.

Patients are responsible for submitting reports in a structured manner directly to regulatory or industry and advocacy groups and through less structured settings such as patient groups and social media in developing economies.

Healthcare professionals, particularly physicians, are responsible for passive

surveillance methods such as spontaneous reporting of adverse events as well as methods for active surveillance such as the compilation of patient records, registries and patient-accumulated databases.

Industry's responsibilities in post-marketing processes are related to country-specific requirements to submit reports such as periodic safety update reports and periodic benefit-risk evaluation reports. Medical Scientific Liaisons within industry are charged with informing healthcare professionals of regulatory issues. Finally, industry must conduct phase IV trials for approved medicines as required.

Regulatory agencies act as recipients of reports leading to actions such as the provision of feedback information to patients and prescribers. They can additionally issue warnings, limit the prescription of medicines or remove a drug from the market altogether. Agencies are also accountable for accepting risk management or risk minimisation plans from industry or establishing post-authorisation requirements and commitments and for conducting periodic re-evaluations.

Post-authorisation in developing economies

Regulatory agencies in emerging jurisdictions may not have strong ties to public health delivery programmes, which may limit their ability to implement and manage pharmacovigilance systems.

There are differences in the roles of stakeholders in developing economies compared with mature economies. For healthcare professionals, these differences include issues such as the fact that medicines are often obtained outside of a pharmacy and without prescription. Public health campaigns may be separated from regulatory connections and nurses may play a more prominent role.

For patients in developing economies, social media may be the fastest way of learning about medical issues but internet access remains problematic, especially in rural areas and there is a greater reliance on healthcare professionals for this access. Additionally, cultural context may determine what information the patient is willing or able to contribute and traditional medicine may assume a greater role. Finally, grass roots organisations may provide education about safe medicine use by patients.

Among regulators, there is a huge variability among economies for resources, training and capability; therefore, mutual recognition and information exchange among regional regulators is essential to ensure drug quality and enforcement actions.

Industry in emerging economies is also highly diverse, including multinational and national companies that range from small to huge. In fact, the local presence of a multinational company may be limited and depend on local distributors. Despite this, industry is bound by a social contract that holds them responsible not only for the supply of medicines but for their stewardship.

Recommendations

- Stakeholders must recognise the effect of global diversity on post-authorisation issues including cultural differences, variability in healthcare systems, internet technology infrastructure, data collection capabilities and diversity of healthcare professionals involved in data collection and information dissemination.
- A mutual reliance among stakeholders across and within countries is required, including a commitment to greater and timely information sharing and support for data collection.
- There is a need for a unified approach to post-authorisation commitments, which currently differ among organisations

PANEL: REFLECTIONS ON ROUNDTABLE DISCUSSIONS

Dr Petra Dörr, *Head of Communication and Networking, Deputy Director, Swissmedic*

- **Reliance:** Reliance on the assessments of reference regulatory authorities from the premarketing through the post-approval period is a concept that is echoed through many of the discussions at this and other Workshops about risk-based regulatory review and information sharing. In accordance with Article 13 of its Therapeutic Products Act, Switzerland has relied on the assessments of other established regulators since 2002. Where applicable, Swissmedic relies on reference authority assessments from first-line approval through post-marketing surveillance. In order to facilitate reliance approaches, stringent regulatory authorities should consider making the results of their regulatory assessments publicly or more widely available to regulators from smaller and emerging markets as part of regulatory best practices.
- **Convergence:** The regulatory community is moving toward convergence, which allows for more flexibility at regional and national levels if compared to the concept of harmonisation.
- The WHO has recently issued Good review practices guidelines for regulatory authorities based on work performed in APEC. Hopefully, a broadly acceptable benefit risk framework could be incorporated in the next revision of this document as it plays such a major part of regulatory review.

Luiza Novaes Borges, *Health Surveillance and Regulation Specialist, Brazilian Health Surveillance Agency*

- The recognition of the importance of a structured benefit-risk approach is no longer in question. We fully recognise the advantages of this approach and its ability to strengthen our decision-making process; however, methods for implementation in the face of agency limitations in size and resources remain to be resolved. In consideration of this issue, our agency may engage in a partnership with CIRS to develop a feasibility and pilot study for the use of a benefit-risk framework in Brazil.

Gloria Hung, *Asia Regional Director, Regulatory, Pfizer, Hong Kong*

- Industry is always an advocate for harmonisation or convergence because of the complexity of tailoring global submissions to individual agencies, each with specific requirements that entail specific expertise, quality control and compliance review. Identifying the methodology and ultimate goal for convergence can be challenging; however and may require a stepwise approach.
- Smaller and emerging regulatory agencies may not be developing needed experience and expertise because of reliance on prior review or on processes such as the Certificate of Pharmaceutical Product (CPPs), requiring regional efforts in regulatory training and education.
- It would be helpful to industry if there were more structured and constructive regulatory pre-consultation mechanisms, especially in local markets where information regarding medical practice, guidelines, epidemiology or other issues may be vital to local submissions of global dossiers.

Lawrence Liberti, *Executive Director, Centre for Innovation in Regulatory Science*

- An important issue which emerged from the Syndicate discussions and which is associated with multiple benefits and challenges was collecting patient perspective and input on benefit-risk evaluation. One potential method to incorporate patient perspective into company benefit-risk evaluations would be to include patient-reported outcomes or other relevant data from the efficacy section of a dossier. Another technique, which was suggested to me by a patient advocate, would be a tripartite approach wherein patients would be able to report benefits and harms associated with their particular therapies during their participation in a clinical study simultaneously to both industry and to regulators. This direct, independent reporting may provide a way around the negative reaction or “flaming” that some patients have received from fellow patients when they have reported adverse or negative reactions to trial medications in social media.
- Patient-driven pharmacovigilance methods may also need to vary from country to country because of the availability of specific media and should not be constrained by past

practices. In Africa, for example, telephone landlines are relatively rare so patients have moved directly to cell phone and smartphone use, which may represent an opportunity to institute novel approaches for data collection.

Section 3: Presentations

Structured benefit-risk assessment – why?

Dr Tomas Salmonson

Chair, Committee for Medicinal Products for Human Use, European Medicines Agency, UK

The centralised EU review process

Since its inception in 1952, the European Union has expanded from 6 to 28 countries. Each of those countries has one vote in regulatory decisions for new medicines made by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) in which joint decisions are taken by a majority of representatives from member states. This process results in one decision for a medicinal product, with one European label, one document for prescriber information and one patient leaflet and one market for pharmaceutical development.

There are three different routes for a CHMP review: a centralised procedure (CP; Figure 3), a mutual recognition procedure (MRP) and a decentralised procedure (DCP). The route that is selected depends on the type of product and

authorisation history in the EU, regulatory and marketing strategy and company preference.

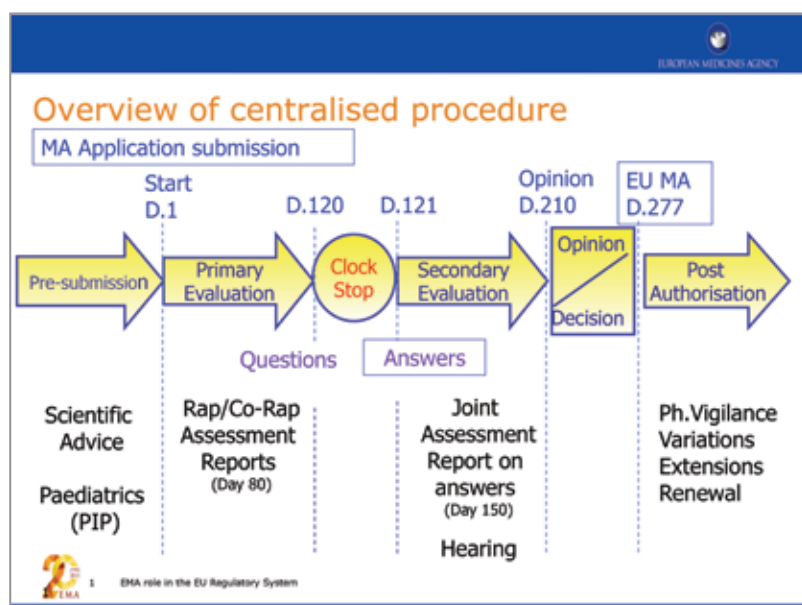
Today, the EMA has seven committees: the CHMP, the Committee for Medicinal Products for Veterinary Use (CVMP), the Committee for Orphan Medicinal Products (COMP), the Committee for Herbal Medicinal Products (HMPC), the Paediatric Committee (PDCO), the Committee for Advanced Therapies (CAT) and the Pharmacovigilance Risk Assessment Committee (PRAC), which continues regulatory overview of a product across its life cycle.

Although there is good regulatory harmonisation in the EU as the result of EMA processes, there is little alignment among downstream stakeholders in the review process, including health technology assessment bodies; payers; national, regional and local committees; prescribers and patients. To convince these participants of the validity of a unified regulatory decision requires transparency, trust and communication. Accordingly, there has been an increasing effort to involve external experts and patients during the benefit-risk assessment during an EMA product review. Currently, patients are only involved in EMA regulatory decision making through participation in scientific advisory groups but the EMA will be conducting pilots with patient panels, comprising 20 to 30 patients who will submit written questionnaires and then participate in a group discussion led by a professional interrogator. It is anticipated that this approach will be used in the oncology setting to establish a balance between outcomes such as progression-free survival and adverse events.

The EMA Effects Table

The EMA Benefit-Risk Project was conducted to improve transparency, communication and consistency of benefit-risk assessments and to move the thinking regarding benefit-risk decisions from an implicit to explicit process. Four Work Packages were completed in this project: a description of current practices; an evaluation of the applicability of current tools and methods; field tests of tools and methods; and the development of a benefit-risk tool kit. The last Work Package, which is for a pilot and training is ongoing.

Figure 3. The CHMP centralised review procedure



The Benefit-Risk Toolkit that was proposed as part of Work Package Four consisted of Multi Criteria Decision Analysis (MCDA), a quantitative method that allows higher precision and sensitivity analysis and that requires substantial resources to use; along with an Effects Table, a qualitative method that permits the compact display of effects and information in support of the benefit-risk balance (Figure 4). The Effects Table can be generally applied and can be used as the basis for quantitative methods.

The Effects Table is currently being piloted for EMA benefit-risk evaluation. In this descriptive approach, a medicine's beneficial (favourable) and potentially harmful (unfavourable) effects are selected for evaluation on the basis of their importance, including both primary and secondary endpoints. The magnitude of these effects must be understood by evaluators and the impact of any uncertainties surrounding these effects discussed, along with potential methods of resolution. Once the important benefits and risks have been evaluated and compared against one another, a value judgement is rendered as to a positive or negative benefit-risk balance. Although this is a relatively straight-forward process, maintaining consistency is challenging and the EMA is currently investing in training evaluators in its use. The first training activity was a workshop held in January 2015 for twelve of the most experienced CHMP assessors.

Structured benefit-risk assessment . . . is an important tool that allows regulators to use transparency to build trust.

Challenges and opportunities for structured benefit-risk assessment

Years after the introduction of benefit-risk assessments in Europe, a number of challenges remain including the over-reliance on primary endpoints as parameters for evaluation to the exclusion of other clinically relevant findings. Additionally, some experts may be still uncomfortable in explicitly providing the rationale for their benefit-risk evaluations. Other key issues include the potential for excessive repetition of information and the need to explicitly state uncertainties to avoid prolonged discussions and to clearly identify value judgements.

Structured benefit-risk assessment is important to regulators for its ability to facilitate discussions within and between regulatory agencies, enable interactions with applicants, to expedite decision making and to effectively transfer knowledge to non-EU regulatory stakeholders and to downstream healthcare participants. Ultimately, it is an important tool that allows regulators to use transparency to build trust.

Figure 4: Sample EMA Effects Table



 EUROPEAN MEDICINES AGENCY

Caprelsa for thyroid cancer

	Effect	Description	Unit	Placebo	Vandetanib	Uncertainties/ Strength of evidence	References
Favourable	PFS (HR)	From randomization to progression or death (blinded independent review)	N/A	1	0.46 95% CI: (0.31, 0.69)	Large effect in overall population. Consistent and significant effect on PFS but not OS (too early?)	See Discussion on Clinical Efficacy.
	PFS (median)	Weibull model	Months	19.3	30.5	Only a very low number of patients with definite RET mutation negative status at baseline. Lower efficacy?	Single-arm study in RET negative patients post-approval.
	ORR	Proportion of complete or partial responders (>=30% decrease unidimensional) RECIST	%	13	45	No clear effect on PRO/ QoL (missing data)	See Discussion on Clinical Efficacy.
Unfavourable	Diarrhoea Grade 3-4	Increase of ≥7 stools per day over baseline; incontinence; Life-threatening	%	2.0	10.8	Duration of follow up in the pivotal study is short vs. the need for long duration of treatment.	Risk of dehydration and renal/cardiac risks (see SmPC 4.4)
	QTc related events Grade 3-4	QTc >0.50 second; life threatening; Torsade de pointes	%	1.0	13.4	Risk of developing further major cardiac SAEs including Torsades de pointe?	Restrict to symptomatic and aggressive disease (see SmPC 4.1).
	Infections Grade 3-4	IV antibiotic, antifungal, or antiviral intervention indicated; Life-threatening	%	36.4	49.8		Explore lower dose (see See Table 20. Summary of the RMP)

2

Development of frameworks for benefit-risk assessment: their role and importance for international regulatory cooperation

Dr John Skerrett

*Deputy Secretary for Regulatory Services,
Department of Health, Canberra, Australia*

Current benefit-risk methodologies

Although benefit-risk assessment is the central and fundamental regulatory decision that is made before a medicine can reach the market, it is rarely defined specifically in legislation. An effective benefit-risk framework provides a structured support for this necessary function, facilitating the review and systematic articulation of each of the benefits and risks of a medicine and their respective weightings. It can also assist international regulatory collaboration, which may be particularly important as more regulators utilise reviews made by trusted regulators to enable faster decision making. Additional value for these frameworks lies in their ability to facilitate the communication and visualisation of benefits and risks and improve public accountability by increasing the transparency of regulatory decisions.

A range of differing approaches for benefit-risk evaluation has been used, including those developed by the US FDA, EMA, CIRS and the CIRS-Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team (PhRMA BRAT). Some of the approaches employ decision or value trees, while others use tables, weighting systems or comparisons with alternative therapies or with best practice therapy. All of these methodologies; however, have similar goals and place an emphasis on using communication tools for different audiences.

Several quantitative benefit-risk methodologies have been described in the literature but these typically involve weighting according to relative importance of different factors and the strength of evidence around particular benefits and risks and thus entail subjectivity both in the selection of the methodology and in the expert judgement used to make the benefit-risk evaluation. These quantitative methodologies may additionally suffer from biases if clinical trial data is used from a small subset of patients who may not be

wholly representative of those who will use the medicine once commercialised. They also pose a fundamental challenge in objectively weighting the chance of rare serious adverse events against the potential for widespread benefits, especially as clinical trials may not detect rare but important adverse events. Current quantitative approaches may also be less useful when multiple benefits and harms exist for the use of a medicine in the treatment of differing indications or disease severities. Ultimately, these approaches may be used more frequently in health technology and reimbursement assessments, where economic factors are also required to be incorporated into decision making.

As discussed by Dr McAuslane (p 34), the CIRS Universal Methodology for Benefit Risk Assessment (UMBRA) is an overarching framework that provides a platform for the coordinated development of benefit-risk assessment methodologies. The UMBRA documentation system, consisting of the Benefit-Risk Template and User Manual was evaluated by a consortium of regulators from Australia, Canada, Switzerland and Singapore in retrospective feasibility and validation studies. The revised template was then evaluated by this group in the prospective review of several products. Although the consortium did agree that there should be a process for better communication of benefits and risks, they did not reach a unanimous decision regarding the utility of the UMBRA template. In addition, its interaction with existing forms in use by the different regulators and the ability of the template to compare a product with other drugs in the same class or to analyse adverse events was not confirmed.

However, regulators from these countries have agreed to share templates and complete guidance in the future to facilitate eventual parallel reviews using a common template. Other plans in this regard include working toward an aligned benefit-risk section in Public Assessment Reports, noting that at present there are differences in the nature of these reports among participating jurisdictions.

Regulators can often have the same data sources (such as application dossiers) but reach different conclusions regarding a medicine's benefit-risk profile and hence, its suitability for market authorisation. These different decisions may be challenging to publicly justify in the absence of a systematic, consistent approach to benefit-risk communication. Examples of differences in market authorisation decisions between the US

FDA and EMA are shown in Figure 5.

Benefit-risk assessment at TGA

Australian Public Assessment Reports (AusPARs) are prepared both for approved and rejected new chemical entities (NCEs) and late withdrawals from the evaluation process, applications for extension of indications, new drug combinations, salts of NCEs and for biosimilars. The online publication of an AusPAR explains the rationale for accepting or rejecting a medicine application and includes assessment summaries for quality, safety and efficacy, pharmacovigilance requirements and proposed risk minimisation activities along with an overall conclusion and benefit-risk assessment. The AusPAR consists of a summary of the steps in the evaluation process that led the TGA either to approve or not approve a medicine rather than a formal benefit-risk matrix.

The TGA is faced with the challenge of consistently applying benefit-risk evaluations across its reviews. The Advisory Committee for Prescription Medicines and Advisory Committee for Safety of Medicines are not directly asked by the TGA if they recommend approval for new medicines but are rather asked for their opinion regarding issues such as the proposed indication and dosing for a new medicine and their views on its benefits and risks. TGA market authorisation decisions are made by individual medical officers on the regulator's staff rather than by a committee or by the Minister.

Figure 5. Different marketing authorisation decisions from similar regulatory agencies.

Some medicines approved in the USA but rejected in Europe after active consideration		
Gemtuzumab ozogamicin	Acute myeloid leukaemia	2000 (withdrawn 2010)
Milnacipran	Fibromyalgia	2009
Ixabepilone	Breast cancer	2008
Lorcaserin	Anti-obesity	2013
Phentermine / topiramate	Anti-obesity	2013
Tofacitinib	Rheumatoid arthritis	2013
Mipomersen	Homozygous familial hypercholesterolemia	2013
Medicines approved in Europe but rejected in the USA after active consideration		
Pirfenidone	Idiopathic pulmonary fibrosis	2010
Mifamurtide	Osteosarcoma	2009
Sugammadex	Reversal of neuromuscular blockade	2008
Vildagliptin	Type 2 diabetes	2007
Laropirant/ nicotinic acid	Hypercholesterolemia	2008 (withdrawn 2013)
Sitaxentan sodium	Pulmonary arterial hypertension	2006 (withdrawn 2010)
Miglustat	Gaucher disease	2009
Testosterone	Transdermal patch for libido (women)	2006

The question as to whether benefit-risk frameworks are applied more consistently when committees are advisory, as they are in the Australian TGA and the US FDA, versus when those committees have the final decision-making role as is the case with the EMA Committee for Medicinal Products for Human Use (CHMP) has not been resolved. It should be noted, though that CHMP members are medicines regulators from a range of EU jurisdictions. Several information exchange processes are used to encourage consistency of benefit-risk evaluations in the TGA; however, it is recognised that it is more challenging to establish uniformity in evaluation of medicines between different therapeutic classes.

Challenges to the assessment of benefits and risks

Uncertainty regarding a new medicine must be distinguished from the potential risks of a medicine but benefit-risk frameworks may not be the appropriate tools to identify these uncertainties. Additionally, benefits and harms are usually asymmetric; that is, using established endpoints and measurement methods, new medicine trials typically anticipate benefits for most patients and harms in only a few patients and these harms can be multiple, unexpected or confounded by the disease being treated or complicated by co-morbidities. These factors can make the impacts of a medicine hard to assess statistically and assessments may be further impacted by withdrawal bias in many clinical trials.

Other challenges to the use of benefit-risk frameworks include that clinical trials are typically of shorter duration than real-world use of the product. Clinical trials usually measure the efficacy rather than effectiveness of a medicine and are usually conducted in patient populations that lack major co-morbidities. Additionally, patient medication non-adherence among trial participants can result in the overestimation of the effective dosage in patient populations with accompanying under-estimation of harms. On the other hand, long-term and clinical effectiveness clinical trials tend to become observational rather than blinded studies and these are often associated with selection bias.

To avoid the potential exclusion of beneficial drugs from the market because of uncertainties regarding adverse events, clinical trial duration must be long enough for potential harms to emerge and benefit-risk conclusions must

be amenable to revision as new information about the benefit-risk profile of the drug is obtained. Observational data from a larger and diverse patient group with co-morbidities will allow benefit-risk assessments to be adjusted throughout a product life cycle. The greater use of comparative effectiveness trials in recent years may more closely reflect the likely decisions to be made in routine clinical practice but there are often only limited differences in benefit or risk between medicines within a class. Furthermore, the choice of comparator medicine or use of a particular (high or low) dose for the comparator can introduce biases.

New regulatory models for market authorisation such as the use of reviews by trusted international regulators to facilitate decision making; for example, in jurisdictions such as Singapore, Chinese Taipei and Mexico add additional complications to benefit-risk evaluation; other complications may be introduced when regulators apply approaches for accelerated approvals and adaptive licensing of medicines. Although regulators may work closely with sponsors on clinical trial designs for medicines that have been designated as fast track or priority review and in the case of provisionally or adaptively licensed medicines, a development plan may be agreed to provide information on risk versus benefit to enable subsequent authorisation in a defined group of patients, the phase 3 clinical trials may not have been completed at the time of regulatory review. This may create additional challenges for benefit-risk assessment for these products. Although it is critical not to confuse uncertainty with risk or harm in these evaluations, subjective assessment of benefit-risk for unblinded treatments (as would be the case for the follow-up studies) must be avoided if possible. For these products, benefit-risk assessment in a wider population will require ongoing studies and the provision of data to collaborating regulators. Additionally, policies for withdrawing medicines from the market if they are subsequently found to have limited benefits should be devised.

Other challenges to benefit-risk evaluation can include:

- The small patient groups evaluated in trials of “personalised medicines” presents challenges for adequate statistical powering of the trials. In addition benefit-risk for the medicine will potentially differ between disease subpopulations treated with the medicine.

... International collaboration on benefit-risk assessment is critical and it will be increasingly important to both understand and explain when different decisions are reached by different regulators using the same data.

- Surrogate endpoints, when they are used in determining benefit-risk, need to be promptly validated.
- Toxicology assessments are more complex and more uncertain for newer types of medicine products, which could include, proteins, biosimilars and combination products.
- “Off-label” medicine use and the potential diversion for abuse may not be able to be factored in assessments in many countries under their regulatory frameworks.
- There is a current drive to incorporate more patient-defined endpoints such quality of life in the evaluation of medicines but it is recognised that patents’ tolerance for risk in the expectation of potential benefit may vary considerably from the tolerance that regulators – who operate in the glare of public scrutiny - may have.

Conclusions

TGA routinely applies detailed benefit-risk assessment in reaching regulatory decisions but we do not utilise a single template for these evaluations. Nevertheless, international collaboration on benefit-risk assessment is critical and it will be increasingly important to both understand and explain when different decisions are reached by different regulators using the same data.

A common benefit-risk framework: Can it facilitate decision-making and improve communication?

Dr Thomas Kühler

*Regulatory Policies & Intelligence, Novo Nordisk A/S,
Denmark*

Advantages and challenges to benefit-risk frameworks

Benefit-risk assessment is the core of regulatory decision making and represents the most difficult yet exciting process in the development of new medicines. Because different people interpret the available data for medicines in different ways, benefit-risk assessment will always involve some degree of subjective judgement by experts; however, it may be desirable for decision making to shift to a more explicit process. This shift would be facilitated by the use of a structured benefit-risk framework.

The medicine's label is the driver of the drug development process and sponsors could potentially use a benefit-risk framework as a means for organising, interpreting and communicating the value proposition for the drug. A framework could fulfil industry's need for a mechanism for communicating benefit-risk assessments to stakeholders beyond regulatory agencies such as health technology assessment organisations and health insurance payers. The structured, graphical nature of the currently available frameworks also make them amenable to soliciting perspectives from stakeholders who are not necessarily trained in the drug development process or in the

scientific evaluation of the benefits of a product compared with its risks, such as patients or healthcare professionals.

Structured approaches to benefit-risk assessment also offer potential benefits to regulators such as a means for providing transparency and auditability for the rationale for regulatory decisions, which may be particularly useful when those decisions are challenged (Figure 6). Frameworks may also facilitate the establishment of regulatory memory, which would allow evaluations to be applied to a class of drugs and which could be used to update assessments as new data become available. These advantages can enhance consistency and robustness in decision-making processes.

Benefit-risk assessments are currently commonly conducted throughout a drug's life cycle. They play an important role in Module 2 of the Common Technical Document. In the post-marketing setting, Periodic Benefit-Risk Evaluation Reports (PBRER), Periodic Safety Update Reports (PSUR), license renewals and variations accommodate new data about medicines as they are used in the real world. In the future, frameworks may also be used in soliciting patient perspectives. However, the number of available approaches to benefit-risk assessment can present a challenge, including those developed by the CIRS-Pharmaceutical Research and Manufacturers of America Benefit-Risk Assessment Team (PhRMA BRAT), the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Consortium on Benefit-Risk Assessment (COBRA). Because there may be as many tactics for presenting benefit-risk assessments to regulators as there are sponsors the lack of a common benefit-risk template could result in miscommunication and suboptimal industry-regulatory agency discussions.

Figure 6. The advantages of benefit-risk framework benefits for regulators.



Novo Nordisk experience

Novo Nordisk has taken a measured approach to the evolving use of benefit-risk frameworks and has sponsored doctoral research in this area as individual projects and as efforts within the Innovative Medicines Initiative (IMI). In addition, the company has investigated the use of the CIRS-PhRMA BRAT model as well as other, semi-quantitative models. However, one pilot project that tested the use of a structured benefit-risk framework as a means of driving drug development resulted in the perception that use of the framework was complicated and resource intensive and suggested that the outcome of the assessment may not be robust.

There is an emerging recognition that an aligned, common approach to benefit-risk assessment is needed. To this end, industry needs greater clarity on what the regulatory agencies expect. Whilst industry has accommodated regulators' requests for specific formats for benefit-risk data, they generally, are unsure as to how their own benefit-risk analyses will be received and whether their validity will be questioned.

Conclusions

Benefit-risk frameworks should be explored as tools for planning the drug development process. They could also be used as systematic means to build regulatory memory and seem amenable to soliciting and incorporating patients' views and accommodating patient-reported outcomes. Tools for benefit-risk assessment are already integral parts of life cycle management activities; however, industry needs clear guidance and predictability in their use. Although complete harmonisation is probably not a realistic expectation, a convergence of approaches may be both desired and achievable.

Benefit-risk frameworks should be explored as tools for planning the drug development process. They could also be used as systematic means to build regulatory memory and seem amenable to soliciting and incorporating patients' views and accommodating patient-reported outcomes.

Development of UMBRA and its utilisation as an overarching template for a systematic structured approach to benefit-risk assessment of medicines

Dr Neil McAuslane
Director, Centre for Innovation in Regulatory Science, UK

UMBRA

The CIRS Universal Methodology for Benefit Risk Assessment (UMBRA) is an overarching framework that provides a platform for the coordinated development of benefit-risk assessment methodologies that can be used internationally during drug development, the regulatory review and in the post-approval period, thereby increasing the transparency, predictability and consistency with which benefit-risk assessments are conducted and communicated effectively.

The steps for assessment contained within multiple international benefit-risk methodologies such as those used by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), CIRS Benefit-Risk Template and the CIRS Benefit-Risk Action Team (BRAT) can all be explicitly or implicitly mapped to the eight steps of the UMBRA framework: (1) establishing the decision

... the UMBRA Benefit-Risk Summary Template may afford an understanding of the reference agency benefit-risk evaluation and the ways in which it maps to the overarching framework, while providing a structured approach for reaching a local decision regarding the benefit-risk profile of new medicines.

context; (2) building a value tree; (3) refining the value tree; (4) assessing relative importance; (5) evaluating the options; (6) evaluating the uncertainty; (7) concise presentation of results and (8) reaching a final recommendation based on expert judgement. The use of these common principles and a toolbox of different methodologies should facilitate benefit-risk evaluation in a range of international regulatory environments.

The advantages to the use of UMBRA include its ability to provide a training tool for both regulatory agencies and pharmaceutical companies involved in the development and assessment of new products, to enhance the objectivity and transparency of the decision-making process, to review the consistency of regulatory decisions on marketing authorisation applications and to carry out more balanced and objective benefit-risk reassessments in post-authorisation.

UMBRA Benefit-Risk Template

A documentation system for the evaluation of benefit-risk consisting of the Benefit-Risk Template and User Manual was constructed based on the EMA reflection paper on benefit-risk assessment methods.¹ As mentioned by Dr Skerrit (p 29) This system was evaluated by a consortium of regulators from Australia, Canada, Switzerland and Singapore in retrospective feasibility and validation studies and then the revised template was evaluated by this group in the prospective review of several products. There was general agreement among these evaluators that there is value in this systematic approach and they each are currently determining how the template can best be used within their individual agencies.

iSABRE

This work was extended to Southeast Asia in the CIRS iSABRE (international Summary Assessment for Benefit-Risk Evaluation) feasibility study, in

Figure 7. Revisions to the Benefit-Risk Summary Template enacted for the feasibility study.

Pilot Study: New Summary Template



Product Name:
Indication:

Table of Contents		
Benefit-Risk Summary		
1.1	Background (Decision Context)	Go to Page
2.1	Overall Summaries	Go to Page
3.1	Clinical Study Summary	Go to Page
4.1	Table of Pooled overall incidence of events	Go to Page
5.1	Identified Benefits and Risks	Go to Page
6.1	Relative Importance and Values	Go to Page
7.1	Conclusion	Go to Page



which regulatory agencies in China, Indonesia, Malaysia, Philippines and Chinese Taipei assessed the potential of the Summary portion of the UMBRA Benefit-Risk Template for use in their agencies' evaluations of new medicines.

All participants in the feasibility study were positive about both the structure and content of the template and agreed that a systematic structured approach to documenting benefit-risk evaluations had value within their agency. iSABRE participants determined that their agency reviews already included a number of steps required in the UMBRA Summary Template but that the reviews may not specify these steps in a systematic structured way. They additionally identified modifications to the Summary Template that were felt would improve both internal communication and documentation including changes to the layout of the template, new sections for consideration and aids to facilitate use by reviewers. Changes to the template that were enacted as a result of this feasibility study included the addition of boxes for entry of local decision context and possible interethnic differences and an effects table in the final section of the template and a reordering of the template sections. Additionally, it was felt that more explicit instructions or clarification and worked examples would be useful additions to the user manual.

Following the feasibility study, seven reviewers from four agencies participated in the iSABRE pilot study in 2014; they evaluated the use of revised versions of both the electronic Benefit-Risk Template Summary (Figure 7)

and User Manual as an appropriate means for documenting benefit-risk decisions within regulatory agencies responsible for maturing pharmaceutical markets.

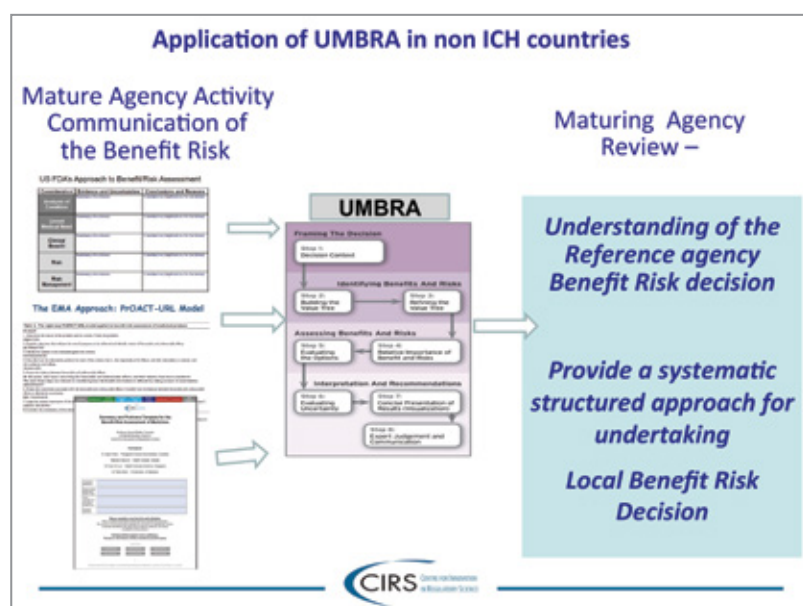
Participants in the iSABRE pilot rated the Benefit-Risk Summary Template as good to excellent in navigation, clarity of instructions and applicability and comprehensiveness of guidance. They additionally indicated that the template has advantages of the systems currently in use in their organisation, contributes to achieving consistency of decisions between regulatory agencies and promotes effective communication to stakeholders.

For regulatory agencies in maturing markets, the use of the UMBRA Benefit-Risk Summary Template may afford an understanding of the reference agency benefit-risk evaluation and the ways in which it maps to the overarching framework, while providing a structured approach for reaching a local decision regarding the benefit-risk profile of new medicines (Figure 8).

Reference

1. European Medicines Agency. Reflection paper on benefit-risk assessment methods in the context of the evaluation of marketing authorisation applications of medicinal products for human use, 2008. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500069634.pdf

Figure 8. Maturing regulatory agencies can provide clarity for mature regulatory agency benefit-risk decisions, which can be mapped to the UMBRA framework.



Benefit-risk assessment for medicinal products in Taiwan

Li-Ling Liu

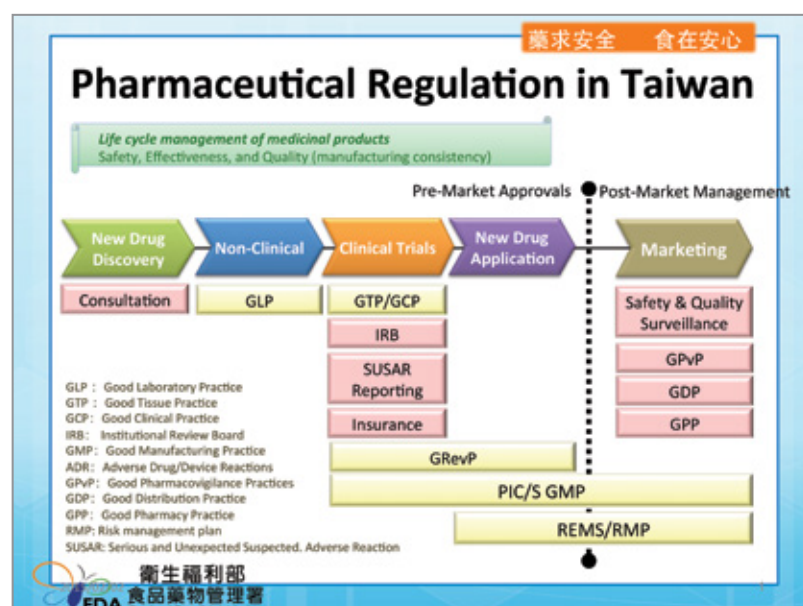
Director, Division of Medicinal Products, Taiwan Food and Drug Administration, Ministry of Health and Welfare, Taiwan

TFDA

Taiwan has a population of 23 million people, 99.8% of whom are covered by the single-payer National Health Insurance. In 2013, the Taiwan pharmaceuticals market was valued at US\$2.75 billion. The Taiwan Food and Drug Administration (TFDA) was formed in 2010 within the Department of Health (DoH) by the integration of four bureaus, Food Safety, Pharmaceutical Affairs, Food & Drug Analysis and Controlled Drugs, with the mission of protecting and promoting public health. In 2013, the DoH was restructured and elevated as the Ministry of Health and Welfare. The TFDA comprises seven divisions, the major divisions being concerned with food safety, medicinal products, medical devices and cosmetics and controlled drugs.

The TFDA regulates pharmaceutical products through a system of lifecycle management. Safety, effectiveness and quality are ensured through the use of good laboratory practices, good clinical practices, good manufacturing processes, good distribution practices and the use of appropriate risk management

Figure 9. TFDA lifecycle management of pharmaceuticals incorporates good clinical, manufacturing, review and distribution practices.



plans (Figure 9). Before marketing, scientific, evidence-based review incorporates good review practices, which promote efficiency, transparency, clarity, predictability, consistency and high quality (Figure 10).

Through Taiwan's Drug Injury Relief System, funded by a 0.02% to 0.2% levy on the annual revenue of pharmaceutical companies, patients receive compensation for death, disability or serious illness caused by the proper use of legal medicines, excluding traditional medicines and vaccines.

Benefit-risk assessment

Pharmaceutical products have become the mainstay in the prevention, treatment and diagnosis of disease. However, modern medicines, while being biologically effective, also have potential for harm. The regulator performs an essential public health task by ensuring that safe and effective human drugs and biological products are available to improve the health of people. Balancing the desirable and undesirable effects of drugs is the core task of drug regulatory agencies; however, determining that balance is complex because of

- difficulty in estimating the probability of desirable and undesirable effects due to limited and sometimes conflicting data;
- multiple objectives such as maximising benefits while minimising risks;
- differences in stakeholder perspectives;
- the difficulty of trading off effects of differential importance;
- a lack of agreement on what valuation criteria to use and
- the heterogeneity of effects across patient populations.

As of July 2012, Taiwan has required adherence to the International Conference on Harmonisation (ICH) Common Technical Document (CTD) format, Module 2.5.6, which requires benefit and risk conclusions in dossier submissions. The TFDA has observed variability in the approaches taken by applicants in presenting benefit-risk assessment. The ICH M4E (R2), regarding standardising the content and presentation of benefit-risk information in regulatory submissions is under review and is envisioned that such standardisation will increase efficiency in communication of benefit-risk assessment between industry and regulators.

Many other factors in addition to benefit and risks inform the benefit-risk evaluation such as the nature and severity of the disease, unmet medical needs, availability of other therapies and Certificates of Pharmaceutical Products (CPPs) from other countries. In addition to ICH, several international organisations such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), Health Canada and CIRS have developed benefit-risk frameworks or guidance for the use of frameworks some of which incorporate consideration of these factors.

However, regulators are challenged with establishing transparency of the regulatory process and making reproducible and defensible decisions in the absence of an accepted, validated, international benefit-risk assessment model employing a quantitative valuation, which regulators would recognise and use in their assessment of a new drug application.

Conclusions and future prospects

Convergence and harmonisation are needed for benefit-risk structures and processes and for standard data exchange models that will streamline the transfer of data between different stakeholders using the electronic CTD. Uncertainties must be taken into account and it should be understood that any methodologies only act as decisions aids.

Future prospects for the TFDA include enhanced international, regional and cross-strait regulatory collaboration. The development of quantitative

Convergence and harmonisation are needed for benefit-risk structures and processes and for standard data exchange models that will streamline the transfer of data between different stakeholders . . .

and semi-quantitative tools and guidances and frameworks for benefit-risk assessment and the revision of assessment report templates to incorporate a structured framework for benefit-risk criteria are also planned. Workshops will be organised with all stakeholders and specialists in decision-making theory and benefit-risk framework development and training programmes for regulatory assessors and sponsors will be held in support of these efforts.

Figure 10. TFDA good review practices promote efficiency, transparency, clarity, predictability, consistency and high quality.



Philippines: Feedback on the utilization of the common benefit risk framework (SABRE)

Pia Angelique Priagola

Food-Drug Regulation Officer III, Center for Drug Regulation and Research Food and Drug Administration, Philippines

Drug regulation in the Philippines

The vision of the Food and Drug Administration (FDA) of the Philippines is to be an internationally recognised centre of regulatory excellence safeguarding the health of Filipinos and their mission is to ensure the safety, efficacy, purity and quality of the products it regulates through effective implementation of the national regulatory framework, consistent with international best practice. To this end, the agency is committed to establishing science-based standards as the basis for regulatory policies and to continually improving and maintaining the agency's competence, delivering quality public service with integrity.

Marketing authorisations for various products that are regulated by FDA are processed by separate centers namely the Center for Devices Regulation Radiation Health and Research, Center for Food Regulation and Research, Center for Drug Regulation and Research (CDRR) and Center for Cosmetic Regulation and Research. CDRR functions include the licensing and accreditation of establishments, marketing authorisation, post-marketing surveillance and clinical research of pharmaceutical products including biologicals. It is separated into two divisions and a variety of subunits to address its wide range of functions.

The regulatory framework in the CDRR addresses four key functions. Licensing and accreditation of establishments is carried out through the observance of a variety of guidelines including those for good manufacturing practice, good distribution practice, good clinical practice and good laboratory practice. Pre-marketing

assessment evaluates quality, safety and efficacy of innovative medicines and the quality and interchangeability of generic drugs. Post-marketing surveillance assesses the ongoing safety or benefit-risk balance and quality of approved medicines with quality testing and compliance monitoring. Finally, use of a benefit-risk framework provides for communication with stakeholders.

As reported by Dr. McAuslane at this Workshop, the Philippine FDA was a participant in the CIRS International Summary Approach to Benefit-Risk Evaluation (ISABRE) feasibility and pilot studies, in which regulatory agencies in China, Indonesia, Malaysia, Philippines and Chinese Taipei assessed the potential of the Summary portion of the UMBRA Benefit-Risk Template for use in their agencies' evaluations of new medicines. The Philippine FDA experienced several challenges in the employment of this evaluation tool, including a lack of experience in its use and the subjective nature of assignment of values and weights to benefit and risk parameters. In addition, it was felt that decision making may be influenced by the prevalence of particular diseases in different parts of the country, as well as the various modalities available for healthcare. Finally, use of the Summary Template would require reviewer training and education. Despite these challenges, the Philippine FDA is reviewing and updating its review processes and investigating the incorporation of the use of the CIRS UMBRA Summary Template into its current review framework.

The agency looks to the future for opportunities to fulfill its mission by improving the efficiency, clarity and transparency of the review process, advocating a robust yet flexible and risk-based regulatory system, reviewing and updating existing policies and regulations to align with international standards and collaborating with other drug regulatory agencies. The Philippine FDA currently collaborates with regulatory agencies in ten other countries in the Association of South East Asian Nations (ASEAN). The UMBRA Summary Template should facilitate this and other collaborative efforts. Furthermore, it will allow enhanced coordination and communication among regulators, academia and other stakeholders.

The UMBRA Summary Template . . . will allow enhanced coordination and communication among regulators, academia and other stakeholders.

Assessment of benefits and risks in agencies across Asia: Utilisation of a framework approach – challenges, opportunities and future perspective

Azura Abdullah

Head of Unit/Section for New Drug Products, Centre for Product Registration, National Pharmaceutical Control Bureau, Ministry of Health, Malaysia

Assessing benefits and risks

Benefits can be defined as the demonstrated beneficial effects of a treatment, determined from measurable, objective efficacy endpoints and *risks* as the treatment's unfavourable effects, which before approval are determined largely from the safety concerns reported in controlled clinical trials. Balancing the benefits and risks of a product requires the critical judgement of regulators. A benefit-risk assessment is an important component of the regulatory process for a new medicine and its importance continues throughout the post-approval period.

Challenges

Major challenges in benefit-risk assessment have been identified, including ranking and weighting the benefits and risks that are identified in clinical trials. Assessments must also take into account differences in views, opinions and approaches for benefit-risk evaluation between regulators and the pharmaceutical industry, between regulators and other regulators and among all other stakeholders. Additionally, clinical trial results must be extrapolated to a real-world setting and a balance established between regulatory and treatment decisions; that is, although a product may have been judged to have a positive benefit-risk profile for a certain patient population, that balance may not

An appropriate, reliable, structured approach to assessment will help to improve the consistency of assessments and provide for reproducible outcomes, which will help to facilitate and improve the regulatory decision-making process.

be positive for a specific patient. Furthermore, effective benefit-risk assessments must incorporate the integration of information from a variety of sources in addition to clinical trials including, safety reports, information from the Internet and data from other agencies. Finally, a common understanding among reviewers and stakeholders must be developed and there is a need for additional experience, expertise and guidance in benefit-risk evaluation.

Opportunities and future perspective

As discussed by Dr McAuslane and other presenters at this Workshop, the CIRS international Summary Approach to Benefit-Risk Evaluation (iSABRE) framework was evaluated by regulators in Malaysia as well as in China, Indonesia, Philippines, Singapore and Taiwan. Regulators in Malaysia found that elements of the summary template are already included in their current review processes, although not as part of a specific template or format. Evaluators concluded that a benefit-risk framework acts as a method for communication between industries, agencies and other stakeholders and facilitates the development of better risk communication and risk management strategies. An appropriate, reliable, structured approach to assessment will help to improve the consistency of assessments and provide for reproducible outcomes, which will help to facilitate and improve the regulatory decision-making process.

Practical applications and utilisation of a structured approach to benefit-risk assessment:

Singapore's experience

Dr Yee Hoo Looi

Regulatory Consultant, Therapeutic Products Branch, Health Sciences Authority, Singapore

UMBRA Summary Benefit-Risk Template

The Universal Methodologies for Benefit-Risk Assessment (UMBRA) is an overarching eight-step framework that provides underlying principles for the process of making a quality decision. The framework is supported by the Benefit-Risk Assessment Template and an associated User Manual. The use of this framework has been studied by the Centre for Innovation in Regulatory Science (CIRS) in association with the Australian Therapeutic Goods Administration (TGA), Health Canada, the Singapore Health Sciences Authority (HSA) and SwissMedic (the ACSS Consortium) to determine if a structured, systematic standardised approach to the benefit-risk assessment of medicines would facilitate the opportunity for work-sharing between the agencies.

The consortium first conducted a pilot functionality study on a paper-based benefit-risk assessment template, followed

by a retrospective feasibility study using an electronic version. A prospective study was then conducted using a revised template. Results of the prospective study led to the hypothesis that the Summary portion of the template (Figure 11), which collates the relevant conclusions, could be used as a stand-alone tool for documenting and communicating benefit-risk decisions.

Singapore review of the Summary Template

Accordingly, twelve HSA reviewers participated in a retrospective study of the Summary Template in order to assess its appropriateness to document and communicate benefit-risk decisions. In the study, the reviewers transferred relevant information from the completed clinical assessment reports to the Summary Template for recently reviewed abridged new drug applications encompassing a wide range of benefit-risk profiles.

Most of the reviewers found the Summary Template to be fit for purpose in documenting relevant information supporting the study outcomes, regulatory decision and the benefits and risks under consideration but also indicated that more training on the understanding and application of relative importance weighting was required. Some reviewers additionally remarked that the contribution of adverse events to the overall decision should be the focus of the report, with less emphasis on the details that are required by the template. In assessing the Template applicability, reviewers specified that it has some advantages over the current HSA systems for benefit-risk assessment and could aid in achieving consistency of decisions between agencies and promoting effective communication to various stakeholders.

Although the overall findings were very positive, reviewers expressed concern about duplication of work required to use the template in addition to current systems. Some also stated that the subjective judgements of individual organisations may limit the achievement of consistency. Nevertheless, the study concluded that the Summary Template could be useful in comparing the basis for regulatory decisions between jurisdictions. Users also expressed a high degree of willingness to share the template (Figure 12).

Potential audiences for template output include media and the public domain, other regulatory agencies, patients and patient-advocacy groups, health technology assessment agencies and healthcare professionals. However,

Figure 11. The Summary Benefit-Risk Template was evaluated by Singapore Health Sciences Authority reviewers.

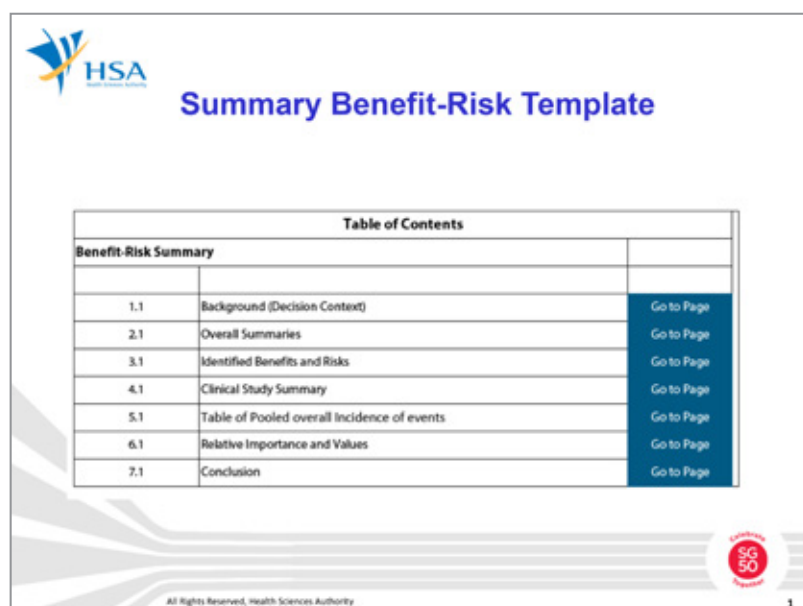


Table of Contents		
Benefit-Risk Summary		
1.1	Background (Decision Context)	Go to Page
2.1	Overall Summaries	Go to Page
3.1	Identified Benefits and Risks	Go to Page
4.1	Clinical Study Summary	Go to Page
5.1	Table of Pooled overall Incidence of events	Go to Page
6.1	Relative Importance and Values	Go to Page
7.1	Conclusion	Go to Page

All Rights Reserved, Health Sciences Authority

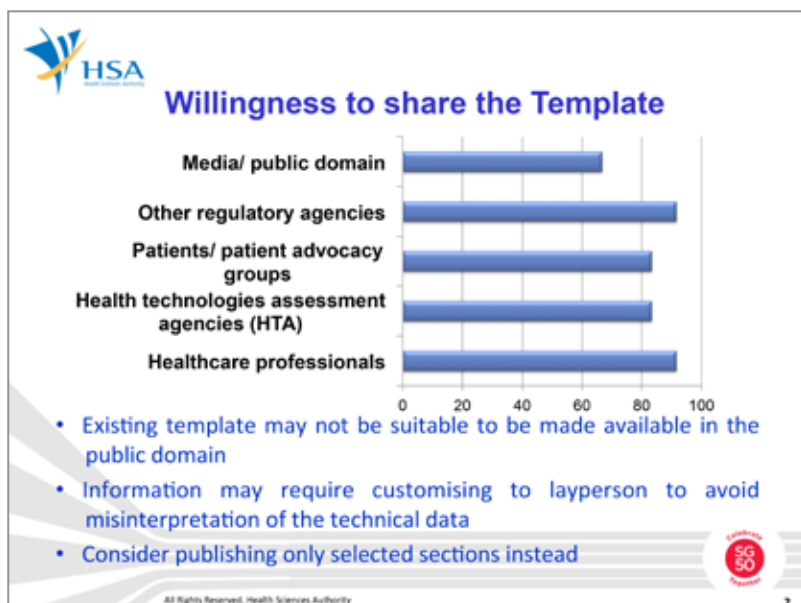


Figure 12. HSA evaluators are willing to share the template.

customisation for laypersons may be required to avoid misinterpretation of technical data and publication of only selected portions of the current template should be considered.

... the Summary Template could be useful in comparing the basis for regulatory decisions between jurisdictions.

The HSA review showed that the practical and potential applications of the Summary Template include its ability to provide documentation of benefit-risk assessments to ensure internal consistency in decision making and to act as an audit tool, benefit-risk communication vehicle and training tool for the advancement of regulatory standards.

In addition to the previously mentioned need for training in the understanding and application of relative importance weights and duplication of efforts presented by the Summary Template, an additional challenge in the use of the tool is the requirement for reviewer and management buy-in and approval.

Indonesia's experience on use of the framework to communicate and facilitate discussion by the National Committee on Drug Evaluation

Dra Nurma Hidayati

Director of Drug and Biological Products Evaluation, National Agency of Drug and Food Control, Indonesia

Drug regulatory system in Indonesia

Drug regulation in Indonesia is the responsibility of the National Agency of Drug and Food Control (NADFC). The vision of the NADFC is to become an innovative, credible and internationally recognised drug and food regulatory authority for protection of the public through the achievement of their primary mission, which is to conduct pre-market evaluation and post-marketing control based on accepted international standards.

The NADFC regulatory framework is designed to produce good regulatory decisions that ensure

the safety, efficacy and quality of medicines. The determination of efficacy and safety must be aligned with international standards while incorporating the responsiveness and flexibility needed to meet the needs of the population within the agency's jurisdiction. Adherence to the principles of Good Review Practice ensures transparency, clarity and consistency in NADFC processes, all critical for maintaining the credibility of the agency.

To ensure the robust nature of decision making, the agency uses a risk-based approach in which decisions are based on the scientific evidence, in the context of the reviewers' knowledge and experience, as well as the needs of the community. This process also covers post-approval monitoring of safety and effectiveness and provides for good documentation and effective communication.

The principles of risk-based evaluation are applied to all new medicines. The scientific and evidence bases for products are evaluated, including information from pre-clinical studies, product development, clinical protocol design and data from clinical studies. An appropriate benefit-risk assessment is conducted and the

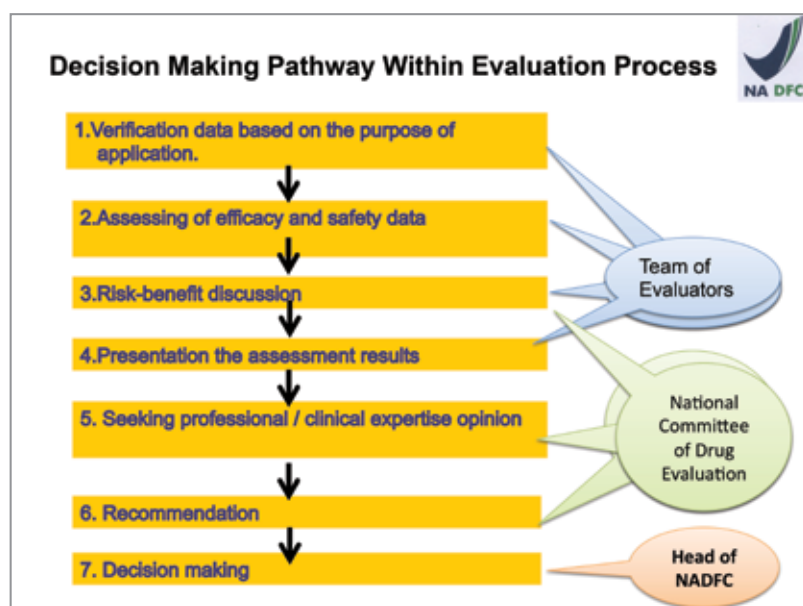
safety of the product is assessed by identifying and evaluating safety issues related to the product or to its therapeutic class. Quality control of the production process is applied to ensure a safe and consistent product, taking data on chemistry, manufacturing and controls (CMC), stability and the validation process into consideration.

Participants in decision making

The NADFC has one internal review centre and four external centres from universities throughout Indonesia, each with a team of evaluators. Review centre meetings are conducted five times per month to discuss the results of the evaluations of the safety, efficacy and quality of potential new medicines. The review centres pass on their conclusions and recommendations from on these evaluations to the National Committee on Drug Evaluation, who are recruited from universities and other relevant institutions and who include experts in the fields of clinical pharmacology, pharmacy and biology, as well as relevant clinicians.

The National Committee conducts at least one meeting per month to make final decisions regarding new medicines, employing the services of ad hoc experts as necessary. All National Committee participants are required to sign a statement of independence attesting to their lack of conflicts of interest but ultimately, responsibility for final decisions rests with the Head of the NADFC (Figure 13).

Figure 13. The NADFC decision-making pathway



A structured and systematic approach to benefit-risk assessment, based on knowledge and experience as well as on scientific justification, will produce consistent, clear and predictable decision making.

Both the review centre evaluation teams and the National Committee conduct benefit-risk evaluations as part of their assessments. Decisions are based on an evaluation of the clinical, non-clinical and quality data contained within a product dossier as well as an assessment of other relevant data such as input from related ad-hoc experts, national public health needs, medical literature and other published public assessment reports from regulatory agencies such as those in Europe, the United States and Australia. Applicants receive a letter of decision on the assessment results and the NADFC also publishes a public assessment report.

Conclusions

Good regulatory decision making is the key to achieving a high-quality system for the regulation of medicines. A structured and systematic approach to benefit-risk assessment, based on knowledge and experience as well as on scientific justification, will produce consistent, clear and predictable decision making. Such a framework has been incorporated by the National Committee on Drug Evaluation to generate recommendations for its decision making.

Use of the framework to facilitate internal decision making

Dr I-Chun Lai

Team Leader/Medical Reviewer, Division of New Drugs, Center for Drug Evaluation, Taiwan

The CIRS Summary Benefit-Risk Template and CDE Template

As discussed by Dr McAuslane (p 34), the use of the Summary Template from the CIRS Universal Methodologies for Benefit-Risk Assessment (UMBRA) framework was recently assessed for facilitating internal decision making by regulatory agencies in Southeast Asia, including the Center for Drug Evaluation (CDE), Taiwan.

The current CDE template for evaluating medicines consists of eight parts, numbered 0 to 7. The benefit-risk assessment is incorporated into Sections 1 (the Executive Summary) and 7 (the Clinical Section).

Use of the Summary Template was not intended to replace the current CDE template but rather to summarise the evidence and facilitate the benefit-risk assessment.

Example: tofacitinib

The assessment of Xeljanz (tofacitinib) provides an example of the CDE use of the CIRS template. Tofacitinib is an oral, small-molecule inhibitor of Janus kinase approved by the US Food and

Drug Administration (FDA) in 2012 for patients with moderate to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. However, the European Medicines Agency (EMA) refused marketing authorisation for the drug in 2013.

The tofacitinib regulatory dossier included five pivotal studies, one testing the drug as monotherapy and four used with a background of disease-modifying anti-rheumatic drugs (DMARDs). The primary endpoints in all five studies were the American College of Rheumatology 20% response rate (ACR 20), the Health Assessment Questionnaire Disability Index (HAQ-DI) and Disease Activity Score for 28-joint counts less than 2.6 (DAS28<2.6). One study with background DMARD treatment also included the van der Heijde modified Total Sharp Score (mTSS), a measure of radiologic response. All of these are considered acceptable relevant efficacy endpoints.

In Figure 14, a portion of Section 3.1 (Clinical Summary) of the CIRS template has been used to summarise the results for one of the pivotal studies for tofacitinib. This study employed four treatment groups, 5-mg and 10-mg tofacitinib and two placebo groups. The study results showed statistically and clinically significant differences between 5-mg tofacitinib and placebo and between 10-mg tofacitinib and placebo for the endpoints of ACR 20, HAQ-DI and DAS28<2.6 and improvement in clinical response and physical function were identified as the primary benefits. Key risks included serious infection, opportunistic infection, malignancy and major adverse cardiovascular events (MACE). The template was used to document similar results for the other pivotal studies except that in the one clinical study with mTSS as an endpoint, a statistically significant difference from placebo was shown only for the 10-mg tofacitinib group which was insufficient for a claim of radiologic improvement. These findings were also summarised in Summary Section 3.2 (Clinical conclusions) of the template.

The CDE prepared tables summarising tofacitinib benefits and risks for Section 6.1 of the CIRS template, with weightings of the relative importance of each benefit and risk. Similar tables were also completed for Section 7.1.1 of the template, which according to the CDE evaluation resulted in some repetition and duplication of effort. A possible solution for this issue might be to present only those benefits and risks that are considered of high importance

Figure 14. Using the CIRS summary template to document the benefits and risks of tofacitinib.

Summary 3.1 Clinical Study Summary				
Study Ref. Type	Study Design (N) (Duration) -NI/S/O -Primary objective -Primary efficacy parameter	Treatment	Conclusion	Provide the key benefit(s) or risk(s) identified by this study
1045 Pivotal	R, DB,PC (611) (6m) -Superiority -Efficacy, safety vs Pbo -ACR 20 -DAS 28 -HAQ-DI	1.Tof 5mg bid 2.Tof 10mg bid 3.Pbo 5mg bid 4.Pbo 10mg bid	•Stat sig difference between Tof 5mg/ 10mg vs Pbo •5mg similar to 10mg	•Benefit: Improvement in clinical response, physical function • Risk: Serous infection, opportunistic infection, malignancy, MACE

R: randomized, DB: double blind, PC: placebo controlled, NI: non-inferior, S: superiority, O: Observational study, MACE: major adverse cardiovascular events

Benefit Risk Balance		
	US FDA, Taiwan CDE	EMA
Benefit	• 5mg and 10mg: Sufficient evidence to support clinical and physical response • inadequate evidence for both dose for radiographic response	• inadequate evidence for both dose (esp 5mg) for radiographic response
Risk	• 5mg: better safety profile	• safety concerns related to immunosuppressant actions
Conclusion	• approved 5mg • no radiographic improvement in approved indication	• refusal of MA

Figure 15. The differences in the benefit-risk evaluation for tofacitinib among the FDA, Taiwan CDE and EMA.

in Section 7.1.1.

The CIRS Summary Template was also used to compare the benefit-risk evaluations of different regulatory agencies (Figure 15). In approving tofacitinib, the FDA found sufficient evidence that both 5 mg and 10 mg of tofacitinib provide clinical and physical response. For example, in one study, an ACR 20 response was achieved by 59% of patients with the 5-mg dose and 65% with the 10-mg dose, compared with 26% with placebo. In another study, the corresponding ACR 20 response rates were 50%, 51% and 28%. Although there was inadequate evidence for both doses to support a claim of radiographic response, this endpoint was considered to be of moderate importance by the US FDA and

The CDE evaluation showed the CIRS Summary Template to be practical in assisting logical thinking and in conducting a benefit-risk assessment.

Taiwan CDE and was not required for approval. The 5-mg dose was found to have a better safety profile than the 10-mg dose. In contrast, because the EMA found insufficient evidence to support radiographic response, which they regarded to be an important endpoint and because of additional safety concerns related to immunosuppressant actions of tofacitinib, they did not approve the product.

Conclusions and suggestions

The CDE evaluation showed the CIRS Summary Template to be practical in assisting logical thinking and in conducting a benefit-risk assessment.

Section 3.1 was regarded as useful for reviewers but it was suggested that its visual nature may become too complex if many pivotal studies needed to be presented, making it more challenging to see key benefits and risks at a glance. As previously mentioned, repetition between Sections 6.1 and 7.1.1 should be addressed. Finally, guidance is required in weighting benefits and risks, particularly for the results of clinical trials with multiple treatment options, which may be solved by providing more information and guidance in the CIRS Summary Template User Manual.

Company assessment of local benefit and risks prior to submission

Dr Susan Forda

Vice President, Global Regulatory Affairs, Eli Lilly, UK

Benefit-risk determinations for new medicines are made from early-phase development through post-authorisation from the perspectives of stakeholders that include industry, regulators, clinicians and patients. These evaluations are influenced by differences in regulatory policies, procedures and requirements, by local medical practices and guidelines and disease prevalence and by the amount and quality of patient input.

Structured benefit-risk analysis used in development decisions

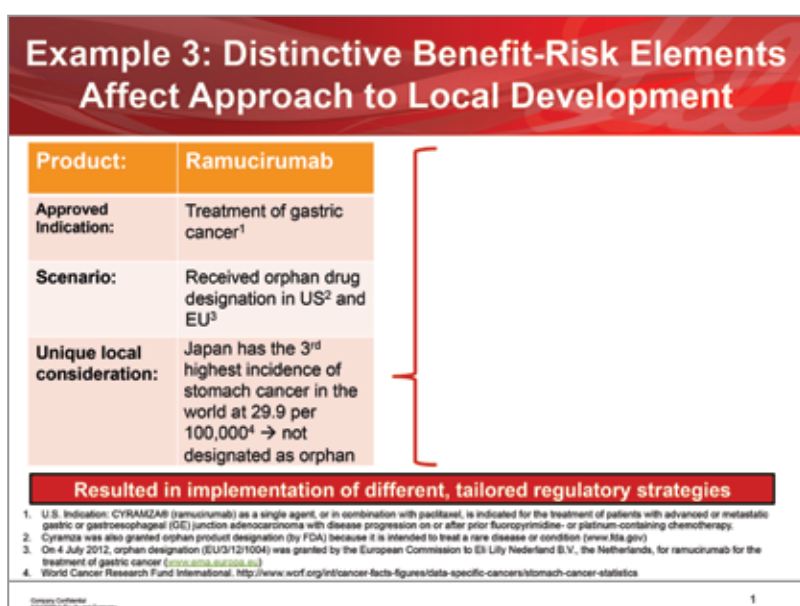
Structured benefit-risk analysis particularly assists company decision making. At the end of phase 2 development, this assessment is performed to decide if a product should move forward into phase 3, evaluating safety and efficacy, advantages over standard of care, an understanding of possible alternatives, potential development tradeoffs and what treatments stakeholders value. For example, in an evaluation of a cardiovascular medicine at the end of phase 2, specific considerations raised with the development team included further characterisation of the unmet medical need and the characteristics of the patient

population, including better characterising relevant subgroups. In addition, the analysis was used to clarify how the drug would differentiate itself from similar treatments. Using a structured benefit-risk approach in this evaluation enabled more robust decision-making by the development team.

National or regional benefit-risk considerations can play an important role in global development decisions. These considerations include medical practice nuances, disease or condition prevalence rates, the availability of quality clinical trial sites, impact of therapeutic guidelines and treatment standards, intrinsic and extrinsic ethnic differences and the nature of the medicine. The clinical trial development strategy for a treatment of Type 2 diabetes mellitus is an example of the effect of regional considerations on benefit-risk evaluation. The prevalence of Type 2 diabetes is approximately 8% in Japan; 9% in China; 10% in Taiwan; 11% in the US and 21% in Saudi Arabia. In addition to these differing rates, which may occur because of ethnic, dietary, lifestyle or cultural factors, the treatment of this disease is also extremely variable. The oral alpha-glucosidase inhibitor, acarbose is widely prescribed in Asia, with prescription rates per 1000 patients at 16 in Japan, 10 in China and 33 in Taiwan. However, this drug is almost unknown in the United States where it is used by only 0.01 of 1000 patients. In designing a clinical trial for an anti-diabetic agent in Asian countries, investigators would need to consider if concomitant use of acarbose might impact the investigational medicine's pharmacokinetics or pharmacodynamics and the effect of drug-drug interactions would need to be evaluated during trials and after approval. Additionally, there may be a negative potential impact on patient recruitment if concomitant use of acarbose is not allowed. Finally, insights into local characteristics such as dietary impact, medical practice and patient preferences would need to be determined.

The submission strategy for the monoclonal antibody ramucirumab is another example of the ways in which distinctive benefit-risk elements affect an approach to local development. Ramucirumab was approved in the United States and EU for treatment of gastric cancer, using an orphan drug registration pathway. However in Japan, which has the third highest incidence of stomach cancer in the world at 29.9 per 100,000⁴, the drug could not be granted orphan status, which resulted in a different, tailored submission strategy for that country (Figure 16)

Figure 16. National disease prevalence considerations affected ramucirumab submission strategy in Japan.



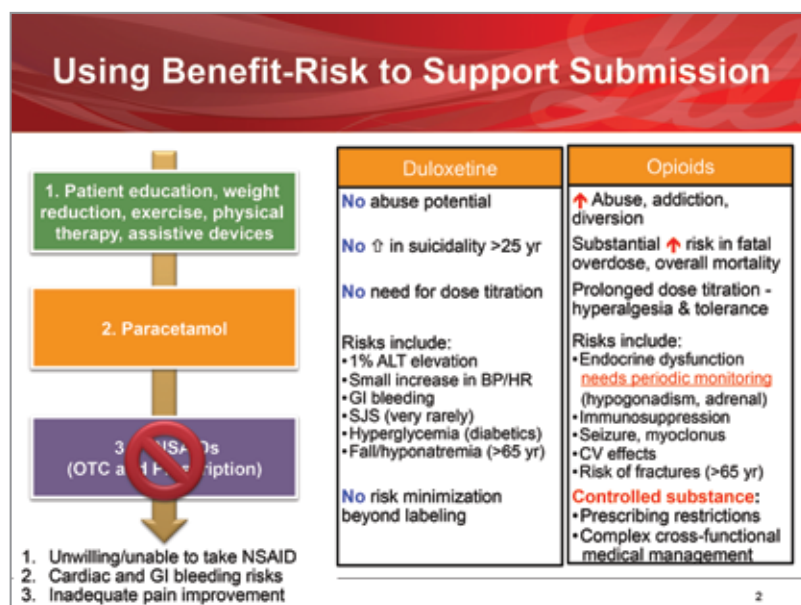


Figure 17. Using benefit-risk analysis to support a regulatory appeal.

Structured benefit-risk assessment supporting submission

When the Committee for Medicinal Products for Human Use (CHMP) rejected the submission for duloxetine—which is approved in the US—Lilly appealed this decision by identifying an unmet medical need in a patient population with a very limited choice of safe and effective medicines and then used a strictly structured benefit-risk analysis of the favourable and unfavourable effects of duloxetine and the uncertainties raised by the CHMP to present an overall assessment of the medicine's benefit-risk balance (Figure 17). Although ultimately the approval outcome was unfavourable, the appeal raised awareness within the company regarding the utility of structured benefit-risk as a submission tool.

An example of the use of structured benefit-risk after approval demonstrates the difference in response from two regulatory agencies who have reviewed the same benefit and risk data. After a clinical trial that was being conducted in support of a submission for a second indication was terminated because of a safety signal, Lilly requested core data sheet changes and the issuance of a global 'dear healthcare professional'

communication letter and reported the study findings at a scientific conference. In response, the EMA requested extensive amendments to the summary of product characteristics whilst the US FDA, which considered the absolute risk for harm to be low, has not taken action on this issue.

Finally, benefit-risk analysis can reveal particular benefits to a subset of patients. When Lilly submitted the dossier for the use of pemetrexed for first-line treatment of non-small-cell lung cancer (NSCLC), the regulatory authority requested the results of a pre-planned subset analysis, which demonstrated significantly superior benefits in the form of survival time among patients with non-squamous, as opposed to squamous, NSCLC. The result was approval of pemetrexed as a first-line treatment for metastatic NSCLC and a subsequent approval for second-line treatment for non-squamous NSCLC.

Dr Forda concluded her presentation by remarking that patient input is necessary to inform the benefit-risk discussion and that increased and enriched patient participation in the assessment of benefit-risk throughout the product life cycle will enhance the possibility of global alignment of benefit-risk assessment. This alignment may also be positively impacted through the ongoing update to Section 2.5.6 of the ICH Clinical Overview for Benefit-Risk Considerations and greater harmonisation of global regulatory policies and procedures such as review templates, patient requirements and review timelines.

...global alignment of benefit-risk assessment may be positively impacted by ... greater harmonisation of global regulatory policies and procedures such as review templates, patient requirements and review timelines..

The utilisation of a common benefit-risk framework across countries:

A critical component for regions interested in undertaking shared assessments

Barbara J Sabourin

*Director General, Therapeutic Products Directorate,
Health Products and Food Branch, Health Canada*

Director General, Therapeutic Products Directorate, Health Products and Food Branch, Health Canada

There are a number of potential goals for international regulatory collaboration including standard setting, work-sharing and other, larger government agendas and these partnerships offer multiple advantages.

Sharing expertise, experience, resources and communication channels with other regulators produces better outcomes. Working in real-time on emerging issues can assist with building common regulatory frameworks. Resources can be better used, with targeting and value-added considerations. Additionally, collaboration can contribute to the adoption of best practices, including risk-based approaches.

Currently, Canada is active in numerous collaborative initiatives in pharmaceutical regulation including the International

... the Health Canada Pharmaceutical Safety Efficacy Assessment Template has been recently modified to incorporate the steps in the CIRS UMBRA framework

Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the International Coalition of Medicines Regulatory Authorities (ICMRA), the International Conference of Drug Regulatory Authorities (ICDRA), the Pharmaceutical Inspection Convention/ Pharmaceutical Co-operation Scheme (PIC/S), the Asia-Pacific Economic Cooperation (APEC) and the World Health Organization (WHO) which includes the Pan American Health Organization (PAHO) and the Pan American Network for Drug Regulatory Harmonization (PANDRH).

Collaboration on generics

Health Canada is actively engaged both bilaterally and multilaterally with its international partners in the area of generics. Initiated in 2011, the Regulatory Cooperative Initiative with Australia works to match, share and use reports and build confidence through staff exchanges. This programme has demonstrated that international collaboration can translate into meaningful actions to help address common global regulatory challenges. The generics project for the Australia, Canada, Singapore, Switzerland (ACSS) Consortium was also initiated in 2011. The International Generic Drug Regulators Program (IGDRP), encompassing more than 14 jurisdictions and launched in 2012, is an information-sharing pilot project with the European Union to share assessment reports in real time. In addition, Canada participates in the International Coalition of Medicines Regulatory Authorities (ICMRA) Generics Project. Health Canada's participation in these initiatives has helped drive multilateral projects on a broader scale with other key regulators

The collective efforts of the participating agencies have resulted in tangible deliverables on a variety of priority work areas in the field of generic medicines. These priority work areas have largely been identified through examining the similarities and differences across the different jurisdictions and selecting those that had the greatest potential for alignment. Examples include the development of common assessment tools such as common application forms for sponsors, common assessment

Figure 18. Enabling factors for international collaboration.



templates and guidance for reviewers.

Experience with international collaboration on generics has demonstrated that significant planning and investment are required to build relationships and confidence. Key collaborative tasks include identifying priority areas, developing work plans with clear deliverables and timelines, convening regular meetings and conducting staff exchanges. Collaboration also requires a forum with a specific mandate and leadership to promote collaboration and link strategically with other international initiatives.

A number of factors are needed to enable collaboration such as a common glossary or lexicon, which allows understanding of differences in terminology and potential standardisation. Other enabling factors include industry support and engagement, cooperation and buy-in at both the working and senior executive levels, mechanisms to share confidential information such as a memorandum of understanding, secure information technology systems and staff training and development (Figure 18).

A common benefit-risk framework: Challenges and opportunities

Although the use of a common framework is an important factor in international collaboration, there are challenges in its use including differences in data packages submitted to each agency and jurisdictional regulatory and technical requirements, as well as the clinical context and practice of medicine relevant to

regulatory decisions. In addition, regulatory staff must agree that using foreign reviews enables more efficient reviews without compromising standards.

Despite the challenges; however, the use of a common framework offers important opportunities. It allows agencies to share work and conduct joint reviews, communicating information more broadly with industry partners and other stakeholders, such as patient groups and health technology assessment agencies. These frameworks also allow a clearer understanding of the rationales underpinning differing marketing and labeling decisions in different jurisdictions such as clinical context and the practice of medicine. In addition, enhanced collaboration is possible with Risk Management Plans and Periodic Safety Update Reports in the post-approval setting.

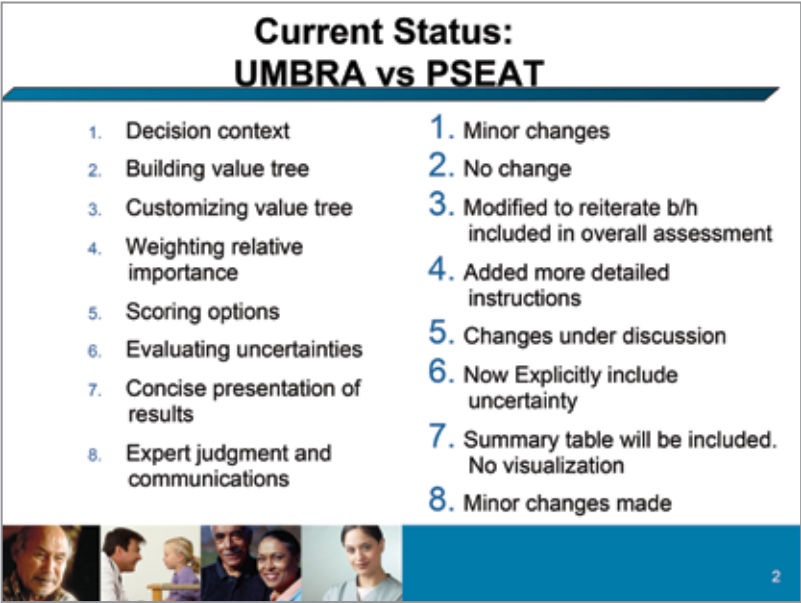
In its efforts to utilise a common framework for benefit-risk assessment, the Health Canada Pharmaceutical Safety Efficacy Assessment Template (PSEAT) has been recently modified to incorporate the steps in the CIRS Universal Methodologies for Benefit-Risk Assessment (UMBRA) framework and a new version will be implemented in 2015 (Figure 19).

Conclusions

Implementation of a common benefit-risk framework is a journey, with many steps that will differ among agencies, depending on their individual situations and pressures and their intentions for use of the templates. However, the issue is no longer whether but how to best use a common benefit-risk framework in a consistent and transparent manner that contributes to the efficiency and quality of the drug review process.

National, regional and international strategies are needed for the use of a common benefit-risk framework to develop practical, relevant, incremental and flexible approaches that result in tangible benefits. Experience from other initiatives, such as IGDRP and ACSS generic programmes can and should be leveraged in implementation of a common international benefit-risk assessment template.

Figure 19. The Health Canada Pharmaceutical Safety Efficacy Template has been updated to incorporate steps in the CIRS UMBRA framework.



Enabling the translation of reference agencies' decisions to the local jurisdiction for benefit-risk assessment

Dr James Leong

Head of Education, Centre of Regulatory Excellence,
Duke-NUS Graduate Medical School, Singapore

Referencing

The term *referencing* refers to the translation of established regulatory reference agencies' decisions regarding pharmaceutical dossiers to a local jurisdiction. Referencing does not mean direct adoption of other agencies' regulatory decisions, nor does it represent the loss of the right to make independent or different decisions nor remove or eliminate an agency's need to fill resource gaps such as regulatory competencies within its own structure.

In August 2014, the World Health Organization (WHO) issued a draft of Good Review Practices: Guidelines for Regulatory Authorities for comment. This draft enumerates ten principles of good review including balance, consideration of context, basis in evidence, identification of signals, investigation and solving of problems, creation of linkages, utilisation of critical analyses, thoroughness and good documentation and management. The guidelines also identify four key elements for a review strategy: the review

must consider public health priorities; include an understanding of other regulatory actions for the same application; involve an understanding of specific intrinsic and extrinsic factors and identify major scientific questions and resolutions.

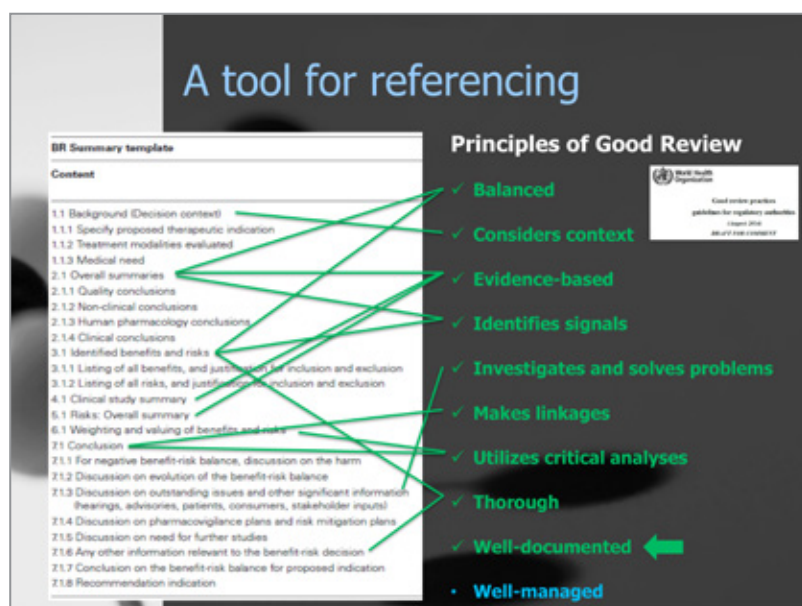
The Guidelines recognise that applying a review strategy is resource dependent and the availability of expertise must be taken into consideration. However, they specify that the basis on evidence of the review must be in accord with legal frameworks and regulatory guidelines, that internal processes must be robust and that benefit-risk assessment methodologies must be employed. Furthermore, the review process must be documented and communication with stakeholders maintained.

In their efforts to fulfil these guidelines, regulators face a number of challenges including resource limitations, increasing workloads and gaps in competencies. In addition, healthcare stakeholders demand timely access and efficiency, transparency and accountability of regulatory decisions and consistency of standards and the rapid evolution in the sciences often outpaces regulatory processes. These issues create the need for an effective approach to reduce the burden on regulators while fulfilling the quality and standards of good regulatory decision making.

To this end, the referencing or leveraging of the work of established regulatory agencies by local authorities can utilise the resources and expertise of these agencies to relieve the work burden and complement ongoing efforts to enhance regulatory capabilities and build confidence for regulatory authorities in emerging markets. Furthermore, referencing an understanding of the perspectives of other agencies is good review practice, contributing to the robustness of decisions. Referencing can be of particular benefit to a community of similar epidemiologic profile to that of a reference agency, helping to build and support the bases of regulatory decisions that are applicable to a region.

Despite the benefits of referencing; however, there are also potential barriers. The number of publicly available reports is limited and use of those reports that are available may require a memo of understanding or a formal agreement. Additionally, the ease of locating the reports can vary and because the quantity of information hampers the communication of the essential messages, the understandability of the bases of decisions and contributing factors may be

Figure 20. The CIRS Benefit-Risk Summary Template aligns with WHO principles of good review.



obscured. Then too, the objectives of a given report may not be suited for the same purpose in a different jurisdiction. Finally, the lack of internal policies that support referencing in regulatory processes may require change management.

A tool for referencing

As detailed by Dr McAuslane (p 34) a Benefit-Risk Template based on an European Medicines Agency (EMA) reflection paper¹ was developed by a consortium of regulators from Australia's Therapeutic Goods Administration (TGA), Singapore's Health Sciences Authority (HSA), Health Canada and SwissMedic in collaboration with CIRS. The summary portion of this template was then extracted to produce a stand-alone Benefit-Risk Summary Template whose simplified format would best meet the needs of regulatory agencies in jurisdictions with developing pharmaceutical markets. Based on established criteria for assessment of benefits and risks, the Benefit-Risk Template and Benefit-Risk Summary template, support the CIRS Universal Methodologies for Benefit-Risk Assessment (UMBRA) eight-step benefit-risk assessment framework.

Part of a recent study performed by Dr Leong and colleagues involved the transfer of information from publicly available assessment reports from four jurisdictions into the Benefit-Risk Summary Template. The objectives of the study were to compare the formats of the assessment reports and the summary template and to examine the utility of the Benefit-Risk

Given the minimal differences among the existing report formats of reference agencies, it may be timely to consider the use of a universal benefit-risk template.

Summary Template for extracting information and communicating benefit-risk decisions.²

The structure of the Benefit-Risk Summary Template was found to align well with the previously cited WHO principles of good review (Figure 20). The template improved the quality of communication by listing benefits and risks, with justification for their roles in assessing the benefit-risk balance and the reasons for their inclusion or exclusion. It also provided values and weights for the identified benefits and risks and afforded the opportunity for visualisation of outcome. The template was found to use guided discussions and structured questions to illustrate key discussion points leading to benefit-risk decisions.

Given the minimal differences among the existing report formats of reference agencies, it may be timely to consider the use of a universal benefit-risk template. If used as a universal template, the Benefit-Risk Summary Template could trace and document the evolution of the benefit-risk balance of a product, using data from various jurisdictions and allowing meaningful comparisons, which would lead to increases in consistency, transparency and quality in decision making. It should be recognised; however, that even with a universal template, to develop an appropriate decision for its jurisdiction, each agency still must make its own critical evaluation, thereby also developing and enhancing its competency.

An example of referencing

The HSA offers three routes of evaluation for new drug applications, on a risk-stratification basis. A full review takes place over a period of 270 working days and is used for a product that has not been approved by any drug regulatory agency at the time of submission. An abridged review occurs over 180 working days and is used for a product that has been approved by at least one drug regulatory agency at the time of submission. An abridged review allows a non-clinical overview in place of the usual requirements and leverages existing approvals. Abridged reviews reduce the required review

Figure 21. Documentation for abridged or verification new drug applications.

An example of referencing

Table 5. Dossier Submission Requirements for an NDA.

Documents	Location in		Module/Part required for		
	ICH CTD	ACTD	Full NDA	Abridged NDA	Verification NDA
Administrative Documents	Module 1	Part I	Yes	Yes	Yes
Common Technical Document Overview and Summaries	Module 2	Incorporated in Parts II, III and IV	Yes	Yes	Yes
Quality documents	Module 3	Part II	Yes	Yes	Yes
Non-clinical documents	Module 4	Part III	Yes	ICH: No ¹ ACTD: Overview only	ICH: No ¹ ACTD: Overview only
Clinical documents	Module 5	Part IV	Yes	Study report(s) of pivotal studies and synopses of all studies (phase I-IV) relevant to requested indication, dosing and/or patient group	Study report(s) of pivotal studies and synopses of all studies (phase I-IV) relevant to requested indication, dosing and/or patient group

¹ Non-clinical overview included in Module 2 of the ICH CTD.

CORE
Centre of Regulatory Excellence
of State Health and Medical Research

time for non-clinical data but the chemistry manufacturing controls (CMC) review remains unchanged. In many cases, the prior approving agency is a major reference agency, allowing the use of publicly available reports for referencing.

A verification review, takes place over 60 working days and is used for products with similar indications, dosing regimens, patient groups and/or directions for use that have been approved by at least two of the following HSA reference agencies: US Food and Drug Administration (FDA), Health Canada, TGA, EMA or Medicines and Healthcare products Regulatory Agency (MHRA). To use a verification process, a submission must be made within three years from the product's first approval date, the quality of the product must be identical to that currently approved by the chosen primary reference agency and the product cannot require a more stringent assessment as a result of differences in local disease patterns or medical practices. In addition, the product cannot have been rejected, withdrawn or approved via appeal process or pending deferral. Furthermore, the proposed uses should be the most stringent amongst those approved by the reference agencies (Figure 21).

Use of the verification process leverages converging opinions from two established sources, reducing the time required to review data and allowing an expedited market decision and lessening burdens on HSA staff.

There are challenges associated with the use of referencing including the fact that the suitability of the approach within legal and regulatory frameworks differs across jurisdictions. In addition, the use of verification reviews could open a floodgate for applications with shorter timelines, increasing rather than reducing demands on local agencies and compromising the environment for experiential learning. A framework is therefore particularly needed to develop agency competency.

Building trust

In considering how enabling the translation of reference agencies' decisions to the local jurisdiction for benefit-risk assessment could underpin trust and understanding among agencies Chen and colleagues wrote

"trust is enforced when organizations develop shared goals, form social relational embeddedness and initiate influence strategies. In addition, inter-organizational trust leads to better inter-organizational collaboration and knowledge sharing."³

Achieving understanding among regulatory agencies involves the attainment of technical comprehension and interpretation, as well as mutual agreement or cooperation. The common goals of regulatory agencies are to develop and enhance good review practices and increase efficiency and referencing should be evaluated as an approach to meet those goals. The Benefit-Risk Summary Template should be further explored as a tool to facilitate understanding of benefit-risk decisions and to enable extrapolation of suitable conclusions for local context, which can potentially function as part of a regulatory submission or complementary to a Certificate of Pharmaceutical Product (CPP).

References

1. European Medicines Agency. *Reflection paper on benefit-risk assessment methods in the context of the evaluation of marketing authorisation applications of medicinal products for human use*. Found at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500069634.pdf Accessed May 2015.
2. Yeen JLW, Salek S, Walker S. Strategy for communicating benefit-risk decisions: a comparison of regulatory agencies' publicly available documents. *Front Pharmacol*. 04 December 2014, doi: 10.3389/fphar.2014.00269.
3. Chen YH et al. How to facilitate inter-organizational knowledge sharing: The impact of trust. *Inform Manag*. 51:568-578.

The role of frameworks in building quality into regulatory decisions

Dr Justina A. Molzon

Former Associate Director for International Programs, Food and Drug Administration, USA

The rising tide of guidelines for best practices in the development and regulation of medicines began with good manufacturing practices (GMP) and has expanded to include good clinical practices (GCP) and good pharmacovigilance practices. Increased granularity within GCP has resulted in good documentation practices, good clinical data management practices and good clinical laboratory practices and the trend has also now gone expanded to include good review practices (GRevP), good management practices, good submission practices and good pharmacovigilance practices.

Because of the complexity of disciplines and specialties involved in the drug review process, a consistent approach to evaluating submissions and expressing conclusions is needed and many of these guidelines such as GRevP have emerged from the need for transparency and consistency. In addition, regulatory processes should incorporate agreed upon best practices and a common style and review format will help regulators, industry and the public understand the review process from data, to interpretation, to recommendations and decisions and subsequent regulatory actions.

To further that understanding and because regulatory reviews are made available to the public through web postings, the US FDA requires that they be written such that the American public understands the recommendations and decisions; each agency review discipline has its own template to ensure an articulate, understandable presentation in a common style and review format that will help regulators and the American public.

In addition to furthering understanding, implementation of GRevP helps to achieve the desired regulatory review outcomes by ensuring that those involved in the review process have the critical thinking skills and tools needed to

optimise scientifically sound, evidence-based decisions. In addition, GRP facilitates progress toward regulatory convergence by facilitating the exchange of review reports and of increased mutual understanding amongst regulatory authorities.

The World Health Organization (WHO) has developed a GRevP document based on the precepts developed by the Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonisation Steering Committee (RHSC) through a series of workshops. At the time of this Workshop, the WHO GRevP document was expected to be published in May 2015. Section 6.2 of the document specifies that a GRevP should ultimately enable a reviewer or review team to understand the benefit-risk profile of a medical product, given the indication and context of use. The WHO GRevP guideline further states that adoption of a benefit-risk framework is critical to promote interactions between drug regulatory authorities.

In fact, the adoption of GRevPs will facilitate convergence among international regulatory authorities. Adherence to these best practices ensures that reviews are similar across different regions. Regulators are, ultimately, responsible for the wellbeing of their citizens and must determine benefit-risk in the context of their own countries; therefore, regulatory decisions might differ amongst jurisdictions. However, by following GRevP, the information that led to those decisions decision would be presented in a consistent manner.

Aligned regulatory requirements allow companies to make global submissions for needed medicines within a compacted timeframe. In regions where regulators have limited resources, the authorities would benefit from assessing the reviews conducted by other regulatory authorities, allowing them to refocus their efforts on pharmacovigilance and benefit-risk issues relevant to their own population. Finally, shared standards can simplify communication between regulatory authorities; exemplifying what author David Grewal calls "The emergence and consolidation of transnational and international networks that link people –or groups of people – through the use of shared coordinating standards."¹

Reference

1. Grewal DS. *Network power: The social dynamics of globalization*. Boston: Yale University Press, 2008.

Because of the complexity of disciplines and specialties involved in the drug review process, a consistent approach to evaluating submissions and expressing conclusions is needed...

Building quality into the decision-making process

Professor Stuart Walker

Founder, Centre for Innovation in Regulatory Science, UK

Good decision-making practice: the role of frameworks

Beginning in 2010, the Centre for Innovation in Regulatory Science (CIRS) has enlarged and built on its two decades of work in the area of the benefit-risk evaluation of medicines by examining the science of decision making as it relates to medicine development and regulation. CIRS activities in this regard include Workshops, doctoral research and the global monitoring and evaluation of good review and submission practices.

Multiple consultancy organisation are currently providing advice on corporate decision making, including how to embed decision-making capabilities into an organisation, the impact of leadership and culture on quality decision making and the elements of good decision making. Another source of guidance, the book *Smart choices: A practical guide to making better decisions* by Hammond and colleagues,¹ contains eight steps for better decision making that have become known by the acronym PROACT-URL: 1. Define the decision Problem; 2. Clarify the Objectives; 3. Decide on the Alternatives;

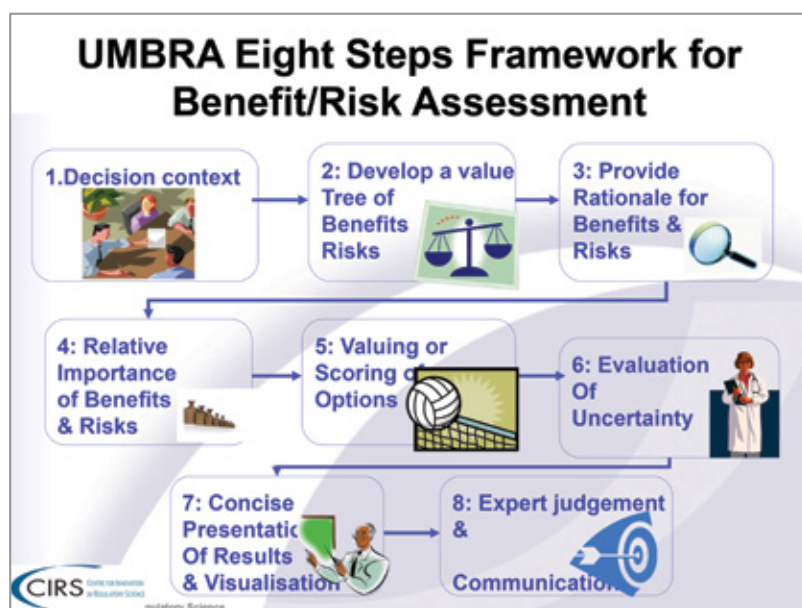
4. Describe the Consequences; 5. Assess the Tradeoffs; 6. Evaluate the Uncertainties; 7. Account for Individuals Risk Tolerance and 8. Effectively review current and future decisions (Link). These steps were influential in the design of the European Medicines Agency Roadmap to 2015.² The overarching CIRS Universal Methodology for Benefit-Risk Assessment (UMBRA) framework also contains eight steps for the area of decision making specific to benefit-risk evaluation to which all current benefit-risk approaches can be mapped (Figure 22).

Doctoral research conducted by Dr Ronan Donelan at Cardiff University in collaboration with CIRS and supervised by Professors Stuart Walker and Sam Salek resulted in the development of the Quality of Decision-Making Orientation Scheme (QoDoS©) instrument for appraising the quality of decision making. Dr Donelan conducted semi-structured interviews about decision making with key opinion leaders in regulatory agencies, pharmaceutical companies and clinical research organisations. These interviews resulted in a 94-item list of themes and sub-themes in decision making, which were reduced through analysis and content validation to 76 items and further reduced through factor analysis to a 47-item instrument. The QoDoS tool examines the decision-making approach and culture within an organisation and an individual's decision-making competence and style, using questions that measure the frequency (not-at-all to always) at which various aspects of decision making are encountered.³

Through the results of opinion leader input in the development of the QoDoS tool, ten steps for good decision making emerged.

1. Employ scientific rigor and understand the decision context.
2. Apply knowledge and experience.
3. Examine the integrity of the information.
4. Use an objective approach and be aware of biases and preferences.
5. Consider uncertainty and examine alternative solutions.
6. Assign values and relative importance to decision criteria.
7. Re-evaluate as new information becomes available.
8. Evaluate internal and external influences.

Figure 22. The CIRS Universal Methodology for Benefit-Risk Assessment (UMBRA) as the basis for the development of a decision-making tool



9. Apply a structured approach to aid transparency and record trail.
10. Perform impact analysis and effectively communicate the bases of the decision.

Results of a sample assessing this decision tool showed that 40% of participants never received any training in decision-making science, whilst 30% received some training. A majority of individuals (60%) use a structured approach to decision making but only 35% of their organisations use such an approach and transparency in decision making was practiced by 40% at the organisational level but less than 30% at the individual level.

A good decision-making framework: Is this critical to success?

Stakeholders in medicines development have indicated to CIRS that decision making is a topic of growing importance. Participant recommendations from the June 2012 CIRS Workshop entitled "The benefit-risk toolbox included one that specified "learn from QoDoS pilot experience; further assess its value for baseline and ongoing analysis of the quality of decision making and identify [decision making] training needs." At a CIRS Workshop held in Beijing in 2013, aspects of a good decision framework were identified during a Syndicate discussion (Figure 23).

Accordingly, the CIRS project plan for 2015 to 2017 includes the implementation of a programme that will identify the general principles of a good decision framework and

A majority of individuals (60%) use a structured approach to decision making but only 35% of their organisations use such an approach

the processes and practices that build quality into decision making within drug development, regulatory review and health technology assessment. The objectives of this programme are to:

- Review and evaluate current frameworks that enable quality to be built into decision making;
- Identify and document current decision-making practices with respect to major decisions such as the initiation of global development, the decision to submit to a regulatory agency, the decision to approve a medicine by a regulatory agency and the HTA decision to make a recommendation for reimbursement;
- Develop and validate a framework and documentation system for a structured, systematic, transparent and logical approach to decision making
- Recommend and advocate the use of good decision-making practices within companies and agencies to improve the efficiency and effectiveness of decision making for all stakeholders.

Figure 23. Attributes of a good decision framework, from CIRS Workshop, Beijing, January 2013.

Attributes of a good decision framework

Potential Attributes	Benefits
Structure , Clarity, Consistency	Allows comparison between decision in comparable situations/ products and review/challenge of the decision by others
Clear Roles and Responsibilities	Clear decision makers and advisors/contributors, encompasses debate, a range of perspectives
Efficiency and Effectiveness	Timely, provides benefit to those in receipt of decision
Constraints, Biases and Context	Identifies uncertainties, biases, limitations, subjectivity/ objectivity context and rationale of the decision or question being asked Human factor in decision making
Transparent	Allowing confidence with the decision and trust of the decision maker
Considers impact	Consider impact to a range of stakeholders, is forward looking and acknowledges the potential need to revisit decisions over the life cycle continuum
Helps range of stakeholders	Other reviewers, other agencies, sponsors, competitors, payers, physicians, patients, public citizens

From Syndicate recommendations CIRS Workshop, Beijing, 2013

References

1. Hammond JS, Keeney RL, Raiffa H. *Smart choices: A practical guide to making better decisions*. Boston: Harvard Business Review Press, 1999.
2. European Medicines Agency. Road Map to 2015. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101373.pdf Accessed May 2015.
3. Donelan R, Walker S, Salek S. Factors influencing quality decision making: regulatory and pharmaceutical industry perspective. *Drug Safety*. 2015; 24:319-328.

A structured benefit-risk framework: Can it ensure “quality of decision”?

Professor Hans-Georg Eichler

Senior Medical Officer, European Medicines Agency

What is a quality decision?

Before considering whether a structured benefit-risk framework can ensure the quality of decision, the definition of a quality regulatory decision must be established. That definition cannot hinge on the decision's outcome since uncertainties that persist regarding the mechanism of disease, the pharmacology of treatment and the psychology of patient adherence may result in a poor outcome for an appropriate regulatory decision. Furthermore, if the quality of regulatory decisions is determined by the satisfaction of stakeholders, Meijer and colleagues have postulated that other factors are required, saying “Besides good results, engagement from stakeholders in regulatory processes is needed to produce stakeholder satisfaction.”¹

Daniels and Sabin have pointed out that whilst achieving a unanimous regulatory decision is an elusive goal, in the face of this uncertainty of outcome and lack of consensus regulators can be responsible for an accountability for the “reasonableness” of their decisions.² The three elements of this accountability are transparency, relevance and revisability. That is,

documentation of regulatory decisions should show the underlying rationale and the decision-making methods that were used, allowing for discussion of any disagreements. The decision's relevance can be outlined by explaining why specific data were important or not important to the regulators. Finally, a revisable decision is one which can evolve as new information is incorporated into the benefit-risk assessment of a product.

Determining whether a structured decision framework adds the transparency and relevance to regulatory decisions that is required for accountability should be considered in light of the decision rule employed by regulators. This rule asks if the benefits of a medicine outweigh its risks and if the uncertainty surrounding those benefits and risks is acceptably low. Canadian regulators have called this concept benefits, harms and uncertainty or B-H-U.

The toolbox of available benefit-risk decision frameworks, which includes the EMA Effects Table (Figure 24), entail a trade-off between precision in results and the degree of complexity and effort required for use. Regardless of their level of complexity; however, these methods all involve uncertainty. These uncertainties include those regarding precision, external generalisability, extrapolation, the potential for bias or fraud and the unknown unknowns.

As regulatory science moves from a holistic to a deconstructed approach, a structured framework allows an explicit valuing and weighting of factors that may previously been implicitly assessed. Frameworks may also enable the accrual of structured patient input, including the weighting of factors that are important to these stakeholders.

Whether structured frameworks would affect the outcome of decision making currently remains unknown because of a lack of experience in their use. Outcomes may be ultimately affected by the attitude of decision makers toward risk. Neither maximum risk tolerance, with its attendant approval of potentially dangerous drugs, nor maximum risk aversion, with its resulting unavailability of important new medicines, have a positive impact on public health. Regulators are charged to find the balance of risk tolerance and risk aversion that results in the greatest benefit to public health.³

Conclusions

Structured frameworks for benefit-risk assessment will likely add to transparency and

Figure 24. The toolbox of available benefit-risk decision frameworks, includes the EMA Effects Table.

B-R: transparency and relevance? (EMA/CHMP Effects Table)						
Effect	Description	Unit	Placebo	Vandetanib	Uncertainties/Strength of evidence	References
Favourable	PFS (HR)	N/A	1	0.46 95% CI: (0.31, 0.69)	Large effect in overall population. Consistent and significant effect on PFS but not OS (too early?)	See Discussion on Clinical Efficacy.
	PFS (median)	Months	19.3	30.5	Only a very low number of patients with definite RET mutation negative status at baseline. Lower efficacy?	Single-arm study in RET negative patients post-approval.
	ORR	%	13	45	No clear effect on PRQ/QoL (missing data)	See Discussion on Clinical Efficacy.
Unfavourable	Diarrhoea Grade 3-4	%	2.0	10.8	Duration of follow up in the pivotal study is short vs. the need for long duration of treatment.	Risk of dehydration and renal/cardiac risks (see SmPC 4.4)
	QTc related events Grade 3-4	%	1.0	13.4	Risk of developing further major cardiac SAEs including Torsades de pointes	Restrict to symptomatic and aggressive disease (see SmPC 4.1).
	Infections Grade 3-4	%	36.4	49.8		Explore lower dose (see See Table 20. Summary of the RMP)

relevance to decision making by making the value judgements of regulators explicit. The frameworks may also help to improve the 'light to heat ratio', by shifting the focus of public discourse from questioning the competence or motives of regulators to discussing differences in opinions and perspectives on the basis of the rationales presented by the use of the framework. With all of the available frameworks; however, addressing uncertainty will likely remain the most significant challenge.

Use of the frameworks may or may not affect the outcomes of regulatory decisions, which are most influenced by decision makers' attitudes toward risk, yet these tools will likely enhance—but probably not ensure—the quality of regulatory decisions.

Use of the frameworks may or may not affect the outcomes of regulatory decisions, which are most influenced by decision makers' attitudes toward risk and these tools will likely enhance—but probably not ensure—the quality of regulatory decisions.

References

1. Meijer A, Boon W, Moors EI. Stakeholder engagement in pharmaceutical regulation. *Pub Admin*. 2013;91:696-711.
2. Daniels N, Sabin JE. Accountability for reasonableness: an update. *BMJ*. 2008;337:1850.
3. Eichler H-G, Bloechl-Daum B, Brasseur D et al. The risks of risk aversion. *Nature Rev Drug Disc*. 2013;12:907-916.

Building quality into the decision-making process:

The role of frameworks to an emerging-markets agency

Dr Joey Gouws

Registrar of Medicines, Medicines Regulatory Authority, Department of Health, South Africa

The Southern Africa Development Community

The Southern Africa Development Community (SADC) is a regional organisation encompassing 15 countries, with a total population of 277 million people or approximately 4% of the world population. To provide additional perspective for this statistic, it should be recognised that 15% of the world population consumes approximately 90% of finished pharmaceutical products.

Within the SADC, regulators who are faced with an increased workload and limited resources realise that growing concerns about the safety of medicines require advances in pharmacovigilance systems and strengthening of regulatory capacity. Global declarations recognise this need such as a 2010 World Health Assembly resolution that requires that the quality, safety and availability of blood for

transfusion be ensured. In addition, there is a worldwide call for regulatory oversight of herbal medicines to ensure quality and safety and an international requirement to provide regulatory oversight of medical devices and in vitro diagnostic devices to ensure safety, quality and performance. Finally, recent legislation in the European Union that reformed the roles for importing active pharmaceutical ingredients for medicinal use requires the immediate regulatory oversight of manufacturers.

Quality decision-making processes

In 1999, the World Health Organization (WHO) defined the elements of effective medicine regulation as good regulatory practice and standards, adequate and appropriate human, financial, technical and physical resources, supported by appropriate standard operating procedures (SOPs) and policy guidelines. WHO also called for regulation based on risk and set limits on the discretionary powers of regulators.

The mandate of each national regulatory authority (NRA) is to protect the public through quality decisions. NRAs strive to implement good regulatory review practices among their assessors, ensure robust regulatory decisions and actions and endeavour to implement a quality management system. For their part, applicants expect scientific integrity, communication, transparency and consistency in the review process. The quality of regulatory dossiers, however, affects the way in which reviews are

conducted and the possibility of a successful review outcome.

Within a NRA, the quality management system is influenced by the size of the agency, its resources and competencies, particular objectives, agency processes and the organisational structure. Successful quality management implementation requires a commitment by senior management and is the responsibility of everyone within the organisation. As defined by WHO in 2014, review tools should include standard operating procedures, templates and reviewer learning activities including training courses, mentoring, orientation packages and discussion sessions.

The requirements for effective quality management have been defined by WHO and the Centre for Innovation in Regulatory Science – CIRS. (Figure 25).

Framework of quality management system

The Medicines Regulatory Authority (MRA) in South Africa uses a quality cycle process. The four key components of this process are predefined procedures captured in key documents including assessment templates, guidelines and SOPs, daily execution of directives, monitoring and review practices and improvement in reviews due to evolving science or the adoption of new practices.

Decision-making processes include the use of decision frameworks, external experts, internal meetings, time frames for completing and communicating reviews and peer review by

... the implementation of good regulatory review practices including decision-making frameworks will allow the optimisation of available regulatory resources in even the smallest of emerging markets.

internal and external reviewers. The benefit-risk assessment process follows a structured approach (Figure 26).

The MRA has adopted the Common Technical Document and a pilot programme has evaluated the use of the electronic Common Technical Document in 44 applications. Although currently, regulators and evaluators in South Africa could be characterised as risk averse, the need for change in this regard has been recognised.

Quality across borders

An initiative has been launched within the SADC countries of Zambia, Zimbabwe, Botswana and Namibia (ZaZiBoNa) to ensure the quality of decision-making across borders through the use of joint assessments and WHO format and guidelines. South Africa will join this initiative in 2015. In the ZaZiBoNa project, the Secretariat is located in the host country, which selects products for evaluation. Applicants are involved in the review process and a rapporteur reports for all the countries. Before a ZaZiBoNa meeting, the host country performs the first evaluation of the product. During the meeting, the evaluation is discussed and consensus developed, a list of consolidated questions is provided to the applicant and a report is prepared. ZaZiBoNa then holds a second meeting to assess the applicant's response after it is received and a final decision is made after which, each country is free to make its own decision regarding the product. To date, ZaZiBoNa has held four meetings and assessed fifty dossiers

Conclusions

Regulators in countries with emerging pharmaceutical markets face a number of challenges surrounding decision making. Each agency has to determine the public health priority represented by potential new medicines, given the policies of its government. These regulators need to understand the intrinsic and extrinsic factors that are relevant to their population, such as genotypes and phenotypes, disease manifestation and study populations, identifying major scientific

Figure 25. Requirements for a quality management system.



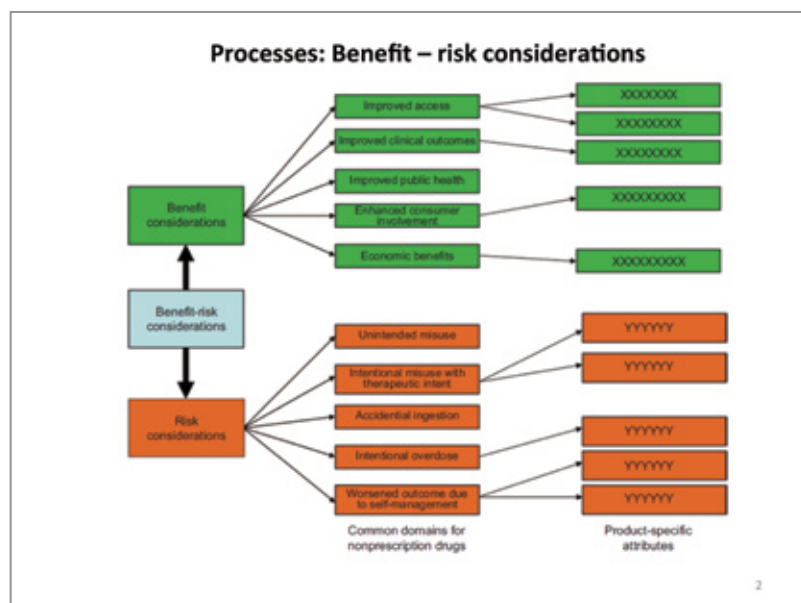


Figure 26 Benefit-risk assessment in the South African MRA.

questions and possible resolutions to those questions, using the information necessary for marketing authorisation versus the information that must be collected in the post-marketing period. Finally, the benefit-risk profiles of these medicines must be understood, particularly as they relate to patient safety and the actions of other regulatory agencies on the same application appreciated. Consideration of these factors and the implementation of good regulatory review practices including decision-making frameworks will allow the optimisation of available regulatory resources in even the smallest of emerging markets.

Appendix: Workshop Attendees

REGULATORY AGENCIES		
Azura Abdullah	Head of Unit/Section for New Drug Products, Centre for Product Registration	National Pharmaceutical Control Bureau, Malaysia
Luiza Novaes Borges	Health Surveillance and Regulatory Specialist	Brazilian Health Surveillance Agency
Alasdair Breckenridge	Former Chairman	Medicines and Healthcare Products Regulatory Agency, UK
Dr Ming-Hsiao Chan	Director, Division of New Drugs	Center For Drug Evaluation (CDE), Taiwan
Dr Kai-Ling Chang	Reviewer, Division of Pharmaceutical Science	Center For Drug Evaluation (CDE), Taiwan
Dr Chi-Hsun Chen	Senior Team Leader, Division of New Drugs	Center For Drug Evaluation (CDE), Taiwan
Ke-Hsin Chen	Section Chief, International Cooperation	Food and Drug Administration, Ministry of Health and Welfare, Taiwan
Dr Chin-Wei Chiao	Reviewer, Division of Medicinal Products	Food and Drug Administration, Ministry of Health and Welfare, Taiwan
Dr Petra Doerr	Head of Communication and Networking, Deputy Director	Swissmedic
Prof Hans-Georg Eichler	Senior Medical Officer	European Medicines Agency
Dr Churn-Shiouh Gau	Executive Director	Center for Drug Evaluation, Taiwan
Dr Joey Gouws	Registrar of Medicines	Medicines Regulatory Authority, Department of Health, South Africa
Dra. Nurma Hidayati	Director of Drug and Biological Products Evaluation	National Agency of Drug and Food Control (NADFC), Indonesia
Dr I-Chun Lai	Team Leader, Division of New Drugs	Center For Drug Evaluation (CDE), Taiwan
Dr John Lim	Deputy Director of Medical Services Executive Director,	Ministry of Health, Singapore Centre of Regulatory Excellence, Duke-NUS
Dr Chih-Liu Lin	Deputy Executive Director	Center for Drug Evaluation, Taiwan
Dr Hsien-Yi Lin	Senior Reviewer, Division of Medicinal Products	Food and Drug Administration, Ministry of Health and Welfare, Taiwan
Dr Yi-Chu Lin	Associate Researcher, Division of Medicinal Products	Food and Drug Administration, Ministry of Health and Welfare, Taiwan
Li-Ling Liu	Director, Division of Medicinal Products	Food and Drug Administration, Ministry of Health and Welfare, Taiwan
Dr Yee Hoo Looi	Regulatory Consultant	Health Sciences Authority, Singapore
Dr Justina Molzon	Former Associate Director for International Programs	Food and Drug Administration, USA
Pia Angelique Priagola	Food – Drug Regulation Officer III	Food and Drug Administration, Philippines
Dato' Eisah Rahman	Senior Director of Pharmaceutical Sciences	Pharmaceutical Services Division, Ministry of Health, Malaysia
Po-Yu Wang	Section Chief	Food and Drug Administration, Ministry of Health and Welfare, Taiwan
Dr Tzong-An Wang	Team Leader/Medical Reviewer, Division of New Drugs	Center For Drug Evaluation (CDE), Taiwan

PHARMACEUTICAL COMPANIES AND ASSOCIATIONS		
Dr Harindra Abeysinghe	Vice President, Head of Asia Pacific Regulatory Affairs	Johnson & Johnson Pte Ltd, Singapore
Tracy Baskerville	VP, Regulatory Affairs, Area and Affiliate	AbbVie, USA
Jayanthi Boobalan	Asia Regulatory Country Strategist	Pfizer, Malaysia
Zila Munir-Cheung	Senior Manager – Regulatory Affairs	Biogen Idec, UK
Serena Chow	Senior Director	Janssen, Taiwan
Dr Susan Forda	Vice President, Global Regulatory Affairs International	Eli Lilly and Company Ltd, UK
Dr David Guez	Director, International Therapeutic R&D Special Projects	Institut de Recherches Internationales Servier, France
Christophe Helbert	Project Director	Institut de Recherches Internationales Servier, France
Gloria Hung	Asia Regional Director, Regulatory	Pfizer, Hong Kong
May Hwang	Sr. RA Manager	Novartis, Taiwan
Dr David Jefferys	Senior Vice President, Global Regulatory, Government Relations, Public Affairs and European Product Safety	Eisai Europe Ltd, UK
Sadia Kaenzig	Communications Manager	International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
Prof Thomas Kühler	Senior Director/Professor	Novo Nordisk A/S, Denmark
Thean Soo Lo	Director, AP Regulatory Policy Lead	Janssen, Singapore
Janet Lu	Deputy Site Head of Roche Product Development in Asia Pacific, Head of Regulatory Asia Pacific	Roche (China) Holding Ltd, China
Caroline Mendy	Manager, Regulatory Policy	International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
Estelle Michael	Senior Director	AstraZeneca, UK
Shigeru Nakaji	Executive Directors, Development department	Astellas, China
Dr Ashley Preston	Head of International Regulatory and Scientific Policy	Merck Serono, Singapore
Irene Rau	Regulatory Affairs Director	GlaxoSmithKline Pharmaceutical Company, Taiwan
Dawn Ren	Global Safety Leader, TA Primary Care, GPV	Bayer Healthcare Co Ltd, China
Dr Michael Rozycki	Vice President, Regulatory Affairs Asia Pacific	Allergan Inc, Singapore
Dr Isao Sasaki	Director, Asian Regulatory Affairs, Regulatory Affairs-Japan	Astellas Pharma Inc, Japan
Jessica Thongcharen	Associate Director, Pharmacovigilance	Takeda Development Center Asia, Singapore
Alec Tiong	Head, Regulatory Affairs, Japan & Asia-Pacific	AbbVie, Singapore
Kum Cheun Wong	Head, Asia Pacific Policy & Liaison, Drug Regulatory Affairs	Novartis Asia Pacific Pharmaceuticals Pte Ltd, Singapore

ACADEMIC INSTITUTIONS		
Prof Bruno Flamion	Professor of Physiology and Pharmacology	University of Namur, Belgium
Dr James Leong	Head of Education, Centre of Regulatory Excellence	Duke-NUS Graduate Medical School, Singapore
Assoc Prof Silke Vogel	Associate Professor / Deputy Director, Centre of Regulatory Excellence	Duke-NUS Graduate Medical School, Singapore
Centre for Innovation in Regulatory Science (CIRS)		
Patricia Connelly	Manager, Communications	
Lawrence Liberti	Executive Director	
Dr Neil McAuslane	Director	
Prisha Patel	Manager, Emerging Markets Programme	
Professor Stuart Walker	Founder	