IMPLEMENTING AN INTERNATIONALLY ACCEPTABLE FRAMEWORK FOR THE BENEFIT-RISK ASSESSMENT OF MEDICINES:

How close are we to this objective?

20-21 JUNE 2013
WASHINGTON, DC, USA

WORKSHOP REPORT

CIRS Centre for Innovation in Regulatory Science

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Report date: May 2014

Section 1: Executive Summary

Background to the Workshop

At the annual CIRS Benefit-Risk Workshop in 2012, there was an agreement among those who are developing methodologies for assessing the benefits and risks of medicines that there are four key stages for these evaluations, namely; framing the decision; identifying the benefits and risks; assessing the benefits and risks; and developing interpretations and recommendations. An overarching eight-step framework developed at this Workshop underpins the four stages:

1. Developing a decision context
2. Building a value tree
3. Refining the value tree
4. Assessing the relative importance of parameters
5. Evaluating options
6. Assessing uncertainty
7. Concisely presenting results – visualisation
8. Issuing final recommendations

The overarching framework provides the basis for a common agreement on the principles for benefit-risk assessment and all the methodologies for evaluation that are currently being developed by regulators and pharmaceutical companies have either implicitly or explicitly incorporated most of the eight steps. Over the past year, an implementation and usage guide has also been developed for the overarching framework through the CIRS Universal Methodologies for Benefit-Risk Assessment (UMBRA) initiative.

Two issues within the conduct of benefit-risk assessment remain to be resolved, one being the assessment of relative importance and the other the evaluation of uncertainty. However, in some methodologies they may not be considered as specific steps. Moreover, the process of determining relative importance has been identified as particularly difficult, due to perceived complexity, subjectivity and the lack of standardised methodology.

CIRS has recently investigated these issues with companies and agencies as part of the UMBRA initiative and proposals for consideration with regards to the applicability of the UMBRA Framework were discussed and debated at this Workshop. Stakeholders in the development and regulation of medicine sought to determine if the overarching framework and the methodologies that have been developed and that are now being used routinely within companies and agencies are fit for purpose and if not, what the main concerns were.

Workshop Objectives

- **Discuss the progress** made by the different groups in 2013 in defining and implementing a benefit-risk methodology framework and specific methodologies within their organisations
- **Further the thinking** around assessing relative importance and uncertainty within the context of making explicit benefit-risk decisions and how these should be approached
- **Develop proposals for the implementation** of the overarching UMBRA framework and discuss its use from molecule to marketplace in the life cycle of medicines

Introduction

Day 1 Chair, Dr Ed Harrigan, *Senior Vice President, Worldwide Safety and Regulatory, Pfizer, USA* reminded Workshop participants that much progress has been made in the area of the benefit-risk assessment of new medicines in the past decade. This progress includes pilot programmes for the use of structured benefit-risk assessment methodologies by global regulatory agencies and work toward developing a common lexicon. However, much work remains, as the position of these methodologies progresses from pilot programmes to everyday use – work that would hopefully be advanced by the current Workshop.

Key points from presentations

SESSION: IMPLEMENTING A COMMON FRAMEWORK FOR BENEFIT-RISK ASSESSMENT: HOW ARE THE DIFFERENT METHODOLOGIES PROGRESSING?

Dr James Shannon, *Chief Medical Officer, GlaxoSmithKline, UK* argued that it is now time for a benefit-risk decision-making framework to be used routinely in the development and regulation of new medicines, saying that although the methodologies may differ in nature and usability, an agreed overarching framework would provide a common language and enable industry, regulators and patients to engage in transparent dialogue to determine the trade-offs involved in the use of a medicine and understand the context of the decision, including the severity of the unmet medical need that it addresses and the quality and reproducibility of the scientific evidence that supports its use.

Dr Sinan B. Sarac, *Senior Medical Officer, Danish Health and Medicines Authority* agreed that there are multiple benefits to the use of a structured approach for both industry and regulators. Industry could take control of the evaluation of their products by discussing, valuing and weighting the results themselves and proactively including a structured benefit-risk assessment in their dossiers and regulators could use their own structured assessments to increase the consistency of their decisions and to enhance their credibility by transparently communicating their decision making to the public. The lack of the routine use of structured benefit-risk assessment by the developers and regulators of medicine, however, is the result of multiple, often conflicting factors.

The Consortium on Benefit-Risk Assessment (COBRA) is an association of representatives from Health Canada, the Therapeutic Goods Administration of Australia, Swissmedic and the Health Sciences Authority of Singapore seeking to develop a qualitative framework for the benefit-risk assessment of medicines to allow a systematic standardised approach to the appraisal of medicines during regulatory review and post-marketing to facilitate the opportunity for joint or shared reviews within the group. Reporting on the results of a pilot of the COBRA template in Health Canada, **Barbara Sabourin**, *Director General, Therapeutic Products Directorate* reported that for Health Canada, participation in the COBRA pilot study identified areas for improvement in the review processes and identified new concepts to build into existing procedures and has also "socialised" the concept of different methodologies for benefit-risk evaluation within the review community.

Introducing new or modified ways of doing things in large organisations is challenging and implementation of the benefit-risk assessment process at the FDA will require a change-management approach. **Dr Patrick Frey**, *Director, Office Program and Strategic Analysis, CDER, FDA, USA* explained that to this end, the FDA began to obtain buy-in from senior leadership from the very beginning of the framework development and the support of senior leadership facilitated frequent engagement with review teams during the pilot project. Currently, all levels of staff are engaged in determining a reasonable approach for framework implementation.

Intended to be used for relatively straightforward benefit-risk assessments, the EMA Effects Table was developed as a compact and clear display of salient findings for a new drug, which is simple to build and communicate and which can be generally applied. In building the Effects Table, the reviewer focuses only on the important effects of a medicine and those effects are not weighted for their relative importance. After a CHMP trial of the use of the Table in the evaluation of ten medicines, Dr **Francesco Pignatti**, *Head of Section, Oncology. Haematology & Diagnostics, European Medicines Agency* reported that it is currently being piloted by the EMA as an element of the Assessment Report, with assessors being trained and monitored in its use. In addition, the CHMP is encouraging companies to use the template in the presentation of dossiers to the EMA.

The benefit-risk template developed by COBRA is a tool showing the progressive logic and bases of benefit-risk decisions, which also correlates to and supports the Universal Methods for Benefit-Risk Assessment (UMBRA) framework. The template has been evaluated through a prospective study by COBRA members and regulators from Indonesia, Philippines, China, Malaysia, South Korea and Chinese Taipei (the Southeast Asia Benefit-Risk Evaluation [SABRE] group) are also assessing the potential of the summary portion of the template. **Dr Neil McAuslane**, *CIRS Director*, outlined the perspective of nine pharmaceutical companies, however, who said that although the COBRA methodology is informative and applicable to assessing benefits and risks and has the potential to become a common platform for

regulatory review, it needs to be mapped to current regulatory processes and documentation and would require significant enhancements that would include modifications that would allow it to be used as part of a life cycle management approach. CIRS will evaluate the sponsors' feedback in detail and discuss with companies what would be of value to them and to consolidate and potentially publish agency comments regarding their use of the template.

Professor Deborah Ashby, *School of Public Health, Imperial College London* reported on the progress of Work Package 5, the second- stage evaluation of several formal methodologies for the assessment of the benefits and risks of six medicines by the IMI PROTECT Consortium (Innovative Medicines Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium). The roadmap toward recommendations developed by PROTECT calls for five discrete stages of benefit-risk evaluation: planning, evidence gathering and data preparation, analysis, exploration, conclusions and dissemination of those conclusions. In addition to the preparation of a peer-reviewed publication, patient and public involvement studies are currently being conducted and a website that will synthesise the findings of PROTECT WP5 and provide interactive features is being developed.

SESSION: BENEFIT-RISK DECISION MAKING: ASSESSING RELATIVE IMPORTANCE AND UNCERTAINTY: HOW ARE THESE BEING APPROACHED AND WHAT NEEDS TO BE CONSIDERED

There is still resistance to the formal weighting of benefits and risks despite the fact that this weighting is a component of many accepted decision-making practices. Nevertheless, most decision makers understand that there is a need for quantitative tools to address more complex decisions that must incorporate data, uncertainty and necessary value judgements. **Dr Bennett Levitan**, *Director, Epidemiology, Janssen Research and Development* discussed five of the many types of methods used to derive benefit-risk weighting: zero/one weighting, categorisation, point allocation, swing weighting and conjoint analysis as well as common approaches to applying weights in benefit-risk decisions. The advantages and disadvantages of the models in terms of their theoretical justification, the identity of the parties assessed, the time and expertise needed to implement and the ease with which the results are communicated all affect their utility according to various stakeholder needs.

Dr Marilyn Metcalf, *Senior Director, Benefit Risk Evaluation, GlaxoSmithKline, USA* outlined the ways in which weighting informs pharmaceutical companies' internal benefit-risk work. It helps identify treatments with durable effects and minimal adverse events that provide convenience for patients' desired activity levels and enables decisions as to whether medicine development should continue based on the disease or condition it treats, alternative therapies and potential treatment populations. Companies need to study the outcomes that will inform patients' decisions, who need to know if the medicine is right for them based on their health history, lifestyle and personal goals and preferences. Weighting these elements provides perspective and can be a backbone for deeper discussions about a product's benefit-risk.

The FDA structured approach is an attempt to transparently show the benefits and risks considered in an evaluation, to identify the alternative treatment options that were taken into account, to consider ways to manage risks, to focus on what is known and unknown about the drug and then to make as rational and explainable a decision as possible. However, evaluations are not all binary "yes/no" decisions. It may also be necessary to consider whether a drug will be a second-line treatment, whether special tests will be required before use or as a part of safety or efficacy monitoring, which dosage should be used or whether a special safety description (i.e., a Box Warning) is required. **Dr Robert J. Temple**, *Deputy Center Director for Clinical Science, Center for Drug Evaluation and Research, U.S. Food and Drug Administration* provided examples in which the agency had to make difficult decisions based on both clear and uncertain data and instances in which drug-associated adverse events led to non-approval or withdrawal or approval with the implementation of risk management programmes.

The assessment of the benefit-risk balance of new medicines is inherently challenging and uncertainty regarding benefits and risks adds complexity to the assessment. **Dr Paul Seligman**, *Executive Director, US Regulatory Policy, Amgen Inc* said that there are a number of ways to improve understanding of and conversations around uncertainty such as an open discussions of uncertainty in sponsor-regulator interactions, an increase in regulatory guidance and training on how to evaluate and describe uncertainty

and the building of education on uncertainty into the FDA's upcoming public meetings. Sponsors and regulators must clearly define where uncertainty exists and discuss the impact of uncertainty on the benefit-risk assessment. Semi-quantitative and quantitative methodologies may be useful in assessing the impact of uncertainty on the assessment but the methodologies for and assessment of uncertainty in benefit-risk decision making are still evolving.

Dr Gerald J. Dal Pan, *Director, Office of Surveillance and Epidemiology, US Food and Drug Administration* discussed the multiple issues inherent in evaluating benefit and risk in the post-approval setting. Integrating data from multiple sources can present challenges when the sources of that data measure different things with varying degrees of rigour; understanding real-world effectiveness can be difficult when balancing emerging real-world safety issues with efficacy data obtained from clinical trials. Because medicines are not assigned to patients randomly in real-world situations, robust methods are required to adjust for confounding. Finally, because any result can be significant if a database is large enough, results require careful interpretation. Methods to balance benefit and risk must include an understanding of the impact of risk management on these events in the post-launch period.

The impetus behind the evolution of the Periodic Safety Update Report (PSUR) to the Periodic Benefit-Risk Evaluation Report (PBRER) was a desire on the part of regulators to have a greater emphasis on a balanced analysis of important factors, particularly a scientific evaluation of the benefit-risk profiles of medicine. **Dr Rebecca Noel**, *Senior Research Scientist, Eli Lilly and Company* reported that the advent of the PBRER should strengthen the practice of pharmacovigilance and the explicit discussion of benefit and risk and a focus on risk in the context of benefit encourages a more thoughtful, critical and integrated analysis. PBRERs have become a very effective tool to help focus the spotlight on the need for an integrative, evaluative approach to benefit-risk assessment, serving as a platform and as a motivation and leverage to develop and use a more structured approach to benefit-risk evaluation earlier in the product life cycle and in submissions.

Prof Hans Hillege, *Professor in Cardiology, Management Board, Department of Epidemiology, University Medical Center Groningen, The Netherlands* provided an online demonstration of the Aggregated Data Drug Information System (ADDIS), a software system that bridges the gap between aggregated clinical data and evidence-based drug regulation, using state-of-the-art methods for benefit-risk decision making. This software can be deployed not only in the regulatory domain but also in the decision-making domain of stakeholders such as developers, HTA agencies, hospital and community pharmacists, medical specialists, general practitioners and patients. The ADDIS system demonstrated that an on-demand application answering different efficacy/safety questions in an efficient, transparent and accountable way within and across different drugs is feasible. It showed that a more consistent standardised data model for aggregated clinical data would contribute to the harmonisation of benefit-risk assessments.

The objectives of the CIRS Benefit-Risk Taskforce are to facilitate knowledge exchange in the area of the benefit-risk assessment of medicines; facilitate the exchange of information, reports and published papers to relevant parties; ensure the effective knowledge sharing and the exchange of learnings from these various initiatives; and to make recommendations on proposals for workshops, surveys or research that should be undertaken to develop the appropriate toolbox for benefit-risk assessment. *CIRS Founder*, **Professor Stuart Walker** concluded the Workshop by summarising the achievements of the Taskforce to date and laying out plans for the future.

Recommendations from across the Syndicates

1. Global regulatory agencies should clarify and articulate all factors that lead to the benefit-risk decision, including their relative importance.
2. As new methodologies come into use, all parties are encouraged to gain familiarity with those methodologies sufficient to inform benefit-risk discussions.
3. Conduct a comparison of benefits and risks identified by sponsor with those identified by patients; the differences will illustrate the impact of patient inputs and subsequently to convince regulators of the validity of the selected parameters as part of a submission.
4. There is no average patient. All patients and caregivers will be biased in some way and patients continually called upon to provide input may experience "input fatigue", which will alter their opinion. It is therefore, recommended that academia investigate suitable rigorous methodology to balance relevant opinions and bias, while recognising the divergence among patients and being cautious not to "average out" results.
5. After reviewing the methodology to increase representation, including caregivers and to cover perspectives throughout the life cycle of a medicine, CIRS should repeat the survey conducted March 2013 to determine the hurdles and solutions on incorporating patients' voices.
6. Give a greater role to the patient's perspective in the post-marketing setting.
7. Incorporate the HTA/payer perspective: Use the UMBRA framework to develop aligned benefit-risk tools and models.
8. Initiate pilots on disease-specific models with multi-stakeholder involvement.
9. Develop methodologies for assessing benefit in the post-marketing setting and the hierarchy of benefit and risk evidence.

Workshop Programme

DAY 1: 20 JUNE 2013	
SESSION: IMPLEMENTING A COMMON FRAMEWORK FOR BENEFIT-RISK ASSESSMENT: HOW ARE THE DIFFERENT METHODOLOGIES PROGRESSING?	
Framing the Workshop	**Lawrence Liberti**, *Executive Director, CIRS*
Day 1 Co-Chair's welcome and introduction	**Dr Ed Harrigan**, *Senior Vice President, Worldwide Safety and Regulatory, Pfizer, USA*
Moving from pilot programmes to routine use in development and review - If not now, when? **Industry viewpoint** **Regulatory viewpoint**	 **Dr James Shannon**, *Chief Medical Officer, GlaxoSmithKline, UK* **Dr Sinan Sarac**, *Senior Medical Officer, Danish Health and Medicines Authority*
Benefit-risk framework development: Current status and forward plans **Four Agency Consortium**	 **Barbara Sabourin**, *Director General, Therapeutic Products Directorate, Health Canada*
A structured approach to benefit-risk assessment in drug regulatory **EMA perspective** **Utilisation of UMBRA by agencies and companies**	**Dr Patrick Frey**, *Director, Office Program and Strategic Analysis, CDER, FDA, USA* **Dr Francesco Pignatti**, *Head of Section, Oncology. Haematology & Diagnostics, European Medicines Agency* **Dr Neil McAuslane**, *Director, CIRS*
IMI PROTECT – What are the recommendations from this initiative with regard to the best way to communicate results and to whom?	**Prof Deborah Ashby**, *Professor of Medical Statistics and Clinical Trials Co-Director of Imperial Clinical Trials Unit, School of Public Health, Imperial College London, UK*
SESSION: BENEFIT-RISK DECISION MAKING: ASSESSING RELATIVE IMPORTANCE AND UNCERTAINTY: HOW ARE THESE BEING APPROACHED AND WHAT NEEDS TO BE CONSIDERED	
Chairman's introduction	**Prof Sir Alasdair Breckenridge**, *Former Director, MHRA*
Assessing relative importance – An overview of the current major approaches to weighting	**Dr Bennett Levitan**, *Director, Quantitative Safety Research, Department of Epidemiology, Janssen Research Foundation, USA*
The FDA's approach to assessing relative importance	**Dr Robert Temple**, *Deputy Center Director for Clinical Science, CDER, FDA, USA*
An industry viewpoint on weighting	**Dr Marilyn Metcalf**, *Senior Director, Benefit Risk Evaluation, GlaxoSmithKline, USA*
Building uncertainty into the benefit-risk framework – Ensuring stakeholder understanding of the role of uncertainty in the decision	**Dr Paul Seligman**, *Executive Director, US Regulatory Policy, Amgen Inc*

Syndicate Sessions	
Syndicate A: Assessing relative importance – what guidance should be given as to how this step should be implemented by agencies and companies?	
Chair **Rapporteur**	**Prof Deborah Ashby**, *Professor of Medical Statistics and Clinical Trials Co-Director of Imperial Clinical Trials Unit, School of Public Health, Imperial College London, UK* **Dr Consuelo Blosch**, *Executive Medical Director, Global Safety, Amgen Inc, USA*
Syndicate B: How should patients contribute to the regulatory decision?	
Chair **Rapporteur**	**Barbara Sabourin**, *Director General, Therapeutic Products Directorate, Health Canada* **James Leong**, *Senior Regulatory Specialist, Health Sciences Authority, Singapore*
Syndicate C: Utilisation of the benefit-risk framework in the post-approval setting – What are the key considerations?	
Chair **Rapporteur**	**Dr Ronald Robison**, *Vice President, Regulatory Affairs, Patient Services and R&D QA, AbbVie Inc, USA* **Dr Isabelle Stoeckert**, *Vice President, Head Global Regulatory Affairs Europe/Canada, Bayer Pharma AG, Germany*

DAY 2: 21 JUNE 2013	
SESSION: SYNDICATE SESSIONS AND FEEDBACK	
Chairman introduction	**Prof Sir Alasdair Breckenridge**
Feedback of Syndicate discussion and panel viewpoint following each Syndicate discussion	
Panel discussion **Company representative** **Regulatory FDA viewpoint** **Patient viewpoint**	 **Dr Ed Harrigan**, *Senior Vice President, Worldwide Safety and Regulatory, Pfizer, USA* **Dr Theresa Mullin**, *Director, Office of Strategic Programs, CDER, FDA, USA* **Dr Mary Baker**, *President, European Brain Council*
New pharmacovigilance guidelines – One year on are companies using a structured approach to benefit risk and how are agencies using this internally to inform their views? **Regulatory viewpoint** **Company viewpoint**	 **Dr Gerald Dal Pan**, *Director, Office of Surveillance and Epidemiology, CDER, FDA* **Dr Becky Noel**, *Senior Research Scientist, Eli Lilly & Company, USA*
Making better use of clinical trials – Development of Aggregated Data Drug Information System (ADDIS) for aiding the benefit-risk assessment of new medicines	**Prof Hans Hillege**, *Professor of Cardiology, Management Board, Department of Epidemiology, University Medical Center Groningen, The Netherlands*
The Benefit-Risk Taskforce: What has been achieved and what action is required for the next 12 months?	**Prof Stuart Walker**, *Founder, CIRS*

Section 2: Syndicate Discussions

Three Syndicate Discussion Groups were asked to discuss aspects of the implementation of a benefit-risk framework.

Syndicate Discussion A

Assessing relative importance – what guidance should be given as to how this step should be implemented by agencies and companies?	
Chair	**Prof Deborah Ashby**, *Professor of Medical Statistics and Clinical Trials Co-Director of Imperial Clinical Trials Unit, School of Public Health, Imperial College London, UK*
Rapporteur	**Dr Consuelo Blosch**, *Executive Medical Director, Global Safety, Amgen Inc, USA*

Background

At the annual CIRS Benefit-Risk Workshop in 2012, there was an agreement among those who are developing methodologies for assessing the benefits and risks of medicines that there are four key stages for these evaluations, namely; framing the decision; identifying the benefits and risks; assessing the benefits and risks; and developing interpretations and recommendations. An overarching eight-step framework developed at this Workshop underpins the four stages:

1. Developing a decision context
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3. Refining the value tree
4. Assessing the relative importance of parameters
5. Evaluating options
6. Assessing uncertainty
7. Concisely presenting results – visualisation
8. Issuing final recommendations

The overarching UMBRA framework provides the basis for a common agreement on the principles for benefit-risk assessment and all the methodologies for evaluation that are currently being developed by regulators and pharmaceutical companies have either implicitly or explicitly incorporated most of the eight steps. There is, however, one particularly challenging issue within the context of conducting a benefit-risk assessment – the assessment of relative importance. There is agreement within agencies and companies that some weighting of the benefits and risks of new medicines necessarily occurs. This weighting can take place at the level of the simple inclusion or exclusion of elements or through the deployment of more sophisticated methods that evaluate elements across the qualitative/quantitative spectrum, from purely qualitative, to semi-quantitative, to fully quantitative. There is, however, limited consensus regarding the methodology for determining relative importance and a perception that the process is highly complicated.

In December 2012, CIRS brought together experts from the pharmaceutical industry and academia to debate and discuss the critical issue of the utilisation of relative importance (weighting) within a benefit-risk framework, with a particular emphasis on the regulatory agency perspective. A "straw man" proposal for assessing relative importance was drafted from this meeting, which this Syndicate was asked to review and requested to make recommendations on the guidance that should be given as to how this step should be implemented by agencies and companies.

Objectives

The objectives of this Syndicate group were to discuss:

- The key elements of the proposal for an approach to assessing relative importance as part of a structured approach to benefit-risk assessments
- The key current challenges to agencies/companies to assessing relative importance in the submission and review process

- The straw man proposal and make recommendations on what methodologies can and should, be considered by companies and agencies when assessing relative importance as part of a structured approach to benefit-risk.

Questions for consideration

The straw man proposal

It is proposed that a key step in the decision-making process for the approval of a new medicine is the relative importance that regulatory agencies assign the submitted benefits and harms. Thus, reviewers should consider including a more explicit way of providing stakeholders (patients, physicians, companies) an insight into how the agency considered the relative importance of each of the benefits and harms in making the benefit-risk assessment. It is also proposed that agencies should consider qualitative approaches, or a point-allocation system as fit- for-purpose in providing insight into how they have weighed the relative importance of the evidence in the submitted application.

Other discussion questions

1. What benefit-risk assessments do companies currently include in the submission of a new medicine and what role does assessing relative importance have in the way the benefits and risks are expressed?
2. What do agencies currently do during the review to assess the relative importance of the benefits and harms of a new medicine and is the approach taken implicit or explicit?
3. Does the Syndicate believe assigning relative importance to benefits and harms to be a critical component of any benefit-risk assessment – Please provide insights on this from both a company's and agency's perspective.
4. Is how agencies assign relative importance a key factor in why different agencies can come to different outcomes when faced with the same data set?
5. If agencies adopt or provide a more explicit articulation of how they have assigned relative importance will there be a need for companies to be more explicit in their views in their submissions?
6. What are the major challenges for agencies to adopt a more explicit approach to assigning relative importance to benefits and harms as part of the decision-making process?
7. What are the challenges and implications if agencies adopt a more explicit approach to assessing relative importance in the review of new medicines?

Critical issues

After a discussion of the straw man proposal, Syndicate A provided this revised version (revisions in bold)

It is proposed that a key step in the decision-making process for the approval of a new medicine is the relative importance that regulatory agencies assign to submitted benefits and harms. **At the moment, this is done implicitly. The FDA, EMA and other agencies have made steps toward communicating the benefit-risk evaluation. On the positive side, a thoughtful application of a benefit-risk framework can be used as an effective communication tool.** Thus, agencies should consider including a more explicit way of providing stakeholders, which include patients, physicians, companies **and HTA organisations**, an insight into how the agency reviewers consider the relative importance of each of the benefits and harms in making the benefit risk assessment. It is also proposed the agency should **clarify and articulate all factors that led to the benefit-risk decision, including their relative importance. As new methodologies are coming into use, we encourage all parties to gain familiarity of those methodologies sufficient to engage an informed benefit risk discussions.**

The majority of submissions do not require a weighting assessment methodology but rather can accomplish the goal with a qualitative assessment. Weighting should be considered for assessments in which a number of benefits and risks need to be evaluated concurrently or for situations in which an unexpected or worrisome risk has emerged from a well-designed clinical trial or for which sub-group analyses have identified an issue. Although companies can specify the need for a weighted evaluation in advance, it is preferable that the weighting occur after submission, at which time the full scope of the data is known. Weighting should definitely be considered for use by those conducting health technology assessments, where comparative assessments are typically conducted.

Selected weighting assessment methodologies can be established and re-used for an indication across companies. The expectation is that the beneficial and harmful events will be constant

across various indications and an unexpected event may necessitate starting over with a selected methodology.

Global regulatory coordination and discussion should occur as much as possible, to allow the selected weighting methodology for an indication to be relevant for multiple regulatory agencies. One approach to this type of assessment will not fit all stakeholders; that is, patients, healthcare providers, companies and HTA organisations. Accordingly, various types of written or visual communication should be readily available, for example, one employing technical language and the other using plain language with simplified explanation, developed at approximately an eighth grade level for patient stakeholders. Key messages, however, should be consistent and coherent across stakeholder communication.

Strategies

There should be ongoing discussions between sponsors and global regulatory agencies and full use must be made of the current benefit-risk assessment approaches. This highlights the need for personnel within agencies with the expertise in and a willingness to explore the more complex methodologies such as swing weighting, conjoint analysis and point allocation, as companies have begun to use methods that are more complex that simple zero-one categorisation.

Recommendations

- Globally, regulatory agencies should be in a position to clearly identify and articulate all factors that lead to the benefit-risk decision, including their relative importance.
- As new weighting methodologies come into use, all parties are encouraged to gain familiarity with those methodologies sufficient to engage inform benefit-risk discussions.
- The straw-man statement regarding weighting, as revised by the Syndicate group, should be adopted.

Syndicate Discussion B

How should patients contribute to the regulatory decision?	
Chair	**Barbara Sabourin**, *Director General, Therapeutic Products Directorate, Health Canada*
Rapporteur	**James Leong**, *Senior Regulatory Specialist, Health Sciences Authority, Singapore*

Background

As pharmaceutical companies and regulatory agencies develop methodologies for the benefit-risk evaluation of new medicines and for communicating this evaluation to stakeholders, there has been a growing awareness that the patient's voice is a critical component. Moreover, the patient's role is believed by many to be the central focus 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 that may differ from that of regulators. During the post-approval period, the ongoing assessment of a products benefit-risk profile can be placed in the perspective of the end-user, the patient.

At a CIRS Workshop held in March 2013, *The patient's voice in clinical development: Can patients contribute to the benefit-risk assessment of new medicines?* there was agreement that R&D and regulatory review will continue to evolve and become more patient-centric. A key component of this will be based on information/data on the benefits and harms being solicited directly from patients at different points in the development of a medicine. This perspective will be of value to inform both the R&D and the regulatory review processes at the disease level as well as on specific products.

While industry and agencies are in agreement regarding the high value that they place on patient input, there are real or perceived barriers to engaging with patients in a meaningful manner. These include: resource issues, conflict of interest, accepted methodologies to capture their input (see tables on page 15 for outline of some barriers perceived by patients, regulators and companies). However, it is believed that with new thinking, education, utilisation and acceptance of appropriate methodologies and technologies, that it should be possible for patients to increase their contribution to R&D and the review of medicines.

Patient input to decision making needs to be credible and this Syndicate group was asked to discuss how patients should contribute to the regulatory review and decision-making processes and to make recommendations on what needs to be done by companies, patients, patient advocacy groups and regulators for this input to become an integral activity in the R&D and review of medicines.

Objectives

The objectives of this Syndicate group were to discuss:

- From company and agency perspectives, how patients currently contribute to the regulatory decision on the benefits and risks of new medicines
- The key current challenges to companies and agencies to obtain information from patients on benefits and harms that will be of value to the review process
- A future landscape in which information/data directly from patients on benefits and harms would be central to informing the decision made in the review of new medicines
- Recommendations of how the environment needs to change in both the short- and long-term for patient information and data on benefits and harms to inform the regulatory review process

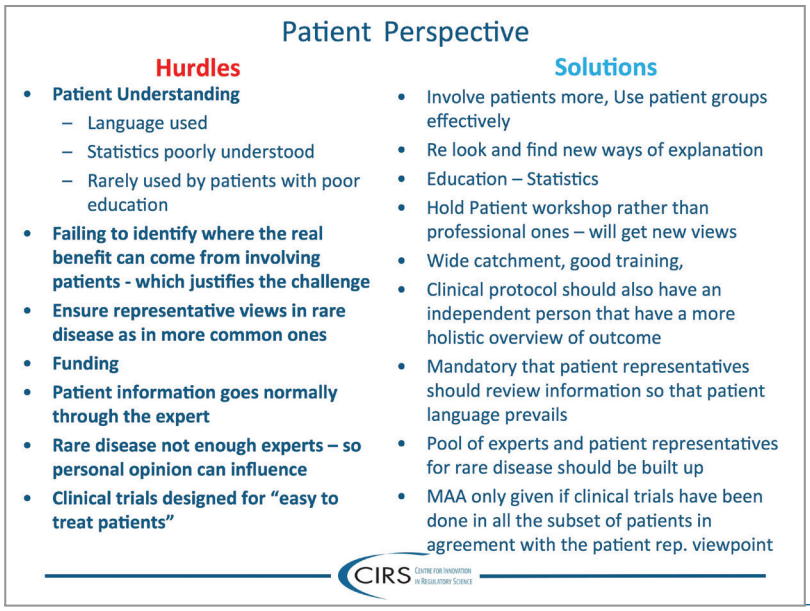
Questions for consideration

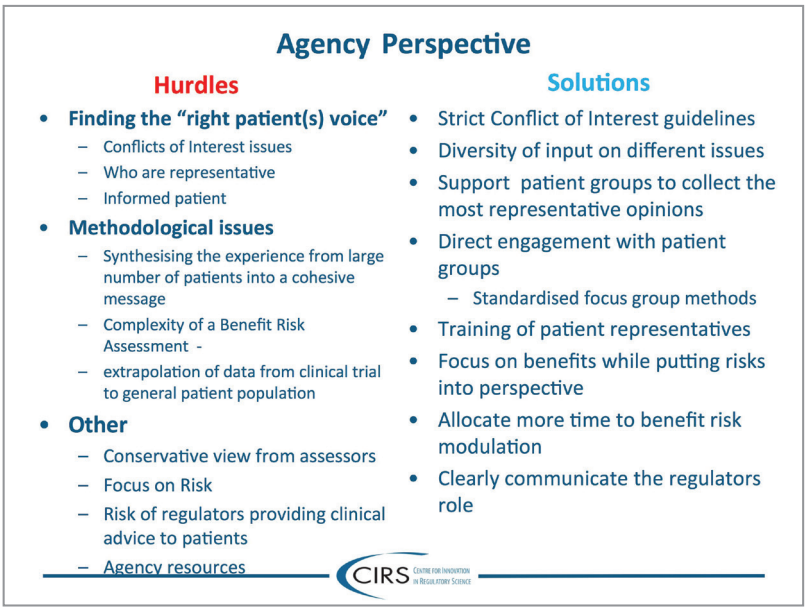
Use the following tool to capture ideas regarding the current environment of patient involvement in providing information on benefits and harms in the review process.

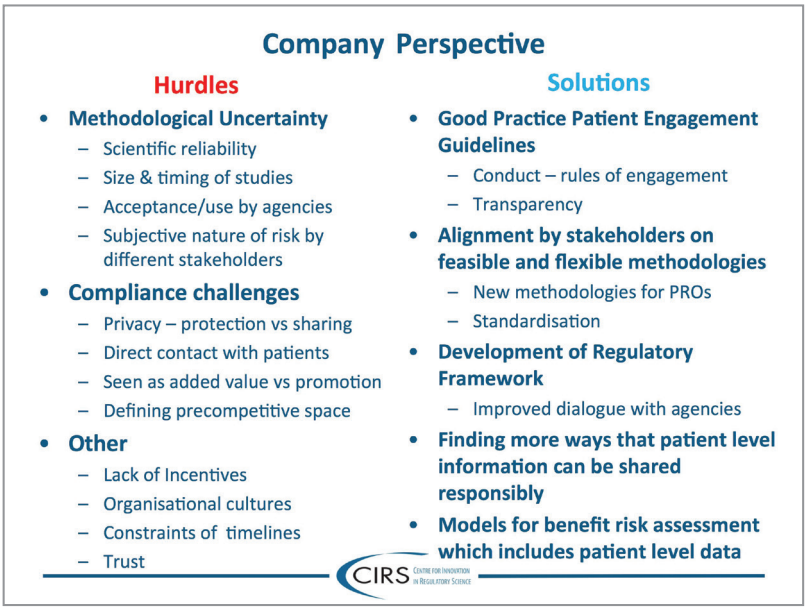
Type of Information	Patient involvement that can inform the regulatory decision	Timing of interaction	Approaches that can be used at this stage for eliciting patients' views?	What are the key challenges from an agency and patient perspective?
Therapy area guideline development				
Specific disease experience				
Design of clinical trials				
Opinion/ information on Benefits				
Opinion/ Information on Harms				
Perspective on relative importance of benefits and harms				
Understanding of potential trade-offs				

What do you think is the future landscape for how patients should contribute to the regulatory decision-making process? Please consider the potential drivers, what changes are required to the current process, as well as potential approaches that would be worth exploring. This could include new technologies, as well as simple elicitation of information (such as listing of benefits and risks for a particular disease/ product and asking patients what relative importance they would assign them).

Data taken from a survey conducted by CIRS in March 2013, where the question was asked: What are the three major hurdles today for eliciting/ including patient information on the benefit-risk balance of medicines?







Critical issues

There are hurdles to the acquisition and use of patient input for regulatory decision making that are relevant to all stakeholders:

- The acceptance of patient-reported outcomes and other patient input by regulators is growing but uncertainty remains around certain patient-reported outcomes (PROs) and existing relevant factors pertaining to patients cannot easily fit into current models for decision making.
- Despite the growing recognition of the importance of the necessity of patient input, sponsors continue to submit dossiers based largely on traditional types of data parameters (i.e. clinical endpoints from controlled clinical studies). Meanwhile, resource constraints may mean that current initiatives to acquire novel forms of patient input may be limited to only a few disease areas and internal company policies and legal constraints may preclude direct interactions with patients to inform them of benefits and risks of novel products.
- Even though patients' and caregivers' opinions may be biased, their views are of importance. Patients' lack of understanding of the development and regulatory processes and generally limited communication among regulators and industry on this topic limits the contribution patients may be able to make to decision making.
- Healthcare professionals have not been sufficiently engaged in the efforts to involve patients in informed decision making about their own care.

In addition, there are multiple challenges to the use of patient-reported outcomes:

- Implementing patient-reported outcomes in clinical trial development may require the incorporation of additional robust methodologies into already complicated protocols and will add additional costs and time to those associated with investigating primary endpoints. This may appear disadvantageous to sponsors, particularly if not requested by regulatory authorities.
- There may be a lengthy period required for the validation of patient-reported outcome processes.
- There is currently a lack of information that correlates patient input to clinical outcomes and a lack of the systematic data that is typically the result of clinical trials.

Strategies

Partnerships

An important step in this process is to create awareness of the existence of partnerships between patient groups and regulators that have as their outcome the goal of building trust. There is a perceived worry that certain partnerships may induce a bias. To help maintain the independence of patients and to protect their interests, partnerships between patients and academia should be fostered. Partnerships

between patients or advocacy groups and sponsors are seen as helpful to provide up to date information especially in diseases with limited therapeutic options. In light of the observation that most agencies have not developed their own strategies to help support patient groups, it is the role of sponsors in this collaboration to collect patient input and to demonstrate to regulators the independent nature of its value. Consequently, partnerships between patients and relevant government agencies remains an area of opportunity.

Well-organised coordinated patient groups provide a unified voice and a consortium of all stakeholders with increased dialogue among all parties can help to improve ways to increase patient participation.

Methodology

A cohesive framework is required for all stakeholders with efficient rigorous standardised methods to engage patients early (before the start of trials) especially to help create meaningful endpoints. The stage can be set by defining the context; that is, the disease background and available treatments and concurrently identifying a particular subpopulation with unmet medical needs. Providing validated methods for obtaining patient-reported outcomes will ensure that interpretation of the results will be aligned with clinically meaningful outcomes.

Efforts to acquire patient input should cut across related diseases using standardised methodologies, allowing correlation rather than interpretation in silos. A variety of social media could be enlisted to capture patient voices and widen the input perspectives.

Recommendations

- Conduct a comparison of benefits and risks identified by sponsor with those identified by patients; the differences will illustrate the impact of patient inputs and subsequently could be used to confirm the validity of the selected parameters used in a submission.
- There is no "average" patient. All patients and caregivers will be biased in some way and patients continually called upon to provide input may experience "input fatigue", which will alter their opinion. It is therefore, recommended that academia investigate suitable rigorous methodologies to balance relevant opinions and bias, while recognising the divergence among patients and being cautious not to "average out" results.
- After reviewing the methodology to increase representation, including caregivers and to cover perspectives throughout the life cycle of a medicine, CIRS should repeat the survey conducted March 2013 to determine patient perspectives on the hurdles and solutions to incorporating patients' voices.

Conclusions

Stakeholders must acknowledge the need for further patient inputs in clinical development and for regulatory decisions, particularly focussing on the role of patient-reported outcomes. Partnerships, standardisation of methodology and education for all stakeholders on the importance of patient involvement is required. Focus groups may help identify important societal issues and change mind-sets, including how regulators view benefit-risk assessment. The next generation of R&D will be more patient-centred and a key component of this will be based on information on the benefits and harms directly solicited from patients that will inform the development and regulatory review processes both at the disease and specific product levels.

Syndicate Discussion C

Utilisation of the benefit-risk framework in the post-approval setting – What are the key considerations?	
Chair	**Dr Ronald Robison**, *Vice President, Regulatory Affairs, Patient Services and R&D QA, AbbVie Inc, USA*
Rapporteur	**Dr Isabelle Stoeckert**, *Vice President, Head Global Regulatory Affairs Europe/ Canada, Bayer Pharma AG, Germany*

Background

One of the key objectives of establishing a formal framework for benefit-risk assessment is to enable a systematic and structured approach to understanding what information and perspectives had been considered to assess and make decisions on the benefit-risk balance. The development of a new medicine requires a continual learning process, as new information is obtained during the development process as well as throughout the initial regulatory review and the post-approval use of the medicine. If the framework is to be of value, it must be of use in the pre-, peri- and post-approval settings.

Thus, both companies and agencies require that any framework be flexible insofar as being applicable to evolving scenarios, as knowledge increases about a new medicine. This has led agencies and companies to focus on the importance of benefit-risk assessment in the post-approval phase as a mechanism to provide a better understanding both of the benefits and risks of medicines. This has been shown in the recent evolution of the ICH E2 guideline which now requires companies to provide continually updated information on the benefit-risk balance. This process includes an ongoing structured benefit-risk evaluation.

As agencies and companies utilise benefit-risk methodologies for the marketing approval decision, the questions are

- How will these function in the post-approval setting?
- Are they fit for purpose as they are?
- How can they best be applied?
- How do companies and agencies truly assess the benefits of medicines post- approval?

Indeed, agencies and companies are currently using or discussing potential early-release models for new medicines and evidence generation post-initial approval for products approved through these accelerated procedures will need to have particular efficacy and safety endpoints evaluated as a condition of early approval. Therefore, as these new medicines are evaluated over time, it is clear that good documentation and structured approaches will be required to enhance clarity and transparency about the benefit-risk balance.

The role of a structured benefit-risk framework and its attendant methodologies is seen as essential not only as a way of assessing the growing body of benefit-risk information post-approval but also as a key component for the building trust in these early approval models. These models must also include a clear mechanism to recommend withdrawal of a medicine from the marketplace if certain benefit-risk criteria are not met. This Syndicate was asked to consider the post-approval stage of a medicine's life cycle and to address the question: Utilisation of the benefit-risk framework in the post- approval setting – What are the key considerations?

Objectives

The objectives of this Syndicate group were to discuss:

- The current status of applying structured benefit-risk assessments post-approval and the potential issues as part of an ongoing process
- The key current challenges to companies and agencies to obtain benefits and harms information, following approval
- Are the current methodologies fit-for-purpose for use in the post-approval phase and is the UMBRA framework relevant in the post-approval period (see figure, page 19) as a suitable structure for benefit-risk assessment in this phase?
- Recommendations on the elements or functionality that need to be considered, both short- and long-term to enable the

various methodologies to be used effectively in the post-approval phase

Questions for consideration

Q1: Does the UMBRA framework apply equally to the post-approval setting as it does to pre-submission and, if not, what specific elements or functionality need to be considered? Does the framework need to be modified and if so in what way?

Q2: What are the probable challenges specific to utilising the framework in the post-approval setting and what are the potential solutions? Please consider this from an agency's perspective in having to review the information, in addition to a company's perspective in collecting and submitting information in compliance with the agency's requirements.

Q3: How does the group foresee the future post-approval landscape for measuring benefits and risks? What are the tools/methodologies/ data collection/ new techniques that need to be developed to be able to use the framework, or a systematic structured approach, to benefit-risk, following initial approval? Are there special considerations for application particularly in the context of conditional approvals?

Critical issues

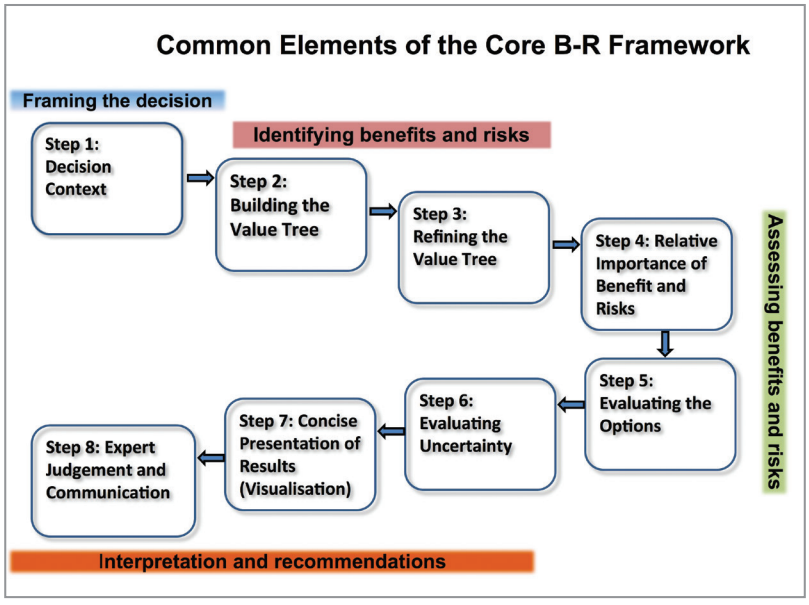
Is there a role for the UMBRA benefit-risk framework?

It was the consensus of this Syndicate that a framework is indeed important for industry as knowledge constantly grows through data acquired through post-authorisation safety studies and registries. Regulators likewise require a framework to continuously assess benefit-risk from new post-marketing commitments such as risk management plans (RMPs), risk evaluation and mitigation strategies (REMS) and periodic benefit-risk evaluation reports (PBRERs). A framework can help these decision makers justify their actions internally to senior management as well as to external stakeholders.

A structured, qualitative approach is appropriate for most decision processes such as PBRER or RMPs and preferably the same approach would be employed pre- and post-approval for a particular product. However, there is less freedom for sponsors to design benefit-risk modelling in the post-marketing setting, as the general requirements for presentation are laid out by regulators. Regulators need to establish an internal dialogue within their organisation among the different reviewing groups that are conducting the pre- and post-approval assessment in order to bring continuity to the life cycle review.

Other important issues in post-marketing benefit-risk assessment abound:

- It is important to consider how to balance the results of clinical trials with the results from post-approval safety and observational studies because each type of study carries its own varying degree of certainty.
- Sometimes, medicines have been approved based on surrogate markers that have become out-dated. Correlating these with real-world evidence may be a challenge for post-approval assessments.
- There is a potential for imbalance in the post-approval benefit-risk profile of medicines now on the market as there has been a historic asymmetry of data accumulation in the post-approval period, with an almost exclusive focus on safety not necessarily counterbalanced by relevant effectiveness data.
- Decision makers are faced with an increasing number of additional sources of signals for medicines in the post-approval time period including events reported from adverse drug reaction (ADR) databases, post-authorisation efficacy studies (PAES) / risk evaluation mitigation strategies (REMS) / risk management plan (RMP) actions and registries, health economic outcome studies, database studies by academia and social media.



- There is a global impact when one individual agency makes a decision to approve or withdraw a medicine.
- There are new players and new values to be considered, in particular those involved with health technology assessment who focus on relative effectiveness.
- Changes in the therapeutic environment must be considered; new drug approvals could theoretically alter the benefit-risk of previously marketed drugs if the new products have a better profile.
- An aging population faces increased risks from co-morbidity and co-prescription.
- Physicians and their professional associations should be more involved and understand that if treatment guidelines are changed for the rapid uptake of a newer therapy, risk signals are likely to be observed much earlier than benefit signals.

Strategies

Cooperation in benefit-risk assessment should be fostered among all stakeholders and within each organisation through the use of a clear framework and methodology that is used in both the pre- and post-authorisation settings. A more tailored approach may be required to implement disease-specific models that need to be aligned across regions for global assessments.

The post-marketing setting must become a multi-stakeholder setting enriched with the perspectives of healthcare providers, health technology assessors and particularly patients. This goal requires the development of tools for value elicitation from patients for incorporation into benefit-risk models. Regulators can become informed regarding patient needs and understand the relevance of symptom management in everyday life in a structured way through the use of specific tools and structure patient input (as is being done by the US FDA). The rationale for the use of patient-reported outcomes relevant to both health technology assessment and regulatory reviews should be further explored. Companies should become more proactive in this field, striving to maximise cross-functional interactions, using the precompetitive period to develop opportunities for intercompany patient outreach projects of common interest and starting earlier to integrate an HTA perspective into development.

A single high-level benefit-risk approach that can be easily mapped to existing regulatory and HTA expectations will allow transparency on points of alignment and value differences. Clarity on the regulator's expectation for the ongoing demonstration of a product's benefits should be established, including how best to use the results of observational studies and registries. It may be helpful in this regard to create a "catalogue" of acceptable benefits and to acknowledge the uncertainties of risk signals, taking the time and effort to develop methods that ultimately increase the certainty of these findings.

Are our frameworks, for example, UMBRA, fit for the post-approval phase? What else is needed for data collection and review?

The Syndicate concluded that the UMBRA framework provides a good basis for post-approval benefit-risk assessment. The same high-level principles can be applied; tools and methodologies that map to UMBRA will need refinement and tailoring to disease or therapeutic class. Many new aspects should be considered post-approval. Additional stakeholders' perspectives become even more critical and methods for the combination of evidence from different sources such as registries and observational and clinical studies into one tool should be explored.

Recommendations

- Give a greater role to the patient's perspective in the post-approval setting.
- Incorporate the HTA/payer perspective: Use the UMBRA framework to develop aligned benefit-risk tools and models.
- Initiate pilots on disease-specific models with multi-stakeholder involvement especially in a pre-competitive environment.
- Develop methodologies for assessing benefit in the post-approval setting, which in particular help characterise for each disease a hierarchy of benefit and risk evidence.

Panel Discussion of Syndicate Results: Key points

Dr Ed Harrigan, *Senior Vice President, Worldwide Safety and Regulatory, Pfizer, USA*

- Using a structured benefit-risk format could help to organise what can be a chaotic world of data in the post-marketing arena and there is certainly a good reason to continue to continue to use a structured approach for benefit-risk assessment in the post-marketing timeframe when you have used it for the product's pre-registration documentation. I am sure we will begin to do that by default as we become more accustomed to using the structured framework pre-marketing.
- The point made by Syndicate C regarding the asymmetry of evidentiary standards is a topic that requires careful consideration. The patient perspective and real-world benefit data may differ from the controlled setting, which historically generates the benefit data on which the drug development community rely. This means that we will be acquiring and describing benefit data that could potentially be of a lower quality standard that is less credible than that which have been developed during the pre-registration period; trying to balance that against risk data, which although they are again, not controlled data, appropriately carry more weight than the corresponding benefit data could be challenging. So, even though this could be a "race to the bottom", with the lowering of evidentiary data standards for safety and effectiveness during the post-marketing period, it is more likely to lead to an upgrade in the ability to capture credible data for both benefits and risks. This will likely require that industry make more directed innovative investments, to enhance data collection on both on the benefit and the risk side.
- I agree that there is a pre-competitive opportunity to promote consensus in particular disease areas such as stroke, epilepsy or rheumatoid arthritis, in terms of the relative valuation of benefits and risks. This approach has the potential for growth as companies and regulators become more familiar with using a structured approach to bringing the patient voice into the landscape.
- We must exercise caution when discussing the monitoring of social media as a source of information in the post-marketing period, because it is an area without well-defined contextual boundaries and mining those sources for meaningful data could prove to be extremely problematic.

Dr Theresa Mullin, *Director, Office of Strategic Programs, CDER, FDA, USA*

- One of the themes that emerged from Syndicate B from the regulator's perspective is the range of opportunity to acquire patient input and that the value of gaining that input changes throughout the product development life cycle. It may be that later in the life cycle, it is possible to be more inclusive in obtaining input and ideas for patient-related outcomes that might help to expand the benefit dimensions of an available product, although undoubtedly, there are issues surrounding this concept that will need to be better understood.
- The patient landscape is extremely complex and the issues and challenges vary by region. Divergence in reimbursement policies, local regulatory issues and societal differences complicate the identification of a "representative patient" and the selection of optimal outreach and engagement methods. The goal is to collect reliable and credible information without the reality or perception of conflict of interest. A central focus of FDA patient interactions has been to aim for useful, effective, productive partnerships that make the best use of limited resources.
- The development and qualification of patient-reported outcomes that will generate a higher yield and be regarded as a less risky investment for the private sector is likely to become an important agenda item for regulators.
- In their discussion of relative importance, Syndicate A made the point that regulators should be more explicit regarding the rationale for decision making and clearly articulate all the factors involved. In the United States, while that information is available for all approved drugs, the issue that was raised is that for approximately 10% to 20% of medicines, more complex issues will arise that some feel merit additional analysis that that could provide additional insight. This is clearly an area requiring further discussion, understanding and methodology development.
- Some of the ideas expressed regarding the acquisition and evaluation of post-market efficacy and benefit information such as

compiling a catalogue of domain benefits that are acceptable to regulators, establishing a hierarchy of evidence and incorporating evidence from different sources are extremely interesting and should be further explored. Along those lines, the FDA is looking to develop better guidance on the use of meta-analysis as part of the FDA commitments for the next authorisation of the Prescription Drug User Fee Act (PDUFA).

Dr Mary Baker, *President, European Brain Council*

- We need to reflect if the system that we have is truly fit for purpose. In part because of the successes of healthcare and the pharmaceutical industry, the average life span has grown dramatically, from 42 years a century ago in London to 100 years in Japan today. This achievement, however, represents significant healthcare challenges. For example, most clinical trial exclusion criteria eliminate participation by anyone over 65 years old, a significant majority of the world's population.
- At the other end of the scale, people who would have died in infancy are now surviving but will require ongoing special management. Women who are delaying childbirth because of new educational and employment opportunity are experiencing fertility issues. Work remains to be done on the effects of medicines on the unborn that are used to treat chronic conditions in mothers such as epilepsy, bi-polar disorder and schizophrenia.
- Meanwhile, diseases and patients are being broken down into many types and niches, potentially limiting the possibility of blockbuster drug development rewards for industry. In addition, the rise of litigation has led to an obsession with safety that stifles innovation, increasing regulation and ultimately, the price of medicine. This rise in medicine prices has led in part to the complexities surrounding health technology assessment.
- All of us will eventually become patients, so patients and indeed everyone involved in healthcare must join together to proactively examine how society can meet these challenges and work cooperatively to discover what the healthcare system of the future should look like.

General discussion

- The EMA very much encourages companies in all stages to include a population that reflects the real world. There is the temptation to try to maximise your chances to detect something in a very homogenous population - sometimes this is easier to do in the post-approval setting and we should find ways to use post-marketing data to reality check how effective these drugs are in the broader treatment population.
- I think industry has become more inclusive of patients and you still have that problem that the less controlled the environment, the lower the quality of data that results, so the challenge is to control as many variables as you can in order to get the most useful data. I think maintaining high expectations for the diligent post-marketing collection of quality information with realism around what is doable would lead in the right direction.
- It is not really true that incorporating exclusions into protocols results in better-quality data. Rather, failing to include all these real-world considerations results in a limited data set that makes the uncertainty around the generalisability of the results greater for the regulator. Inclusion criteria should be broadened and some of our talented statisticians can help us to figure out how to deal with these trial complexities.
- Inclusion and exclusion criteria represent an attempt to mitigate the extremes but there are definitely efforts underway to expand inclusion criteria, particularly in disease states like oncology in which the average patient age is over 70 and comorbidities are frequently involved. This is an area on which we need to continue to focus.
- I think it is important that we address this properly and in a strategic way. Just including a few older patients with co-morbidity in trials is not going to give us the generalisable answers we need, because we're not going to have power to actually determine the important questions. We can predict that the population is ageing and we should be able to understand key morbidities from existing databases. I see no problem with pivotal trials being conducted in clean, homogenous populations and then prioritising special studies in additional populations.
- This is really very similar to a sub-group analysis. Putting aside whether sub-groups are pre-specified or identified post-hoc by machine learning or other techniques,

benefit-risk assessment is really an independent question. You identify a group of people, you have the data relevant for them and then you ask the same questions for that sub-group as you would of the population as a whole. You just may have greater variability of the data in the sub-group since it is much smaller but I don't think it is a different problem.

- We do have a precedent, which is paediatric exclusivity, which encourages companies through a patent extension to look at this sub-group. So one could imagine, for example, geriatric exclusivity, or a co-morbidity exclusivity. You do have to give some incentive to companies who are increasing the risk by adding heterogeneity to their populations in the study. Or you do not touch the main study and you have auxiliary studies, for which companies are incentivised for a couple of years.
- The market exclusivity idea is interesting and from my perspective that is a carrot and there is also a stick. And the stick, which is actually being discussed in many countries, including Canada, is not giving market authorisation unless you have done the studies in the population in which the drug will be used – all populations in which the drug will be used. As regulators and as industry and as patients, we need to come to grips with what both of these approaches might mean. The carrot approach does not always work; neither does the stick approach. It limits access to products for other patients. But somehow we have to get to the bottom of this and make sure the information about how drugs behave in people with co-morbidity is available to treating physicians and patients so they can make informed choices.

Section 3: Presentations

Moving from pilot programmes to routine use: If not now, when?

An industry viewpoint

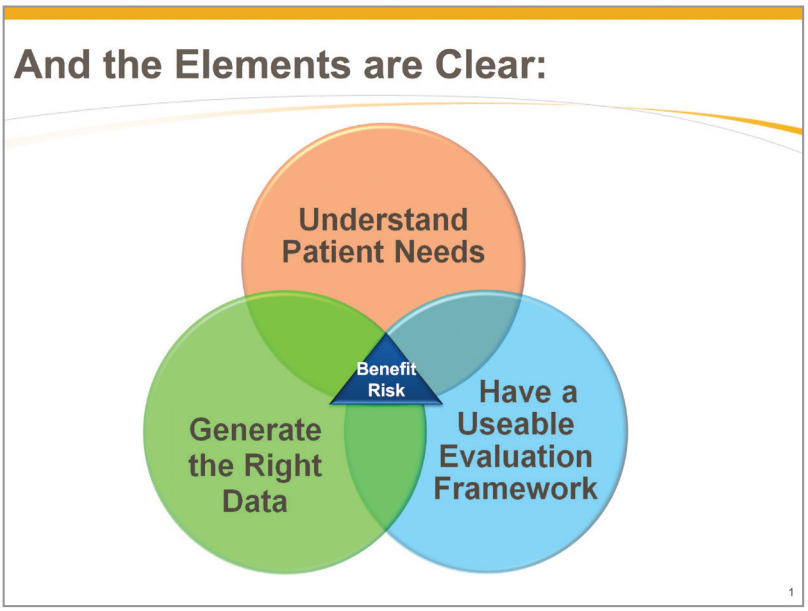
Dr James Shannon

Chief Medical Officer, GlaxoSmithKline, UK

At the June 2012 CIRS Benefit-Risk Workshop on benefit-risk assessment, it was agreed that the four stages of the benefit-risk assessment were framing the decision, identifying the benefit and risks, assessing the benefit and risks and making interpretations and recommendations. It was further decided that these stages are underpinned by an eight-step framework. In addition to the use of a functional benefit-risk framework, the other necessary elements for the assessment of new medicines are equally clear: an understanding of patient needs and the generation of the appropriate data to address those needs (Figure 1).

Although at first glance these conclusions may seem somewhat self-evident, they provide a necessary structure with which to drive the process of evaluation forward. Moreover, these elements may not be quite as simplistic as might be assumed. For example, a medicine's developers may be unsure if the patients studied in clinical trials are truly representative of an entire population. Understanding of patient needs may be misguided or led by traditional, paternalistic doctor-patient assumptions. Additionally, the type of framework that should be employed in evaluations; that is, quantitative, qualitative or other type or even the need for a framework at all has yet to be agreed.

Figure 1. The elements of benefit-risk decision making.



As discussed by authors Kent and Hayward, by using the mean results of clinical trials, the real and sometimes important difference in treatment results and therefore in the benefits and risks of a medicine for individual patients of different ages, genders or races may be lost. That is, within the normal distribution of treatment effects, there will be patients who experience significant benefits or harms and some who will derive no benefit or risk no ill effects at all.[1] These differences must be better understood going forward.

Differences in patients' individual motivation for treatment use must also be acknowledged and understood as those differences will affect the level of potential benefits they expect or harms they are willing to risk. For example, although all medicines carry some risk, to be acceptable to patients, the risks associated with preventative treatments must be extremely low and the benefits must be durable, whereas patients may be more willing to risk potential adverse events associated with effective treatments for acute, life-threatening illnesses.

Numerical differences for a composite endpoint from a clinical trial are not meaningful to patients or clinicians. Rather than being driven by regulatory requirements, data collected for a new medicine should answer questions about the medicine's benefits and risks from the patient's perspective, questions such as how good are the benefits, how severe are the

. . . an agreed overarching approach would provide a common language and enable industry, regulators and patients to engage in transparent dialogue to determine the tradeoffs involved in the use of a medicine and understand the context of the decision . . .

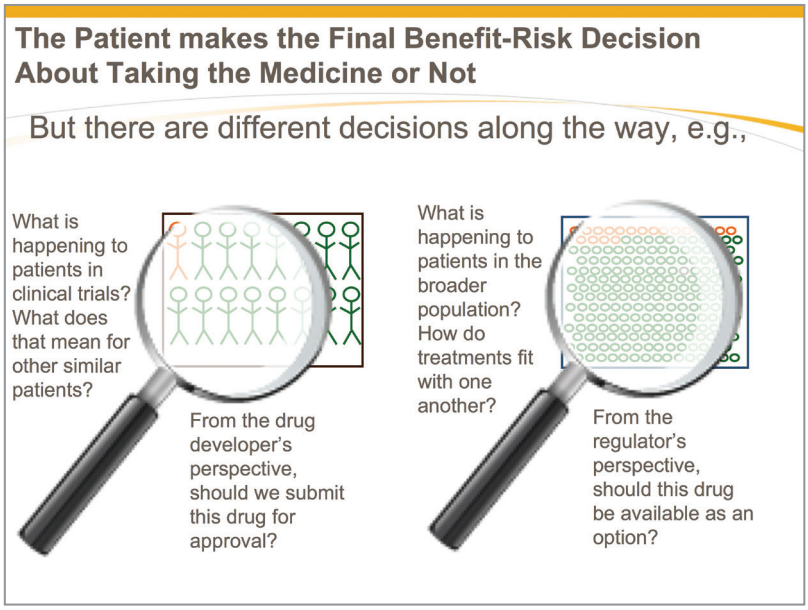


Figure 2. Benefit-risk decision making occurs before patients are faced with their individual determinations about a medicine.

harms, how quickly do either occur, how long do they last and what is the likelihood of their occurrence? Can the harms be avoided or if they occur, can they be managed?

Before a medicine is available, the company and regulators are making decisions throughout the development review process but ultimately, the patient will make the final decision to take a medicine. The company must determine if for example, a chemotherapy with significant effects on survival but extremely poor tolerability should be submitted for regulatory review, without really knowing if individual patients would decide to risk significant harm for significant benefit. Regulators must then determine the best course of action from a societal rather than an individual patient perspective, deciding if the medicine should be approved and if approved, whether it should be restricted to certain populations (Figure 2).

Although benefit-risk decision-making frameworks may differ in nature and usability, an agreed overarching approach would provide a common language and enable industry, regulators and patients to engage in transparent dialogue to determine the trade-offs involved in the use of a medicine and understand the context of the decision, including the severity of the unmet medical need that it addresses and the quality and reproducibility of the scientific evidence that supports its use. Clear communication of that context to all stakeholders is a vital component of this understanding. Moving forward, the routine use of established methodologies based on a common framework will enable shared understanding and decision making, ultimately resulting in better health outcomes.

Reference

1. Kent D, Hayward R. "When Averages Hide Individual Differences in Clinical Trials: Analyzing the results of clinical trials to expose individual patients' risks might help doctors make better treatment decisions." *Amer Scientist*. 2007;95:60-68.

Structured benefit-risk assessments – moving from pilots to routine use: A regulatory viewpoint

Dr Sinan B. Sarac

Senior Medical Officer, Danish Health and Medicines Authority

Current status

Simplistically, it could be stated that structured benefit-risk assessments of new medicines will routinely occur when regulators demand their use. Realistically, however, the generalised lack of their use by both the developers and regulators of medicine is the result of multiple, often conflicting factors.

It is commonly accepted that one of the primary purposes of these structured assessments is to put the benefits and the risks of new medicines into perspective in order to enhance the transparency and ease of communication in decision making but there remain challenges to their use within both industry and regulatory agencies. For example, the developers of medicines may feel that the mandated use of assessment tools challenges their decision-making capabilities or simply that it is unwise to expend effort and resources on work not required by regulators. For their part, regulators may fear that data interpretation might be obscured through the use of complex evaluation tools and they may believe that capable reviewers should not need structured frameworks to render decisions.

At a national level, structured approaches to benefit-risk assessment are not being routinely used. On a European level, however, centralised

. . . structured benefit-risk assessments of new medicines will routinely occur when regulators demand their use.

regulatory documents contain a benefit-risk assessment section in which beneficial and unfavourable effects of medicines and the uncertainties in knowledge that surround these parameters are documented and discussed and conclusions are drawn. Although this use seemingly involves structure, the process is an intuitive and implicit evaluation of the decision context, the options to be appraised and the results and the value judgement that is made may not always be communicated in a transparent fashion.

The Benefit-Risk Effects Table

The main output of the benefit-risk assessment methodology project of the European Medicines Agency seems to be the use of the benefit-risk Effects Table, in which the benefits and risks of a drug are described, units of measurement are assigned to parameters and performance and uncertainties are defined. Although this methodology is somewhat structured, value judgements are still implicit and weighting, visualisation and the formal communication of uncertainty are missing. (Figure 3) Some of these challenges can be overcome, however. Simple numeric or high, medium, low scales can be used to assign and communicate values. To enable visualisation, the use of the Effects Table can be complemented with the use of a forest plot or tornado diagram. The transparent communication of uncertainty of clinical trial data to healthcare professionals and patients, however, remains a difficult challenge that requires additional considered thought and investigation.

Figure 3. The EMA Effects Table is missing certain parameters.

Rationale for structured assessments

Regulators and industry members should be ready to adopt the use of structured approaches to benefit-risk assessment now and although both groups seem to be on the verge of a paradigm shift in benefit-risk assessment, movement is slow and each seem to be reluctant to be the first to take that final decisive step. However, the rationale supporting the use of the framework is strong. There is experience with its use as regulators in several member states in Europe have responded positively to their current participation in the CIRS pilot project for benefit-risk assessment in Europe. Additionally, there are multiple benefits to the use of a structured approach for both industry and regulators. Industry could take control of the evaluation of their products by discussing, valuing and weighting the results themselves. Instead of putting the fate of new medicines solely in the hands of the regulators, they could proactively include a more structured benefit-risk assessment in their dossiers. Regulators could use their own structured assessments to increase the consistency of their decisions and to enhance their credibility by transparently communicating their decision making to the public.

Speculations!

If the Committee for Medicinal Products for Human Use (CHMP) decides to use the EMA Effects Table in their Day 80 Assessment Reports (D80 ARs) and the European Public Assessment Reports (EPARs) it may be in routine use throughout Europe by 2014. Weighting and visualisation, which are not included in the Effects Table may then be the next item on the CHMP agenda, or the CHMP may await the results of the Innovative Medicines Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics (IMI PROTECT) Work Package 6 evaluation of benefit-risk methodologies (see p 35) in the third quarter of 2014 before moving forward with regard to visualisation and weighting. In either case, the expedited use of structured assessment approaches will enhance transparent and effective communication, allowing healthcare stakeholders to assemble all the individual pieces of new medicines in order to see the greater picture.

COBRA: Where are we now?

Barbara Sabourin

Director General, Therapeutic Products Directorate, Health Canada

Benefits and challenges for the benefit-risk template

The Consortium for Benefit-Risk Assessment (COBRA) is an association of representatives from four mid-size regulatory agencies, Health Canada, the Therapeutic Goods Administration of Australia, Swissmedic and the Health Sciences Authority of Singapore. The group is seeking to develop a qualitative framework for the benefit-risk assessment of medicines to allow a systematic standardised approach to the appraisal of medicines during regulatory review and post-marketing to facilitate the opportunity for joint or shared reviews within the group.

COBRA members envision that using a structured framework approach would allow the systematic articulation and weighting of individual benefits and risks of new medicines and the communication and visualisation of these parameters. The framework also offers the potential to provide process consistency among agencies and the ability to compare regulatory decision making, particularly across medicines within a class, as well as the potential to act as a tool for collaborative work and as a platform for peer-to-peer discussion.

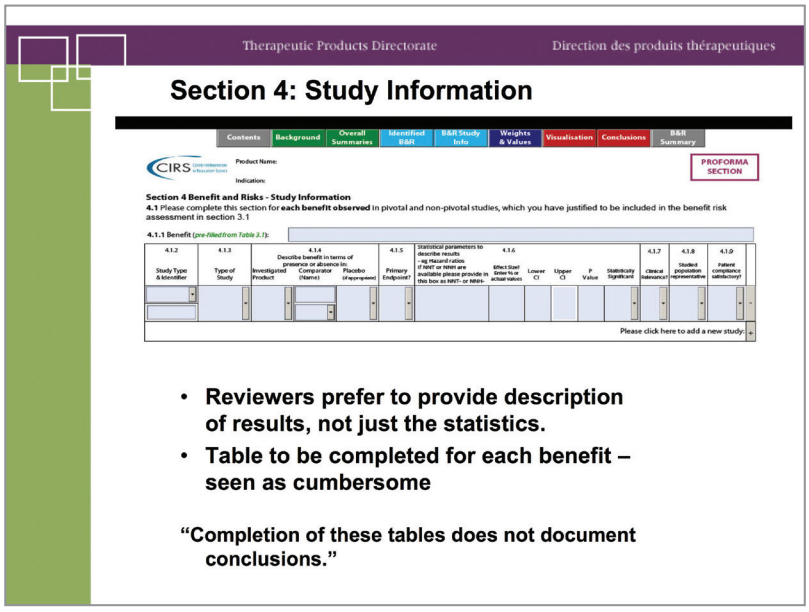


Figure 4. After using the COBRA benefit-risk template in a pilot study Health Canada, regulators provided comments.

COBRA members have evaluated the template approach to benefit-risk assessment, co-developed and piloted by CIRS. While the approach has been found to be helpful in guiding benefit-risk assessments, there have been challenges inherent in its use. Perhaps most important is whether the template is to be used in addition to or as a replacement for existing documents within each of the agencies' assessment reports and whether each jurisdiction would be making its own decisions when using a common report. The length and level of detail of the document and its use in product life cycle management were also topics that needed to be further addressed by the COBRA group. As with other benefit-risk methodologies being developed, the weighting and visualisation of benefits and risk have proved to be especially challenging.

As the result of a pilot study that examined the retrospective use of this template methodology for the benefit-risk evaluation of a medicine that had been approved by all four agencies, amendments were made to the template in December 2012 and a draft User Manual was developed. The group is currently in the process of conducting a pilot study in the prospective use of the benefit-risk template in the review of a drug submission at each of the agencies. TGA has completed the pilot, the study is in progress at HSA and Swiss Medic was unable to complete the study within the specified timelines. Because of concerns about meeting their 300-day review timelines, Health Canada completed a modified review in which the benefit-risk template was filled in using an already completed review.

Health Canada prospective pilot reviewer comments

Health Canada reviewers reported some technical issues with use of the benefit-risk template format, a fillable PDF. These issues, which are typical of this type of format, were not considered substantive. Additionally, users were unsure where to insert additional information not covered in the template. In their review of the specific sections of the template; that is, *Background, Overall Summaries, Identified Benefits and Risks, Benefit and Risk Study Information, Weights and Values, Visualisation and Communication*, Health Canada reviewers found the Background section to be generally fit for purpose. This section was similar to the *Pharmaceutical Safety and Efficacy Assessment* template in use by the agency, except that there were no sections for the regulatory history of

the submission or the review strategy that was used. Health Canada regulators additionally remarked that the *Benefits* section of the benefit-risk template only allowed inclusion of benefits with statistical information and not benefits that are not quantifiable, although there was another place in the template to include this information.

Reviewers preferred to provide description of results rather than just the statistics used in the *Study Information* section of the template and completing an entire table for each benefit was seen as cumbersome. One reviewer also commented that "Completion of these tables does not document conclusions (Figure 4)." The *Clinical Studies* section of the benefit-risk template departed from the Health Canada Pharmaceutical Safety and Efficacy Assessment template, which asks reviewers to distinguish between pivotal, non-pivotal and supportive trials using scientific and clinical judgement and then to provide a summary of the individual study reports, critically assessing study, design and safety and advocacy findings, using a list of different questions for reviewers to consider such as Were the objectives relevant to the indication(s) sought? The format used by Health Canada requires the reviewer to focus on individual studies rather than individual benefits and risks and Ms Sabourin noted that training and change management processes may be required to allow Health Canada reviewers to become more comfortable with looking at information in this manner.

Regardless of the choice of decision model, the values that are applied in the evaluation are typically those of the regulator, even though some research has shown that regulator values can be poor surrogates for those of patients. However, whilst the use of patient preferences in benefit-risk decision making is expected to increase the transparency and openness and possibly even the quality of decision making, it is also associated with challenges such as the fact that patients may not be fully informed about all aspects of a product's benefits and risks, their perspectives can be seen as anecdotal, their preferences may evolve and these opinions may be difficult to obtain reliably and without bias.

It has been recognised that flexible decision frameworks may be required to handle all types of evaluations at the EMA and regulators are exploring the ways in which decisions are made at the agency, examining the tools necessary to make all types of explicit and transparent decisions. They are seeking consensus as to the best methods for achieving collaboration among all stakeholders including patients but optimal methods for eliciting patient preferences without bias are yet to be determined and EMA regulators will continue to explore the use of different methods and values in the decision making process.

Consortium members will incorporate the learnings from the project and integrate them into their own review practices

In evaluating the *Conclusions* section of the template, reviewers felt that regulatory decisions should also incorporate the consideration of precedents in a given therapeutic class, clinical practice, the benefits or harms of a particular route of administration or dosing regimen and professional judgement. It was not evident to reviewers how to incorporate these factors in the benefit-risk template.

Conclusions and next steps

For Health Canada, participation in the COBRA pilot exposed areas for improvement in the review processes and identified new concepts to build into existing procedures. It has also "socialised" the concept of different methodologies for benefit-risk evaluation within the review community. Like other jurisdictions, Canada is continually challenged by resource constraints. Participation in the COBRA project as well as in other programmes that allow agencies to gain confidence in each other's processes and to explore resource sharing may alleviate these constraints by the eventual use of reviews from other jurisdictions, particularly in the areas of chemistry and manufacturing.

CIRS will compile the results of all reviewer evaluations and publishing these findings to realise their full impact is under consideration. Consortium members will incorporate the learnings from the project and integrate them into their own review practices and members will continue projects to develop common review templates across the four agencies.

FDA benefit-risk framework: Current and future efforts in 2013–2014

Dr Patrick Frey

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The FDA has developed its conceptual framework for benefit-risk assessment through the use of case studies of prior regulatory decisions, conducting interviews of reviewers in key disciplines on select, challenging decisions to identify the range of benefits and risks that were evaluated. The agency also constructed question-based prompts to guide completion of this framework by reviewers and is pilot-testing the template in pre-market reviews, evaluating and further refining the framework and its documentation and focusing on its implementation in the review process.

Five decision factors comprise the framework rows: an analysis of the condition to be treated, current treatment options, benefits, risks and risk management. The reviewer considers the key information that supports a medicine's association with each of the factors or the uncertainties that surround that association and then draws a conclusion. Finally, all the analyses are tied together in a succinct written summary of the benefit-risk decision and the rationale behind that decision, including any important differences of opinion that may have arisen among the review team and how those differences were resolved (Figure 5).

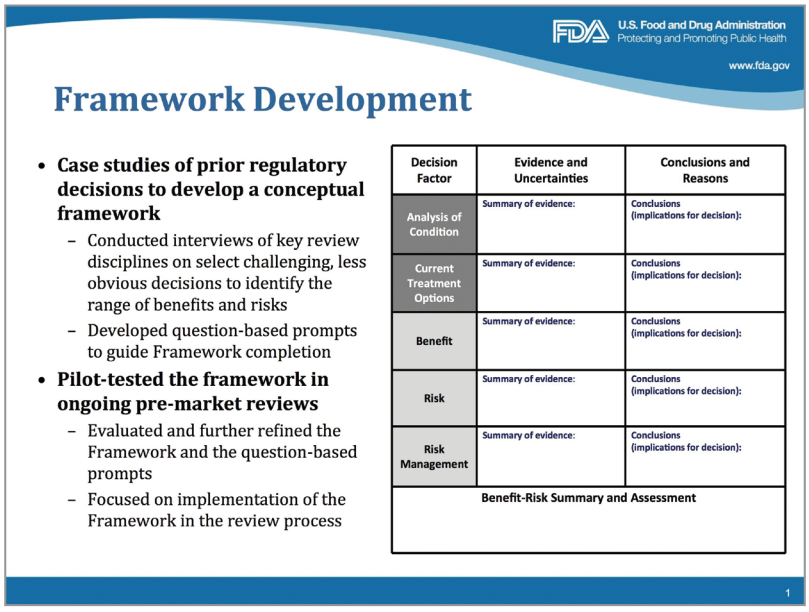

Figure 5. The FDA benefit-risk framework was developed through interviews with reviewers of case studies of prior FDA decisions and subsequent testing in ongoing reviews.

As part of the commitments entailed in the fifth authorisation of the Prescription Drug User Fee Act (PDFUA V) the FDA developed a 5-year plan that describes the agency's approach to implementing a benefit-risk framework. The plan calls for the revision of review templates, decision memo templates and the Manual of Policies and Procedures to incorporate use of the template, the conduct of two public benefit-risk workshops from the regulator's perspective and the development of an evaluation plan to ascertain the impact of the framework and its ability to address stakeholder needs. In addition, in its new Safety and Innovation Act, the US Congress requires that the FDA implement a structured benefit-risk assessment framework as part of the drug review process.

The staged timeline for implementation of the framework calls for its use in the review of new drug and biologic license applications for new molecular entities during 2014-2015, in efficacy supplements for new or expanded indications in 2016 and in all original new drug applications in 2017. During that time, a Change Control Board will be established to oversee the implementation, FDA reviewers will be trained on a bank of examples of the use of the framework and the frameworks used in evaluations will be posted on www.FDA.gov following approval actions.

The FDA received written comments on this plan from industry, patient advocates and other stakeholders, with the majority of comments originating from patient advocacy groups. Comments, which included suggestions that the framework be used earlier in the drug development process, not be duplicative, be fully integrated into the review process and be used to facilitate drug applicant meetings are all being considered by the FDA.

In 2012, the framework was tested in a pilot in which reviewers in the Office of New Drugs were asked to begin using the tool in the review of one new molecular entity at mid-cycle, further refining it through the remainder of review. Frameworks were finalised with the primary reviewer at the end of the review process and reviewed by the signatory authority. Interviews were then conducted with eighteen staff members to obtain input on the value and utility of the framework.

Most reviewers thought the framework

demonstrated utility in structuring thinking or facilitating team collaboration. Some also acknowledged its value as a communication tool to external stakeholders; however, some were concerned about the effort required to perfect a document for external publication. The majority of reviewers indicated that the primary clinical reviewer should create the first draft of the framework. Other implementation considerations mentioned included the fact that input from other disciplines would be important as would clear and reasonable expectations of what the final framework should look like. It was also suggested that the FDA should clarify how disagreements and different perspectives will be addressed and consider using the framework to streamline other aspects of the review process.

The FDA is currently engaging senior leadership in the Office of New Drugs to discuss implementation of the framework. One possibility is that the concepts of the framework be integrated into and align with the current Clinical Review Template. However, introducing new or modified ways of doing things in large organisations is challenging and implementation of the benefit-risk framework at the FDA will require a change management approach, as was suggested by a discussion Syndicate at the annual CIRS Benefit-Risk Workshop in June 2012, where it was also remarked that a framework must be "of value, understandable and visible and compatible with current thinking." To this end, the FDA began to obtain buy-in from senior leadership from the very beginning of the framework development and the support

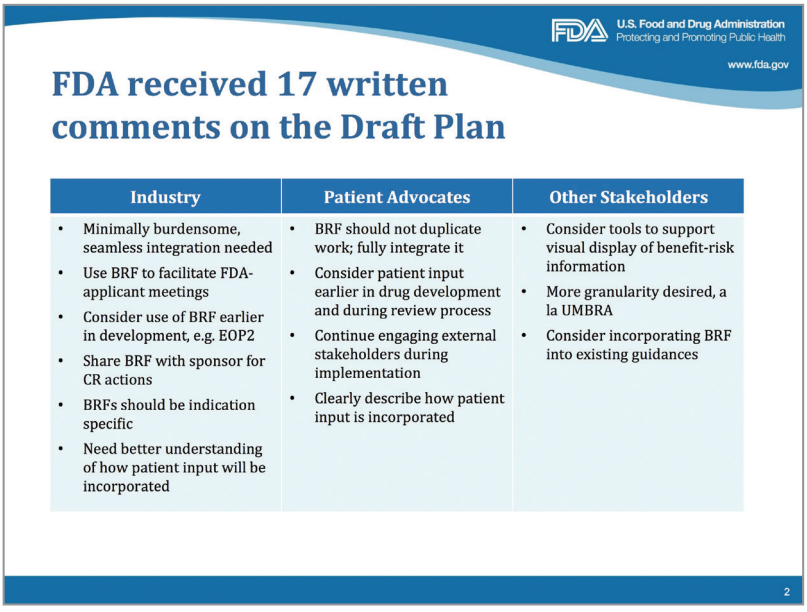

Figure 6. The FDA has announced its list of patient-focussed drug development meetings to be held 20013-2015.

. . .the FDA recognised that the review process could benefit from a systematic approach to obtaining patients perspectives on disease severity and unmet medical need.

of senior leadership facilitated frequent engagement with review teams during the pilot project. Currently, all levels are now engaged in determining a reasonable approach for framework implementation.

Because the assessment of a drug's benefits and risks involves analysis of severity of condition and current state of the treatment armamentarium and because patients who live with a disease have a direct stake in drug review process and are in a unique position to contribute to drug development, the FDA recognised that the review process could benefit from a systematic approach to obtaining patient perspective on disease severity or unmet medical need. Accordingly, as part of the PDUFA V enhancement, the FDA will conduct 20 public meetings to obtain patient perspective on specific disease areas.

These meetings continue the dialogue and engagement with the patient community on patient-focused drug development (PFDD) that began during PDUFA V discussions, address important considerations and challenges in establishing a process for conducting PFDD meetings and may help inform best strategies for future meetings. Thirty-nine diseases were nominated for public consideration from a wide range of therapeutic areas that could be characterised by one or more of the following factors:

- Chronic, symptomatic and affect functioning and activities of daily living
- Important aspects of disease currently not formally captured in clinical trials
- Reflect a range of severity
- Severe impact on identifiable sub-populations (e.g. children or elderly)
- Represent a broad range in terms of size of the affected population
- Currently no therapies or very few therapies, or the available therapies do not directly affects how a patients feels, functions, or survives

The FDA received approximately 4,500 public

docket comments after which the review divisions in the Centers for Drug and Biologics Evaluation and Research were given the opportunity to provide their perspectives on the disease areas that should be covered. Meetings to be held from 2013-2015 were announced (Figure 6) and there will be the opportunity for additional public comment before meetings to be held in 2016-2017 are decided. As each meeting is concluded a report will be posted on the FDA website. The report for the first meeting on Chronic Fatigue Syndrome/Myalgic Encephalomyelitis, held on 24-25 April 2013 can be found here.

EMA Benefit-Risk Project

Dr Francesco Pignatti

Head of Section, Oncology. Haematology & Diagnostics, European Medicines Agency

The objective of the EMA Benefit-Risk Project is to improve the consistency, transparency and communication of benefit-risk assessment and to move from implicit to explicit evaluations. Within the project, four of five work packages have been implemented to achieve this goal: 1) Description of current practice; 2) Applicability of current tools and methods; 3) Field tests of tools and methods and 4) Development of tools and methods for benefit-risk. The fifth work package, Pilot and training is ongoing.

Benefit-risk assessment has been defined as describing the favourable and unfavourable effects associated with a new medicine and the strength of evidence or the lack of evidence supporting the association. The Benefit-Risk Project has identified several tools to measure benefit-risk. Multi Criteria Decision Analysis (MCDA) allows for a high-precision evaluation and sensitivity analysis of new and complex situations. A type of MCDA, the PrOACT-URL framework evaluates the PRoblem, Objectives, Alternatives, Consequences, Tradeoffs; Uncertainty, Risk tolerance and Linked decisions surrounding a medicine.

Intended to be used for relatively straightforward assessments, however, the EMA Effects Table was developed as a compact and clear display of salient finding for a new drug, which is simple to build and communicate and which can be generally applied (Figure 7). In building the Effects Table, the reviewer focuses on the important effects of a medicine and those effects are not weighted for their relative importance. The table reflects conclusions based on the data, which may not be exact if the data are pooled results or are based on assumptions and this "less certain" data can be expressed as free text in some of the table columns (Figure 8).

The CHMP conducted a pilot trial of the Effects Table from January to May 2013, in which two new drug applications were assessed each month using the tool after the first round (day 120 list of questions) or after the second round of assessment (day 180 list of outstanding issues), for a total of ten drugs. The Table was completed by assessors and circulated to CHMP members in parallel to the usual assessment reports and feedback was collected from assessors and CHMP members. Industry's use of conjoint analysis at phase 1 and 2 development has been limited despite the fact that obtaining benefit-risk perspectives from patient respondents can provide benchmarks for pharmaceutical development decisions and can help industry understand the overall clinical value of a product, that is, its benefit-risk tradeoffs. An understanding of the tests that can be performed to reduce bias and confounding

Figure 7. Example of the EMA Benefit-Risk Effects Table.

EUROPEAN MEDICINES AGENCY

	Name	Description	Unit	Placebo	300 mg	Uncertainties	Reference in the text
Benefits	Progression-free survival Hazard Ratio	Date of randomization to the date of objective progression or death	unitless	1	0.46	Only a very low number of patients with definite RET negative status at baseline	Major Objection No. 1, Discussion on Clinical Efficacy (page 44)
	Progression-free survival (median)	Date of randomization to the date of objective progression or death (Weibull model)	months	19.3	30.5	From Weibull model – distributional assumptions probably do not hold	
	Objective Response (RECIST)	Proportion of complete or partial responders (at least a 30% decrease in the sum of the longest diameter from baseline)	%	13	45	Not a good surrogate. May provide some symptom relief (assumed)	
Risks	Diarrhoea CTC 3 Grade 3-4	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; …	%	2.0	10.8	Duration of follow up in the pivotal study is quite short with regard to the need for long duration of treatment and therefore the risk of developing	Major Objection No. 2, Discussion on Clinical Safety (page 65), Scientific Advisory Group answers to CHMP
	QTc related events CTC[3] Grade 3-4	QTc >0.50 second; life threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	%	1.0	13.4	further major Cardiac SAEs including Torsades de pointe. Could the risk be underestimated? How well can oncologists monitor in clinical practice?	See R MP
	Infections CTC[3] Grade 3-4	IV antibiotic, antifungal, or antiviral intervention indicated; …; Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	%	36.4	49.8		Discussion on Clinical Safety (page 66)

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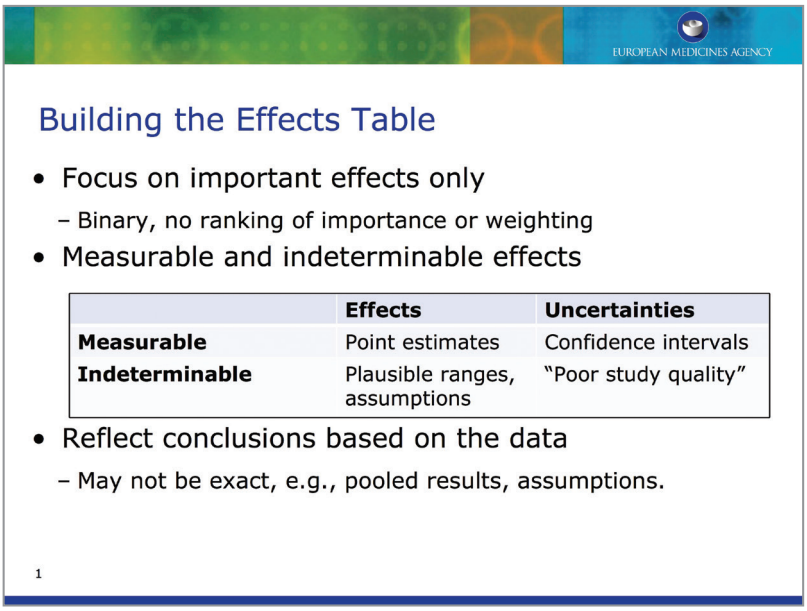


Figure 8. The EMA Effects Table is useful in evaluations of simplistic or less certain data.

may increase acceptance and uptake of this methodology.

Positive feedback from reviewers included comments that said that the Effects Table allowed for decomposition of the benefit-risk assessment into relevant components; that it was sufficiently easy to follow; was useful in the presentation of critical issues in discussions and provided focus for the important issues without the distraction of less important factors.

Negative comments were also received. Some reviewers noted that the Effects Table was too simplistic and did not provide the flexibility to represent the data in a clear and comprehensive way, allowing the presentation of relative and absolute data by study and by dose. It was also remarked that the table was more helpful in the earlier stages of assessment and needed to focus on the certainties as well as uncertainties. In addition several reviewers mentioned that the lack of the inclusion of weights was a limitation of the Effects Table because it seemed to imply that all criteria had the same value. Finally, as the data were already summarised in the Assessment Report, it was commented that completing the Table represented additional work for reviewers.

Some reviewers noted that the Effects Table was too simplistic. . .[while others] mentioned that the lack of the inclusion of weights was a limitation because it seemed to imply that all criteria had the same value.

For their part, CHMP members commented that whilst the Table was very useful, it should contain more quantitative information and it may represent considerable work for assessors. They also remarked that the Table would not be useful when it was too lengthy or not self-explanatory and more consistency would be required when constructing the Table, with less variability in layout and with an accompanying key to abbreviations provided.

Through the pilot, the EMA learned that the Effects Table was useful as a compact display of salient findings of benefit-risk evaluation that can be effectively communicated and generally applied. It was concluded, however, that the table should be used to complement rather than replace text and that its use requires training and monitoring. The Effects Table is currently being assessed by the EMA as an element of the Assessment Report, with assessors being trained and monitored in its use. In addition, the CHMP is encouraging companies to use the template in the presentation of dossiers to the EMA. Finally, the use of patient preferences is being evaluated and as other tools are identified by the PROTECT project, the EMA will explore their integration into the use of the Effects Table.

Utilisation of UMBRA by companies and agencies

Dr Neil McAuslane

Director, Centre for Innovation in Regulatory Science

Unmet need for an overarching benefit-risk system

Notwithstanding the significant efforts of pharmaceutical companies and regulatory agencies, both stakeholder groups have recently observed that the need for an overarching system to evaluate the benefit-risk of new medicines still remained unmet.[1,2] In fact, at the annual CIRS Benefit-Risk Workshop in 2012 it was agreed that a toolbox of methodologies for benefit-risk assessment should be developed containing tools such as the EMA PrOACT-URL or the systems developed by CIRS, the FDA or the Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team (PhRMA BRAT).

It was also the consensus of Workshop participants that all of these methodologies could be mapped to the overarching UMBRA eight-step framework. The UMBRA (Universal Methodologies for Benefit-Risk Assessment) framework provides a common platform for the development, assessment, implementation and refinement of an internationally acceptable, structured, systemised, standardised approach to the benefit-risk assessment of medicines. In addition, this platform facilitates the objectivity and transparency of regulatory assessment and reassessment and the predictability of regulatory process and promotes the consistency of regulatory decisions and the ability to communicate those decisions. In furtherance of this goal, CIRS is developing a lexicon for use with the UMBRA framework to maintain congruence with other benefit-risk initiatives.

The COBRA benefit-risk template evaluation

Based on an EMA reflection paper on benefit-risk assessment methods,[3] the template developed by the Consortium for Benefit-Risk Assessment (COBRA) that was discussed by Ms Sabourin (page 27) is a tool showing the progressive logic and bases of decisions that also correlates to and supports the UMBRA framework (Figure 9)[4]. In the year after the 2012 CIRS Benefit Risk Workshop, the template was modified through a series of reiterations and mapped to the UMBRA framework.

The template has been evaluated through a prospective study by COBRA members and regulators from Indonesia, Philippines, Thailand, Malaysia, South Korea and Chinese Taipei (the Southeast Asia Benefit-Risk Evaluation [SABRE] group) are also assessing the potential of the summary portion of the template to provide structured documentation to their benefit-risk decisions. In addition to these agency evaluations, because some regulators have indicated that it might be helpful to have data submitted in the same structure as it would be reviewed, the template was also sent to 13 pharmaceutical companies to determine if it had any applicability for use in the development and submission of a new medicine and if any modifications or additions should be made to increase its suitability for these purposes.

Abbott, Amgen, AstraZeneca, Bayer, Biogen, GSK, J&J, Lilly, Merck Serono, Novartis, Pfizer, Roche and Takeda were sent the latest version of the electronic template and user guide, which were developed for use by regulatory agencies, as well as a brief protocol for the evaluation. Feedback from 9 companies has been received: at 4 companies, individuals and teams reviewed the template and provided general comments, whilst teams at 2 companies provided general comments and 3 companies provided detailed comments using a case study approach. These diverse forms and methods provided a good perspective of companies' views, including potential modification enhancements and alternative approaches.

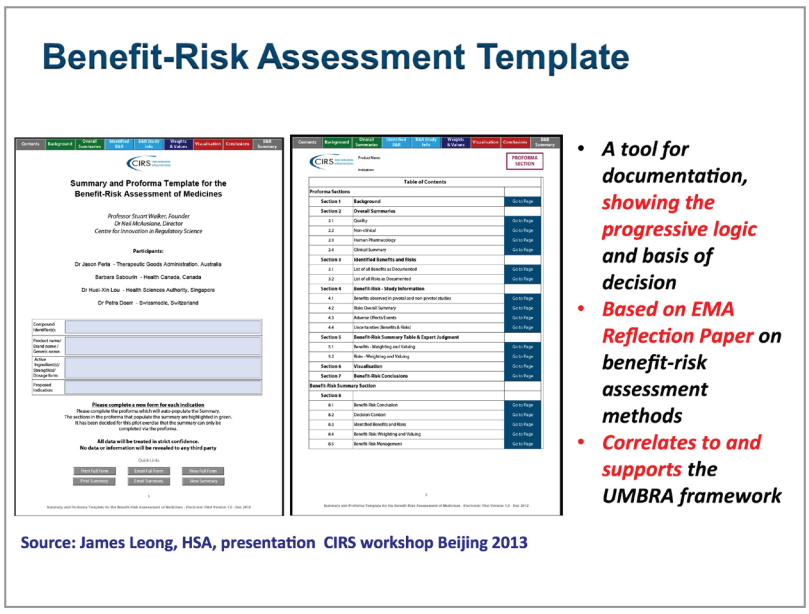


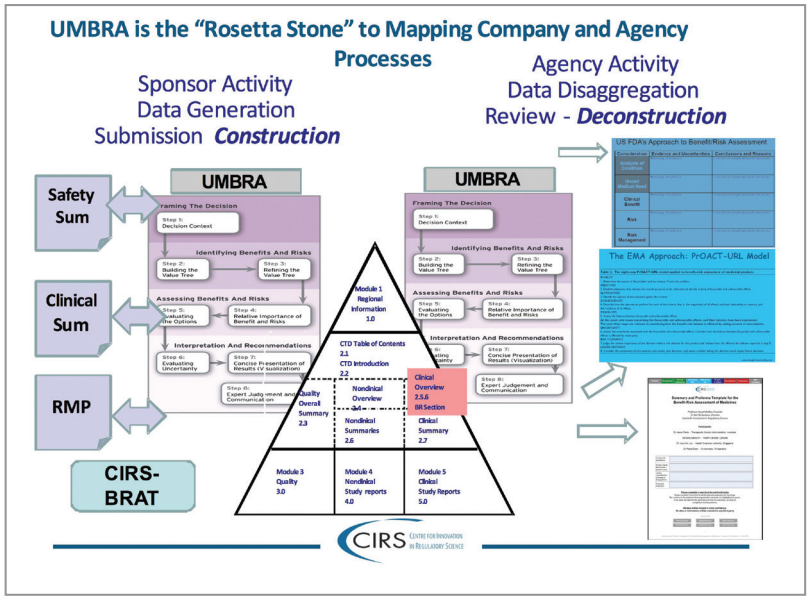
Figure 9. The template developed by the Consortium for Benefit-Risk Assessment (COBRA) Group.

Results of company evaluation

Although company responses were diverse, the template was regarded as generally not suitable for use by companies. Respondent themes included:

- Processes developed at companies and agencies differ according to differing needs. That is, companies must construct and aggregate evidence for medicines during development, whilst it is the responsibility of agencies to deconstruct or disaggregate that evidence. The template was seen as more helpful as a deconstruction tool.
- Although the template does overlap with the electronic common technical document, specifically in the clinical overall summary and risk management plan, it is not currently required for companies to provide such documentation in this format.
- The template lacks the ability or flexibility to accommodate the complexity of data and analyses of those data undertaken by companies.
- Using the template involves a duplication of effort and information, thereby building in inefficiencies.
- Rather than being useful as part of a life cycle approach to benefit-risk evaluation, the template was perceived as a document for use at submission only.
- Quality control issues may emerge related to the various sources of information required to complete the benefit-risk template.

Figure 10. The UMBRA benefit-risk framework can be used as a Rosetta Stone for the benefit-risk processes and documentations of primary stakeholders.



Evaluators of the template, however were divided into:

1. those who saw little opportunity for use of the template because their company already had a well-defined approach to benefit-risk evaluation that was practiced throughout the company and that was integrated into the business process there and
2. those who felt that with specific enhancements the template could meet their company's needs because an integrated approach had not yet been developed there.

Five companies provided specific areas where the template could be enhanced. The enhancements centred around restructuring sections to provide flexibility and the ability to accommodate the complexity of data and analyses undertaken by companies to consolidate and integrate narrative discussion so that individual benefits and risks are not taken out of context. Specific improvements called for enhanced risk management and risk mitigation sections, the inclusion of value trees and visualisation tools, the removal of duplication, the utilisation of hyperlinks and additional guidance documentation.

From the perspective of responding companies, although the benefit-risk template is informative and applicable to assessing benefits and risks and has the potential to become a common platform for regulatory review, it needs to be mapped to current regulatory processes and documentation. To be used by companies, the template would require significant enhancements that would include the use of a life cycle approach.

The companies suggested that moving forward, CIRS should work more directly with sponsors to construct a flexible approach that better fits company processes; map and cross reference the template to required regulatory documents produced by companies with a focus on benefit-risk such as clinical overviews, risk management plans and periodic benefit-risk evaluation reports. Additionally, CIRS should evaluate development of a new tool that will aid companies in the creation of a living document that will also allow agencies to map specifically to their documentation needs, allowing for a structured approach to evaluating the pertinent information for making a benefit-risk decision. To this end, the BRAT approach, which also maps to UMBRA and which CIRS is helping to disseminate, may be a more appropriate tool

The overlap of the steps of the UMBRA framework and activities used by pharmaceutical companies and regulatory agencies points to the potential to use the framework as a type of Rosetta Stone that each group of stakeholders could use to map their processes and documentations to those used by other groups.

for sponsors to use to construct the benefit-risk profile

Importantly, company respondents saw the UMBRA 8-step benefit-risk framework as informative and applicable in assessing benefits and risks with the potential to provide a structured common framework approach. Because many of the elements of the UMBRA framework and template are encompassed in regulatory documents, including the clinical overview of the common technical document and risk management plans, an alternative approach was suggested to refresh the guidance of the overview to the common technical document to include UMBRA and to establish a "points to consider" companion document, allowing the inclusion of appropriate clinical context. Parts of UMBRA and the benefit-risk template that are not currently incorporated could be added such as guidance on structured benefit-risk assessments, the weighting of benefits and risks and the potential inclusion of the visualisation of benefits and risks and a framework checklist.

Conclusions and the way forward

The overlap of the steps of the UMBRA framework and activities used by pharmaceutical companies and regulatory agencies points to the potential to use the framework as a type of Rosetta Stone that each group of stakeholders could use to map their processes and documentations to those used by other groups (Figure 10).

References

1. Lumpkin MM, Eichler HG, Breckenridge A, Hamburg MA, Lönngren T, Woods K Advancing the science of medicines regulation: the role of the 21st-century medicines regulator. *Clin Pharmacol Ther.* 2012;92:486-493.
2. Forda SR, Bergström R, Chlebus M, Barker R, Andersen PH. Priorities for improving drug research,development and regulation *Nat Rev Drug Discov.* 2013;12:247-248.
3. Committee for Medicinal Products for Human Use. *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 Accessed December 2013.
4. Liberti L, McAuslane N, Patel P, Connelly P. *Regulatory Review – How do agencies ensure the quality of the decision? The role of decision frameworks in the review of new medicines: What are the challenges and solutions that can facilitate agencies to make quality decisions?* Workshop report: Beijing, PR China: 24-25 January 2013. Available at www.cirsci.org. Accessed December 2013.

Benefit-risk assessment and communication: Recommendations of the IMI-PROTECT initiative

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There are multiple stakeholders involved in decision making for new medicines, including pharmaceutical company officials, who make decisions about what compounds to develop for which indications; regulators, who make decisions regarding a medicine's quality, safety, efficacy and benefit-risk balance for individuals and public health; payers and reimbursement agencies, who decide the medicine's cost-effectiveness; healthcare providers, who make decisions based on prescribing lists and finally, patients, who ultimately decide which medicines to use.

The task of regulators is to make good, defensible decisions regarding what medicines should receive a license for which indications, based on the available evidence of risks and benefits. It is increasingly important to be able to justify and explain these decisions to patients and other stakeholders. Can more formal approaches to decision making and especially more modern methods of graphic display help regulators do this better? Certainly there are challenges to formalisation. For example, there is a plethora of quantitative methods for benefit-risk assessment and not a general consensus. Additionally, there may be competing priorities, value preferences and requirements from the different stakeholders. Finally, there are various elicitation methods to inform these methodologies such as simple elicitation, decision conferencing and discrete choice experiments.

Using a case study format, the IMI PROTECT initiative evaluated several formal frameworks for the assessment of the benefits and

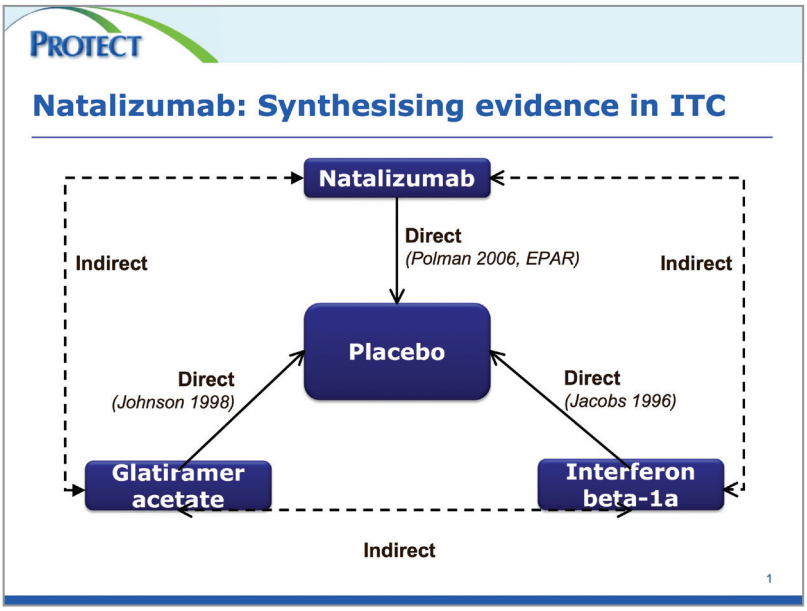

Figure 11. Indirect treatment comparison can be used in the evidence gathering and data preparation stage of benefit-risk assessment.

risks of six medicines. The IMI PROTECT consortium (Innovative Medicines Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) is a public-private partnership coordinated by the European Medicines Agency. The PROTECT project has received support from the Innovative Medicines Initiative Joint Undertaking (www.imi.europa.eu), resources of which are composed of financial contribution from the European Union's Seventh Framework Programme and EFPIA companies' in kind contribution.

The case study used by PROTECT was of an evaluation of the benefits and risks of natalizumab, compared with placebo, interferon β1-A and glatiramer acetate for the treatment of relapsing remitting multiple sclerosis. Natalizumab was first approved in 2004, withdrawn due to concerns regarding associated occurrence of progressive multifocal leukoencephalopathy (PML) and subsequently re-evaluated and reintroduced because of public demand. Like the first-stage PROTECT analysis, this second stage was developed through the use of publicly available data and was not intended as a commentary on any specific regulatory decisions.

The roadmap toward recommendations developed by PROTECT calls for planning, evidence gathering and data preparation, analysis, exploration, conclusions and dissemination of those conclusions. The important planning stage encourages stakeholders to focus on critical issues related to benefit-risk assessment, encourages sufficient thinking and thorough discussions between stakeholders to clearly define the purpose and context of the benefit-risk assessment, ensures clear detailed summary documentation of discussions and results and allows future analyses and updates to utilise the same foundations. The key points that should be documented at the planning stage of a benefit-risk assessment are the decision problem, the comparators, the benefits and risks to include, the perspectives that should be taken into account, the sources of evidence, the resources available to the decision maker and the time horizon (short-term versus long-term benefits and risks).The methodologies recommended for use in this stage of the case study were PrOACT-URL and the model developed by the Pharmaceutical Researchers and Manufacture of America Benefit-Risk Action Team (PhRMA BRAT), whilst tree diagrams and structured tables were the visualisation techniques employed.

During the evidence gathering and data preparation stage, assessors identify and extract evidence relevant to the benefit-risk assessment in relation to the set criteria, determine what data are to be collected from the anticipated type of benefit-risk analysis, aggregate multiple sources of evidence which may require the use of estimation techniques and encourage systematic handling of missing data. This stage requires the engagement of clinical, statistical, epidemiological and database expertise. Methods that can be drawn on during this step include indirect or mixed treatment comparison (ITC/MTC) (Figure11) and probabilistic simulation method (PSM), whilst visualisation techniques include structured and colour-coded tables, effects table such as used in PrOACT-URL, a source data table such as is used in the PhRMA BRAT methodology, network graphs and forest plots.

During the analysis stage, assessors evaluate data collected at previous stages in a benefit-risk assessment, quantifying the magnitudes of benefits and risks and weighs or integrates quantitative measures of the benefit-risk

The task of regulators is to make good, defensible decisions regarding what medicines should receive a license for which indications, based on the available evidence of risks and benefits.

balance, depending on the type of analysis. Methodologies recommended at this stage include metric indices, which are numerical representations of benefits and risks such as number needed to treat/number needed to harm (NNT/NNH); impact numbers, quality-adjusted life years (QALY); quality-adjusted time without symptoms and toxicity (Q-TWiST), benefit-risk ratio (BRR) and incremental net health benefit (INHB). Quantitative frameworks, which model benefit-risk trade-off and balance benefits and risks are also recommended such as multi-criteria decision analysis (MCDA) and stochastic multi-criteria acceptability analysis (SMAA) as are utility survey techniques, which elicit stakeholders' preference information such as discrete choice elicitation (DCE). Appropriate visualisation techniques at this stage include those that elicit value preferences such as tree diagrams and method-specific visualisations such as swing-weighting 'thermometer' scale (Figure 12) and drop-down lists; those that present descriptive analysis results such as tables and forest or interval plots and those that present quantitative analysis such as difference display and stacked bar and grouped bar charts.

During the exploration stage, assessors evaluate the robustness and sensitivity of the main results to various assumptions and sources of uncertainties, assess the further consequences of a decision, consider any impact or added value to a risk management plan. This stage requires both statistical and clinical input.

Methodologies recommended at this stage include ITC/MTC; utility survey techniques such as DCE, analytical hierarchy process (AHP) and swing-weighting, PSM and SMAA. Recommended visualisation techniques include box, distribution, scatter and forest or interval plots, tornado diagrams and interactive visualisations

The conclusions and dissemination stage, represents the point at which a conclusion is reached and the results and consensus from the benefit-risk assessment are communicated to a wider audience. This stage includes an explicit statement of the findings and conclusions that could influence future actions, emphasising a transparent audit trail of the whole assessment process. It ensures the "big picture" overview is not lost.

Key methodological considerations as this stage:

- What question(s) was the benefit-risk assessment aimed at addressing?
- What answer(s) were found?
- Is/are the answer(s) highly sensitive to the treatment effects data, the choice of analysis method, or the preference data?
- What is the supporting information on which the conclusion is based?

Key visualisation considerations

- Know the intended audience – consider knowledge/interests
- Refer to established visual design principles and guidelines
  - Concretised in the GSK Graphics Principles[1]

In addition to the preparation of a peer-reviewed publication, patient and public involvement studies are currently being conducted and a website that will synthesise the findings of PROTECT WP5 and provide interactive features is being developed.

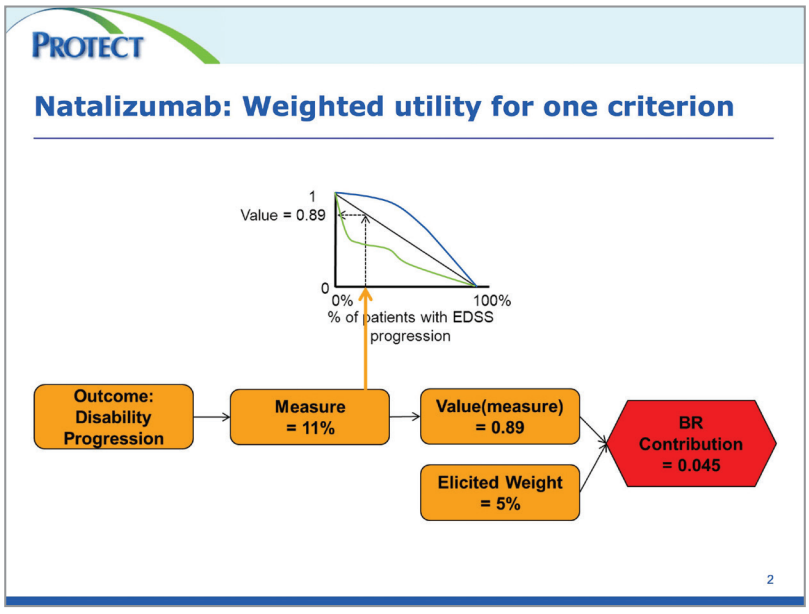

Figure 12. Weighted utility analysis can be used during the analysis stage of benefit-risk assessment.

Reference

1. Duke S. *Best practice recommendations*. Found at https://ctspedia.org/do/view/CTSpedia/BestPractices Accessed February 2014.

Assessing relative importance: An overview of current major approaches to weighting

Dr Bennett Levitan

Director, Epidemiology, Janssen Research and Development

There is still resistance to the formal weighting of benefits and risks despite the fact that this weighting is a component of many accepted decision-making frameworks such PrOACT-URL, UMBRA and BRAT. This resistance might be traced to the fact that medical decision making usually occurs through the intellectual integration of data and is typically communicated with words rather than by the use of a numeric system such as those employed in formal weighting. Moreover, the value judgements incorporated into weighting may be considered "less scientific" and the quantitative approach may be regarded as a means to derive an answer rather than the means to obtain clarity. In addition, no consensus has yet emerged regarding which of the many methods should be used, nor has guidance been developed for their use. Finally, some regulators may regard weighting as a novel process that is subject to the introduction of industry bias. Despite these concerns, most decision makers understand that there is a need for quantitative tools to help clarify more complex decisions that must incorporate data, uncertainty and necessary value judgements, even though this type of decision may not occur frequently. Dr Levitan discussed five of the many types of methods used to derive benefit-risk weighting: zero/one weighting, categorisation, point allocation, swing weighting and conjoint analysis.

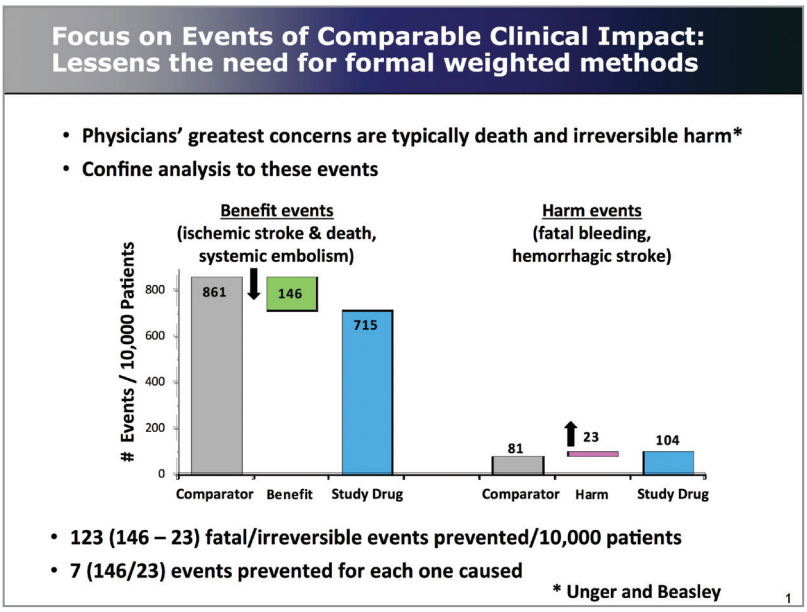

Figure 13. Weighting benefits and risks of comparable clinical impact for two drugs.

Common approaches to obtaining weights

Zero/One weighting: This is a type of informal weighting in which the identification of relevant outcomes is one of the first steps in which the values of the decision maker come into play, as outcomes are weighted as relevant or not. This assessment is performed implicitly when developing a clinical protocol, statistical analysis plan, value tree or benefit-risk approach.

Categorisation: Another type of informal weighting in which decision makers or clinical experts assign each endpoint to a category in an n-point scale. Existing, validated scales such as the Common Terminology Criteria for Adverse Events can be used.

Point allocation: This is a type of trade-off or allocation method in which decision makers start with well-defined attributes; for example, headache relief = reduction from severe or moderate pain to mild or no pain in two hours; rapid onset = reduction from severe or moderate pain to mild or no pain in one hour and myocardial infarction (MI) = the number of MIs per 1,000 patient-years. Next, potential incremental changes in the attributes are defined; for example, 1% increase in headache relief; 1% increase in rapid onset; an increase in 1 MI per 1,000 patient-years. The incremental change that has the greatest impact on decision making is then selected and assigned100 points. Values between 0 and 100 are allocated to the incremental changes in the other attributes, reflecting their clinical importance relative to the attribute with the greatest impact. Finally, all weights are scaled back so that they equal 100. The overall results can then be visually portrayed to stakeholders to ensure buy-in.

Swing weighting: This trade-off or allocation approach is one of the more common approaches used in multi-criteria decision analysis. It is similar to point allocation and is based on a full range of attributes. It is critical to specify the range for each attribute that is relevant to the decision; for example, the proportion patients with headache relief (reduction from severe or moderate pain to

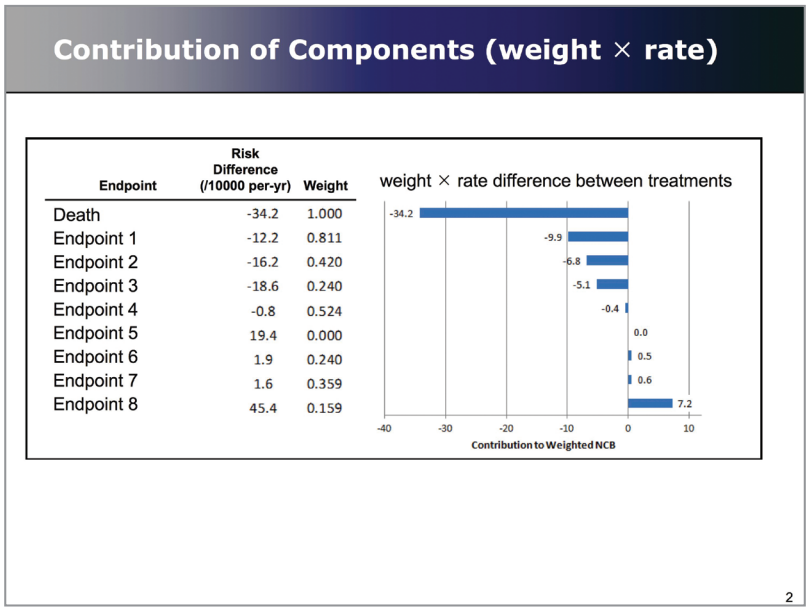

Figure 14. Calculating the benefits and risks of two therapies by the weighted contribution of their attributes.

mild or no pain within 2 hours after treatment) should range from 20% to 80% and the number of MIs per 1000 patient-years (MI defined per clinical criteria) range from 0 to 40. Decision makers identify the attribute whose "swing" from lowest to highest value in its range would have the greatest impact on the decision, which in this case would be the number of MIs per 1,000 patient-years from 0 to 40. For each other attribute, an assessment would be made of the fraction of this value that would be achieved by swinging the other attribute from its lowest to highest value; for example, the proportion patients with headache relief swinging from 20% to 80% would have 1/5 the impact on the decision as the swing for MI.

Stated Preferences are those preferences elicited by using hypothetical situations; for example, asking a decision maker whether Treatment A or B is preferable, while Revealed Preferences are those preferences that are revealed by choices in real-world situations such asking a decision maker whether Treatment A or B was selected. Although the use of Revealed Preference data might appear to be most advantageous, Stated Preference surveys can assess treatments that are not yet available whilst Revealed Preference data suffer from many confounders such as the effects of differing insurance plans and access and decisions made by other stakeholders. Furthermore, there may be little variability in key treatment attributes being surveyed and these data may be difficult and time consuming to obtain.

A stated choice survey is one in which a

. . . most decision makers understand that there is a need for quantitative tools to help clarify more complex decisions that must incorporate data, uncertainty and necessary value judgements . . .

responder indicates their preferred option from a set of alternatives. For example, respondents are asked whether Treatment A or Treatment B would be their preferred therapy when both treatments are associated with a 15% chance of disabling stroke; Treatment A is associated with a 10% risk of non-fatal myocardial infarction, Treatment B, a 15% risk and Treatment A is associated with a 20% risk of bleeding with transfusion, Treatment B, a 10% risk.

A type of stated choice survey, a **conjoint analysis** was conducted by Pharmaceutical Research and Manufacturers of America Benefit-Risk Assessment Team/Next Steps Working Group (PhRMA BRAT /NSWG) among 200 high-functioning migraine sufferers. The survey determined that the most important attribute for two migraine therapies was an associated risk of myocardial infarction and suggested that respondents would accept a 2/1000 annual chance of myocardial infarction to relieve activity limitations during migraines. Interestingly, this is likely to be a substantially higher risk than regulators would be willing to accept.

Common approaches to applying weights

A focus on events of comparable clinical impact lessens the need for formal weighted methods and because physicians' greatest concerns are typically death and irreversible harm[1], analysis can be confined to these events. For example, a medication that prevents 146 fatal or irreversible events such as ischaemic stroke and death and systemic embolism in 10,000 patients but causes 23 instances of fatal bleeding or haemorrhagic stroke, prevents 7 events for each 1 event that it causes (Figure 13).

In another example of the practical application of weighting, a forest plot could be created in which the outcomes for two therapies are vertically stacked by order of decreasing weight rank, with the events of greatest impact on top and the least severe on the bottom along a horizontal scale of risk of occurrence. In this way it can easily be seen not only which effects favour each therapy and how important those effects are.

Summary
Based on Speaker's Knowledge and Biases

	Who is Assessed?	Time to implement	Expertise needed to implement	Transparency / Ease of communicating Results	Theoretical Justification
0/1 weighting	Small group of experts	Hours	Low	Easy	N / A
Categorization	Small group of experts	Hours	Low	Easy	N / A
Direct entry	Small group of experts	Hours	Low	Easy	No
Point allocation	Small group of experts	Hours	Medium	Moderate	Probably
Swing weighting	Small group of experts	Hours	Medium	Moderate	Yes
Conjoint Analysis	Population – 100's*	Months	High	Moderate - Hard	Yes
Best-worst Scaling	Population – 100's *	Months	High	Moderate - Hard	Yes

* Patients, physicians, caretakers, etc.

3

Figure 15. The advantages and disadvantages of different models for weighting the benefits and risks of medicines.

As previously discussed with the example of the migraine therapies, in the maximum acceptable risk application, a ratio of weights is used to give a threshold for acceptable trade-offs. For example, the survey that suggested that patients will accept a 2/1000 annual chance of myocardial infarction to relieve activity limitations during migraines could be used to evaluate any migraine therapy by its associated risk for myocardial infarction.

Finally, the contribution of endpoints for therapies can be calculated by multiplying their weight times their rate of incidence versus comparator therapies (Figure 14).

The advantages and disadvantages of the models in terms of their theoretical justification, the identity of the parties assessed, the time and expertise needed to implement and the ease with which the results are communicated (Figure 15) all affect their utility according to various stakeholder needs.

Reference

1. Beasley BN, Unger EF, Temple R. Anticoagulant options--why the FDA approved a higher but not a lower dose of dabigatran. *N Engl J Med*. 2011;364:1788-1790.

FDA's approach to assessing relative importance

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Rationale for a structured approach

The FDA's structured approach to benefit-risk assessment is an attempt to transparently show the benefits and risks considered in an evaluation, to identify the alternative treatment options that were taken into account, to consider ways to manage risks, to focus on what is known and unknown about the drug and then to make as rational and explainable a decision as possible.

Although these elements are critical, following this structure does not necessarily result in easy regulatory decisions because judgements will invariably differ as to what is most important and identifying the correct decision is often difficult, even when the data are clear. In addition, in many cases, the data are not clear and the evaluator must weigh importance and the level of uncertainty. Furthermore, evaluations are not all binary "yes/no" decisions. It may also be necessary to consider whether a drug will be a second-line treatment, whether special tests will be required before use or as a part of safety or efficacy monitoring, which dosage should be used or whether a Box Warning is required.

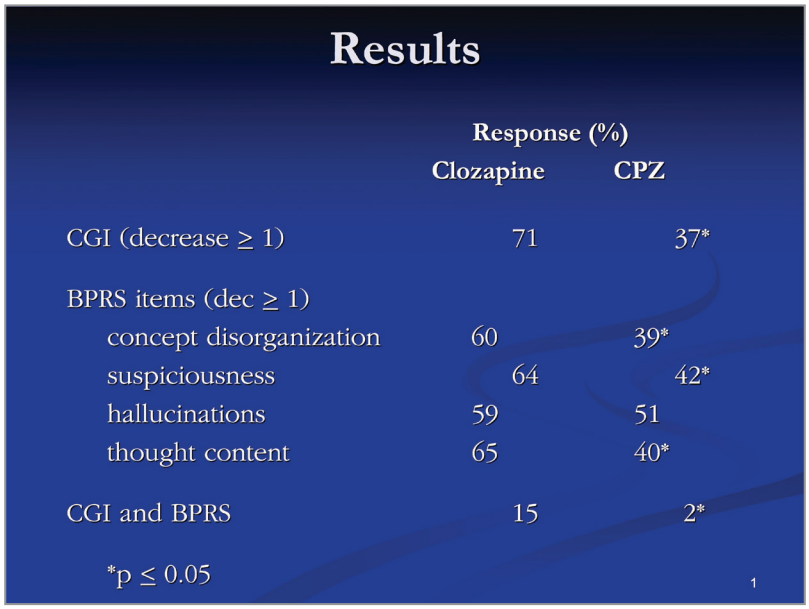

Figure 16. The anti-psychotic drug clozapine was approved despite an associated risk of agranulocytosis because of its clear superiority over an alternative therapy.

Clear data and a difficult decision

The FDA decision for dabigatran, an oral anticoagulant approved in the United States in 2010, is an example of a difficult evaluation involving clear data. The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study compared dabigatran 110 and 150 mg twice daily with warfarin titrated to appropriate international normalized ratio (INR) for the prevention of stroke and systemic emboli in approximately 15,000 people with atrial fibrillation. Results showed that

- Dabigatran 150 mg was clearly better than warfarin or dabigatran 110 mg in decreasing overall occurrence of stroke (1.1% vs 1.5%-1.7%).
- Dabigatran 110 mg was less effective than warfarin in the prevention of thromboembolic stroke and dabigatran 150 mg was significantly better.
- Dabigatran at both 150 and 110 mg was much better at preventing haemorrhagic stroke, which warfarin seems to cause.
- Therefore, dabigatran 150 mg was better than warfarin and dabigatran 110 mg was not inferior to warfarin but was inferior to dabigatran 150 mg.

Bleeding, sometimes serious, is a side effect of anticoagulant use. Dabigatran 150 mg has similar effects to warfarin in respect to bleeding and dabigatran 110 mg is quite a bit better than warfarin. Therefore, dabigatran 150 mg is clearly superior to warfarin in its desired effects, especially in the prevention of intracranial haemorrhage but is associated with more bleeding than dabigatran 110 mg. Although dabigatran 110 mg is not superior to warfarin in its desired effect, it does have an effect and causes less bleeding.

The FDA Advisory Committee was split in its recommendation, with 6 members voting to only approve the 150 mg dosage of dabigatran and 4 voting to approve both the 110 and 150 dosages. The EMA and Health Canada approved both doses. Ultimately, the FDA approved only the 150 mg dosage, with the rationale that it is better to not experience strokes even if a treatment is associated with bleeding; that is, strokes were judged to be more important than non-fatal bleeds. Obviously, not everyone agrees with this decision.

Uncertainty and a difficult decision

The FDA decision for rosiglitazone, an insulin sensitiser first approved in the United States in 1999, is an example of a difficult decision involving uncertain data. Rosiglitazone's predecessor, troglitazone was withdrawn because of the occurrence of severe (fatal) liver injury. The reported fatality/transplant rate was debated and ranged from 1 in 1000 to 1 in 5000. Interestingly, troglitazone was withdrawn only when later drugs rosiglitazone and pioglitazone were shown not to be hepatotoxic.

A 2007 meta-analysis showed that an increased rate of myocardial infarction and a borderline increase in cardiovascular death (but decreased incidence of stroke) was associated with rosiglitazone. These results were not supported by the larger and longer study Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD). There was, however, scepticism about the RECORD study, which was not blinded and in 2010, after Advisory Committee consideration, the FDA greatly limited use of rosiglitazone and not pioglitazone (which had reported associations with bladder cancer).

Therefore, a statistically borderline meta-analysis ($p > .05$) compared with uncertainties about a large, directed and open-level cardiovascular trial that showed no risk led to major restrictions on the use of rosiglitazone but no restrictions on pioglitazone despite small margin mortality comparisons through epidemiology studies (hazard ratio, 1.1 – 1.3). The rationale for this decision was based on the existence of many other oral hypoglycaemic therapies (including pioglitazone) and the fact that although the heart attack/mortality finding was not strong, there was clearly some evidence of risk for a large, vulnerable population and the perception that the contradictory RECORD study was severely flawed.

Serious adverse events: non-approval and withdrawal

Some drugs are associated with rare but lethal adverse reactions. In addition to these events, regulatory decisions must also consider other parameters such as the availability of alternative treatments.

Each of the following drugs were either denied approval or withdrawn because they are associated with serious but rare adverse events that other drugs of its class do not have:

The FDA's structured approach to benefit-risk assessment is an attempt to transparently show the benefits and risks considered in an evaluation . . . to consider ways to manage risks, to focus on what is known and unknown . . .

- lumiracoxib – hepatotoxicity
- ximelagatran – hepatotoxicity
- romfenac – hepatotoxicity
- astemizole – Torsade de Pointes (TdP)
- terfenadine – TdP
- cisapride – TdP
- valdecoxib – Stevens-Johnson Syndrome
- cerivastatin – rhabdomyolysis

Serious adverse events: approval and risk management

There are, however, drugs which are associated with serious adverse effects but which also have a documented advantage over alternatives. It is generally believed there should be more than one drug for a condition, allowing testing to determine whether a drug worked in people who did not respond to available therapy or could be tolerated by people who could not tolerate the available drug, although this type of testing is infrequently performed.

Captopril (which caused agranulocytosis) showed clear superiority in patients with hypertension for whom "triple therapy" (hydrochlorothiazide, hydralazine, reserpine) was ineffective and was approved only for that subpopulation.

Bepridil (a calcium channel blocker) was superior to diltiazem in angina patients not responding to diltiazem and was marketed until recently for that group of patients despite associated QT prolongation and deaths from TdP. Some might question if angina therapy is worth this serious risk.

The anti-psychotic clozapine causes potentially fatal agranulocytosis in approximately 1.5% of patients. Clozapine was tested in a four-week randomised, double blind trial versus chlorpromazine in patients hospitalised with schizophrenia for whom haloperidol was ineffective. The results showed that clozapine was significantly more effective in producing improvement in Clinical Global Impression Scale

and Brief Psychiatric Rating Scale items (Figure 16) and were the basis for the drug's subsequent approval with a risk management system.

Comparison trials do not always reveal these significant differences, however. Many physicians treating arthritis have insisted that the individuality of response means that many arthritis treatment options are required. However in a study comparing rofecoxib 25 mg and celecoxib 200 mg in celecoxib non-responders all of the non-responders did well on treatment, with no difference in response to the two therapies. Note that without a celecoxib control, rofecoxib would have appeared extremely effective in this non-responder population.

Benefits and risks that make a difference in decision making

So what makes a benefit important? The more important the benefit, the more risk (and perhaps less safety data), would be tolerated. A drug that for example:

1. Treats serious disease (or aspect of one) with no alternative therapies, such as many cancer treatments; clearly stated in subpart I of IND regulation 312.80.
2. Has documented advantage over existing therapy for serious or sometimes non-serious and troublesome diseases, either works better; for example tysabri, or lacks an important adverse effect, even if it has one of its own; for example acetaminophen lacks NSAID GI effects but is associated with liver problems.
3. Treats those in whom existing therapies are ineffective, allowing tolerance of considerable risk; for example, clozapine, captopril, bepridil; and not always for a serious disease; for example, angina.
4. Provides distinct mechanism for a disease that does have good treatments, allowing tolerance of some serious risks; particularly critical for diseases for which drugs leave many inadequately treated, for example, epilepsy, multiple sclerosis, rheumatoid arthritis

The risks of major interest or those that are "game changers" are of two kinds: those presented by drugs such as flosequinan, rofecoxib and encainide, which may be associated with an increased risk of death or irreversible morbidity, usually modest (2-fold or less) for cardiovascular issues such as coronary artery disease, arrhythmia, congestive heart failure, stroke, pulmonary emboli valvulopathy or other effects such as fractures or cancer risk. Or those drugs associated with a markedly increased risk of a life-threatening and still rare adverse event, when alternative therapies lack that risk:

Adverse event	Drug
SJS	valdecoxib
DILI	iproniazid, ticrynafen, benoxaprofen, bromfenac, troglitazone, pemoline
TdP	terfenadine, astemizole, grepafloxacin, cisapride
Anaphylaxis	zomepirac
Acute renal failure	suprofen
Rhabdomyolysis	cerivastatin (worse than others)

Therefore, a lethal and rare adverse event associated with a drug for a disease with options for alternative treatment will lead to withdrawal or non-approval but may be found acceptable if no alternative therapy existed. As a general rule, symptomatic and reversible side effects are acceptable, even if a drug does not have a clear advantage over alternatives and this profile would rarely, if ever, lead to a non-approval. In part, this reflects the view that additional drugs are good to add to an armamentarium and that all of their benefits may not be known and may emerge later and their adverse effects are monitorable and reversible.

There are many illustrations of the value of new pharmacologic approaches whose added benefits are not yet fully characterised. New anti-hypertensives, angiotensin-converting enzyme inhibitors, beta-blockers, angiotensin receptor blockers and calcium channel blockers have major additive effects and many novel uses. New anti-depressants treat a wide range of related illnesses and have different adverse effect profiles. Calcium channel blockers, which started as anti-angina drugs are now used to treat a range of illnesses. The display of the elements leading to a decision and the analysis of the associated factors and data are enabled with the FDA structured benefit-risk framework critical to all stakeholders in healthcare.

The weighty topic of relative importance: An industry viewpoint

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Why use social media?

GlaxoSmithKline has been very proactive in ensuring that benefit-risk assessments be considered by all key contributors in the medicines development process. The benefit-risk initiative was begun at GlaxoSmithKline at the end of 2011 and by 2012, with guidance from the Benefit-Risk Group, most product teams had presented formal benefit-risk summaries and the Group had received Safety Board and Safety Leader feedback. In 2013, the Benefit-Risk Group responded to that feedback, while product teams began to proactively seek their advice and find synergies between benefit-risk assessment and other activities such as clinical trial protocols and safety updates, thereby achieving consistency in benefit-risk communication. Over 170 employees have received basic benefit-risk training and advanced training was planned for the fourth quarter of 2013.

Weighting is only one component of benefit-risk assessment (Figure 17). Teams are encouraged to frame their assessments by a consideration of the disease context, the unmet need, how benefits and risks for the product are measured,

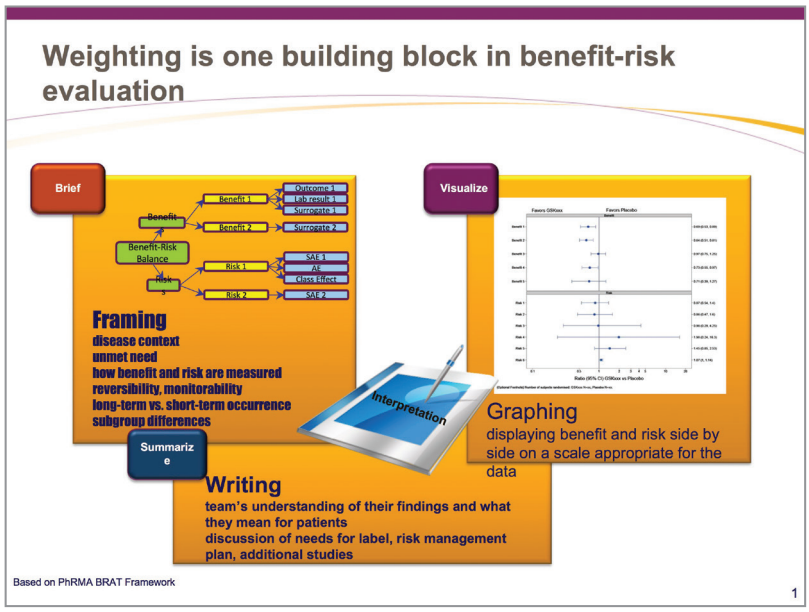

Figure 17. The weighting of benefits and risks are only part of their evaluation.

. . .ultimately, the patient, once informed, is the definitive decision-maker concerning the benefit-risk balance.

the reversibility and monitorability and long-term versus short-term occurrence of associated adverse events and the differences in efficacy and safety among population subgroups. The written assessments of teams should contain that group's understanding of their findings and what they mean for patients as well as a discussion of the needs for label, a risk management plan and any necessary additional studies. Visualisation of a product team's benefit-risk assessment should display the benefits and risks side by side on a scale appropriate for the data.

As part of their training, GSK product teams are instructed to consider a medicine's benefits; that is, the evidence for its efficacy in terms of the frequency, incidence, proportion and intensity of clinical outcomes or valid surrogates of outcomes and the timing of onset and durability of these effects. They must consider how the drug works in its target patient population as well as the variability of its effects in subgroups of patients. In addition, the perspectives of various decision makers such as regulators, patients, caregivers and healthcare providers should be evaluated and aligned with information that goes to payers as well. With regard to a medicine's risks, teams must review how severe the associated adverse events are, the frequency and intensity of safety concerns, the timing of onset and of resolution, their predictability, monitorability and reversibility; in whom the events occur and their variability among patient subgroups. As with benefits, the perspective of decision makers regarding risks should be considered as well.

In a preliminary look at multi-criteria decision analysis by the Benefit-Risk Methods Team, a small group of statisticians, safety scientists and benefit-risk scientists chose a case study from the EMA website and used web-based software that provided structured group participation, immediate visualisation and sensitivity analysis. An initial assessment of this process showed that the software output allowed a demonstration of how individual criteria contributed to the overall benefit-risk evaluation and how a sensitivity analysis could be performed by adjusting the weights of the criteria changed the results (Figure 18). Participants liked having

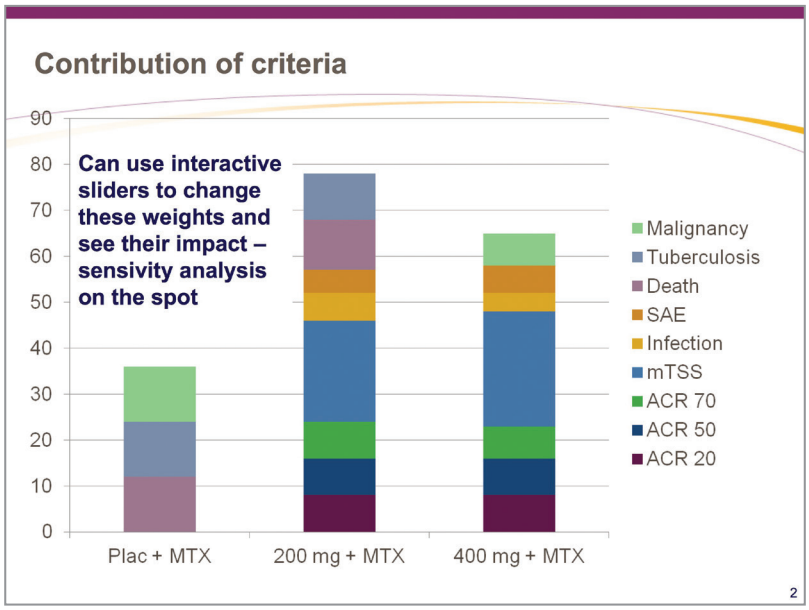

Figure 18. The use of web-based software allowed evaluators to adjust the weights of a criteria to determine their effect on an overall evaluation.

a tool for organising and visualising criteria and appreciated that the software allowed views of inputs from participants, displayed contributions of key benefits and risks to scores and provided calculations such as normalisation. The process provided an opportunity for robust discussion and brought up questions of how benefits and risks were valued and why and underscored the importance of establishing weights before an analysis to avoid bias. In addition, it pushed for clarity of definitions for, for example, the difference between a risk and disease progression.

The Benefit-Risk Group does have practical considerations to be resolved. Facilitation training will need to be provided to instruct group leaders in the best way to elicit complex information from groups such as swing weights and software training will also be necessary to better enable its use. The results of evaluations will need to be interpreted in terms of outcomes for patients. Finally, the entire benefit-risk evaluation process is time consuming and requires a significant commitment of resources and it should be recognised that it will not be required for every decision and consideration must be made of when its use would be appropriate.

Weighting, however, does inform pharmaceutical companies' internal benefit-risk work. It helps identify treatments with durable effects and minimal adverse events that provide convenience for patients' desired activity levels and enables decisions as to whether medicines should continue based on the disease or condition it treats, alternative therapies and potential treatment populations. Companies need to study the outcomes that will inform patients' decisions, who need to know if the medicine is right for them based on their health history, lifestyle and personal goals and preferences. An example of that consideration can be found on the US FDA website discussion of the evaluation of the benefits and risks of alosetron a 5 HT3 antagonist which was approved for the treatment of irritable bowel syndrome in 2000 and voluntarily withdrawn that same year due to the occurrence of serious, potentially life-threatening gastrointestinal side effects. However, in 2002, after intensive lobbying by patient groups and a re-assessment of available data, the FDA approved a supplemental new drug application for the restricted marketing of alosetron to women with severe irritable bowel syndrome. They explained:

"The FDA is aware of the need to balance between access to effective therapies (particularly when conditions are serious, debilitating, or life threatening and when no satisfactory alternative therapy exists) and protection of the public from serious drug-related adverse events. Since the withdrawal of Lotronex, the FDA and GSK have received numerous emails, letters and telephone calls from patients who related how their IBS symptoms were not responsive to any therapy other than Lotronex and how their quality of life was adversely affected by its withdrawal. . . ultimately, the patient, once informed, is the definitive decision-maker concerning the benefit-risk balance."

Companies also need to study outcomes that will inform the decisions of regulators who need to decide if a medicine be made available for the appropriate patients, determining if the benefits have been demonstrated, if the risks can be monitored, mitigated and managed and if the benefit-risk balance remains positive over time.

In conclusion, weights have a place in benefit-risk analysis. They provide perspective and can be a backbone for deeper discussions. Although the numbers assigned to the weights do not necessarily translate well, the relationships among criteria might and the more general issues of importance should translate, if given in the proper context. Ultimately, weights should provide transparency for thornier issues and GSK will continue to explore them as one more useful part of evaluating the benefits and risks of medicines.

Building uncertainty into the benefit-risk framework --

Ensuring stakeholder understanding of the role of uncertainty in the decision

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Uncertainty in benefit-risk assessment

Clinical trials are experiments designed to demonstrate the efficacy and describe the safety of new medicines without exposing subjects to excessive risk in a manner that reduces or avoids confounding. The weighting of benefits and risks will always be conducted based on the information that is available from the studies that are conducted as well as any other information that is available at the time. However, by design, trials may be limited in their ability to generalise the findings to all populations and situations not directly studied. Therefore, drawing conclusions and making decisions in the face of uncertainty has always been and will continue to be part of the complex and challenging art of regulatory science.

In their Work Package IV on benefit-risk tools and processes, the European Medicine Agency articulates two steps related to uncertainty in benefit-risk assessments. The first is to transparently report the uncertainties associated with both the favourable and unfavourable effects of a product. The objective of such reporting is to describe the basis for and the extent of uncertainty in addition to the statistical probabilities. For example, uncertainties may be related to possible biases in the data, the soundness and representativeness of the clinical trials and the potential for unobserved adverse effects. The second step that the EMA describes is to consider how the balance between favourable and unfavourable effects is affected by uncertainty; for example, the extent to which a benefit will be reduced by considering all sources of uncertainty.[1]

Section 3.3 of the FDA draft Structured Approach to Benefit-Risk Assessment from 2013 directly addresses the characterisation of uncertainties in benefits and risks. Noting that, in many cases, the FDA must draw conclusions based on imperfect data, it emphasises the importance of identifying and evaluating those sources of uncertainty. Also, as with the EMA document, the FDA summary stresses the importance of being explicit regarding the impact of uncertainty, both in decision making and in the communication of those decisions.[2]

Types of uncertainty

One type of uncertainty is related to the strength of the evidence in the premarket clinical trial that may be affected by the absence of information, by conflicting findings and by marginal results. Clinical trials are probabilistic experiments. They are also designed to demonstrate a benefit relative to a comparator, such as a placebo or another medicine and by design large groups of patients are routinely excluded in order to improve the ability to either detect the benefit or to limit a safety concern.

A second type of uncertainty relates to what we will learn about a product in the post-market environment. How to evaluate and weight data from a variety of sources derived from a more naturalistic setting and how to reconcile these data with their inherent limitations with the findings from clinical trials and the unknowns at the time a product was approved for wider use remains a challenge.

Sources of uncertainty

There are a number of potential sources of uncertainty that can affect the strength of the evidence including those related to endpoint selection, missing data, patient selection bias and effect differences, potential biases in the data, conflicting findings and marginal results. The sample sizes of clinical trials used to identify benefits and risks in general are insufficiently powered to identify less common or rare adverse effects.

The translation of clinical trial results to a real-world setting may create an uncertainty when the clinical trial population does not adequately represent the actual population in which the therapy will be used particularly when patient subgroups have been excluded or not adequately considered during the conduct of the trial. Furthermore, the limited duration of clinical trials means that the long-term effects of

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a chronic-use therapy remain unknown at the time of approval. In addition, the differential impact of careful, regular follow-up, extensive monitoring and risk reduction activities during the conduct of a clinical trial likewise creates an uncertainty when it comes to both the risks and benefits that patients may experience when the product is used outside the controlled clinical trial environment.

Addressing uncertainty

The clear description of the nature and the basis of all potential important uncertainties is vitally important for sponsors who develop and test products, to government agencies who regulate the conduct of clinical trials and the approval of medicines, to physicians who have to make clinical decisions and to patients who ultimately must trust that the risks of using a product will be substantially outweighed by the benefits they will receive from therapy. All of these stakeholders must consider how the balance between benefits and risks might shift when taking account of these uncertainties. This accounting is more difficult for risks than it is for benefits – the latter being supported by robust clinical trial design and statistical analyses. Risk information on the other hand may be limited or absent rendering models and sensitivity analyses that can assess the potential degree of variability of the magnitude of these risks less robust.

There are a number of semi-quantitative and quantitative methods and statistical tools that have been applied to describe uncertainty and have the potential to bring greater mathematical rigour to decision making and better visualisation of the complex interplay of various factors. Methods include: sensitivity analyses, meta-analyses and Bayesian statistics. Decision trees can be used when uncertainty is the main issue and multi-criteria decision analysis used when there is a need to compare conflicting criteria. Other approaches that could be useful for particular cases include probabilistic simulation, Markov processes and Kaplan-Meier estimators, quality-adjusted life years and conjoint analysis.[3]

Understanding the role of uncertainty in weighting benefits and risks is inherently difficult as each stakeholder brings their own perspective to this understanding. Sponsors worry about the impact of uncertainty on product development. Regulators consider uncertainty and until recently have lacked the tools to articulate how it affected regulatory decision making. Physicians understand uncertainty in the variability of treatment effects recognising that each patient is different. Patients reflecting the heterogeneity of the general population vary in sophistication of their understanding uncertainty.

There are a number of ways to improve understanding of and conversation around uncertainty such as a discussion of uncertainty openly in sponsor-regulator interactions, an increase in regulatory guidance and training on how to evaluate and describe uncertainty and building education on uncertainty into FDA public meetings and communications.

Conclusions

The assessment of the benefit-risk balance of new medicines is inherently challenging and uncertainty regarding benefits and risks adds complexity to the assessment. Sponsors and regulators must clearly define where uncertainty exists and discuss the impact of uncertainty on the benefit-risk assessment. Semi-quantitative and quantitative methodologies may be useful in assessing the impact of uncertainty on the assessment but the methodologies for and assessment of uncertainty in benefit-risk decision making are still evolving.

References

1. European Medicines Agency. *Benefit-risk methodology project Work package 4 report: Benefit-risk tools and processes.* May 9, 2012 Available at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/03/WC500123819.pdf Accessed February2014.
2. US Food and Drug Administration. *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making. Draft PDUFA V Implementation Plan - February 2013* Available at http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf. Accessed February 2014.
3. European Medicines Agency. *Benefit-risk methodology project Work package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment.* August 31, 2010. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/10/news_detail_001129.jsp&mid=WC0b01ac058004d5c1# . Accessed February 2014.

Benefit-risk evaluation in the post-marketing setting

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Integrating data from multiple sources

The goals of drug safety surveillance are to identify and learn more about previously unknown drug-related adverse events and more about how drugs are used in ways that may not promote safe use. This derives from the belief that the safety of medicines is related not only to their intrinsic pharmacologic properties and also to how a very complex healthcare system uses or misuses those medicines. The appropriate method of surveillance depends on the goal and regardless of the method, findings about drug safety must always be communicated to all healthcare stakeholders.

The FDA has relied on passive surveillance since 1969, maintaining that good clinical observation made at the point of care about a suspected adverse drug reaction can inform post-market safety. However, case reports as a whole often lack important clinical details and it is a system that must involve stakeholder participation to work effectively: That is, the system depends on the careful observations of healthcare professionals and patients must be encouraged to accurately report their experiences. In addition, automation has become a critical need for passive surveillance, as the number of reports continues to increase to over 900,000 in 2012. There have been some efforts in the mining of data both in Europe and the United States including the work of IMI PROTECT and the automatic detection of potential adverse events from electronic medical records is being explored.

Clinical trials to best characterise drug safety are designed for the post-approval period and under some circumstances are developed for pre-market testing as well. The challenges to this method include proper endpoint and relevant patient population development as the patients at higher risk for adverse events may not be those tested in efficacy studies. Likewise, placebos, which may be relevant as comparators in tests for efficacy may not be valid choices in trials to determine safety and the clinically relevant size for safety trials may be too large to be feasible. Finally, the ethical issues surrounding these trials were investigated by the Institutes of Medicine, which encouraged the FDA to adopt a standardised yet flexible framework for decision making that would ensure consistency and transparency while allowing the agency to better predict post-approval research needs.[1]

Although the number of observational studies continues to grow, safety trials need to be based on relevant, appropriate data sources. Sources such as insurance-based payment databases, although large, are often missing important indicators for a wide range of health outcomes. In addition, because medicines are not assigned randomly in real-world situations, robust methods such as high dimensional propensity scoring, marginal structural models or instrumental variables are required to adjust for confounding and because any result can be significant if a database is large enough, the clinical relevance of the results require careful interpretation. In fact, observational trials are not a common source of new safety issues. An FDA study of safety-related label changes in 2010 showed that the source for over half of these changes was spontaneous reports. Clinical trials were responsible for less than 20% and very few safety changes resulted from observational studies.

Understanding real-world safety

Examining six recent drug safety issues evaluated by the FDA shows that most have effect measures in the 1.0 to 2.0 range. Although

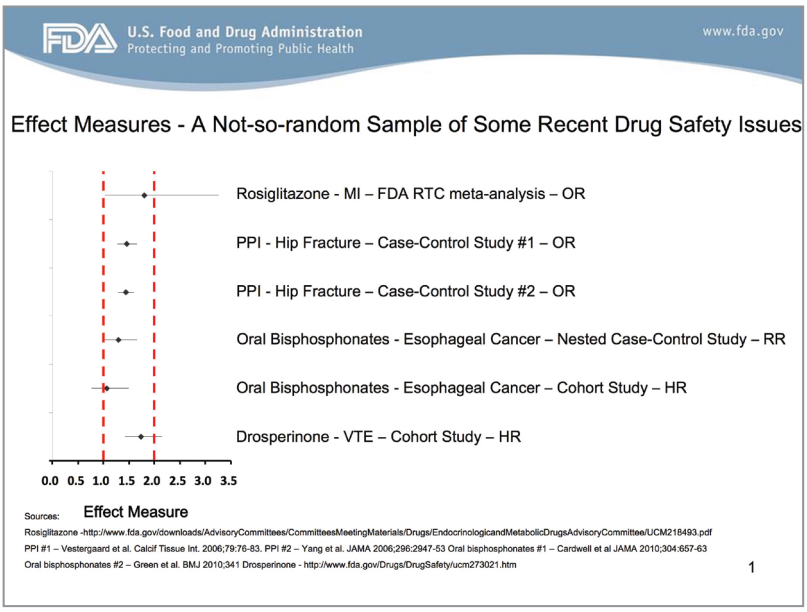

Figure 19. Effect measurement of safety risks for some drugs recently examined by the FDA.

these rates may not be considered to be robust because they could be influenced by uncontrolled confounding parameters, the importance of the risks is actually considerable if considered on an absolute scale (Figure 19).

A method to balance benefit-risk

Although the FDA has always evaluated and balanced the benefits and risks of new drugs, in 2009 the agency initiated a more systematic approach through use of a structured framework. In 2012 the FDA developed a five-year plan for the fifth iteration of the Prescription Drug User Fee Act (PDUFA V) describing the approach to further develop and implement a structured benefit-risk framework in its human drug and biologic review process. A draft of the framework was published 8 March 2013 and a pilot of the framework's use in drug evaluation was started in 2012. The model is currently being further developed with the goal of implementation from 2014 through 2017. As described at this Workshop by Patrick Frey (page 29) the framework is structured with five decision factors, the analysis of condition, the treatment options, the benefits, the risks and risk management. There are the two levels of consideration, evidence and uncertainty and conclusions and reasons and a summary assessment is produced as a result of the assessment.

Understanding the impact of risk management

The Periodic Benefit-Risk Evaluation Report (PBRER) was designed to replace the periodic safety update report (PSUR). The PBRER is a comprehensive analysis of new or emerging information on the risks associated with the use of a product, the benefits of the product in approved indications and its overall benefit-risk profile. The use of PBRERs was approved by the ICH Steering Committee in November 2012 and the corresponding final FDA guidance will be issued in the near future. In the meantime, the FDA has developed procedures to allow applicants to submit the PBRER instead of the PSUR. As regulatory agencies around the world adopt the use of PBRERs they are also adopting a periodic look at benefit-risk.

A risk evaluation mitigation strategy (REMS) is a required risk management plan that uses risk minimisation strategies beyond professional labelling. The FDA can require a REMS before approval if the FDA determines a REMS is necessary to ensure the benefits of the drug outweigh the risks and post-approval if the FDA becomes aware of new safety information and determines that a REMS is necessary to ensure the benefits of the drug outweigh the risks. A REMS can include a Medication Guide, a Communication Plan for Healthcare Providers, Elements to Assure Safe Use (ETASU) and an Implementation System. It must, however, include a timetable for submission of assessments of the REMS.

. . . [the Institutes of Medicine] encouraged the FDA to adopt a standardised yet flexible framework for decision making that would ensure consistency and transparency while allowing the agency to better predict post-approval research needs.

The reauthorisation of PDUFA entailed additional FDA responsibilities with respect to REMS. By the end of 2013 the FDA was required to develop and issue guidance on criteria for requiring a REMS, to hold one or more public meetings to obtain stakeholder input on standardising REMS to reduce the burden on the healthcare system and to initiate one or more public workshops on methodologies for assessing REMS. By the first quarter of 2014, the FDA is required to issue a report of its findings (related to standardisation) and identify at least one priority project in each of the following areas including a work plan for project completion: pharmacy systems, prescriber education, providing benefit-risk information to patients and practice settings. By the end of 2014 the FDA is required to issue guidance on methodologies for assessing REMS.

A REMS Integration Steering Committee (RISC) will oversee three work groups charged with developing policies, tools, techniques and systems needed to standardise REMS to reduce the burden of REMS on the healthcare system and better ways of assessing the impact of REMS on patient care and access to therapies while using informatics tools to more seamlessly integrate REMS into the healthcare system. The REMS Policy Workgroup will develop criteria for determining when a REMS should be required. The REMS Design and Standardization Workgroup will develop and implement an analytically rigorous approach to design of a REMS. The REMS Evaluation Workgroup will develop and recommend a consistent and evidence-based approach for assessing the effectiveness of REMS programs and the burden

on healthcare delivery systems. Moving forward, stakeholders will have the opportunity to contribute to the development of strategies for standardising REMS and integrating them into the healthcare system.

There are multiple issues inherent in evaluating benefit and risk in the post-marketing setting. Integrating data from multiple sources can present challenges when the sources of that data measure different things with varying degrees of rigour. In addition, access to large data sources held by the private sector or by independent academic groups can be limited. Understanding real-world effectiveness can be difficult when balancing emerging real-world safety issues with efficacy data obtained from clinical trials. Finally, methods to balance benefit and risk must include an understanding of the impact of risk management.

Reference

1. Institutes of Medicine. *Ethical and Scientific Issues in Studying the Safety of Approved Drugs.* May 2012. Available at http://www.iom.edu/Reports/2012/Ethical-and-Scientific-Issues-in-Studying-the-Safety-of-Approved-Drugs.aspx. Accessed February 2014.

New pharmacovigilance guidelines: Impact on benefit-risk assessment

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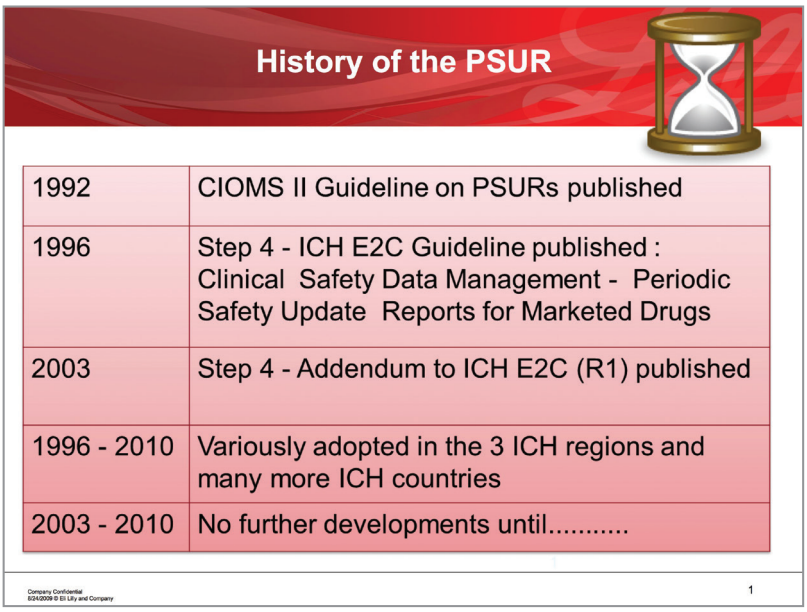
PSUR to PBRER

The evolution of the Periodic Safety Update Report (PSUR) to the PSUR in the format of the Periodic Benefit-Risk Evaluation Report or PBRER should be regarded by stakeholders as an opportunity to refresh and reinvigorate the PSUR, which had not changed its original format since 1992 (Figure 20).

The confluence of change brought about by the EU Pharmacovigilance legislation in 2010 motivated the International Conference on the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) to address the update of the PSUR via this PBRER format. The impetus behind the change to the PSUR was a desire on the part of regulators to have a greater emphasis on analysis, particularly a scientific evaluation of the benefit-risk profiles of medicine, as well as more critical summaries or relevant scientific and clinical information using all available benefit-risk information.

Figure 20. The PSUR retained its original format since its beginning in 1992.



The objectives of PBRERs are to present a comprehensive and critical analysis of new or emerging information on the risks and, where pertinent, new evidence of benefits to enable an appraisal of the overall benefit-risk of a medicine; to contain an evaluation of new, relevant information that becomes available to the sponsor during the reporting interval, specifically, to examine whether new information is in accord with previous knowledge of the benefit-risk profile; to summarise relevant new safety information that may impact the benefit-risk profile and important new efficacy and effectiveness information and to conduct an integrated benefit-risk evaluation when new important safety information has emerged.

Important PBRER sections

The PBRER format (Figure 21) has been enhanced with the addition of new sections. The *Overview on signals: new, ongoing or closed* provides an overview of signals detected, under review and evaluated in the reporting period and references the tabulation of new, ongoing and closed signals. *The Signal and risk evaluation* section contains a summary of safety concerns, signal evaluation, the evaluation of risks and new information, the characterisation of risks and the effectiveness of risk minimisation (if applicable).

The *Benefits evaluation* section represents the seminal change in the thinking behind the evolution of the PSUR, with its focus on safety risks, to the PBRER wherein the emerging benefits of new medicines become an additional focus. This section contains important baseline efficacy and effectiveness information and summarises new information from the beginning of the reporting period, characterised separately by indication, population or route. If significant changes in either risks or benefits have occurred, this summary should provide sufficient information to support their characterisation. This section also lists the epidemiology and natural history of the treated disease, the nature of the benefits of the medicine, the important endpoints and evidence that support the benefits and efficacy or effectiveness as well as trends, patterns and evidence of benefit in important subgroups. In this section, newly identified information on efficacy and effectiveness is listed, generally in approved indications only.

The *Integrated benefit-risk analysis* section brings the benefits and risks into holistic context, requiring an analysis for each indication and population, with consideration of medical need and important alternatives. The analysis should include specification of the key benefits and risks driving the evaluation with the clinical importance, frequency, predictability, preventability, reversibility and seriousness of risks and the strengths, weaknesses and uncertainties of the evidence taken into account. Finally, a clear explanation on methodology and reasoning behind the assessment should be provided.

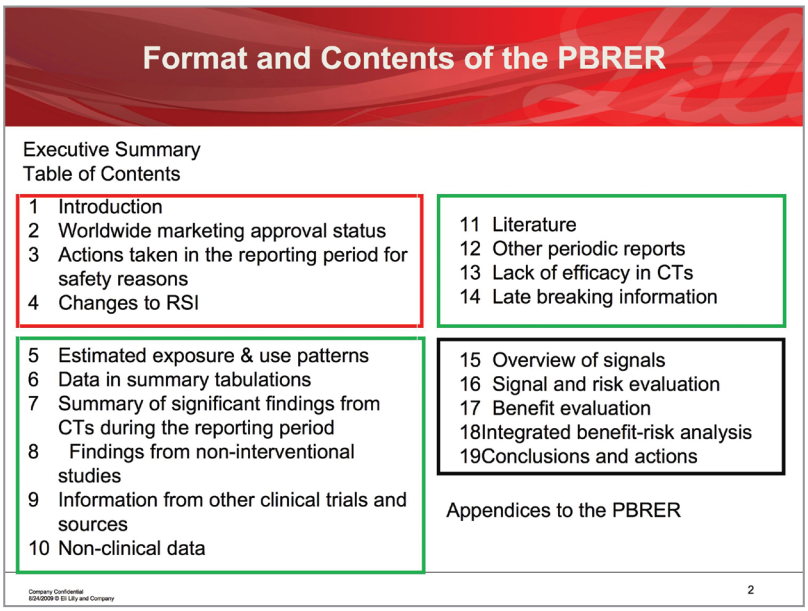


Figure 21. PBRER format, red box = administrative data; green boxes = new information in the reporting interval; black box = evaluative data.

PBRERs can help to serve as a platform and as an impetus and leverage to develop and use a more structured approach to benefit-risk earlier in the product life cycle and in submissions.

Impact of PBRERs

The advent of the PBRER should strengthen the practice of pharmacovigilance and advance the consideration of benefit-risk. The explicit discussion of benefit and risk and a focus on risk in the context of benefit encourages a more thoughtful, critical and integrated analysis. In addition, higher quality PSUR content discourages the data dump, no longer focusing on line listings and case narratives

From a company perspective, based on some informal networking and discussions, some concerns have been expressed surrounding each company's interpretation and the application of the guidance, around the development of new implementation and new process tools and staffing and around the education and guidance of the teams responsible for developing their respective PBRERs, considered to be a more complicated report to prepare, with a steep learning curve for some.

However, because PBRERs are seen as a very effective tool to help focus the spotlight on the need for an integrative, evaluative approach to benefit-risk assessment. PBRERs can help to serve as a platform and as an impetus and leverage to develop and use a more structured approach to benefit-risk earlier in the product life cycle and in submissions.

Dr Noel concluded by providing an example of the significant role assumed by PBRERs as reported in the meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 8-11 April 2013, in which it was noted that for the first time, a periodic safety update report assessment for Protelos / Osseor (strontium ranelate) lead to a recommendation to restrict use of a medicine.[1]

Reference

1. Pharmacovigilance Risk Assessment Committee. *Pharmacovigilance Risk Assessment Committee (PRAC) Report* 8-11 April 2013. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/04/news_detail_001759.jsp&mid=WC0b01ac058004d5c1 Accessed February 2014.

Making better use of clinical trials –

Development of Aggregated Data Drug Information System (ADDIS) for aiding the benefit-risk assessment of new medicines

Prof Hans Hillege

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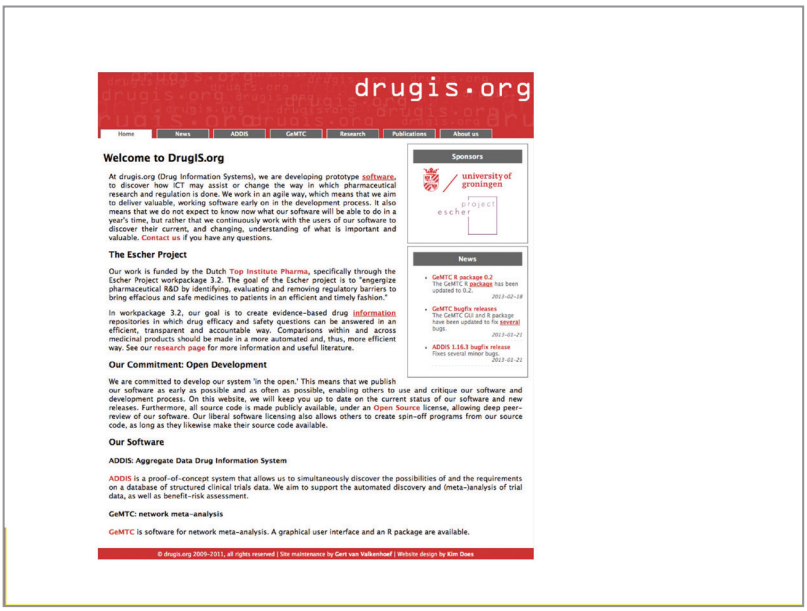
In 1998, the International Society of Drug Bulletins (ISDB) recommended that the European Medicines Agency (EMA) develop a clear policy that ensured consistency from one European Public Assessment Report (EPAR) to the next, as there was at that time a lack of a clear and consistent policy on the reporting of clinical trial data.[1] For example, in the case of the angiotensin II inhibitor irbesartan, details about the optimal dose were missing, only two of the three trials were described in detail, the risk-benefit ratio of irbesartan was not clearly compared with that of enalapril and the adverse effects section of the prescribing information was far more detailed than the efficacy section. These missing details had a direct impact on the clinical assessor who did not have the necessary details to incorporate into an assessment report that could be used to compare the efficacy, safety and appropriate dosages of irbesartan relative to other angiotensin II inhibitors.

Figure 22. ADDIS is free, open source software that can be downloaded at http://drugis.org/addis



Like the EMA, the Dutch Medical Evaluation Board agreed that clinical assessments should be performed using a systematic review format and a proposal was made to create a systematically organised warehouse of drug information. This was envisioned as a web-based drug knowledge network system on an XML platform, containing information at the level of detail required for publication in scientific medical journals, with a relational database system and tabulated and graphical output. Although the initial concept was rejected by clinical assessors, it was revived in 2008 through the Escher project.

In 2008, the Dutch non-profit Top Institute Pharma funded the development of the Escher Project, which is defined on its website as a public-private partnership that studies medicine development and the European regulatory system for medicines. By combining expertise from various disciplines and backgrounds, The Escher Project has provided solid scientific evidence and supported a results-oriented dialogue on reform. By contributing to resolving bottlenecks in the system The Escher Project aims to stimulate innovative medicine development and regulation and bring safe and effective medicines to patients faster. [2]

Results of the Escher Project can be classified into four areas: 1) Evidence generation methods and evidence requirements, 2) Scientific dialogue and stakeholder interaction; 3) The decision-making process and benefit-risk assessment and 4) Health Technology Assessment and evaluating societal impact.

Developed as part of The decision-making process and benefit-risk assessment area, the Aggregated Data Drug Information System (ADDIS) is a software system that bridges the gap between aggregated clinical data and evidence-based drug regulation using state-of-the-art methods for benefit-risk decision making. This software can be deployed not only in the regulatory domain but also in the decision-making domain of stakeholders such as HTA agencies, hospital and community pharmacists, medical specialists, general practitioners and patients.

In developing the prototype for ADDIS it was determined through interviews with major stakeholders of different domains that ADDIS should be an intuitive and user-friendly repository of clinical trials based on aggregated data. It should answer on-demand questions in

an efficient, transparent and accountable way within and across compounds, streamlining benefit-risk decision making. It was intended for use at first for regulatory authorities and for others at a later stage. The key ingredients of ADDIS are a structured database of clinical trials data, containing on-the-fly statistics, evidence synthesis enabling benefit-risk decision modelling. ADDIS is free, open source software that it is hoped others will build on and learn from. It can be downloaded at http://drugis.org/addis (Figure 22).

Professor Hillege demonstrated the use of the ADDIS software, modelling a regulatory dossier, using the Hansen network meta-analyses of anti-depressant therapies[1] and the Edarbi (azilsartan) EPAR as examples. A view of the entire process including the clinical trial repository, evidence synthesis, decision aiding and decision modelling and data acquisition was provided. There are some challenges to the use of ADDIS.

Not everything can be imported automatically. Categorical variables and multiple measurement moments cannot be handled directly because of shortcomings of sources such as ClinicalTrials.gov. That is, not all studies are available at the web site, adverse events data are incomplete and manufacturers are allowed to set a "reporting threshold percentage" for non-serious adverse events. As a result, some events of interest for azilsartan are not reported.

However, the ADDIS system demonstrated that an on-demand application answering different efficacy/safety questions in an efficient, transparent and accountable way within and across different drugs is feasible. It showed that a more consistent standardised data model for aggregated clinical data would enforce harmonisation of benefit-risk assessment and reinforce the EU regulatory network. Although there has been an increasing interest in multi-criteria decision analysis, for benefit-risk analysis of medicines, different models that are both theoretically sound and potentially clinically useful have proven to be far from straightforward and difficult to implement. The ultimate goal will be the development of methodologies and tools for benefit-risk analysis that take into account not only all clinical evidence, benefit-risk trade-offs and thresholds but also the preferences and risk attitude of decision makers.

The first stage of ADDIS was finalised with the completion of the thesis of Dr GHM van Valkenhoef in 2012,[3] and the project is now in its secondary stage. It is envisioned that ADDIS will move forward from a successful desktop proof-of-concept application to a web-based multiuser framework using a CDISC-based aggregated data-model. Extra functionalities and methodologies of the system and the use of real world data for relative effectiveness are expected to be developed within Innovative Medicines (IMI) Get Real application. Additionally, a number of strategic dialogues and collaborations with regulators and HTA organisations are being sought as well as the development of a business model within an open source setting, developing a model that will support the sustainability of the work of ADDIS.

The ultimate goal will be the development of methodologies and tools for benefit-risk analysis that take into account not only all clinical evidence, benefit-risk trade-offs and thresholds but also the preferences and risk attitude of decision makers.

References

1. ISDB. *ISDB Assessment of nine European public assessment* reports published by the European Medicines Evaluation Agency between September 1996 and August 1997. Paris: International Society of Drug Bulletins. June, 1998.
2. Anonymous. *The Escher Project.* Available at http://escher-projects.org/home/ Accessed February 2014.
3. Valkenhoef GHM. *Making better use of clinical trials: Computational decision support methods for evidence-based drug benefit-risk assessment.* Thesis, University of Groningen, 2012. Available at http://dissertations.ub.rug.nl/faculties/medicine/2012/g.h.m.van.valkenhoef/?pLanguage=en&pFullItemRecord=ON. Accessed February 2014.
4. Hansen RA. Efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder. *Ann Intern Med.* 2005;143:415-426.

The Benefit-Risk Taskforce: What has been achieved and what action is required for the next 12 months?

Professor Stuart Walker

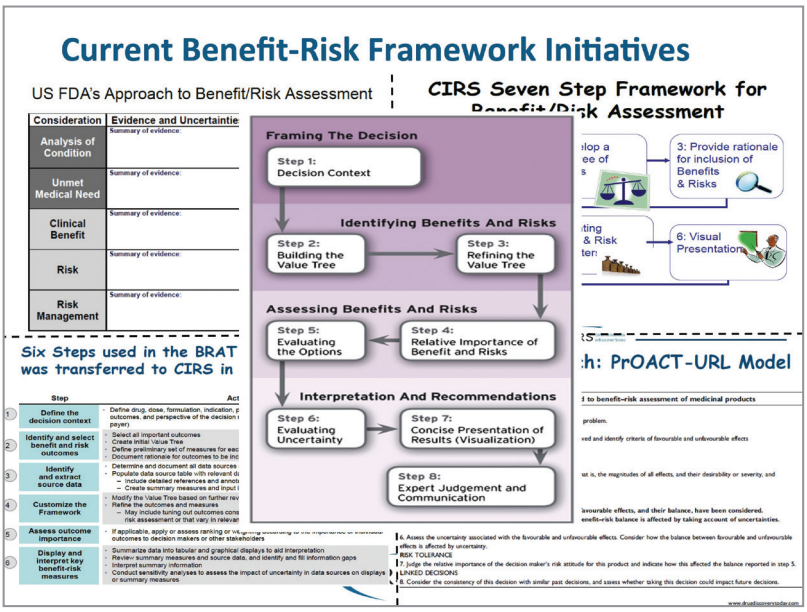
Founder, CIRS

The results of a 2012 CIRS survey contained a recommendation for the coordination of the various activities being carried out around the world with regard to benefit-risk assessment. Accordingly, CIRS invited representatives from a number of regulatory authorities, pharmaceutical companies, academic institutions and patient organisations who were operating in the field of benefit-risk assessment to form the Benefit-Risk Taskforce.

The objectives of the Taskforce are to facilitate knowledge exchange in the area of the benefit-risk assessment of medicines, to facilitate the exchange of information, reports and published papers to relevant parties to ensure the effective knowledge sharing and the exchange of learnings from these various initiatives and to make recommendations on proposals for workshops, surveys or research that should be undertaken to develop the appropriate toolbox for benefit-risk assessment.

One of the first tasks of the Taskforce was to look at the various benefit-risk frameworks, including the five-step framework from FDA, the six-step from the Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team (PhRMA BRAT), the seven-step from CIRS and the eight-step from EMA (Figure 23) and to show that these frameworks could be mapped into the overarching Eight-Step (Universal Methodology for Benefit-Risk Assessment (UMBRA) framework, which had been published in Pink Sheet.[1]

Figure 23. Various benefit-risk initiatives can be mapped to the UMBRA Eight-Step Framework.



The Taskforce subsequently decided that a user guide for the UMBRA framework and a lexicon should be developed, both of which are currently in progress. Other recommendations included the establishment of a database of case studies for benefit-risk assessments and the organisation of a Workshop on The Patient's voice in clinical development (this Workshop took place in Surrey, UK on 12-14 March 2013).

It was additionally recommended that applications of use of benefit-risk framework across life cycle of medicines should be examined, that different methods for communicating benefit-risk to stakeholders be evaluated (such as those evaluated by IMI PROTECT as discussed by Professor Ashby; p 35) and finally, that patients should be surveyed about methods of benefit-risk communication. This particular topic will be a focus in the spring of 2014, when CIRS will convene its third Workshop with a focus on patients and benefit-risk in Surrey, UK, *The Assessment of benefits and harms and their relative importance by patients, industry and agencies: How should they be captured?* This Workshop will of course, be followed by the annual CIRS Benefit-Risk Workshop in June, *Benefit-risk assessment in the post-approval period: How to ensure a life-cycle approach to evaluating the benefits and harms of medicines.*

Professor Walker concluded by advising participants that a meeting of the Taskforce was scheduled to take place after the Workshop that would provide the opportunity for the various stakeholders to bring their fellow Taskforce members up to date with the current status and the forward plans for their various programmes including completed or planned publications. He encouraged Workshop participants to also share any relevant publications that could be circulated to those interested in the topic of benefit-risk (swalker@cirsci.org).

Reference

1. Dombrowski C. International group finds harmony in benefit-risk assessment framework. *Pink Sheet*. 2012: August 27. Available at http://www.pharmamedtechbi.com/publications/the-pink-sheet/74/35/international-group-finds-harmony-in-benefitrisk-assessment-framework Accessed February 2014.

Appendix: Workshop Attendees

Regulatory agencies		
Mohammed Alkudsi	Executive Director, National Drug and Poison Information Centre	Saudi Food and Drug Authority, Saudi Arabia
Prof Sir Alasdair Breckenridge	Former Chairman	Medicines and Healthcare Products Regulatory Agency, UK
Dr Zhen Chen	Deputy Office Director	Center for Drug Evaluation, Chinese Food and Drug Administration, China
Dr Gerald Dal Pan	Director, Office of Surveillance and Epidemiology	Food and Drug Administration, USA
Dr Petra Doerr	Head of Management Services and Networking	Swissmedic
Dr Yi FENG	Associate Director	Center for Drug Evaluation, Chinese Food and Drug Administration, China
Patrick Frey	Director, Office of Program and Strategic Analysis, Center for Drug Evaluation and Research	Food and Drug Administration, USA
Dr John Jenkins	Director, Office of New Drugs, Center for Drug Evaluation and Research	Food and Drug Administration, USA
James Leong	Senior Regulatory Specialist	Health Sciences Authority, Singapore
Dr Theresa Mullin	Director, Office of Strategic Programs	Food and Drug Administration, USA
Dr Francesco Pignatti	Head of Section, Oncology. Haematology & Diagnostics	European Medicines Agency
Jalene Poh	Director (Ag), Therapeutic Products Branch	Health Sciences Authority, Singapore
Barbara Sabourin	Director General, Therapeutic Products Directorate	Health Canada
Dr Sinan Sarac	Senior Medical Officer	Danish Health and Medicines Authority
Dr Robert Temple	Deputy Center Director for Clinical Science, Center for Drug Evaluation and Research	Food and Drug Administration, USA
Dr Mark Walderhaug	Associate Office Director for Risk Assessment, Office of Biostatistics and Epidemiology, CBER	Food and Drug Administration, USA
Pharmaceutical companies and associations		
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Dr Jay Backstrom	Senior Vice President, Regulatory Affairs and Pharmacovigilance	Celgene Corporation, USA
Conny Berlin	Global Head Quantitative Safety Function	Novartis Pharma AG, Switzerland
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Dr Consuelo Blosch	Executive Medical Director – Global Safety	Amgen, USA
Laura Bloss	Executive Director, Global Regulatory Affairs & Safety & Bone TAH	Amgen, USA
Anne Dilley	Director, Epidemiology	Biogen Idec, USA
Dr David Guez	R&D Special Projects Director	I.R.I Servier, France
Dr Edmund Harrigan	Senior Vice President, Worldwide Safety and Regulatory	Pfizer, USA
Deborah Henderson	Head, Global Regulatory Policy	Merck & Co Inc, USA

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Shawn Hoskin	Director, Regulatory Affairs	Novo Nordisk, USA
Dr Diana Hughes	Vice President, Worldwide Safety and Regulatory	Pfizer, USA
Dr David Jefferys	Senior Vice President	Eisai Europe, UK
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Dr Eva Katz	Manager, Epidemiology	Johnson & Johnson, USA
Dr Elias Kouchakji	Executive Director, Therapeutic Area Head, Cardio-Renal, Global Safety	Amgen, USA
Dr Bennett Levitan	Director, Quantitative Safety Research, Department of Epidemiology	Janssen Research Foundation, USA
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Dr Marilyn Metcalf	Senior Director, Benefit Risk Evaluation,	GlaxoSmithKline, USA
Dr Steven Miller	Vice President, Cardiovascular & Metabolism, Global Regulatory Affairs	Janssen Research & Development, USA
Dr Leo Plouffe	Vice President and Head of Risk Management Global Pharmacovigilance	Bayer HealthCare, USA
Ronald Robison	Vice President, Regulatory Affairs, Patient Services and R&D QA	AbbVie Inc, USA
Dr Paul Seligman	Executive Director, US Regulatory Policy	Amgen, USA
Dr James Shannon	Chief Medical Officer	GlaxoSmithKline, UK
Priya Singhal	Vice President, Clinical Trial Safety	Biogen Idec, USA
Dr Meredith Smith	Senior Scientific Director, Risk Management	AbbVie Inc, USA
Jennifer Stevens	U.S. Head, Global Regulatory & Scientific Policy	EMD Serono Inc, USA
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Prof Dr Hans Hillege	Professor in Cardiology, Management Board, Department of Epidemiology	University Medical Center Groningen, The Netherlands
Prof Sam Salek	Director, Centre for Socioeconomic Research	Cardiff University, UK
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