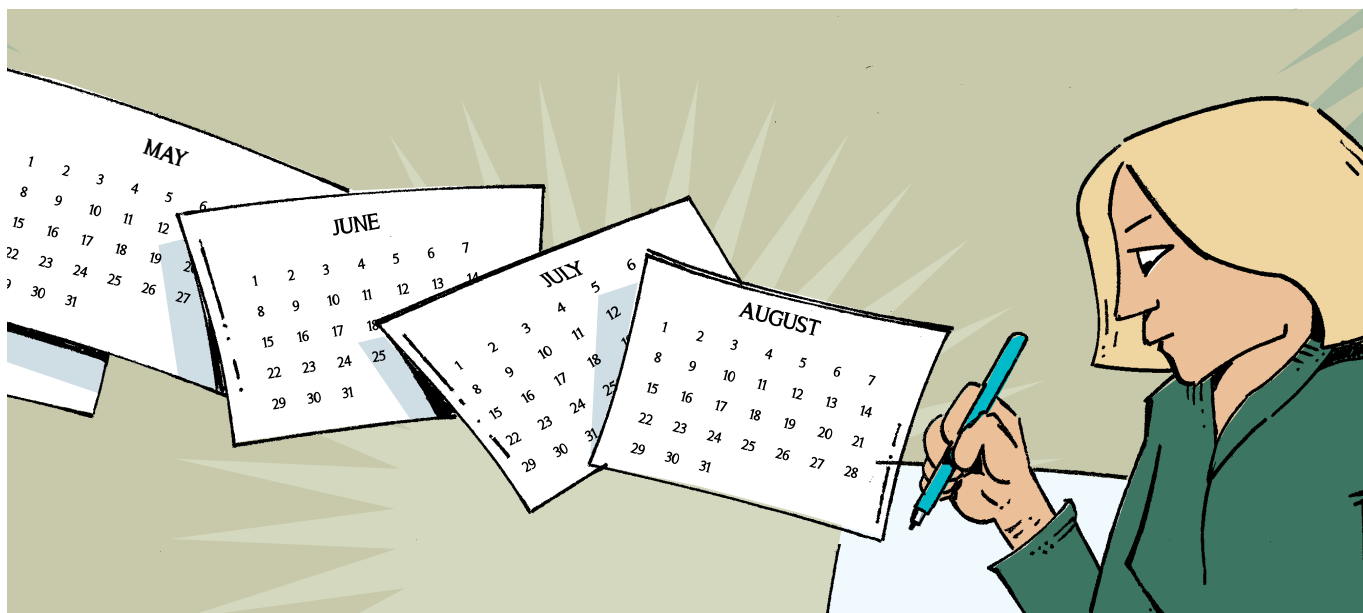




BENEFIT-RISK ASSESSMENT IN THE POST-APPROVAL PERIOD: HOW TO ENSURE A LIFE CYCLE APPROACH TO EVALUATING BENEFITS AND RISKS

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WORKSHOP REPORT

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BENEFIT-RISK ASSESSMENT IN THE POST-APPROVAL PERIOD

Section 1: Executive Summary

Background

One of the criteria for the development of a framework to assess benefits and risks is that it provides the same standardised, structured, systematic approach to the assessment of the benefits and risks throughout the entire life cycle of medicines development. This will lead to not only enhanced documentation and communication of the changing benefit-risk profile of medicines but also to the identification or evolution of appropriate methodologies to measure benefits in the post-approval period.

To date, this has stimulated the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Four Agency Consortium (Swissmedic, Health Canada, Australian Therapeutic Goods Administration [TGA] and the Health Sciences Authority [HSA] in Singapore) as well as companies to evaluate and produce several assessment approaches. An evaluation of these initiatives demonstrates that although each agency may come from a different perspective, a consistency has been achieved in the requirements that describe a benefit-risk assessment. This has led to the creation of the overarching Universal Methodology for Benefit Risk Assessment (UMBRA) framework.

The importance of the post-approval period in providing a better understanding both of the benefits and harms of medicines has been reflected in the recent ICH E2 guideline, which now requires companies to provide a structured benefit-risk evaluation within the Periodic Benefit-Risk Evaluation Reports (PBRERs) and Public Safety Update (PSURS).

The discussion at this Workshop centred on how utilising an overarching framework that covers pre-, peri- and post-approval periods of a product's lifespan can enable an improved understanding of the changing benefit-risk profile as knowledge increases about a new medicine. The challenges, hopes and expectations of structured approaches to evaluating the evidence in balancing benefit-risk in the post-approval period were also explored along with evaluating methodologies that would

be feasible for companies and acceptable to agencies to provide information on the benefits of a new medicine in the post-approval period.

This Workshop also provided an update on the various regulatory methodologies to assess benefits and harms with a focus specifically on both company and agency experience in using a structured approach and how this can translate to the post-approval phase.

Workshop Objectives

- **Discuss how** a universal framework aligns to the structured benefit-risk assessment of medicines across the pre-, peri- and post-approval periods
- **Identify** appropriate methodologies for producing Periodic Benefit Risk Evaluation Reports (PBRERs) as well as the challenges and solutions
- **Recommend** how best to assess benefits in the post-approval period.

Key points from presentations

Use of a structured, qualitative approach best accomplishes the two-fold objectives for the FDA benefit-risk framework: better external communication of the rationale underpinning the Center for Drug Evaluation and Research decisions and internal assurance that the "big picture" for a new medicine is considered throughout complex, detailed reviews. This structured approach best fits the drug-regulatory needs, reflecting the fact that benefit-risk assessment as a qualitative exercise can be supported by extensive analysis of evidence on benefits and risks. **Dr Theresa Mullin**, Director, Office of Strategic Programs, CDER, Food and Drug Administration, USA added that a structured approach to benefit-risk assessment initiated in the pre-approval period can provide useful context and continuity for the evaluation of additional information after approval. By updating and annotating the pre-approval assessment documents with the new information, considerations and conclusions, the new assessment supports internal decision making and knowledge management and

external communication of the reasoning behind regulatory decisions in the post-approval period.

A benefit-risk framework developed during research and development may be able to be used later in a product life cycle but the methods for measurement are likely to be different.

Dr Paul D. Huckle, *Chief Regulatory Officer, GlaxoSmithKline, USA* pointed out that more mature products tend to generate emerging safety signals while not providing long-term efficacy outcome data and need to rely heavily on a variety of data sources to answer benefit-risk questions. The move from clinical trial data to data from observational studies, pragmatic trials, spontaneous reports, social listening, health records and device applications all highlight the need for a variety of analytic methods. The future environment is likely to offer even more options for data collection, pointing to an ongoing need for a consistent approach with agreed standards of data quality and analytical rigor, rather than a single named framework or method. The bigger challenge will be developing a shared understanding that includes the concept of treatment for a patient rather than a medicine for one disease, which will entail consideration of patients' disease stages and their practical management of daily living activities.

The US Food and Drug Administration (FDA) is currently implementing its benefit-risk framework as part of the review process for new medicines. This implementation is required according to the agency's commitment to the fifth iteration of the Prescription Drugs User Fee Act (PDUFA V) and in accordance with statutory requirements. **Patrick Frey**, *Director, Office of Program and Strategic Analysis, CDER, US Food and Drug Administration* reported that the FDA convened a working group to address the integration of its benefit-risk framework into the clinical review template, to revise other aspects of the template to address reviewer and Office of New Drug Management needs and to identify training needs. Once the benefit-risk framework and clinical review template revisions are implemented, future FDA plans include developing a systematic approach to evaluating and dealing with uncertainty in a drug review.

Dr Kimberly Witzman, *Medical Officer, Division of Pulmonary, Allergy and Rheumatology Products, Office of New Drugs, US Food and Drug Administration* discussed the recent use of the US FDA benefit-risk framework in a review of

ivacaftor (Kalydeco; Vertex Pharmaceuticals), a transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients 6 years and older who have a G551D mutation in the CFTR gene. Use of the benefit-risk framework allowed completion of the review in less than 3 months, as it provided a structure for organising information and thinking, allowing a clear presentation of the benefit-risk assessment of the drug. By organising the benefit-risk information effectively, the framework enhanced collaboration with cross-disciplinary team members, division directors and higher-level reviewers within the FDA. Use of a common language allows the framework to accommodate stylistic differences across review teams, across review divisions and from reviewer to reviewer.

The European Medicines Agency (EMA) piloted the use of the Effects Table, a tool designed as a compact display of the effects and uncertainties that are associated with a medicine under regulatory review. **Dr Francesco Pignatti**, *Head of Section, Oncology, Haematology & Diagnostics, European Medicines Agency* said that the table was revised on the basis of a phase I assessment and the revised table and draft guidance were then assessed in a phase II pilot study in which regulators used the tool to examine 12 initial marketing authorisation applications and provided comments on the table and guidance. Although the phase II pilot study was still in progress at the time of this Workshop, interim results were good, with positive average scores on all assessed factors and implementation of the table was forecast for the near future. The EMA also conducted a workshop in which a patient jury successfully used a multi-criteria decision model to evaluate the benefits and risks of two therapies, demonstrating this as a potential methodology for eliciting patient perspectives in the assessment of new medicines.

Use of the CIRS Universal Methodology for Benefit-Risk Assessment (UMBRA) framework is supported by the UMBRA Benefit-Risk assessment template. Use of the summary portion of the template was proposed as a tool for agencies in countries with developing regulatory agencies who needed to both understand the reference agency benefit-risk decision and also to undertake a structured assessment on the benefit-risk for their own population. Accordingly, agencies in China, Indonesia, Malaysia, Philippines, South Korea

and Taiwan participated in the CIRS International Summary Approach to Benefit-Risk Evaluation (ISABRE) pilot study to evaluate the summary template for feasibility and applicability within agencies in these emerging markets. **Dr Neil McAuslane** reported that all the participating agencies were positive about both the structure and the content of the template but identified some changes that could improve internal documentation and communication. At the time of this Workshop, CIRS planned to carry out another pilot study of the modified Summary Template and to discuss the outcomes of this second study at an upcoming meeting of participating agencies.

As representatives of a maturing regulatory agency, twelve reviewers within the Health Sciences Authority (HSA) of Singapore reviewed the summary version of the CIRS Benefit-Risk Template to assess its appropriateness of documentation and communication of benefit-risk decisions. **Dr James Leong**, *Former Senior Regulatory Specialist, Health Sciences Authority, Singapore and current Head of Education, Center of Regulatory Excellence, Duke-NUS Graduate Medical School* said that using recently completed applications to transfer relevant information into the Summary Template, the review accommodated a wide range of benefit-risk profiles and different reviewers' opinions. Study results showed that the summary template was highly fit for purpose in its ability to document relevant information supporting the regulatory decision and the benefits and risks under consideration but that more training on the understanding and application of relative importance (weighting) was required. Although reviewers expressed some particular reservations regarding its use, it was understood that the Benefit-Risk Summary Template might help reviewers meet increasing demands for transparency and accountability and could also provide for alignment and preparation for evolving regulatory science. The use of the template will continue to be explored among agencies in Indonesia, Malaysia, the Philippines, South Korea, China and Taiwan and elsewhere as a potential tool for internal documentation and the possible exchange of information regarding the basis for regulatory decisions.

In the pre-authorisation phase, Health Canada examines both the benefits and risks of a medicine to grant a licence. In the post-approval timeframe, however, the safety aspect of a medicine is emphasised and the evaluation may become less balanced. **Dr Co**

Pham, *Senior Science Advisor, Marketed Health Products Directorate, Health Canada* observed that the accurate measurement of the real-world effectiveness of an approved medicine requires more benefit data from post-market experience. There also needs to be an increase in collaboration among stakeholders to augment the provision of data to accurately weigh the benefit-risk balance and to enhance review capability. Health Canada is actively working to meet the challenges in pharmacovigilance and benefit-risk evaluation. Proposed legislation would strengthen surveillance, require industry to improve labelling, require post-authorisation studies and enhance the recall of unsafe products. Other initiatives that could strengthen these processes include the combination of effectiveness data from PBRERs and risk management plans, collaborative and proactive surveillance of marketed products, the institution of an accepted formal benefit-harm-uncertainty (BHU) framework within Health Canada and the encouragement of high-quality, open communication among stakeholders.

Several challenges for regulatory acceptance of the benefit-risk evaluation of medicines in the post-approval period have been recognised. The FDA has identified two areas of uncertainty in post-approval benefit-risk assessment that require attention: the translation of pre-market clinical trial data to a much wider, real-world patient population and how to address new findings for approved medicines that emerge from sources with varying levels of rigour. Other regulatory issues include channelling bias, off-label use and understanding the benefit-risk profile when a product is used for multiple indications. Furthermore, product comparators may change after approval, altering the decision context for benefit-risk assessment. **Dr Stephen Knowles**, *Senior Director, Global Patient Safety, Medical and Benefit-Risk Management, Eli Lilly and Company* explained that as industry transforms benefit-risk assessments from the development time frame into the post-approval period, using new methodologies, regulatory feedback on post-approval benefit-risk assessments has entirely centred on risk for established products. The best methods for translating post-approval data into regulatory action remain to be determined as does determining the strength of evidence that would be required to change a potential risk to an identified risk and whether a risk that is refuted by studies conducted after marketing could be removed from labeling.

Dabigatran was approved by the FDA in 2010 for

treatment of non-valvular atrial fibrillation.

Dr Gerald J Dal Pan, *Director, Office of Surveillance and Epidemiology, Food and Drug Administration, USA* reported that when a number of adverse events including intracranial and gastrointestinal haemorrhage were spontaneously reported after approval, a US FDA Mini-Sentinel analysis was conducted to determine the significance of these adverse events. The results suggested no public health signal for dabigatran. However, because of study limitations, the FDA conducted a full pharmacoepidemiologic study using Medicare data from more than 134,000 patients and concluded that dabigatran was associated with a lower risk for stroke but a higher risk for gastrointestinal bleeding than the reference drug warfarin. To move toward the routine analysis of safety signals the FDA expects to use Mini-Sentinel with Prospective Routine Observational Monitoring Program Tools (PROMPT), to allow automated, semi-adjusted analyses with several epidemiologic designs. It is envisioned that these sequential analyses will allow for early detection of unexpected outcomes.

Carmen Bozic, MD, *Senior Vice President, Clinical and Safety Sciences, Biogen Idec Inc, USA* presented a case study that demonstrated the high degree of organisational support at Biogen Idec for the use of a structured benefit-risk assessment. Fampridine was approved for improving walking in patients with multiple sclerosis in the US in 2010 but received an initial negative opinion from the Committee for Medical Products for Human Use (CHMP) because of uncertainty regarding the meaningfulness of the primary outcome (timed 25-foot walk), as well as the risk of seizure. Conditional approval was later granted as a result of an appeal that included a graphical categorisation of benefits and risks based on phase 3 data. The required post-approval clinical trial demonstrated significant improvement across multiple thresholds, with a response rate of 48% compared with 28% for placebo. Additionally, the results of a patient risk-benefit conjoint analysis quantified patients' willingness to accept treatment-related risks of 4.6% for seizure (higher than those had been observed) in exchange for an 8-point improvements in walking ability.

Gefitinib was approved in July 2002 in Japan for the indication of locally advanced or recurrent non-small-cell lung cancer (NSCLC). **Dr Akiko Hori**, *Director, Office of Safety II, Pharmaceutical and Medical Devices Agency, Japan* explained that after a higher-than-expected incidence

of interstitial lung disease in patients receiving gefitinib compared with those receiving conventional chemotherapy was observed, two randomised controlled clinical trials were independently conducted by research groups in Japan that showed that first-line gefitinib in patients with advanced NSCLC who were selected on the basis of EGFR mutations improved progression-free survival, with acceptable toxicity as compared with standard chemotherapy. The gefitinib case is unusual in that in most cases, efficacy data are not obtained while post-approval safety data are accumulating resulting in unbalanced benefit-risk profile. To avoid this imbalance, methodologies must be developed for the assessment, description and visualisation of the benefit-risk balance in the post-approval "real world" setting.

The innovative Medicines Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (IMI PROTECT) Work Package 5 consisted of testing and assessing methodologies for the benefit-risk analysis of medicines and developing tools for the visualisation of those benefits and risks. Reporting on the results, **Professor Deborah Ashby**, *Co-Director of Imperial Clinical Trials Unit and Deputy Head, School of Public Health, Imperial College London, UK* said that the choice of an approach to measure the benefits and risks of a medicine should match the complexity of the problem. In most simple problems, a simple descriptive approach is likely to be sufficient. For more complex problems, a descriptive approach supplemented by quantitative tools can facilitate consideration of trade-offs amongst the benefits and risks, address uncertainty and potentially lead to a more comprehensive assessment. To understand the perspective of a particular stakeholder, elicitation of preference values for weighing benefits and risks may be required.

As a component of its commitments to the fifth iteration of the Prescription Drug User Fee Act (PDUFA V), the US FDA has embarked on a programme of patient-focused drug development (PFDD). **Dr Theresa Mullin** informed Workshop participants that as part of the PFDD programme, the agency will convene at least twenty PFDD meetings through 2017 in order to advance a systematic approach to gathering patient input. There has been a good level of in-person and online participation in the meetings that have been conducted to date and the FDA has found the patient input to be both powerful and insightful. It is envisioned

that this input will be useful to FDA staff who are conducting benefit-risk assessments for products under review as well as to drug sponsors who are developing new medicines. The information obtained from the meetings could also be more broadly valuable in helping to identify specific areas of unmet need in a patient population or outcome measures that could be developed for clinical trials.

Numerous types of insights regarding the benefits and risks of medicines in clinical development emerge as the result of patient preference studies such as the determination of thresholds for maximum acceptable risk among patients, the identification of key differences among stakeholders' willingness to accept risk and the rapid determination of the importance of a medicine's potential outcomes from patients and expert jurors. Despite these advantages, challenges exist such as uncertainty regarding acceptance of the findings by regulators, the need to determine optimal timing for the conduct of the studies, the wide variety of available methods, difficulties in enrolling patients in these types of studies and the need to span the gap between population-based and individual patient decisions. **Dr Bennett Levitan**, *Department of Epidemiology, Janssen Research & Development LLC, Pharmaceutical Companies of Johnson & Johnson, USA*, made several recommendations to meet the challenges of patient preference studies, including public-private partnerships to devise initial guidance on the collection and use of patient perspectives and preferences for regulatory review; regulatory and industry joint consideration of mechanisms for adding preference studies to submissions; the development of a consortium of regulatory, academic, industry and patient advocacy groups for creating methodologies to assess patient perspectives and preferences, optimising the use of current standards already developed by organisations such as ISPOR and PCORI and the use of clinical trial patients to maximise the benefits of existing trial infrastructure and making it possible to analyse all trial data in preference subgroup analyses and relating patients' treatment experiences to preference results.

Dr Durhane Wong-Rieger, *President, Canadian Organisation for Rare Disorders, Canada*

maintained that it should be recognised that a patient population is not a homogeneous group and the greater the variability in the group, the greater the challenge for eliciting a representative patient view. In the post-approval period, patient variation can be even greater and even more challenging to capture and individual patient preferences and actions may wreak havoc with the best scientific methods. It is also important to recognise that most patients are not scientists and may make decisions based on emotional impact and intuition rather than on evidence-based probabilities. This results in the major challenge of determining how to integrate what may be personal, intuitive, quality-of-life oriented, value- and emotion-laden judgements with objective, evidence-based, outcomes-oriented, cost-effective evaluations. Ultimately, the ways in which therapy will affect quality of life may be the most important consideration of benefits and harms to patients.

A recent case study compared the use of the CIRS Benefit-Risk template and existing report formats used by the US FDA, EMA and Australia's Therapeutic Goods Administration (TGA) to communicate benefit-risk decisions for ziv-aflibercept (Zaltrap) a treatment for metastatic colorectal cancer administered with other chemotherapy. Results showed that a listing of the benefits reviewed for the regulatory decision was not available. Also missing was information on the risks or harms that were reviewed but not included and the assignment of relative importance along with details of the values assigned to the treatment options. **Professor Stuart Walker**, *Founder, Centre for Innovation in Regulatory Science* hypothesised that in the light of these missing elements, regulatory authorities might consider revising their publicly available communication documents and listing the benefits and risks that were evaluated with justification for their roles in assessing the benefit-risk balance and the reasons for their inclusion or exclusion; valuing the identified benefits and harms of the various treatment options; weighting the identified parameters; potentially providing visualisations to aid in the communication of the evaluation and a guided discussion and structured questions to illustrate key discussion points.

Recommendations from across the Syndicates

1. Study patient priorities; consider using the FDA model of developing guidance following patient-focused drug development meetings.
2. Systematically collect information on patients' prioritisation of the perceived benefits of medicines; use the research performed by IMI PROTECT on the validation of benefit-risk tools.
3. Through use of a collaborative forum following the ICH model, achieve consensus with patients, regulators and industry of the most important and relevant benefit(s) (by disease area).
4. Consider options of data collection for the benefits of new medicines; achieve consensus from regulators and industry on methods for analysis.
5. Once post-approval data on the benefits of new medicine has been accrued, provide incentives for industry to include results in labelling and informational materials.
6. To maximise the accrual of benefit information for approved medicines, a "Benefit Maximisation Plan" toolbox should be developed; CIRS should convene a Workshop on the topic to increase the level of information exchange; implementation efforts should include communication within and across companies and agencies and compliance enhancement activities such as patient support programmes. Clarify the PBRER Lay Summary through the organisation of a technical forum with healthcare professional and lay participation.
7. Collect feedback from stakeholders to determine the impact of PBRERs and to evaluate whether the goals of the PBRERs are aligned with the Pharmacovigilance Risk Assessment Committees and if these goals are being met.
8. Adjust the PBRER format for older products and explore leveraging PBRERs to facilitate access to "older medicines"; potentially with the use of a PBRER as a "submission" dossier.
9. To determine individual patient needs and the relative importance of issues, consider the use of the CIRS UMBRA template be completed by patients.
10. To better understand the harms, tolerability and effectiveness of medicines, endorse a public-private forum on leveraging social media; that is, understanding how to benefit from social interactions in the virtual space.
11. CIRS should survey industry regarding their use of methodologies for the elicitation of patient input and follow with a roundtable discussion on the topic.
12. Encourage discussion about how formally studied patient preference topics could be available publically or shared in some way.
13. Encourage coordination, sharing and partnership among patients, payers, health technology assessment agencies and regulators interested in accruing patient perspectives across the spectrum of patient experience.

Workshop Programme

Day 1: 12 June 2014	
SESSION: UTILISING A BENEFIT-RISK FRAMEWORK: HOW ARE AGENCIES MODIFYING THEIR REVIEW PROCESS AND HOW WILL THIS ENABLE POST-APPROVAL ASSESSMENT?	
Chairman's welcome and introduction	Dr Tomas Salmonson , Chair, CHMP, European Medicines Agency
Does requiring a structured approach to benefit-risk assessment in the post-approval period drive the need for consistent methods in the approval period?	
FDA viewpoint	Dr Theresa Mullin , Director, Office of Strategic Programs, CDER, Food and Drug Administration
Industry viewpoint	Dr Paul Huckle , Chief Regulatory Office, GlaxoSmithKline, USA
Benefit-risk framework development: Current status and forward plans	
FDA framework development and testing	Patrick Frey , Director, Office of Program and Strategic Analysis, CDER, Food and Drug Administration
Discussant – Using the framework	Kimberly Witzmann , Medical Officer, Division of Pulmonary, Allergy and Rheumatology Products, Office of New Drugs, Food and Drug Administration
EMA Framework development and pilot study	Dr Francesco Pignatti , Head of Section, Oncology, Haematology & Diagnostics, European Medicines Agency
An evaluation of the application of UMBRA to ensure a systematic documentation of benefit-risk in non-ICH countries	Dr Neil McAuslane , Director, CIRS
The utilisation of the summary template for benefit-risk assessment of medicines by HSA	Dr James Leong , Senior Regulatory Specialist Health Sciences Authority, Singapore
SESSION: BENEFIT-RISK DECISION MAKING IN THE POST-APPROVAL PERIOD: HOW IS THIS BEING APPROACHED AND WHAT NEEDS TO BE CONSIDERED?	
Chairman's introduction	Dr Tomas Salmonson , Chair, CHMP, European Medicines Agency
Issues in measuring benefit-risk in the post-approval period: What are the challenges for regulatory agency acceptance?	
Agency viewpoint	Dr Co Pham , Senior Science Advisor, Marketed Products Directorate, Health Canada
Company viewpoint	Dr Stephen Knowles , Senior Director, Global Patient Safety, Eli Lilly and Company

New approaches/technologies to capture benefits and risks in the post-approval phase – What are the practical and regulatory challenges?	
FDA viewpoint	Dr Gerald Dal Pan , Director, Office of Surveillance and Epidemiology, Food and Drug Administration, USA
Company viewpoint	Dr Carmen Bozic , Senior Vice President, Clinical and Safety Sciences, Biogen Idec, USA
PMDA perspective	Dr Akiko Hori , Director, Office of Safety II, Pharmaceutical and Medical Devices Agency, Japan
IMI PROTECH initiative	Prof Deborah Ashby , Co-Director of Imperial Clinical Trials Unit and Deputy Head, School of Public Health, Imperial College London, UK
SESSION: SYNDICATE DISCUSSIONS	
Topic A: Collection of benefits and harms in the post-approval period: What are future methodologies	Chair: Prof Robert Peterson , Executive Director, Drug Safety Effectiveness Network, Canadian Institute of Health Research Rapporteur: Anders Lindholm , Pharmacovigilance and Risk Management TA Head, Shire Pharmaceuticals, USA
Topic B: PBRERs: What are company's experiences in providing agencies with structured benefit-risk analysis?	Chair: Prof Bruno Flamion , Professor of Pharmacology, University of Namur, Belgium Rapporteur: Dr Leo Plouffe , Vice President, Head of Risk Management Global Pharmacovigilance, Bayer HealthCare Pharmaceuticals, USA
Topic C: Patient input into the post-approval methods for collection of benefits and harms – what is their role?	Chair: Dr John Bridges , Associate Professor, Johns Hopkins Bloomberg School of Public Health, USA Rapporteur: Dr Rick Hermann , Safety Science Physician, AstraZeneca, USA
DAY 2: 13 June 2014	
SESSION: SYNDICATE DISCUSSION AND FEEDBACK	
Syndicate sessions resume	
Chairman's introduction	Prof Sir Alasdair Breckenridge
Feedback of syndicate discussion and participants viewpoint following each syndicate discussion	
Understanding the benefits, risks and their relative importance to patients: Challenges and recommendations	
Agency viewpoint	Dr Theresa Mullin , Director, Office of Strategic Programs, CDER, FDA
Industry viewpoint	Dr Bennett Levitan , Director, Janssen, USA
Patient viewpoint	Dr Durhane Wong-Rieger , President, Canadian Organisation for Rare Disorders
Communicating benefit-risk decisions to stakeholders	Prof Stuart Walker , Founder, CIRS
Summary and close of Workshop	

Section 2: Syndicate Discussions

Syndicate Discussion A

Collection of benefits and harms in the post-approval period: What are future methodologies?	
Chair	Prof Robert Peterson , <i>Executive Director, Drug Safety Effectiveness Network, Canadian Institute of Health Research</i>
Rapporteur	Anders Lindholm , <i>Pharmacovigilance and Risk Management TA Head, Shire Pharmaceuticals, USA</i>

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 have been considered to assess and make decisions on the benefit-risk balance. The development of new medicines is a continual learning process, as new information is obtained during development 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.

Indeed, at the CIRS June 2013 Workshop it was agreed that the Universal Methodology Benefit-Risk Assessment (UMBRA) framework provides a good basis for post-approval benefit-risk assessment and the group concluded that a structured, qualitative approach is appropriate for most decision processes such as Periodic Benefit-Risk Evaluation Reports (PBRERs) or risk management plans (RMPs). Preferably, the same approach would be employed pre- and post-approval. However, there is less flexibility for sponsors to design benefit-risk modelling in the post-approval 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 lifecycle review. This group also concluded that

- It is important to consider how to balance the results of clinical trials with those 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.
- Developing methodologies for assessing benefits in the post-approval setting is of particular help to characterise each disease in terms of a hierarchy of benefit and risk evidence.

This Syndicate was asked to discuss and make recommendations on what current and future methodologies could provide all stakeholders with equivalent representation of their perspectives of benefits and risks so that there is less information asymmetry in favour of the risks in the post-approval timeframe.

Objectives

- Identify current methodologies that are robust enough to be utilised for both measuring benefits and risks in the post-approval period
- Discuss the key challenges and potential opportunities for methodologies that enable the post-approval measurement of both benefits and risks to be simplified or evolved or utilised in a wider way without losing regulatory robustness
- Recommend how current or new methodologies can be utilised to provide the information as to what needs to be considered and by whom

Questions for consideration

1. What are the major issues in measuring benefits in the post-approval period? Should this be about measuring effectiveness, the need for information for HTA agencies or the role of post-approval trials, registries and record linkage?
2. Has your company's approach to the collection of benefit data changed following the introduction of PBRERs?
3. Are regulatory agencies suggesting new approaches that should be investigated and if so what are these?
4. From which sources should the companies be collecting benefit data?
5. What role does social media or other similar technologies have for the future for collection of benefit information?

Critical issues

This Syndicate decided to focus mainly on the collection of data for the benefits of new medicines in the post-approval period and identified two critical issues that they posed as problem statements.

Problem statement 1: Although the benefit-risk balance is positive at the time of product approval, post-approval benefit-risk evaluation is influenced mainly by additional safety information. New benefit information for a medicine is rarely considered, systematically collected or valued after marketing approval (Figure 1).

Problem statement 2: Study endpoints on which approvals are based such as surrogate markers or non-symptom-related effects are not always of the highest priority to patients. Data on medicines' benefits that are relevant to

patients such as those that affect quality of life need to be developed.

Strategies

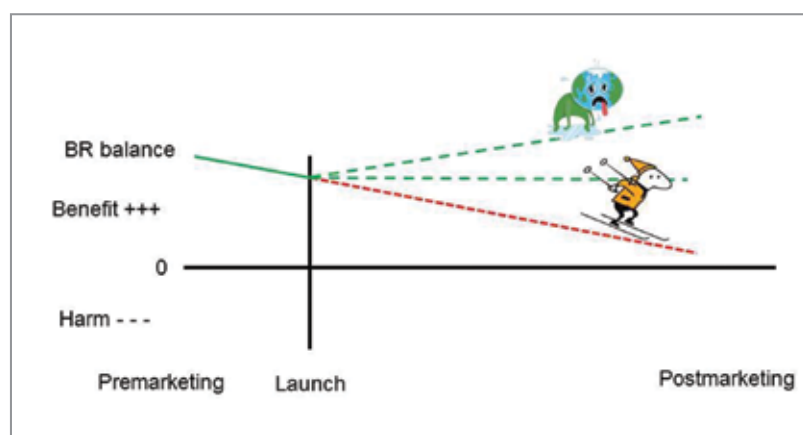
Providing information and education to improve understanding of the methodologies used to collect patient input regarding the benefits and harms of new medicines will increase transparency in decision making. Additionally, the proactive uptake of structured decision-making metrics should also improve the quality of regulatory decisions. Finally, continued patient involvement in the development of therapeutic area guidelines, particularly in the areas of inclusion and exclusion criteria and the identification of primary and secondary endpoints will ensure patient-centric outcomes are part of quality decision making.

A particular challenge in acquiring evidence for the benefits of a newly approved medicine is that the level of evidence required to support those benefits seems to be higher than that required to support harms. That is, the adverse event report from a single individual in a clinical trial can exert a negative impact on a benefit-risk profile whilst evidence that is typically available to support a medicine's efficacy profile such as a patient's anecdotal report may not be regarded as sufficiently robust (Figure 2).

Stakeholder perspectives regarding the priorities for closing the knowledge gaps for newly approved medicines vary. Regulators may remain concerned regarding the medicine's long-term effects, its efficacy among subgroups, the results of concomitant medications and the effects of genomics. Prescribers would like to obtain data regarding a medicine's comparative effectiveness and more clarity is needed regarding the information that would be most important for patients. For their part, although they are aware of the need for more data regarding the benefits of approved medicines, pharmaceutical companies have received limited encouragement from regulators when they have provided benefit information in periodic benefit-risk evaluation reports (PBRERs) and they are limited in their ability to update labelling for an existing indication with new benefit information such as patient-reported outcomes (PROs).

Determining a medicine's benefits after approval requires data from actual use, as the results of randomised clinical trials cannot be generalised to real-world conditions. Real patients belong to a different demography than that of clinical

Figure 1. It is challenging to accrue information regarding a medicine's benefits after approval.



trials with respect to body weight, age and other attributes. They have other concomitant diseases, use other medical and non-medical treatments and results of their treatment must be considered in the light of potential smoking and alcohol use.

Example of methods to study real world patient benefits include large simple studies, which although they may have "clean" data from the use of a clinical trial approach, can be expensive to conduct and produce results that may be affected by a selection bias. Observational studies or surveys can be inexpensive to run but may result in incomplete or missing data and may be also subject to selection bias.

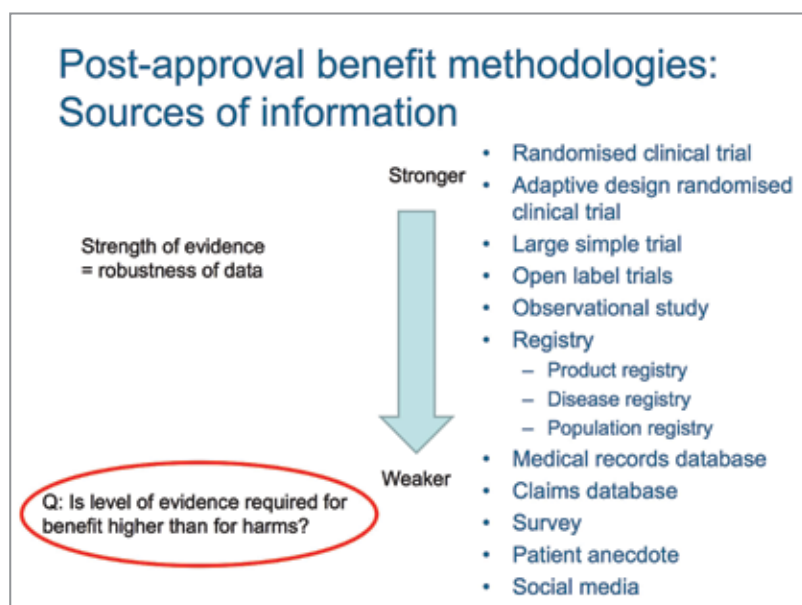
Multiple types of randomised clinical trials can be conducted after approval, each with a different focus. Comparative effectiveness studies are key for HTA assessment and dose optimisation studies can explore or enhance dosing after approval. As previously mentioned, large simple studies can confirm the benefits of a medicine and validate pre-approval findings or determine the long-term benefits and harms for chronic therapy or a medicine's effects in subgroups. Patient-reported outcomes can be used to understand the effects of a medicine that may be most important to the patient.

Observational studies use data sources such as registries and claims and medical records databases. These studies examine real-world scenarios but it is important to obtain a cross-section of patients without selection bias as registry studies are frequently risk focused,

making the detection of benefits more challenging. The linkage of records that is possible in these studies increases the abilities of researchers to study the long-term effects of medicines but it may take a long time to accrue the necessary patients. It may be possible to overcome this challenge by linking patient records to prescription databases. Additionally, the use of registries may be accompanied by issues such as ownership of data, privacy concerns and funding, concerns that may be mitigated by the creation of a disease rather than a therapy registry, the data for which can be randomised post hoc.

Social media may be important sources of information but their optimal use remains to be determined. Challenges include their reliability, the manageability of large amounts of data, the need to develop methodologies to collect usable information and the question as to which media to monitor.

Figure 2. Evidence that is typically available to support claims of efficacy for approved medicines may not be regarded as sufficiently robust.



Recommendations

1. Study patient priorities; consider using the FDA model of developing guidance following patient-focused drug development meetings.
2. Systematically collect information on patients' prioritisation of the perceived benefits of medicines; use the research performed by IMI PROTECT on the validation of benefit-risk tools.
3. Through use of a collaborative forum following the ICH model, achieve consensus with patients, regulators and industry of most important and relevant benefit(s) (by disease area).
4. Consider options of data collection for the benefits of new medicines; achieve consensus from regulators and industry on methods for analysis.
5. Once post-approval data on the benefits of a new medicine have been accrued, provide incentives for industry to include results in labelling and informational materials.

Syndicate Discussion B

PBRERs: What are companies' experiences in providing agencies with structured benefit-risk analysis?

Chair	Prof Bruno Flamion , <i>Professor of Pharmacology, University of Namur, Belgium</i>
Rapporteur	Dr Leo Plouffe , <i>Vice President, Head of Risk Management Global Pharmacovigilance, Bayer HealthCare Pharmaceuticals, USA</i>

Background

Any benefit-risk framework should be flexible enough to incorporate evolving scenarios, particularly as knowledge increases about a new medicine. This has led agencies and companies to focus on the importance of the post-approval period in providing a better understanding both of the benefits and harms of medicines. This has been reflected in the recent Second Efficacy Guideline of the International Conference on the Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH E2), which now requires companies to provide continually updated information on the benefit-risk balance. This process should also include a structured benefit-risk evaluation, not just when new information becomes available but also when medicines are being periodically re-evaluated.

This guideline, although articulating the need for a structured benefit-risk evaluation does not specify detail agency requirements. As a result, companies have designed formats that they believe will satisfy requirements. As a structured benefit-risk evaluation is now mandatory in the post-approval setting, this has been a major focus for companies over the past year.

In December 2013, CIRS held a technical forum to discuss and examine the challenges and experiences of companies as they comply with the requirements of the PBRER and in March 2014, the ICH E2C(R2) Implementation Working Group released a Q&A document to be used alongside the ICH E2C(R2) Guideline: Periodic Benefit-Risk Evaluation Report.

As companies now have experience of implementing this requirement, this Syndicate addressed current challenges and future expectations both internally and across the ICH regions as well as the acceptance or utilisation of the guideline by agencies outside of the ICH region.

Objectives

- Discuss company and agency experience in implementing PBRERs with particular focus on the structured benefit-risk evaluation, including how agencies have responded to company submissions
- Identify the key challenges and potential opportunities within the company in the provision of the requested information
- After discussing the areas in which agencies and companies have issues, recommend how the structured approach in the post-approval stage should be linked to the approval of new medicines

Critical issues

This Syndicate defined the critical issues for this topic through a discussion of the questions for consideration.

- What are the challenges facing the pharmaceutical industry and agencies as a result of the requirement for PBRERs?

From an industry perspective, important challenges that have resulted from the requirement for periodic benefit-risk assessments (PBRERs) include identifying contributors in the necessary cross-functional collaboration and defining the process that is required as well as elucidating unclear expectations for the benefit-risk presentation; that is, determining whether a single statement of a full framework evaluation is required.

Regulatory agencies were traditionally structured to evaluate benefit-risk in the pre-approval setting and safety after approval. However, although the assessment of benefits and risks during post-approval has presented challenges, it has also generated efficiencies and engendered dialogue across regulatory groups and divisions. Both groups share certain concerns regarding PBRERs including determining the definition of a "good" PBRER, establishing an interface with health technology assessment agencies and establishing whether

the public dissemination of PBRERs will exert a positive or negative impact on public health.

- Do you have a submission strategy for ICH regions EU, USA and Japan? Are they evaluated in a similar manner globally?

Most companies do not differentiate for the PBRER across countries or regions but rather anchor PBRERs on core data sheets and risk management programmes although a few companies do customise the reports on a local level.

- Does the ICH E2 Q&A answer your main concerns about the need, construction, submission and evaluation of PBRER's?

Unfortunately, the group reported gleaning little benefit from this document.

- Should the approach for older medicines be viewed differently to newer medicines?

The Syndicate strongly agreed with the need to distinguish newly approved medicines and more well-established medicines with modern submission packages which are best suited for the use of PBRERs from historic medicines for which little data are available. These older medicines often have extensive lists of safety concerns, which exert little real impact on benefit-risk but which present a huge administrative burden. Finally, vaccines are an example of a special category of medicine for which the PBER format is not suitable.

- Do you submit these data to other countries (outside of the ICH regions) and are there any countries where the PBRER's are not accepted?

Syndicate members agreed that PBRERs are sent to all countries of the world and whilst some companies may apply local adaptation to the document, no one could name a country where the PBRER is not accepted.

The group also discussed additional critical issues:

- There are controversies surrounding the required sign off and expectations from the Qualified Person for Pharmacovigilance (QPPV) and challenges in the oversight of data from local studies by health technology assessors.
- Although Section 2.5.6 of the ICH initiative on benefit-risk assessment is focused on submissions rather than on PBRERs, it will set the stage for future PBRERs to be aligned from the time of submission. This reflects

the paradigm shift that occurred in 2009 when the primary focus for pharmaceutical companies changed from bringing medicines to market to enabling market access for those medicines through health technology assessment and keeping them on the market through planned pharmacovigilance.

- Although the PBRER concept is relatively new, the idea of continued data generation after product approval is not. These data have been historically generated by academia and independent investigators but new methods and scientific approaches to accrue information must be developed and the use of social media must be considered.
- Ideally, in the future it will be possible to use benefit-risk frameworks to create stand-alone evaluations for ad-hoc requests.
- An evolution to literature-based data for submission packages is taking place but randomised clinical trials remain the gold standard and the acceptability of different standards of evidence among global regulators is unclear. In the post-approval timeframe, adding observational data may be acceptable to regulators but replacing RCTs with this type of evidence remains a challenge, as the focus remains on safety. This thinking may change with time.

Strategies

The interface of PBRERs and health technology assessments should be enhanced and within the industry there should be a clear process owner for each PBRER who specifies key contributors to this document. For optimal use, PBRERs should also be aligned with and used to provide updates to core clinical data sheets and risk management plans.

Benefit-risk assessment is a stand-alone process, which is integrated into a PBRER and the framework with which the assessment is constructed should be adjusted to the specific medicine being evaluated. For older products, the use of Therapeutic Impact Data should be considered.

Awareness needs to be raised among all stakeholders regarding the need to maximise accrual of benefit data. Industry is already working in this area but there is variable involvement among pharmacovigilance teams and other departments and shared awareness within companies and across agencies could be enhanced.

Recommendations

1. To maximise the accrual of benefit information for approved medicines, a “Benefit Maximisation Plan” toolbox should be developed; CIRS should convene a Workshop on the topic to increase the level of information exchange; implementation efforts should include communication within and across companies and agencies and compliance enhancement activities such as patient support programmes. Clarify the PBRER Lay Summary through the organisation of a technical forum with healthcare professional and lay participation.
2. Collect feedback from stakeholders to determine the impact of PBRERs and to evaluate whether the goals of the PBRERs are aligned with the Pharmacovigilance Risk Assessment Committees and if these goals are being met.
3. Adjust the PBRER format for older products and explore leveraging PBRERs to facilitate access to “older medicines”, potentially with the use of a PBRER as a “submission” dossier.

Syndicate Discussion C

Patient input into the post-approval methods for collection of benefits and harms – what is their role?

Chair	Dr John Bridges , Associate Professor, Johns Hopkins Bloomberg School of Public Health, USA
Rapporteur	Dr Rick Hermann , Safety Science Physician, AstraZeneca, USA

Background

Patients' perspective on benefits and harms and their relative importance is critical to the development and review of new medicines, both at the disease and the therapy level. Although this has been widely discussed in relation to development and approval decisions, the issue raised at the 2013 CIRS Benefit-Risk Workshop was that there needs to be a greater role for the patient's perspective in the post-approval setting. Indeed, at a recent technical forum held by CIRS in December 2013, it was highlighted that "patients are the most underutilised medical resource."

Current methodologies are criticised as overlooking the patient as a resource as well as either being too complex and expensive or as containing issues with scientific reliability or regulatory acceptance. In addition, regulatory agencies have the challenge as how to extrapolate a particular patient's viewpoints on benefits and harms to the general patient population. However, there is agreement from all stakeholders (patients, industry and agencies) that patients need to be engaged in a discussion of benefits and harms and their relative importance. Therefore, an alignment by stakeholders on feasible and flexible methodologies that can be used in the post-approval arena seems critical if this is to be achieved.

This group was asked to discuss the patient's role in the post-approval assessment of benefits and risks, to identify if there are current appropriate methods that could be used and if not, to develop a recommendation for the inclusion of the patient's perspective in the post-approval setting.

Objectives

- Discuss the key challenges to and opportunities for greater patient input in the post-approval period
- Identify current methodologies for patient

input that are robust enough to be utilised in the post-approval period

- Recommend the ways in which current methodologies can provide the information from patients on benefits, harms and tradeoffs, which can be used to inform regulatory decision making

Questions for consideration

1. How is the patient's perspective taken into account in the post-approval evaluation of the benefits and risks of a new medicine?
2. What are the current methodologies and their place in the toolkit for acquiring robust data that are valuable in assessing patients' benefits, harms and tradeoffs?
3. How could current methodologies be simplified for wider use and what are the challenges and opportunities for developing simpler methods for use in the regulatory setting?
4. What is the role and use of social media and patient input and how does a company go about collecting this information and then presenting it to the health authority in a systematic fashion that is of value?

Critical issues

This Syndicate agreed that the need for patient involvement in medicine starts in the pre-approval period. Industry should be performing exit interviews for trial participants to determine their perspective regarding the learnings from the trial and the benefits of treatment. Too often, a standard patient-reported outcome is used that may not apply to the value of a particular outcome or information regarding quality of life is elicited but not weighted. For their part, regulators may need to be convinced of the validity and "correctness" of the patient perspective. One Syndicate discussant provided an example in which no response from regulators was received regarding the submission of the results of a large conjoint

analysis as part of a dossier. Some agencies may contain public members but their participation in decision making may be uneven at best.

To members of this group it seemed that regulators ask “Why doesn’t industry present more non-traditional data?” while industry asks “Why won’t regulators accept anything but hard data?” In fact, however, patient involvement can be confrontational and include politicizing, litigation, media consultants and protests. When regulators open up discussions so that the public can present their concerns and issues, the natural next question from these participants becomes “What will you do about it?” This may be a difficult question to answer if the outcomes that were most important to patients were not measured in the trials in the first place.

Other issues that were discussed include the need to make insurers more accountable to patients and the general public.

Strategies

The US FDA Patient Representative Program could be used as a model for patient participation. The agency provides training to participants and tries to mitigate potential conflict of interest by suggesting that they attempt to think beyond their own experience. Other questions that are posed include

- Can you help expand the set of benefits that need to be measured?
- What symptoms are most bothersome to you?
- What do you think about the current drugs available?
- What patient-related outcome tools should be used?

The FDA also records public testimony and makes these recordings available to its staff.

Precompetitive consortia should be used to design better clinical trials and regulators, patients, academia and industry linked on neutral ground to arrive at solutions? The definition of personalised healthcare should be broadened to include personal preferences, values and settings. The UK National Institutes of Health is working on this issue.

The process of accruing patients’ perspectives needs to more understandable, simpler and cheaper and could perhaps be pared down to a single question “Did it work?” Threshold techniques should be used to identify tradeoffs

that are acceptable to patients.

Social media are an extremely important resource to ensure integration of patients with the other stakeholders across a medicine’s lifecycle and to specifically and formally include patient input into the development of clinical trials but its utility will need to be refined. Scientific use of these media must include training for patients on issues such as adverse event reporting and the high cost and resource intensive nature of properly pursuing this research must be fully understood.

Recommendations

1. To determine individual patient needs and the relative importance of issues, consider the use of the CIRS UMBRA template be completed by patients.
2. To better understand the harms, tolerability and effectiveness of medicines, endorse a public-private forum on leveraging social media; that is, understanding how to benefit from social interactions in virtual space.
3. CIRS should survey industry regarding their use of methodologies for elicitation of patient input and follow with a roundtable discussion on the topic.
4. Encourage discussion about how formally studied patient preference topics could be available publically or shared in some way.
5. Encourage coordination, sharing and partnership among patients, payers, health technology assessment agencies and regulators interested in accruing patient perspectives across the spectrum of patient experience.

Section 3: Presentations

How does structured approach to benefit-risk assessment in the pre-approval support continued assessment in the post-approval period? FDA viewpoint

Dr Theresa Mullin

Director, Office of Strategic Programs, CDER, Food and Drug Administration, USA

Benefit-risk assessment and judgement

The benefit-risk assessment of medicines is a qualitative approach grounded in the quantification of various data elements. At the time of market approval regulators assess a drug's benefits from the efficacy endpoints measured in controlled clinical trials. Risks are assessed from harms reported in clinical trials and other sources such as spontaneous adverse event reports and information from other countries where the drug has already been approved. However, the evaluation of benefit-risk is dynamic and knowledge concerning these factors evolves over the product life-cycle.

Although science provides data to inform analyses of benefit-risk balance it does not

provide decisions. Decisions regarding a medicine's benefit-risk profile may be influenced by statutory and regulatory standards, societal expectations and personal values and perspectives and require judgement on the part of the regulator. Decisions may vary according to stakeholder perspective. Regulators make judgements at the population level, whilst physicians and patients must translate the population-based benefit-risk information to make judgements at the level of the individual patient.

Challenges

Addressing relevant benefit-risk considerations presents a number of challenges. In the pre-market review, large volumes of information are submitted with new drug applications and considerations in the review of these data include the nature of the disease, treatment effects, trial design, the clinical relevance of trial endpoints and study populations. Additionally, attention must be given to the availability of other therapies, risks of other products in class, expected patient compliance, chronic use, the target population, the potential for off-label use, serious risks, efficacy in patient subgroups and labeling. Uncertainties such as in how to extrapolate efficacy and safety from clinical trials to the clinical care setting add to the challenges in this time period.

In the post-approval period, observational data and the results of post-approval commitments are analysed and additional and sometimes extensive safety data emerge. In fact, in 2013, the FDA received more than 876,000 adverse event reports. During this stage, the effectiveness of risk evaluation and mitigation strategies (REMS) are assessed and some of the initial uncertainties that surrounded a new medicine may have been resolved while other uncertainties such as extrapolation of new safety reports and other findings may have arisen.

FDA benefit-risk framework

It was determined that use of a structured, qualitative approach would best accomplish the two-fold objectives for the FDA benefit-risk framework: better external communication of the rationale underpinning the Center for Drug Evaluation and Research decisions and

Figure 3. The FDA benefit-risk framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Sets the context for the weighing of benefits and risks: - How serious is this indicated condition, and why? - How well is the patient population's medical need being met by currently available therapies?	
Current Treatment Options		
Benefit	Characterize and assess the evidence of benefit: - How compelling is the expected benefit in the post-market setting? - How clinically meaningful is the benefit, and for whom?	
Risk	Characterize and assess the safety concerns: - How serious are the safety signals identified in the submitted data? - What potential risks could emerge in the post-market setting?	
Risk Management	Assess what risk management (e.g., labeling, REMS) may be necessary to address the identified safety concerns	

Benefit-Risk Summary and Assessment

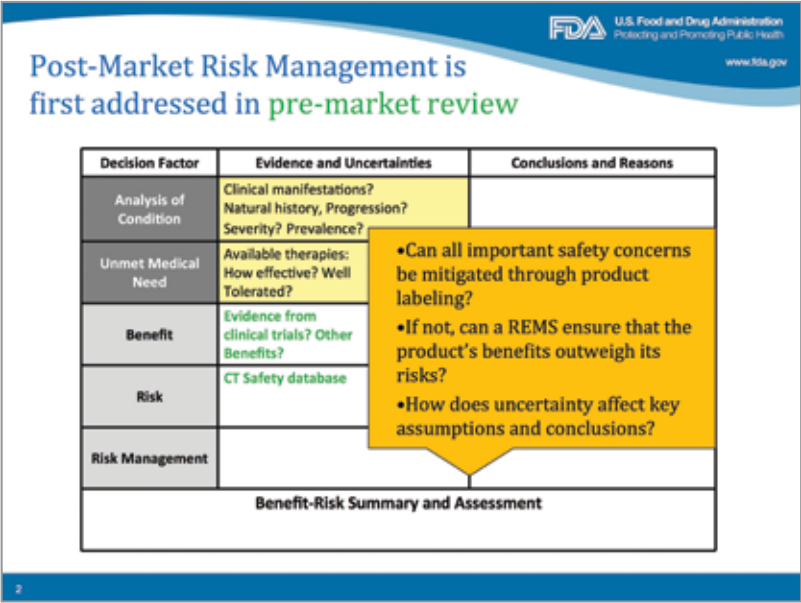


Figure 4. Addressing post-approval risk management in the pre-approval review

internal assurance that the “big picture” for a new medicine is considered throughout complex, detailed reviews. This structured approach best fits the drug-regulatory needs, reflecting the fact that benefit-risk assessment is a qualitative exercise supported by extensive analysis of evidence on benefits and risks. It rigorously communicates in words the basis for decisions while maintaining flexibility to accommodate more complex supporting quantitative analyses that can aid expert judgement.

Information input into the framework establishes the context for evaluating a medicine’s benefits and risks, describing the condition to be treated and the ability of current therapies to meet treatment needs as well as the product’s specific benefit and risk attributes and the proposed risk management plan. It also allows the

A structured approach to benefit-risk assessment initiated in the pre-approval period can provide useful context and continuity for evaluation of additional information after approval.

organisation of evidence and uncertainties for each of these decision factors (Figure 3).

Post-market risk management

Post-market risk management is first addressed in a product’s pre-market review through the answers to three key questions: Can all important safety concerns for this product be mitigated through its labeling? If not, can a REMS ensure that the product’s benefits outweigh its risks? Finally, how does uncertainty affect key assumptions and conclusions? (Figure 4) In product reviews after approval, new relevant benefit-risk information is considered, the original questions are reconsidered and additional questions added: If a REMS already exists for this product, can the current (or a revised) set of elements ensure that the drug’s benefits outweigh its risks?

Conclusions

A structured approach to benefit-risk assessment initiated in the pre-approval period can provide useful context and continuity for evaluation of additional information after approval. By updating and annotating the pre-approval assessment documents with the new information, considerations and conclusions, the new assessment supports internal decision making and knowledge management and external communication of the reasoning behind regulatory decisions in the post-approval period.

Does requiring a structured approach to benefit-risk assessment in the post-approval period drive the need for consistent methods in the approval period? An industry viewpoint

Dr Paul D. Huckle

Chief Regulatory Officer, GlaxoSmithKline, USA

Benefit-risk from an industry perspective

Although pharmaceutical companies may approach benefit-risk assessment from different starting places, they typically share a number of principles and goals and there is an apparent shared industry goal of integrating benefit-risk evaluation more formally throughout the product life cycle. During development, benefit-risk assessments can be used internally to inform product development at key milestones for scientific review boards and safety committees. In the post-approval phase, companies have used different approaches to benefit-risk evaluation, chiefly driven by the requirements of the Periodic Benefit-Risk Evaluation Report (PBRER) and the Periodic Safety Update Report (PSUR).

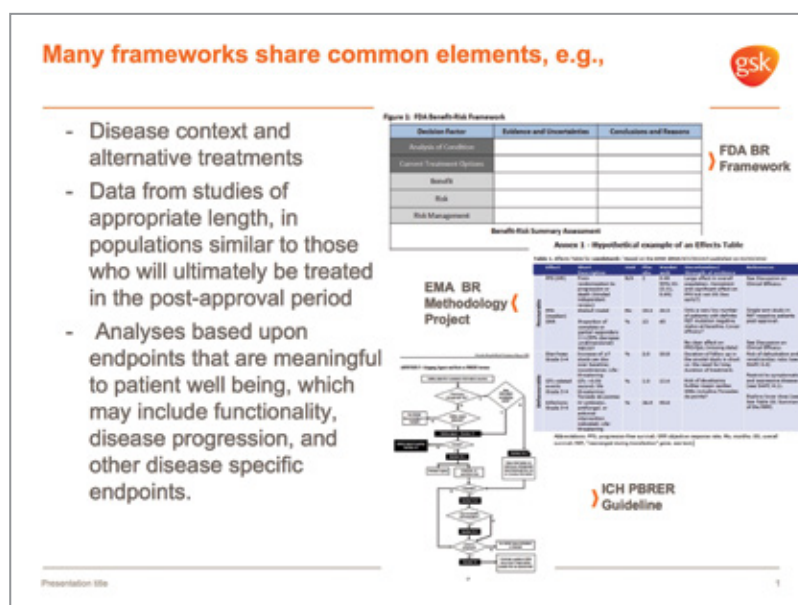
Throughout the continuum of a medicine, a structured framework is an integral part of the process of benefit-risk evaluation and serves the functions of framing the questions to be asked

and allowing data to be visually represented. A variety of analytical methods are available to meet the needs of product teams and many frameworks share common elements. The most widely used frameworks consider disease context and alternative treatments and data from studies of appropriate length in populations similar to those who will ultimately be treated in the post-approval period. These frameworks ask the user to address key concerns, such as the balance between unmet medical need and treatment-associated risk and encourage minimum standards of robust analysis based upon end points that are meaningful to patient well-being, which may include functionality, disease progression and other disease-specific end points (Figure 5).

Industry communication with patients, healthcare providers and other stakeholders is a two-way process that should occur appropriately during development and in the post-approval environment. Trial feasibility, preferences for treatment and device characteristics and regimens and review of patient materials are familiar areas of patient involvement. Innovative trial design, clinical trial data sharing, social listening and use of electronic health records are examples of less-well-trodden ground with patients that merit further dialogue. However, ways to balance the desire for access to information with the desire for privacy must still be determined.

A benefit-risk framework developed during research and development may be able to be used later in a product life cycle but the methods for measurement are likely to be different. More mature products tend to generate emerging safety signals while not providing long-term efficacy outcome data and need to rely heavily on a variety of data sources to answer benefit-risk questions. The move from clinical trial data to data from observational studies, pragmatic trials, spontaneous reports, social listening, health records and device applications all highlight the need for a number of analytic methods. The future environment is likely to offer even more options for data collection, pointing to an

Figure 5. Common elements of benefit-risk frameworks.



Innovative trial design, clinical trial data sharing, social listening and use of electronic health records are examples of less-well-trodden ground with patients that merit further dialogue.

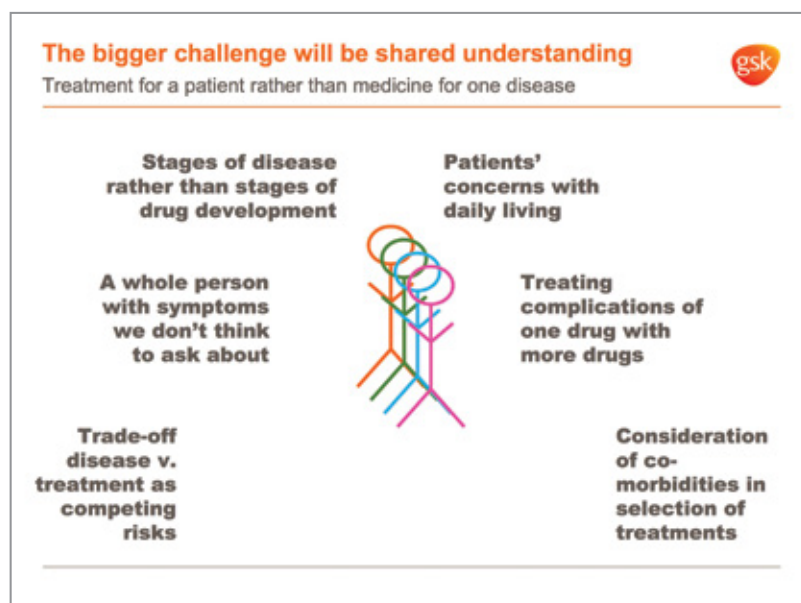


Figure 6. Sharing information may enable understanding of the complexities of drug development, public health and holistic views of patients' needs.

ongoing need for a consistent approach with agreed standards of data quality and analytical rigor, rather than a single named framework or method. The bigger challenge will be developing

a shared understanding that includes the concept of treatment for a patient rather than a medicine for one disease, which will entail consideration of patients' disease stages and their practical management of daily living (Figure 6).

Conclusions

Much progress has been made in the ongoing evaluation of a medicine's benefits and risks. Regulators and practitioners are collecting more information on patients' actual experiences and learning to measure and characterise them in terms of management of diseases, views on trade-offs and goals for treatment. There are many collaborative groups that include patients, representatives, caregivers, advocates, researchers, drug developers, regulators, healthcare practitioners and others working toward practical and meaningful benefit-risk evaluation. Although these stakeholders are still learning how to collect better information regarding a medicine's effectiveness after approval, there is a greater willingness among the groups to learn from one another, which is the most important step of all.

Benefit-risk framework implementation: FDA Update

Patrick Frey

Director, Office of Program and Strategic Analysis, CDER, US Food and Drug Administration

The US Food and Drug Administration (FDA) is currently implementing its benefit-risk framework as part of the review process for new medicines. This implementation is required according to the agency's commitment to the fifth iteration of the Prescription Drug User Fee Act (PDUFA V) and in accordance with statutory requirement.

Through a process of formal feedback, the staff of the Office of New Drugs (OND) indicated that the framework should be integrated into the FDA review process and review templates for new drugs. The OND Office and Deputy Office Directors, and Division and Deputy Division Directors are currently engaged in

identifying potential approaches to framework implementation.

The OND leadership preferred an approach by which the benefit-risk framework is completed as part of clinical reviews and decision memos written for regulatory actions on marketing applications. This approach has two key benefits: It mimics the current review process for writing separate reviews and memos at each level of review and allows transparency in the scientific opinion at each level of review.

It was determined that multi-disciplinary input into the framework would be provided by the OND Cross-Disciplinary Team and the Signatory Authority framework should represent the ultimate regulatory action, noting where disagreements occurred and documenting the resolution of those disagreements.

In September 2013, CDER convened a working group to address the integration of the benefit-risk framework into the clinical review template, to revise other aspects of the template to address reviewer and OND management needs and to identify training

needs. OND representatives on the working group include Office Directors, Division Directors, Cross Cross-Disciplinary Team Leaders, primary reviewers, and training staff. The working group has proposed clinical review template enhancements in three key areas: First, the benefit-risk framework will be located at the front of the clinical review as part of the Executive Summary. Second, a new content area will address the therapeutic context of the regulatory decision, with analyses of the condition and available treatment options. Third, another new content area will address risk management, including analysis and supported recommendation for labelling, post-marketing commitments to resolve residual uncertainties, and Risk Evaluation and Mitigation Strategies.

The OND planned to finalise integration of the benefit-risk framework and CRT revision for review and clearance and implement reviewer training and template functionality through 2014. Implementation of the framework into new drug and biologic licence applications, revisions to the templates of the Cross-Disciplinary Team Leader, Division Director, and Office Director and communication enhancements are anticipated for 2015.

Uncertainty in drug regulation

Despite all the evidence that accompanies a regulatory submission, there can be significant uncertainties surrounding a new medicine. For example, uncertainties in benefit can stem from limits in the scientific understanding of a disease, inconsistencies or contradictory evidence from multiple studies and the relationship between a study population and the patient population who will actually take a drug. Uncertainties may also relate to risk, arising from numerical imbalances in adverse events in treatment and control groups, post-marketing data from sources with varying levels of scientific rigor,

CDER is very interested in more explicit consideration of uncertainty by reviewers and where uncertainty is high, clinical judgement, values, and input from others such as patients or advisory committees may play a greater role.

and the ability of the healthcare system to adequately manage a risky drug.

Explicit consideration of uncertainty was identified as a challenge during a 2012 FDA benefit-risk framework pilot programme. Dealing with uncertainty presents a number of challenges. The FDA does not yet employ a systematic approach to dealing with uncertainty but leadership at the FDA Center for Drug Evaluation and Research (CDER) is very interested in more explicit consideration of uncertainty by reviewers and where uncertainty is high, clinical judgement, values, and input from others such as patients or advisory committees may play a greater role.

The FDA supported an Institute of Medicine workshop on Characterizing and Communicating Uncertainty in the Assessment of Benefits and Risks in February and May 2014. The objective of the workshops was to identify a potential path forward in developing an approach to work through uncertainty that is practical and implementable in the regulatory field and that respects the legal and regulatory framework in which a regulator operates. In recognition that handling uncertainty is not unique to drug regulation, experts from other fields have also been consulted for their insights. Once the benefit-risk framework and clinical review template revisions are implemented, future FDA plans include developing a systematic approach to evaluating and dealing with uncertainty in a drug review.

Using the US FDA benefit-risk framework

Dr Kimberly Witzman
Medical Officer, Division of Pulmonary, Allergy and Rheumatology Products
Office of New Drugs, US Food and Drug Administration

The US FDA benefit-risk framework (Figure 7) was recently used in a review of ivacaftor (Kalydeco; Vertex Pharmaceuticals), a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the CFTR gene. Ivacaftor is the first approved drug that targets the underlying defect in the CFTR chloride channel, for patients with a specific subtype of the disease.

Use of the FDA's benefit-risk framework allowed completion of the review in less than 3 months, as it provided a structure for organising information and thinking, and allowed a clear presentation of the benefit-risk assessment of the drug. In the case of ivacaftor, the framework was especially useful in examining the risk side of the assessment. A specific issue that arose during the review period was that of elevation in transaminase levels (alanine aminotransferase and aspartate aminotransferase) within the clinical trials population. Clinical experience,

By organising the benefit-risk information effectively, the framework enhanced collaboration with cross-disciplinary team members, division directors and higher-level reviewers within the FDA.

however, has shown that patients with cystic fibrosis have frequent changes in transaminase levels, which can be due to the underlying disease and may indicate an exacerbation of the condition. Elevated transaminase levels may also be related to the use of concomitant medications.

Answering key questions about risks by using the framework allows a regulator to communicate the specifics of the risks to patients and prescribers: Is there a range of severity with this risk? Does the risk change over time? Is the incidence of this risk higher than with other drugs in the same therapeutic class? In the case of ivacaftor, the last question was easy to answer, because there are no other drugs in its treatment class.

For ivacaftor, elevated transaminase levels proved to represent a small risk in the context of the therapeutic benefits, which include a potential improvement of 10% to 12% in lung function, beneficial weight gain and significant improvement in symptoms. The framework allowed such information to be captured effectively and presented clearly.

By organising the benefit-risk information effectively, the framework enhanced collaboration with cross-disciplinary team members, division directors and higher-level reviewers within the FDA. Use of a common language allows the framework to accommodate stylistic differences across review teams, across review divisions and from reviewer to reviewer. Because the framework is used in an iterative manner, issues that may emerge after a single reviewer has completed their aspect of the review are easily picked up and dealt with by other team members and the final assessment achieved with the framework is strengthened.

Although the benefit-risk assessment of ivacaftor was fairly straightforward, the advantages of the US FDA benefit-risk framework were further demonstrated to Dr Witzmann in a subsequent, more complex review of a product for which the benefits and risks were not as clearly defined.

Figure 7. The US FDA benefit-risk framework.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Summary of evidence:	Conclusions (Implications for decision):
Current Treatment Options	Summary of evidence:	Conclusions (Implications for decision):
Benefit	Summary of evidence:	Conclusions (Implications for decision):
Risk	Summary of evidence:	Conclusions (Implications for decision):
Risk Management	Summary of evidence:	Conclusions (Implications for decision):
Benefit-Risk Summary and Assessment		

EMA framework development and pilot study

Dr Francesco Pignatti

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

The EMA Effects Table pilot

As part of the five Work Packages of the European Medicines Agency (EMA) Benefit-Risk Project, the agency piloted the use of the Effects Table, a tool designed as a compact display of the effects and uncertainties that are associated with a medicine under regulatory review. Unlike a tool for multi-criteria decision analysis, which allows for higher-precision sensitivity analysis, the Effects Table was developed for use in relatively straightforward regulatory assessments.

A phase I assessment of the Effects Table was conducted in which users were deliberately given limited guidance in its use in order to encourage creativity. On the basis of responses in the phase I assessment, however, the table was revised and appropriate guidance was developed.

The revised table and draft guidance were then assessed in a phase II pilot study in which regulators used the tool to examine 12 initial marketing authorisation applications and provide comments on the table and guidance. Although the phase II pilot study was still in progress at the time of this Workshop, interim results were good, with positive average scores on all assessed factors. Participants demonstrated good

compliance with the guideline even for complex applications (Figure 8).

The pilot study did elicit some negative comments. Some participants found a risk of a focus on the Effects Table resulting in missing the totality of the evidence. A concern regarding potential oversimplification by non-regulators was also expressed and the tool was regarded by some reviewers as being not helpful for assessors or the assessment process but rather as a source of increased workload that was difficult to use for complicated applications that encompassed multiple clinical trials.

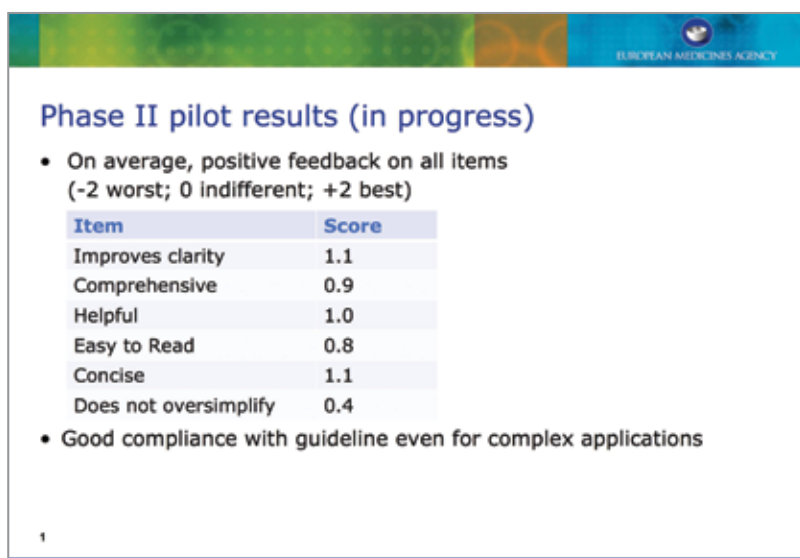
The phase II pilot study was scheduled to be completed in June 2014 with results presented and discussed with the Committee for Medicinal Products for Human Use (CHMP) and other committees and implementation in the fourth quarter of 2014. Similar benefit-risk analysis tools are being developed by some health technology organisations such as the German Institute for Quality and Efficiency in Healthcare (IQWiG) Effects Table and the European Network for Health Technology Assessment (EUnetHTA) Relative Effectiveness Table.

Patient involvement in benefit-risk assessment

Although there are many positive aspects to patient involvement in benefit-risk assessment, there are also multiple challenges such as the tendency to regard patient perspectives as anecdotal and biased. It is also believed that patients may not always be well informed about benefits and risks and may view such information as too technical. In addition, there is no average, representative patient and there are challenges associated with accruing reliable, scientifically rigorous data for patient preferences and sophisticated methods often cannot be applied, because they require extensive training.

With those challenges in mind, the EMA in conjunction with the Patients' and Consumers' Working Party (PCWP) and the Healthcare Professionals' Working Party (HCPWP) convened a workshop in February 2014 to elicit stakeholder preferences with data based on previous regulatory assessments. The workshop conducted separate, parallel MCDA exercises with patient and healthcare professional juries. Each jury was given two hours to build two models using the MCDA Measuring Attractiveness by a Categorical Based Evaluation Technique (MACBETH). The juries used two hypothetical case studies with data that had been modified from European Public Assessment

Figure 8. Positive results in the phase II pilot study of the EMA Effects Table.



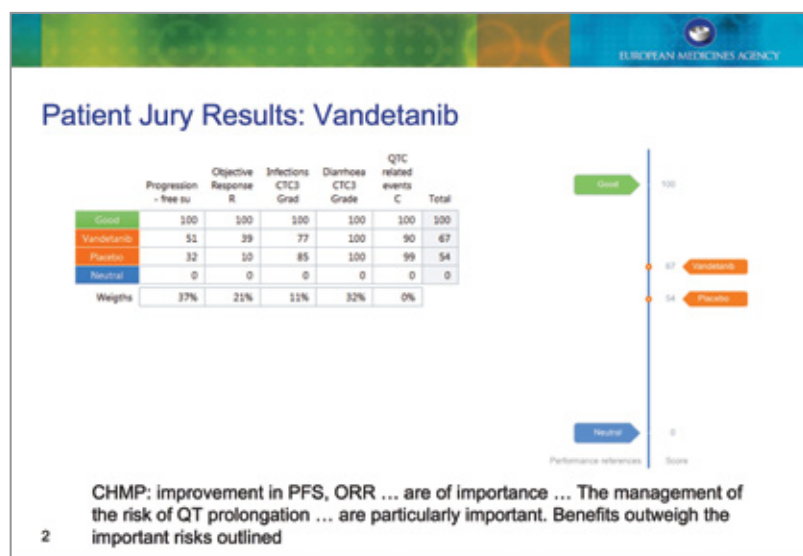


Figure 9. A patient jury at an EMA workshop reached conclusions similar to the CHMP in the evaluation of a medicine to treat medullary thyroid cancer.

Reports (EPARs) for vandetanib in the treatment of medullary thyroid cancer and ixabepilone for breast cancer. The juries examined information on the disease condition; efficacy results and toxicity to devise models for building the value function of the drugs, including a mechanism for assigning weights for various factors in the determination of preferences.

In the case of vandetanib, the analysis of the patient jury results showed that improvement in progression-free survival (PFS) and objective response rate were important for efficacy and that management of QT prolongation in electrocardiograms was an important safety consideration. Overall, benefits were found to outweigh the important risks outlined. In contrast, in the case of ixabepilone, a modest benefit demonstrated in terms of prolonged PFS and a trend towards overall survival was not of sufficient magnitude to outweigh the documented drug toxicity. The patient jury conclusions for both drugs were similar to those originally reached by the CHMP (Figure 9).

... a patient jury, composed mainly of non-experts could successfully build MCDA decision models in a short time... and this type of exercise could empower patients to participate in decision making.

The workshop showed that a patient jury, composed mainly of non-experts could successfully build MCDA decision models in a short time. Although the jury of healthcare professionals, which was composed mainly of "pseudo-experts", did not finish one of the models within the allotted timeframe, the workshop provided the opportunity for informative discussions about weights and trade-offs between the two groups. Jury members reported finding the exercise challenging but very interesting and this type of exercise could empower patients to participate in decision making.

Conclusions

The role of MCDA in decision making remains uncertain but multiple organisations have proposed or developed decision tools for regulators and health technology assessors that are similar to the Effects Table being evaluated by the EMA. These tables facilitate learning and comparisons among therapies and improve accountability. At the time of this Workshop, agreement was still needed from some EMA committees regarding use of the table but responses had been positive.

Based on the results of the EMA workshop, the use of patient juries should be explored as a means to inform benefit-risk assessments.

An evaluation of the application of UMBRA to ensure a systematic documentation of benefit-risk in non-ICH countries

Dr Neil McAuslane

Director, Centre for Innovation in Regulatory Science

UMBRA – a brief introduction

It was the consensus of participants at the June 2012 CIRS Workshop that methodologies for the benefit-risk assessment of new medicines such as the EMA ProACT-URL or the systems developed by the US FDA or the CIRS Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team (PhRMA BRAT) could be mapped to the CIRS eight-step Universal Methodology for Benefit-Risk Assessment (UMBRA) framework. The objective of the development of UMBRA was the provision of a platform for the coordinated development of benefit-risk assessment methodologies that can be used internationally during drug development, regulatory review and post-approval period. The goals were to increase the transparency, predictability and consistency with which benefit-risk assessments are conducted and communicated effectively and to be incorporated within agencies as a cornerstone of good regulatory practice. Advantages of the UMBRA framework include its ability to provide a training tool for both agency and industry staff,

Decision analysis, however, may provide a new pathway for eliciting the patient perspective regarding the benefits and risks of medicines.

to review the consistency of regulatory decisions, enhance the objectivity and transparency of the decision-making process and carry out more balanced and objective benefit-risk reassessments in post-authorisation.

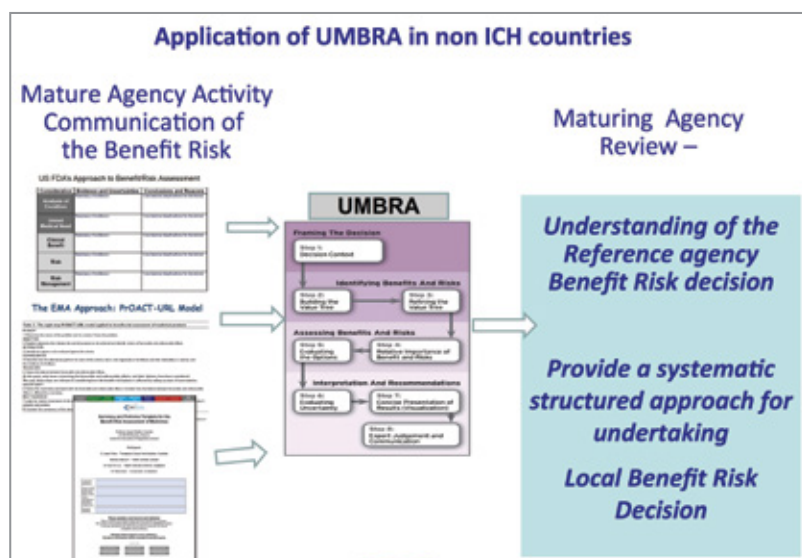
SABRE

Use of the UMBRA framework is supported by the UMBRA Benefit-Risk Template. This template was evaluated and found to be fit for purpose by regulators from Canada, Australia and Switzerland and use of the summary portion of the template was proposed as a tool for agencies in countries with emerging pharmaceutical markets who needed to both understand the reference agency benefit-risk decision and also to undertake a structured assessment on the benefit-risk for their own population (Figure 10).

Accordingly, agencies in China, Indonesia, Malaysia, Philippines, South Korea and Taiwan participated in the CIRS International Summary Approach to Benefit-Risk Evaluation (iSABRE) feasibility study to evaluate the summary template for feasibility and applicability within agencies in emerging markets; to evaluate the benefits as seen by each of the agencies in using a similar approach and framework for benefit-risk assessment; and to determine whether the Electronic Benefit Risk Summary Template is an appropriate mechanism for documenting benefit-risk decisions within these agencies.

Each agency was provided with a protocol, the Electronic Summary Template and a User Manual that included detailed information on how to complete the template. Participants used the Summary Template in the retrospective review of two products in June and October 2013. The products reviewed included anticancer drugs, antibiotics and cardiovascular drugs selected because of positive and negative recommendation, local issues or ethnic factors and high-risk generic reasons. The product reviews were followed by discussion meetings with CIRS, agency reviewers and their management team. The South Korean agency reviewed but did not complete the template and representatives from the authority participated in discussions. In these conferences, the agencies presented case studies highlighting areas in

Figure 10. Use of the summary portion of the template was proposed as a tool for agencies in countries with emerging pharmaceutical markets.





Product Name:
Indication:

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



Figure11. Changes made to the Summary Benefit-Risk Template as a result of the SABRE study.

the template that they found easy or difficult to understand, as well as changes they would like to see and ways the template could be used.

SABRE study outcomes

All the participating agencies were positive about both the structure and the content of the template but identified some changes that could improve internal documentation and communication. The agencies found that the majority of the information within the template was also contained in their own assessment templates and that they undertook a number of the steps specified in the template but not in a systematic or structured manner. Needs that were identified included the placement of the summary of clinical studies before the clinical conclusion and the list of benefits and risks to align with agency review methodology; new sections to address local context issues that influence the benefit-risk balance for a specific country; a box for clinically relevant ethnic issues for each country; the inclusion of a summary effects table; more explicit instructions and clarifications than were contained in the User

... the development of UMBRA was the provision of a platform for the coordinated development of benefit-risk assessment methodologies that can be used internationally during drug development, regulatory review and the post-approval period.

Manual; working examples and translation into local languages.

All the agencies received a report of the study and expressed interest in continuing to the next stage of template evaluation. As a result of the SABRE trial, four key changes have been made to the UMBRA template. A local decision context box and a box for possible interethnic differences have been included; a summary of benefits and risks effects table has been inserted to the final section and portions of the template have been re-ordered to fit with the order of agency processes in drug reviews (Figure 11).

At the time of this Workshop, CIRS planned to carry out another pilot study of the modified Summary Template and to discuss the outcomes of this second study at a meeting of participating agencies. The second study has since been completed and participating agencies met to discuss the results at the Sixth Annual CIRS Regulators Forum in February 2015 (Taipei, Taiwan). This meeting took place in conjunction with a CIRS Benefit-Risk Workshop, which had three principal objectives: (1) to identify the process, procedures and considerations that agencies undertake to make their benefit-risk decision for their jurisdiction and how the process is documented; (2) to discuss how a structured, systematic utilisation of a benefit-risk framework and its documentation with maturing market regulatory agencies can aid both the process and communication within and across agencies; and (3) to make recommendations on how a benefit-risk framework can best be used to optimise internal decision-making and external communication of the decision.

Utilising a benefit-risk framework: How are agencies modifying their review process and how will this enable post-approval assessment?

Dr James Leong

Senior Regulatory Specialist, Health Sciences Authority, Singapore*

UMBRA and the Benefit-Risk Assessment Template

The Universal Methodologies for Benefit-Risk Assessment (UMBRA) is an eight-step overarching benefit-risk framework encompassing the principles that are essential to making a quality benefit-risk decision. UMBRA is supported by the CIRS Benefit-Risk Assessment Template, a tool for documentation that demonstrates the progressive logic and basis for a decision, based on a European Medicines Agency reflection paper.¹ A user manual has also been developed to facilitate use of the template.

A consortium of four international agencies comprising the Therapeutic Goods Administration of Australia, Health Canada, SwissMedic and Singapore's Health Sciences Authority conducted a pilot functionality study of a paper version of the template, a retrospective feasibility study of the electronic version and a prospective feasibility study of

...the summary template was highly fit for purpose in its ability to document relevant information supporting the regulatory decision and the benefits and risks under consideration

the revised template. The outcomes of these studies outlined the template's key attributes, including its provision of a formal structure for benefit-risk assessment and a vehicle for setting internal standards and maintaining consistency for decision making. It was also found that the template allows alignment to the current concept of regulatory processes and enhanced clarity of the decision-making process, that it guides proper documentation and that using it affords the potential for alignment and collaborative work among organisations. Furthermore, the template provides consistency by offering a structure for the systematic articulation of the relative importance of each attribute and fosters clear communication and visualisation of these attributes to various stakeholders.

The prospective study identified changes that were necessary to help achieve the objectives of the template including clarification regarding the template's aims and further guidance in documentation, especially of weights and values. It was further found that more detailed discussion was needed for the provision of safety information and that the user manual should be enhanced to provide these required clarifications as well as to provide examples to illustrate the use of the template. Finally, it was found that a minor rearrangement of document headings would facilitate the flow of information.

Because the prospective study demonstrated the willingness of participants to share the summary section of the template with other stakeholders, it was hypothesised that the summary portion could be used as a stand-alone communication tool, particularly in countries with emerging pharmaceutical markets (Figure 12).

The Singapore HSA study of the benefit-risk summary

As representatives of a regulatory agency within an emerging market country, twelve reviewers within the Health Sciences Authority (HSA) of Singapore reviewed the summary version of the benefit-risk template to assess its appropriateness of documentation and communication of benefit-risk decisions. Using

Figure 12. It was hypothesised that the summary portion of the Benefit-Risk Template could be used as a stand-alone document for benefit-risk evaluation.

recently completed applications to transfer relevant information into the summary template, the review encompassed a wide range of benefit-risk profiles and different reviewers' opinions.

Study results showed that the summary template was highly fit for purpose in its ability to document relevant information supporting the regulatory decision and the benefits and risks under consideration but that more training on the understanding and application of relative importance weighting was required. Reviewers further concluded that although the template facilitated the documentation of study outcome, the contribution of adverse events to an overall decision should be the focus of decision making, with less emphasis on details. Because most agencies already have clinical reports that are used for benefit-risk evaluation, reviewers also expressed concern over the potential for duplication of efforts through use of the template and indicated that the subjective judgements of individual reviewers might limit the template's ability to achieve consistent decision making. Lastly, although it was indicated that the template might allow for communication with a wide range of stakeholders, to avoid misinterpretation of technical data, the publication of only selected sections of the template was recommended for consideration (Figure 13).

transparency and accountability. It can also provide for alignment and preparation for evolving regulatory science, taking into account changes in the benefit-risk balance over the life cycle of a product and the needs of adaptive licensing programmes and responds to new documentary requirements such as Periodic Benefit-Risk Evaluation Reports (PBRERs) and the ICH initiative to include benefit-risk discussion in dossier submissions. The use of the template will continue to be explored among agencies in Indonesia, Malaysia, the Philippines, South Korea, China and Taiwan and elsewhere as a potential tool for the exchange of regulatory information.

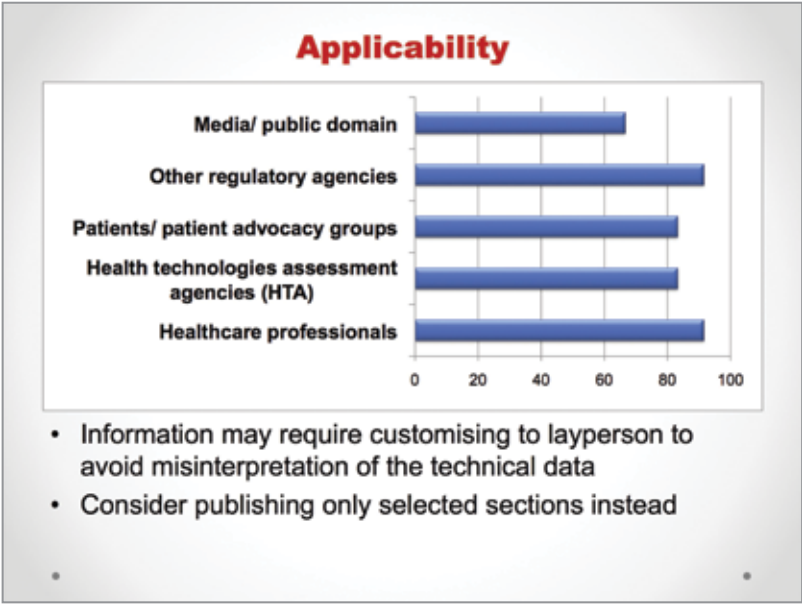
** Since this presentation, Dr Leong has assumed a new position as Head of Education, Center of Regulatory Excellence, Duke-NUS Graduate Medical School.*

Reference

1. Committee for Medicinal Products for Human Use. *Reflection paper on benefit-risk assessment methods on 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 March 2015.

Figure 13. HSA reviewers indicated that the template might facilitate communication with a wide range of stakeholders but might require customisation for laypersons.

Although reviewers expressed some particular reservations regarding its use, it was understood that the Benefit-Risk Summary Template might help reviewers meet increasing demands for



Issues in measuring benefit-risk in the post-approval period:

What are the challenges for regulatory agency acceptance? An agency viewpoint

Dr Co Pham

Senior Science Advisor, Marketed Health Products Directorate, Health Canada

Canadian regulatory framework

In both the pre- and post-approval periods, the Canadian regulatory system is framed around the answers to three key questions:

1. What are the rules for drug approval?
2. What are the requirements for pharmacovigilance by the industry sponsor? and
3. What authority does Health Canada have to request safety, efficacy or effectiveness data from the sponsor?

The answer to the first question is found in Canadian law. Food and Drug Regulation C.08.002 specifies that a new drug submission "shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug..." Whilst Regulation C.08.003.1 states that in examining a new drug submission or supplement to a submission, the Minister "may examine any

information or material filed with the Minister by any person ... to establish the safety and effectiveness of the new drug for which the submission or supplement has been filed." On the basis of these regulations Health Canada can issue a Notice of Compliance (NOC) authorising the marketing of the drug, or it can issue an NOC/c, which grants marketing approval with the condition that the sponsor undertake additional studies to verify the clinical benefit.

In answer to the second question, the market authorisation holder for a new product must track and report drug safety, including serious adverse events reports, annual summary reports, issue-related summary reports and general safety record keeping.

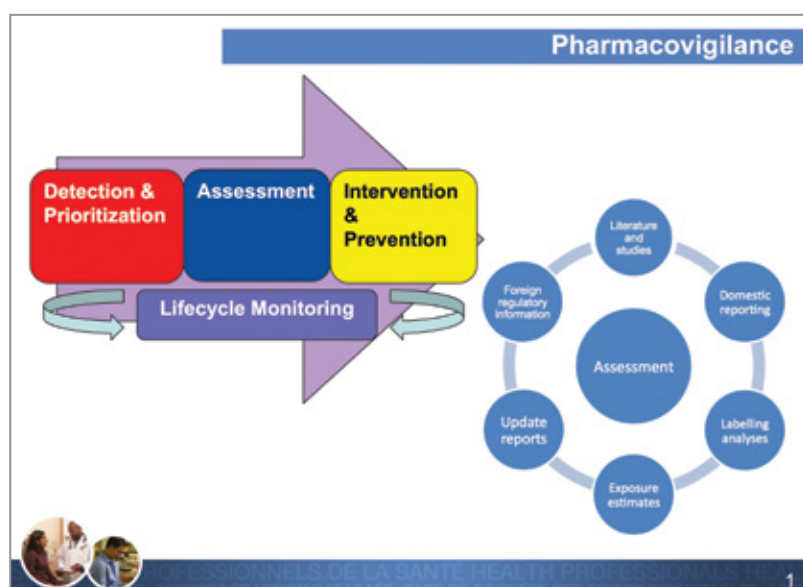
Another regulation provides the answer to the third question. Regulation C.01.013 specifies the requirements for a benefit-risk assessment when the safety data suggest an imbalance in the benefit-risk profile. If such an imbalance is identified, the sponsor may be required to conduct additional studies to verify the clinical benefit of the product.

Pharmacovigilance practices and challenges

In Canada, ongoing risk assessment for medicines is focused on safety and risks are tracked to determine when the balance with benefit is disrupted (Figure 14). Pharmacovigilance is voluntary and industry driven, however, as Canadian law does not mandate that industry provide Health Canada with risk management programmes for approved drugs. When risk management programmes are in place, they are not systematically requested by Health Canada or updated by the sponsors. Periodic Benefit-Risk Evaluation Reports (PBRERs) provide intermittent data from sponsors for approved medicines but these reports cannot be systematically requested and it is unclear how their benefit component will affect the benefit-risk balance for products.

The Canadian Vigilance system comprises voluntary spontaneous reports by citizens and health professionals and mandatory information regarding safety events from sponsors. However, the reporting system is not fully electronic and there remain complexities in determining and interpreting numerator and denominator data. Whilst it is recognised that environmental scanning for safety signals can achieve a high level of results, outcomes, however, are still reactive. The Drug Safety and Effectiveness Network is a developing active surveillance

Figure 14. The process of pharmacovigilance in Health Canada.



research network that aims to provide epidemiologic responses to safety signal queries but does not conduct randomised clinical trials. Post-approval clinical trials that are conducted are driven by industry, have an efficacy focus and are not typically aimed at ongoing safety or effectiveness measures.

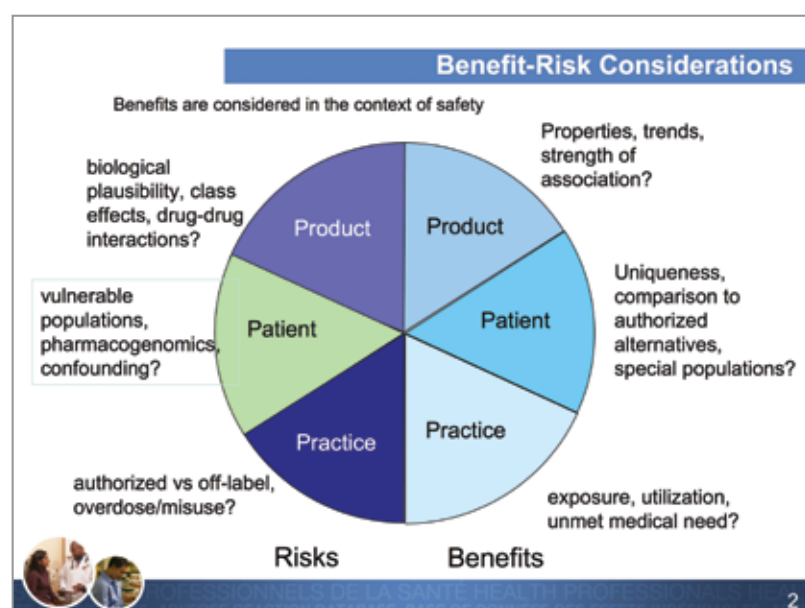
Finally, Health Canada partnerships in pharmacovigilance are still in development. Although there are memoranda of understanding with foreign regulatory agencies, information exchanges with these groups are not always timely or with full disclosure. Provincial and territorial agencies conduct pharmacovigilance activities but the Canadian system is designed for a division of labour and responsibilities and these agencies have different mandates and health objectives from Health Canada resulting in the current paucity of bilateral information exchange.

Measuring benefit-risk throughout the life cycle

In the pre-authorisation phase, Health Canada examines both the benefits and risks of a medicine to grant a licence. In the post-approval timeframe, however, the safety aspect of a medicine is emphasised and the evaluation becomes less balanced.

Post-approval benefit-risk assessment involves a variety of considerations involving the nature of the medicine and healthcare practice (Figure 15). However, the accurate measurement of the real-world effectiveness of an approved medicine

Figure 15. Balancing benefits and risks after the approval of a medicine.



There also needs to be an increase in collaboration among stakeholders to augment the provision of data to accurately weigh the evolving benefit-risk balance and to enhance review capability.

requires more data from post-market experience. There also needs to be an increase in collaboration among stakeholders to augment the provision of data to accurately weigh the evolving benefit-risk balance and to enhance review capability. Better numerator and denominator data from product utilisation and guidance in risk minimisation practices are also required for best post-approval benefit-risk practice.

Although patients can find swing-weighting puzzling at first, once they have experienced it and the concept of comparing added values becomes obvious, the weighting process proceeds smoothly.

Activities on the horizon for Health Canada

The benefit-risk assessment of medicines throughout their life cycle requires openness and transparency among healthcare stakeholders. Health Canada regulatory decisions are developed with the expectation that they will be made available to Canadians proactively and in a timely manner. It is further understood that information intended for the public should be available in plain language, while protecting confidential business information and respecting legislative responsibilities. Accordingly, Health Canada will continue to look for ways to engage Canadians as it undertakes regulatory decision-making processes and to share the results of its consultations.

Health Canada is actively working to meet the challenges in pharmacovigilance and benefit-risk evaluation. Proposed legislation would strengthen surveillance, compel industry to improve labelling, require post-authorisation studies and facilitate recall of unsafe products. Other initiatives that could strengthen these processes include the combination of effectiveness data from PBRERS and risk management plans, collaborative and proactive surveillance of marketed products, the institution of accepted formal benefit-risk framework within Health Canada and the encouragement of high-quality, open communication among stakeholders.

Issues in measuring benefit-risk in the post-approval period:

What are the challenges for regulatory agency acceptance?

A company viewpoint

Dr Stephen Knowles

Senior Director, Global Patient Safety, Medical and Benefit-Risk Management, Eli Lilly and Company

Benefit-risk assessment: When and how

Benefit-risk assessments are required for informed decision making during early clinical development, marketing authorisation applications, Periodic Benefit-Risk Evaluation Reports (PBRERs) and for ad hoc assessments to address new safety concerns.

Several existing frameworks can be used to evaluate the benefit-risk of medicines including CIRS PhRMA BRAT; the CIRS Universal Methodologies for Benefit-Risk Assessment (UMBRA); the FDA framework; Problem, Objectives, Alternatives, Consequences, Trade-offs, Uncertainties, Risk tolerance and Linked decisions (PROACT-URL); and the ICH E2C (R2). These frameworks are qualitative in design and qualitative elements, such as effects tables and key benefit-risk summary tables and visualisation tools such as Forest plots, are confined to the

presentation of supportive data. Although the methodologies have common core concepts, establishing a consensus for their use may be difficult.

Known challenges in the post-approval period

Several challenges for regulatory acceptance of the benefit-risk evaluation of medicines in the post-approval period have been recognised. At approval, the knowledge base about medicines is asymmetrical as the majority of knowledge about a medicine concerns its efficacy whilst its risks remain largely unknown. Furthermore, regulatory agencies can have differing interpretations of the assessments and derive varying conclusions. All are agreed, however, that patient input is important and the use of real-world evidence to inform conclusions about risk and effectiveness is increasing.

The FDA has identified two areas of uncertainty in post-approval benefit-risk assessment that require attention: the translation of pre-market clinical trial data to a much wider, real-world patient population and new findings for approved medicines that emerge from sources with varying levels of rigour.

Many sources for data for approved medicines are available including spontaneous case reports, case series, observational studies and clinical trials, insurance claims data, electronic medical records and adverse event databases. Across these sources, there are differences in methodologies for accrual, levels of evidence, data quality, biases and limitations. Determining how to combine data from multiple sources with different methodologies adds an additional layer of complexity and uncertainty. Despite these challenges, using a structured process for post-approval benefit-risk assessment is possible (Figure 16).

In addition to the previously mentioned expansion in patient population, regulatory agencies face multiple challenges in post-approval benefit-risk evaluation including channelling bias, off-label use and multiple indications. Furthermore, product comparators may change after approval, altering the decision context for benefit-risk assessment.

Patient preferences should be incorporated into benefit-risk assessments. As was illustrated by the reintroduction of Tysabri to the market following patient demand, patients' tolerance of risk may differ greatly from regulators. The challenge, however, lies in the development of

Figure 16. A process for structured benefit-risk assessment in post-approval.

Structured B-R Assessment Process	
Step	Activities/deliverables
Define Context for B-R Assessment	State the specific objective/question to be considered in B-R assessment • Context defined by drug dose, formulation, medical need, indication, population, comparator(s), stakeholder perspective (e.g., regulator, payer, patient)
Identify B-R Outcomes	• Given the context, identify important outcomes likely to influence the B-R balance • Build initial "Value Tree" (graphic) and define outcome measures • Document rationale for including or excluding outcomes
Data Documentation	• Identify data sources (e.g., clinical trials, published literature) • Extract relevant data and populate source tables • Document the rules and decisions for including or excluding data/data sources
Customize the Framework	• Modify the Value Tree based on review of the data and clinical /medical expertise • Refine the outcome measures/endpoints: document decisions • May remove outcomes with higher degrees of uncertainty in level of evidence, relatedness to a product, or relative value to different stakeholders
Assess Outcome Importance	• If applicable, apply ranking or weighting according to the importance of individual outcomes to stakeholders
Display and Interpret Key B-R Measures	• Provide readily understood data displays (graphs /tables) to aid interpretation • Provide relevant information needed for discussion of the B-R Profile • Summaries should aid decision making rather than deliver a conclusion or interpretation in isolation

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a methodology for the incorporation of patient perspective.

The use of effectiveness data from real-world evidence is beginning to inform regulatory decisions; however, changes in key benefits and risks are not captured consistently in observational data. When using this real-world evidence to corroborate clinical trial findings it must be considered if it can also be used to mitigate or negate what had been regarded as key risks. In addition, whether post-approval effectiveness data can be used in labelling in the same way the post-approval safety data are already used remains to be determined. There needs to be an increased focus on methodology and data quality in the post-approval period that will require expertise in pharmacoepidemiology among assessors.

Required post-approval safety studies, including observational studies and registries, are now the norm, adding to the regulatory complexity of ongoing post-approval benefit-risk assessments. This risk evaluation and management can help to minimise risk, allowing the approval of new medicines that might otherwise be rejected. At

Patient preferences should be incorporated into benefit-risk assessments...patients' tolerance of risk may differ greatly from regulators. The challenge, however, lies in the development of a methodology. . .

the same time, risk needs to be assessed on an ongoing basis and the burden on the healthcare system can actually create an impact on access to medicines that reduces benefit.

Industry is now transforming benefit-risk assessments from the development world into the post-approval period, using new frameworks and methodologies. Regulatory feedback on post-approval benefit-risk assessments; however, has entirely centred on risk for established products. The best methods for translating post-approval data into regulatory action remain to be determined as does determining the strength of evidence that would be required to change a potential risk to an identified risk and whether a risk that is refuted by studies conducted after marketing could be removed from labeling.

New approaches and technologies to capture benefits and risks in the post-approval phase – What are the practical and regulatory challenges? FDA Viewpoint

Dr Gerald J Dal Pan

Director, Office of Surveillance and Epidemiology, Food and Drug Administration, USA

The continuum of knowledge about medicines

Knowledge concerning medicines develops over a continuum. In the pre-approval phase, data on a new drug accrue through the controlled development process, leading to an evaluation of its benefit-risk balance. Once a drug is approved, however, data about its benefits may become static, whereas information about its risks continues to accumulate.

Benefit data on older drugs can be particularly difficult to access and generally, only information derived from small clinical trials and case series

are available for medicines for less common conditions. The efficient use of post-approval data demands learning as much as possible about an approved medicine, as quickly as possible and as accurately as possible, recognising that there are trade-offs that involve time, sensitivity and predictive value.

Current US data systems essentially provide insurance claims information. As patients move from one insurer to another, they disappear from one database and reappear in another, truncating follow-up time. At present, there are few or no linkages across coverage systems, little or no data on non-prescription drug use, a lack of or little or no data on important medical characteristics that are not routinely coded and little linkage to external data sources.¹

Mini-Sentinel

In 2008, the US Food and Drug Administration (FDA) initiated development of the Sentinel system for active surveillance for safety of FDA-regulated products. As part of that programme, the Mini-Sentinel pilot programme, which was developed in collaboration with Harvard University Medical School, focuses on monitoring the safety of drugs, vaccines, other

Intracranial (ICH) and Gastrointestinal (GIH) Bleeding Events in New Users of Dabigatran and Warfarin: Mini-Sentinel (Oct 2010 – Dec 2011, Incidence Rate = New Events/100,000 Days at Risk)

Dabigatran		Pre-existing Cond. Requirement	Warfarin	
N	Incidence Rate		N	Incidence Rate
10,569	2.2	Atrial Fibrillation – 183 days	43,351	5.8
9,216	2.2	Atrial Fibrillation – 365 days	34,800	6.1
12,161	2.4	No requirement – 183 days	119,470	5.0
10,464	2.5	No requirement – 365 days	97,267	5.2

1

Figure 17. A Mini-Sentinel analysis showed that the incidence rates for intracranial and gastrointestinal bleeding events were consistently lower with dabigatran than with warfarin.

Figure 18. Pharmacoepidemiologic study results based on 2010-2012 Medicare data showed that dabigatran was associated with a lower risk for stroke and death but a higher risk for gastrointestinal bleeding than warfarin.

biologics and devices through the collection of healthcare data from multiple sources. Mini-Sentinel provides multiple ways to query data:

- Summary tables – pre-calculated tables that are updated quarterly
- Enhanced modular statistical analysis system (SAS) programs – a reusable programme that provide some adjustment for confounding and flexibility in eligibility/exclusion criteria, with more complex outcome definitions
- Prospective Routine Observational Monitoring Program Tools (PROMPT), with semi-automated, increased adjustment for

	Incidence rate per 1,000 person-years		Adjusted hazard ratio (95% CI)
	Dabigatran	Warfarin	
Ischaemic stroke	11.3	13.9	0.80 (0.67-0.96)
Intracranial haemorrhage	3.3	9.6	0.34 (0.26-0.46)
Major GI bleeding	34.2	26.5	1.28 (1.14-1.44)
Acute MI	15.7	16.9	0.92 (0.78-1.08)
Mortality	32.6	37.8	0.86 (0.77-0.96)

Once a drug is approved, however, data about its benefits may become static, whereas information about its risks continues to accumulate.

confounding with propensity score matching; complex statistical designs; sequential testing; and several design options

- Protocol-based assessments – custom SAS programs for in-depth assessments and complete epidemiologic studies

Dabigatran and bleeding complications

Dabigatran was approved in 2010 for treatment of non-valvular atrial fibrillation at which time it was anticipated that a protocol-based assessment of the drug in Mini-Sentinel would be performed. When a number of adverse events including intracranial haemorrhage [ICH] and gastrointestinal haemorrhage (GIH) were spontaneously reported after approval, Mini-Sentinel analysis was conducted to determine the significance of these adverse events.

This analysis compared dabigatran with warfarin among new users of these drugs. Patients were included who, during the 183 days prior to index dispensing, had not received either medicine, had no occurrence of ICH or GIH in an in-patient or emergency room setting and had a diagnosis of atrial fibrillation (AF).

Additional analyses defined new use by single drug, removed the requirement for AF and used an interval of 365 days instead of 183 days. The Mini-Sentinel analysis showed that the incidence rates (new events per 100,000 days at risk) for ICH and GIH were consistently lower with dabigatran (2.2 to 2.5) than with warfarin (5.0 to 6.1; Figure 17). Similarly, the incidence rates for GIH were lower for dabigatran (1.4 to 1.6) than for warfarin (3.1 to 3.7). This suggested an appropriate public health risk for dabigatran. However, study limitations included the lack of adjustment for confounding data or diagnosis exclusions, lack of data on deaths in the absence of medical billing and algorithms that were not validated in observational data.

As a result, the FDA conducted a full pharmacoepidemiologic study in collaboration with the Centers for Medicare and Medicaid, using Medicare data. This observational cohort study of Medicare beneficiaries examined new users of dabigatran and warfarin who had received a diagnosis of AF in the 6 months prior

to the first dispensing of medication. The data were analysed for ischaemic stroke, ICH, major GIH, myocardial infarction (MI) and death.

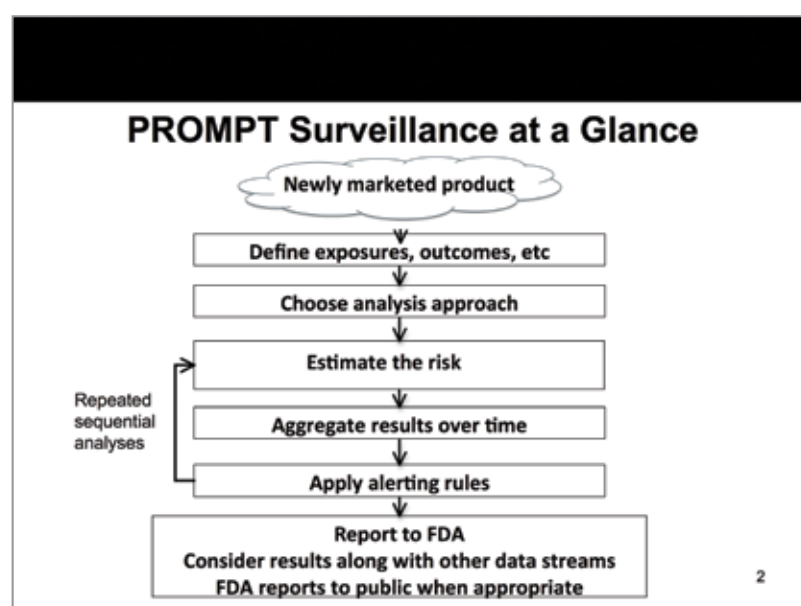
After examining records for more than 134,000 patients over 37,500 person-years of follow-up and adjusting for many potential confounders, the FDA concluded that dabigatran was associated with a lower risk for stroke (incidence rate 11.3 vs 13.9 per 1,000 person-years) and death (32.6 vs 37.8) but a higher risk for GIH (34.2 vs 26.5) than warfarin (Figure 18).²

Directions for the future

The dabigatran studies analysed data for particular points of time. To move toward the routine analysis of safety signals the FDA expects to use Mini-Sentinel with PROMPT to allow automated, semi-adjusted analyses with several epidemiologic designs. These sequential analyses will allow for early detection of outcomes for new molecular entities (Figure 19)

In a PROMPT analysis, the FDA selects the exposure and outcomes of interest and Mini-Sentinel and FDA investigators select among pre-programmed modules of design approaches and determine if one-time or sequential assessments will be used. Investigators then define the subject populations, construct the analytic data set, select among pre-programmed statistical approaches, including propensity score matching, risk estimation and threshold for risk assessment and produce partially adjusted risk estimates across data partners.

Figure 19. US FDA post-approval surveillance using Prospective Routine Observational Monitoring Program Tools (PROMPT).



It remains to be determined if post-approval point-in-time analyses can be replaced by sequential analyses. A number of factors require evaluation: The sequential analysis system relies on coded outcomes for which outcome misclassification is a major concern. In addition, inclusive algorithms have high sensitivity but low predictive value and narrow algorithms have low sensitivity but higher predictive value.

The impact of sensitivity and positive predictive value in planning for sequential surveillance was studied using modeling and simulation in a vaccine example. Results indicated that sequential testing can lower the time to signal detection as non-differential outcome classification generates longer surveillance time and less timely safety signal detection but no misclassification. When sensitivity is high but predictive value is low, the time to signal detection is relatively shorter than when sensitivity is low but the predictive value is high.³

Dr Dal Pan and colleagues also studied the use of post-approval surveillance in orphan therapeutics to determine if sequential analyses in disease-specific distributed research networks could yield potential findings that are important enough to alter the risk-benefit balance of the therapy and that are therefore worth detecting. The researchers concluded that although it is hypothetically possible to discover safety signals with sequential studies significantly faster than with non-sequential studies, low rates of prevalence of orphan diseases made the acquisition of the necessary population sample challenging to attain within the necessary time limits for research.⁴ The FDA will continue to research innovative approaches and technologies to determine the benefits and risks of medicines after approval.

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New approaches/technologies to capture benefits and risks in the post-approval phase –

What are the practical and regulatory challenges? A company viewpoint

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The Biogen Idec approach to structured benefit-risk assessment

There is a high degree of organisational interest and support for structured benefit-risk assessment at Biogen Idec. It is understood that structured benefit-risk methodologies, including frameworks, tools and models, are invaluable in facilitating a good decision. However, frameworks, tools and models assist but do not replace human judgement, which plays an essential role in benefit-risk decision-making.

Benefit-risk decisions at Biogen Idec are a collaboration involving input from safety, clinical development, regulatory and biometrics functions. During the initial marketing application process, as well as the post-approval phase, the company's benefit-risk analytical methods are compatible with the CIRS Universal Methodology for Benefit-Risk Assessment

(UMBRA) overarching framework. Both formal and informal approaches are employed including the CIRS Benefit-Risk Action Team (BRAT) framework, patient risk-benefit conjoint assessments, Markov modelling, number needed to treat/number needed to harm (NNT/NNH) analyses and the FDA benefit-risk framework.

A case study: structured benefit-risk assessment for fampridine in multiple sclerosis.

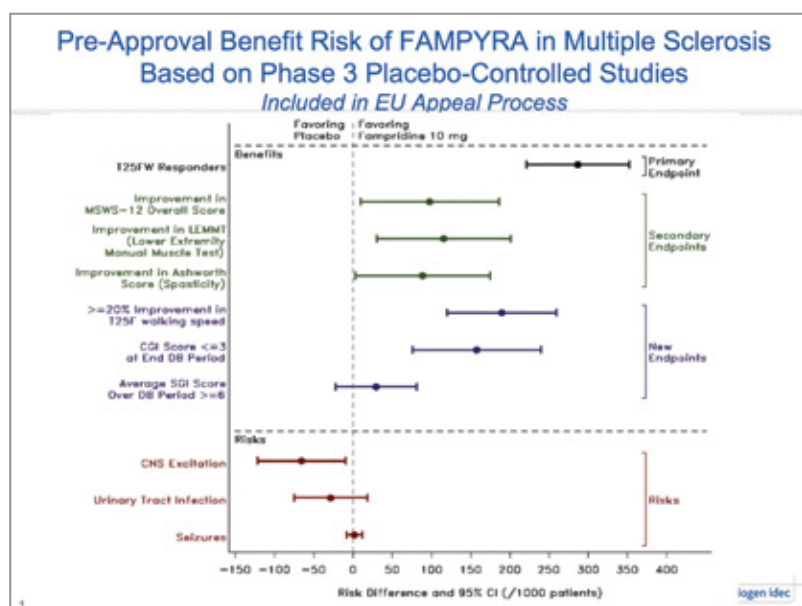
Fampridine (FAMPYRA) is a prolonged-release 4-aminopyridine, which is a voltage-dependent potassium channel blocker. It was approved for improving walking in patients with multiple sclerosis (MS) in the US (2010) and the EU (2011) as well as in other countries. In 2010, fampridine received an initial negative opinion from the EMA Committee for Medical Products for Human Use (CHMP) because of uncertainty regarding the clinical meaningfulness of the primary outcome (timed 25-foot walk), as well as the risk of seizure. An appeal was filed that included a benefit-risk analysis based on Phase 3 placebo-controlled studies. This analysis presented study results showing a graphical categorisation of benefits and risks, with a delineation of those favouring fampridine and those favouring placebo (Figure 20). The evaluation clearly demonstrated the favourable benefit-risk balance for fampridine and conditional approval was granted but with a requirement for an additional study to confirm fampridine's benefit beyond walking speed.

Structured benefit-risk assessment in the post-approval setting

The required post-approval, double-blind clinical study involved 68 patients treated with fampridine and 64 patients treated with placebo in the United Kingdom. Patients received the study medication twice daily for 6 months and walking was assessed by means of the Multiple Sclerosis Walking Score 12 (MSWS-12). Patients treated with fampridine demonstrated significant improvement across multiple thresholds, with a response rate of 48.5% compared with 28.1% for placebo, confirming the efficacy of fampridine in improving walking.

An analysis of the occurrence of seizure from post-approval data showed an incidence of 0.3% per year, based on approximately 100,000 patient-years of treatment. Seizures tended to occur during the first month of treatment, primarily to patients who had risk factors or confounding factors for this event. Most

Figure 20. Pre-approval benefit-risk analysis demonstrating the overall benefit of fampridine.



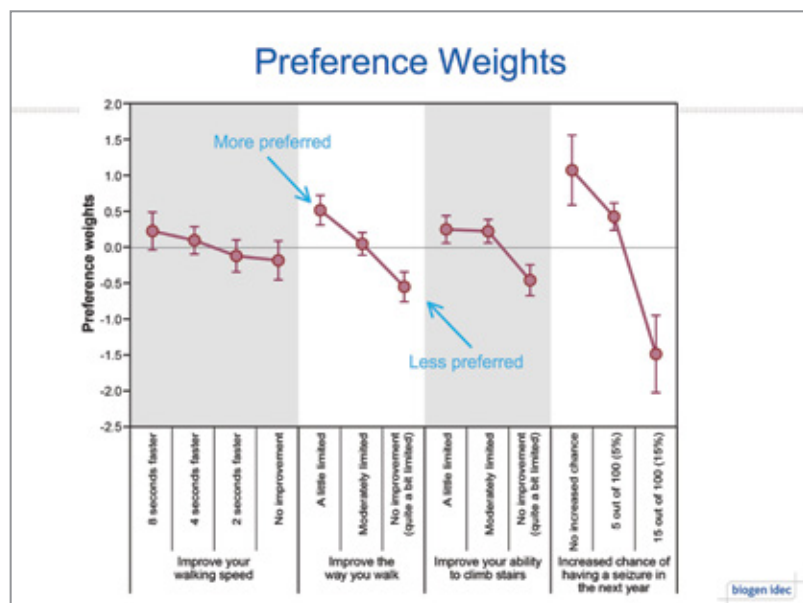


Figure 21. Weighted patient preferences for multiple sclerosis treatment.

seizures were uncomplicated and most patients recovered without sequelae. Additionally, it should be noted that MS itself is associated with an increased risk of seizure.

Because of the post-approval incidence of seizures in patients receiving fampridine, a patient risk-benefit conjoint analysis was conducted to quantify patients' willingness to accept treatment-related risks in exchange for improvements in outcomes. Data were collected from patients who each answered 10 questions that involved a consideration of trade-offs in risks and outcomes. From the responses, a maximum acceptable risk was calculated and patients' preferences were weighted (Figure 21).

Conclusions

The analysis showed that overall, patients were willing to accept a maximum risk of 4.6% for seizure in return for an 8-point improvement

It is understood that structured benefit-risk methodologies, including frameworks, tools and models, are invaluable in facilitating a good decision.

in the MSWS-12. The fact that the maximal acceptable risk of seizure exceeded the incidence of seizure among fampridine-treated patients led to the conclusion that MS patients are willing to accept the risk of seizure in exchange for the walking improvement provided by the medication. This finding and other supportive data were submitted to global regulatory authorities in January 2014.

The case study with fampridine illustrates the utility of using various approaches for the structured assessment of benefits and risks. Experience has shown both strengths and limitations for structured benefit-risk assessment, which assists but does not replace human judgement. These assessments, which may be used in the pre- and post-approval settings, may facilitate transparent discussions and decisions on benefit-risk both internally and with regulators. Whilst no one method fits all cases, multiple methods are available. This multiplicity and lack of a standard model may be considered a limitation, however, as regulators and industry may not be aligned on the best approach. Additionally, because choosing benefits and risks for evaluation can be subjective, the rationale for their selection should be transparent.

Next steps for industry include exploration of a variety of methods to facilitate internal decision making in earlier phases of the pipeline and to engage regulators in the review of pharmaceutical products in early development.

Benefit-risk assessment: PMDA perspective

Dr Akiko Hori

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Risk management plan in Japan

The procedures of the Risk Management Plan in Japan (J-RMP) are required by the Pharmaceutical and Medical Device Agency (PMDA) for new drugs, biosimilars and follow-on biologics for all approval applications submitted on or after 1 April 2013. The J-RMP involves a pharmacovigilance plan, risk minimisation actions and additional activities (Figure 22).

Established in 2012 and supported by funding from the Ministry of Health, Labour and Welfare (MHLW), the Study Group on J-RMP, comprising researchers from academia, regulatory bodies and industry, examines measures to effectively implement the J-RMP. Activities include four key tasks:

- Studying the practical status of pharmacovigilance and risk minimisation activities in Japan and identifying issues to be resolved
- Collecting up-to-date information on risk management regulations and activities in the European Union (EU) and the US

The agency recognises that a structured approach to post-approval benefit-risk analysis is required to facilitate more appropriate decision-making.

- Studying the methodologies of benefit-risk evaluation, especially in the post-approval stage
- Studying the methodologies of evaluation and assessing the outcome of risk minimisation activities.
- It is expected that in 2015, the study group will suggest future directions for the improvement of benefit-risk assessments in Japan.

Current benefit-risk assessment in Japan

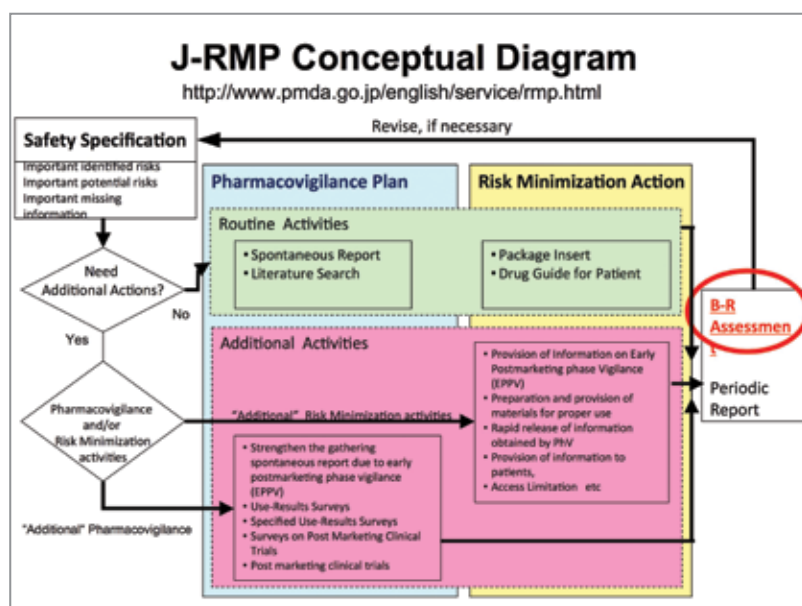
In 2008, the PMDA published *Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drugs*. This guideline uses a checklist approach, summarising the points that must be considered during the evaluation process after a new drug application has been submitted. Considerations for assessment include the development of concept or design, reliability assurances, efficacy, reproducibility of study results, benefit-risk assessment and considerations regarding available treatments for serious or rare diseases and overall societal needs.

The PMDA focuses on a qualitative benefit-risk analysis in its pre-approval evaluation. This analysis examines the question, "Can the recognised risks be controlled and are the risks acceptable when considering the benefits?" The following points must be addressed as part of the assessment:

- Has efficacy been clearly confirmed?
- Have factors related to the recognised risk been clearly identified?
- Has any effective treatment been identified to prevent/inhibit occurrence of the recognised risk?
- Is the recognised risk acceptable, even if it is serious, when considering the benefits?

Each consideration point is described in the review report; the agency recognises that there are currently no standardised visualisation tools for pre-approval benefit-risk evaluation that have achieved international consensus.

Figure 22. Risk Management Plan in Japan (J-RMP)



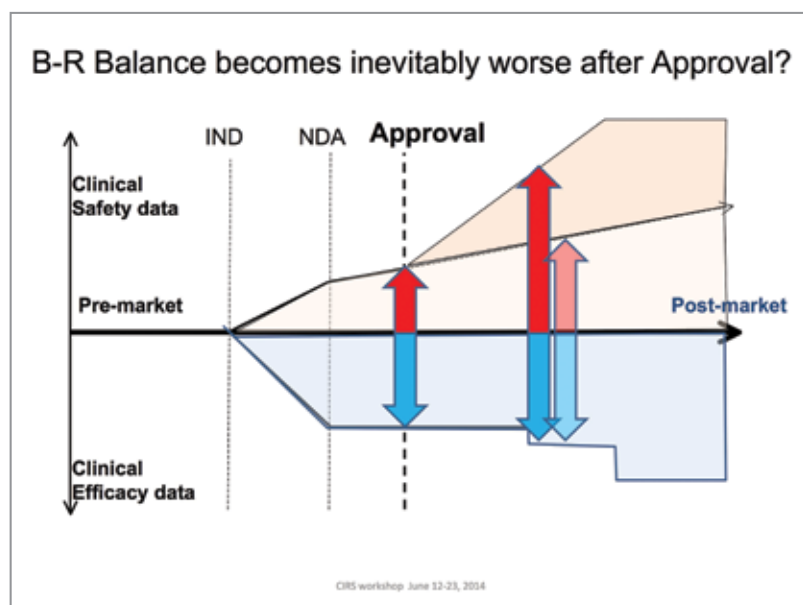


Figure 23. Post-approval benefit-risk balance may be skewed by a lack of accrued efficacy data.

To reconfirm its clinical usefulness, a new drug is reevaluated 4–10 years after approval and a drug containing a new active ingredient is reevaluated 8 years after its initial marketing authorisation. All the collected post-approval data are reviewed and evaluated on the basis of the benefit-risk balance, as a result of which the drug will be classified into three categories. Category 1, which means that there is no need to change indications or dosage and administration, Category 2, which means that indications or dosages and administration must be changed or Category 3, which means that the drug must be withdrawn from the Japanese market. Re-examination reports are posted on the PMDA website in Japanese.

Post-approval benefit-risk assessment of gefitinib

The case of gefitinib provides a unique example of the use of a randomised clinical trial in benefit-risk re-assessment in the post-approval period. Gefitinib was approved in July 2002 in Japan for the management of locally advanced or recurrent non-small-cell lung cancer. Japan was the first country where gefitinib was approved and its approval there was mainly based on a high response rate in Japanese patients demonstrated in a global phase II trials. Three months later, however, a higher-than-expected incidence of interstitial lung disease (ILD) was observed in patients receiving gefitinib

compared with those receiving conventional chemotherapy. As a result, safety measures were taken by the drug sponsor, the MHLW and the PMDA and drug use surveillance and a nested control study was conducted by the sponsor. Additionally, two randomised controlled clinical trials were independently conducted by a research group in Japan in which patients with an epidermal growth factor receptor (EGFR) mutation were randomly assigned to receive gefitinib or standard chemotherapy. The studies' results showed that first-line gefitinib in patients with advanced NSCLC who were selected on the basis of EGFR mutations improved progression-

free survival, with acceptable toxicity as compared with standard chemotherapy. As a result of these trials, the sponsor applied for a re-examination and submitted a supplemental new drug application for gefitinib in advanced EGFR+ NSCLC; approval for this indication was granted in 2011.

The gefitinib case is unusual in that safety and efficacy information were obtained simultaneously, whereas in most cases, efficacy data are not obtained while post-approval safety data are accumulating, resulting in the appearance that the safety profile of a drug is becoming less favourable (Figure 23).

Moving forward

Although PMDA has conducted post-approval benefit-risk assessments and has established internal rules for these evaluations, it has not yet published a document that summarises the basic principles and major points that must be considered in evaluating drugs after launch. The agency recognises that a structured approach to post-approval benefit-risk analysis is required to facilitate more appropriate decision-making. As previously mentioned, the J-RMP Study Group will produce recommendations for the enhancement of benefit-risk assessment in Japan in 2015 by analysing prior regulatory decisions and accruing more experiences with the J-RMP review process. As part of this work, actual points for consideration of benefit-risk assessment at the milestones of the J-RMP must be identified and methodologies developed for the assessment, description and visualisation of the benefit-risk balance in the post-approval "real world" medical setting.

Recommendations for measuring benefit-risk in the post-approval space: IMI PROTECT

Professor Deborah Ashby

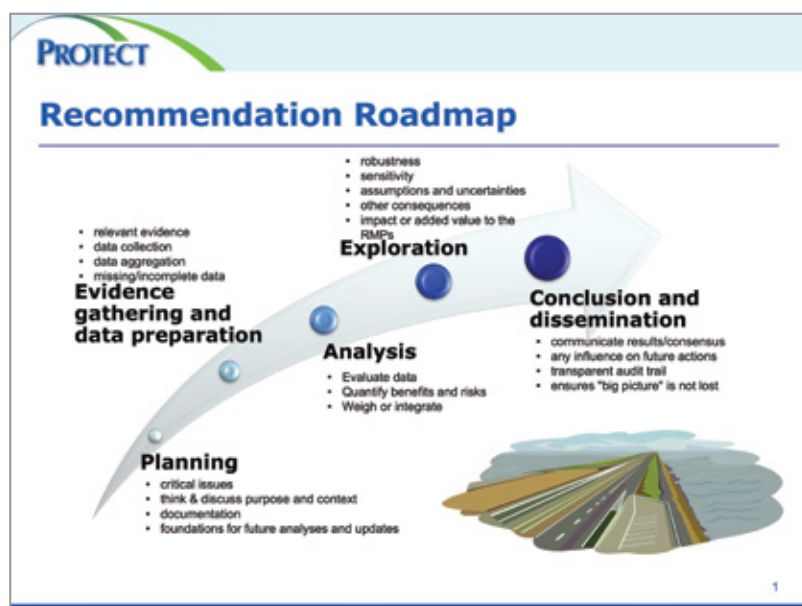
Co-Director of Imperial Clinical Trials Unit and

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IMI PROTECT Work Package 5

Funded under the Innovative Medicine Initiative (IMI), the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) Work Package 5 consisted of testing and assessing methodologies for the benefit-risk analysis of medicines and developing tools for the visualisation of those benefits and risks. The project was jointly led by the European Medicines Agency (EMA) and GSK and took into account individual and population-based decision making that included all stakeholders, including patients, healthcare prescribers, regulators and industry, from post-approval through the product's lifecycle. Toward this end, PROTECT developed a stepwise organisation of benefit-decision making that includes planning, evidence gathering and data preparation, analysis, exploration and conclusion and dissemination, each with a suggested methodological toolbox (Figure 24).

Figure 24. Steps in making benefit-risk decisions.



The choice of an approach to measure the benefits and risks of a medicine should match the complexity of the problem.

Tools for each stage of decision making

During the planning stage, which is arguably the most important step in decision making, the purpose of the evaluation is identified and the context established. This step lays the foundation for future analyses and updates and allows all subsequent steps to fall into place. Useful methodologies in this step include the PROBLEM, Objectives, Alternatives, Consequences, Tradeoffs, Uncertainty, Risk tolerance and Linked decisions (PROACT-URL) and the framework offered by the Centre for Innovation in Regulatory Science - Pharmaceutical Researchers and Manufacture of America Benefit-Risk Action Team (CIRS PhRMA BRAT) programme. Tree diagrams and structured tables provide useful means of visualisation in this step.

At the evidence gathering and data preparation stage, evidence is identified and extracted, it is determined what data should be collected and multiple sources of evidence are aggregated. Methodologies that are recommended for this stage include indirect/mixed treatment comparisons (ITC/MTC) and the probabilistic simulation method (PSM). Visualisation techniques such as structured and colour-coded tables and network graphs enhance the communication of data.

At the analysis stage, data are evaluated, the magnitude of benefits and risks are quantified and quantitative measures are weighed or integrated. Useful analytic methodologies include metric indices that provide numerical representations of benefits and risks, such as number needed to treat/number needed to harm (NNT/NNH) and impact numbers; quantitative frameworks that model the benefit-risk trade-off and balance benefits and risks such as multi-criteria decision analysis (MCDA) and stochastic multi-criteria acceptability analysis (SMAA); and utility survey techniques that elicit stakeholders' preferences such as discrete choice experiments (DCE). There are many methods for visualising data analysis that can be used according to the user's need and preference and some which may be quite complex to construct. These methods include those that are specific to tools such as swing-weighting scales and MCDA

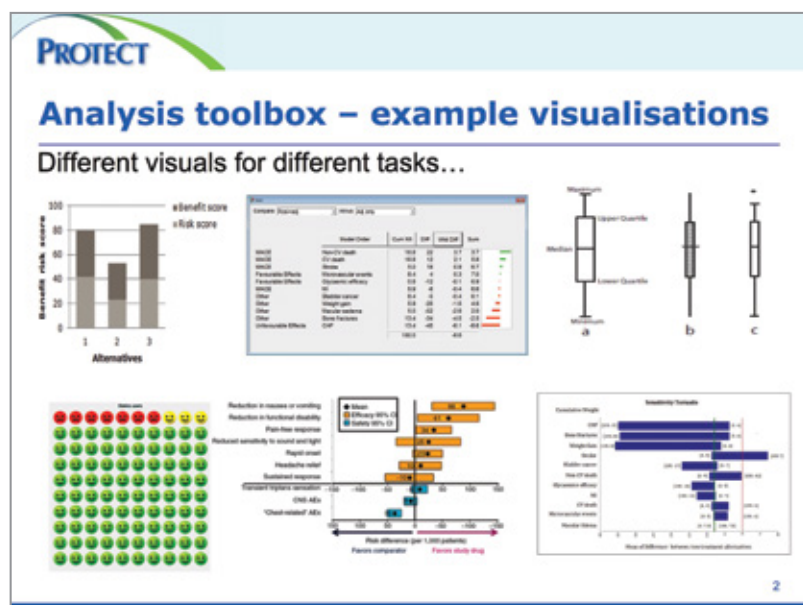


Figure 25. There are multiple options for visualising benefits and risks during the analysis stage of decision making according to user need and preference.

difference displays as well as tables, forest plots and stacked or bar charts (Figure 25).

At the exploration stage, the robust nature and sensitivity of results are assessed and future consequences are evaluated. Recommended methodologies for this stage include ITC/MTC, PSM, SMAA and utility survey

techniques such as DCE, analytical hierarch process (AHP), swing-weighting, Measuring Attractiveness by a Categorical Based Evaluation Technique (MACBETH). Preferred visualisation methodologies include the box, distribution, scatter and forest-interval plots, as well as tornado diagrams and user-interactive techniques.

Conclusions

The choice of an approach to measure the benefits and risks of a medicine should match the complexity of the problem. In most simple problems, a simple descriptive framework is likely to be sufficient. For more complex problems, a framework supplemented by quantitative models can facilitate consideration of trade-offs amongst the benefits and risks, address uncertainty and potentially lead to a more comprehensive overall assessment. To understand the perspective of a particular stakeholder, elicitation of preference values for weighing benefits and risks may be required.

The report of PROTECT WP5 can be found at <http://protectbenefitrisk.eu/> and also <http://www.imi-protect.eu/results/shtml#>.

Clinical context for benefit-risk assessment:

Understanding patients' perspectives — FDA viewpoint

Dr Theresa Mullin

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Understanding patients' perspectives

The US Food and Drug Administration (FDA) recognises that patients are uniquely positioned to inform FDA understanding of the therapeutic context for drug review. However, mechanisms for obtaining patient input have been often limited to discussions related to specific applications under review. In consideration of this need and as a component

The US Food and Drug Administration (FDA) recognises that patients are uniquely positioned to inform FDA understanding of the therapeutic context for drug review.

of its commitments to the fifth iteration of the Prescription Drug User Fee Act (PDUFA V), the FDA has embarked on programme of patient-focused drug development (PFDD).

As part of the PFDD programme, the agency will convene at least twenty PFDD meetings through 2017 in order to advance a systematic approach to gathering patient input. To date, sixteen disease areas had been selected that represent diversity in the range of diseases encountered in regulatory decision making, diseases that are chronic, symptomatic and that affect a patient's functioning and daily activities. Selection also took into consideration diseases that currently

have few or no therapies or for which current therapies do not directly affect how a patient feels or functions. Diseases were also evaluated for which important aspects have not been formally captured in clinical trials, those that encompass a range of severity or that exact a severe impact on identifiable sub-populations such as children or that affected a range of population sizes. At the time of this Workshop, eight PFDD meetings had been held with eight more scheduled to take place (Figure 26).

Patients may also be involved in on-demand EMA functions for specific diseases. These include work in scientific advisory groups (SAGs), the CHMP, the Scientific Advice Working Party (SAWP) and possibly the CAT, PRAC and COMP. In these on-demand functions, patients can be informative regarding the disease and meaningfully contribute to the discussions; for example, patients may offer oral presentations in CHMP meetings, especially in cases in which the CHMP is moving toward a negative decision. However, in SAGs, patients must be prepared and fully participate in deliberations to achieve the full value of patient involvement. Issues that must be determined in patient involvement include whether they should be in attendance during company presentations or in a separate room where an interpreter could translate questions and answers into non-technical language.

Meeting format

Whilst all PFDD meetings are tailored to the needs of a specific disease, they all share a

similar design that encompasses the state of drug development, specific interests of the FDA review division and the needs of the patient population. Discussions are conducted in a way to elicit patients' perspectives on their disease and on treatment approaches and patient input for the meetings is generated in a variety of ways. Before the meeting, polling questions are posed to participants and the results of the poll are used to aid the discussion. Typical questions address issues likely to be significant in the drug development and review processes:

- Which symptoms have the most significant impact on your daily life or your ability to do specific activities?
- How well does your current treatment regimen treat the most significant symptoms of your disease?
- What specific things would you look for in an ideal treatment for your condition?
- What factors do you take into account when making decisions about using treatments, or when deciding whether to participate in a clinical trial?

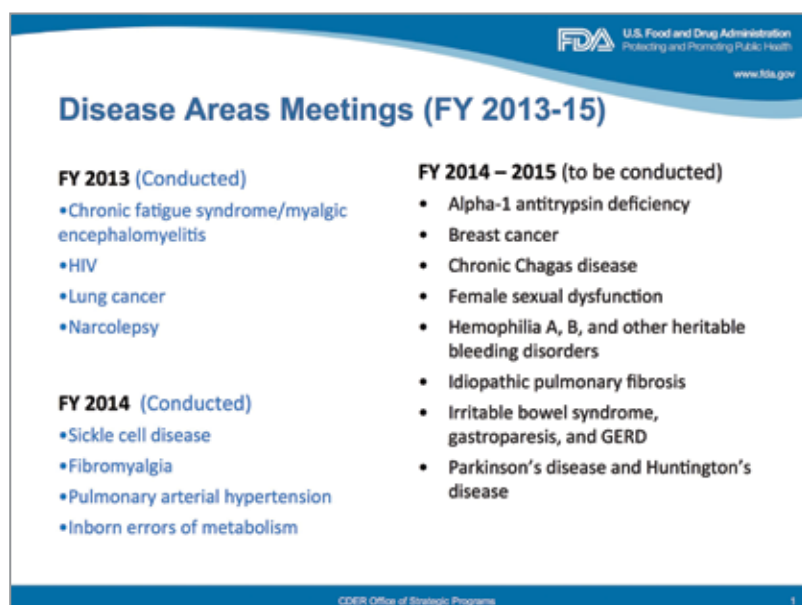
During the meeting, patient panellists make comments and discussion is facilitated with patients in the audience. Patients have provided a great variety of individual, personal, evocative statements in response to the polling questions and to the meeting facilitation such as descriptions of different kinds and degrees of pain (Figure 27). Importantly, many participants have been willing to talk about things they have not previously discussed even with their healthcare providers.

In addition, an interactive webcast and telephone line allow participation by people who are unable to attend the meeting in person. After the meeting, a federal docket allows submission of written comments over a period of a few months.

Attendance

Using websites, social media and flyers, patient advocacy groups such as Unite Narcolepsy have played an important role in publicising PFDD meetings and encouraging patient registration. The groups have also conducted preparatory webinars for the effective use of the patient voice, facilitated docket submissions, organised transportation and hosted social events before and after the meetings.

Figure 26. Sixteen US FDA PFDD meetings have been held or are planned.



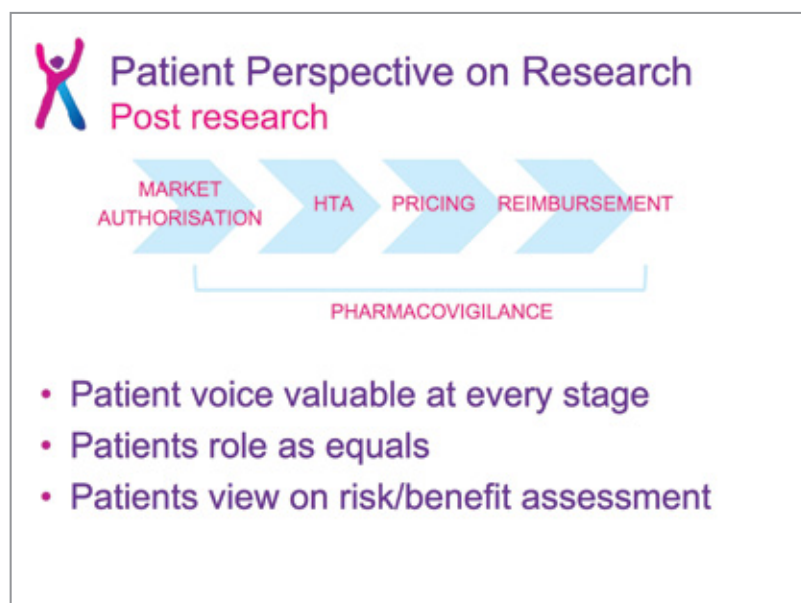


Figure 27. Patients have provided a great variety of individual, personal, evocative statements.

There has been a good level of participation in the PFDD meetings to date. Typically, the number of in-person patient participants has ranged from 30 to 75 and the number of other participants, such as those from the National Institutes of Health or industry, has ranged from 30 to 70. In addition, approximately 125 to 325 participants have accessed the meetings through webcasts and docket submissions for meetings have ranged from 15 to 400, depending on the disease being addressed.

Outcomes

After each meeting, a report is produced that faithfully captures patient input from the multiple information streams. At the time of this Workshop, reports had been produced for the meetings on chronic fatigue syndrome and myalgic encephalomyelitis, lung cancer and human immunodeficiency virus (HIV) and can be found here.

Input from the meetings is useful to FDA staff who are conducting benefit-risk assessments for products under review as well as to drug sponsors who are developing new medicines. This input could also be more broadly valuable in helping to identify specific areas of unmet need in a patient population or outcome measures that could be developed for clinical trials.

The FDA has found the patient input obtained from the PFDD programme to date to be both powerful and insightful. Results have shown that PFDD meetings can be effectively tailored to fit the needs and interests of both the agency and the patient community and with each new meeting the agency continues to learn how to create maximum value in the public meeting process. Lessons learned include how to reach a broad population reflecting a range of experiences and perspectives, how to enable patients to feel that their perspectives have been shared and how to represent the input in an accessible summary report. Finally, there has been significant external interest in the expansion of efforts to gather and use patient input in drug development and review.

Industry perspective on understanding the relative importance of benefits and risks to patients

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Patient-focused drug development and benefit-risk assessment

There is growing international momentum among regulators, industry and patient groups for an increased patient focus in drug/device development and regulatory activities. Clinical development functions that may benefit from incorporating the patient viewpoint include defining the medical context for a potential new treatment; including a clear understanding of the nature of life with the illness and the medical need given available treatments; testing device prototypes; determining the most important endpoints for efficacy and safety; identifying study designs that simplify recruitment; serving as peer advocates during informed consent and sharing the results of assessments of new medicines to the patient community. One of the most critical roles for patients though, is in the assessment of benefit and risks for potential new

There is growing international momentum among regulators, industry and patient groups for an increased patient focus in drug/device development and regulatory activities.

medicines. Patients' health and lives are on the line and they experience the disease, treatment benefits and treatment side effects directly. Patient-focused benefit-risk assessment entails determining the most important endpoints for patients, the relative importance of benefits and harms, and the degree to which patients would accept risk for a given benefit or would require benefit for a given risk.

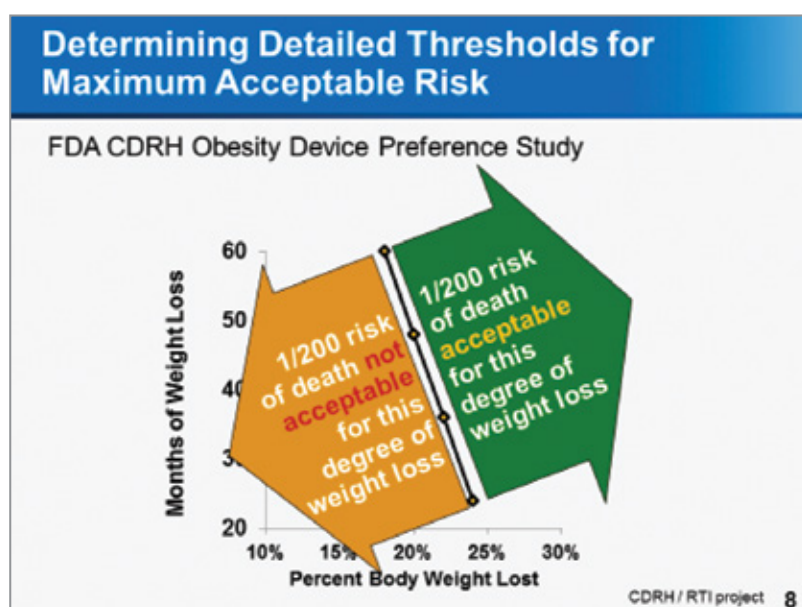
Patient preference studies

Numerous types of insights can emerge as the result of patient preference studies. Results of a recent FDA Center for Devices and Radiological Health Obesity Device project conducted with RTI Health Solutions demonstrated the potential of a preference study to determine detailed thresholds for maximum acceptable risk among patients. In this study, results provide the ability to assess the minimum weight loss and time required to retain that weight loss for patients indicated to accept a 1/200 risk of death from implantation of the device (Figure 28).¹ Another study, which examined preferences for anticoagulants in the treatment of atrial fibrillation showed the ability of a preference study to identify key differences among stakeholders.² In this study, physicians and patients differed in their perceptions of risks; with physicians viewing death as the worst possible endpoint of treatment and patients considering disabling stroke as the least favourable endpoint. Preference studies can also enable the rapid determination of weights from patients and expert jurors. Using a point allocation technique lead by a facilitator at a CIRS Workshop in June 2013, a rough set of measurements of the relative importance of various benefit and harm outcomes in the treatment of migraines with a triptan (Figure 29) was assessed within an hour.¹

Challenges

Despite the advantages of obtaining patient perspective in clinical development through patient perspective studies, significant challenges remain. It is currently unclear whether or how health authorities will use the results of such studies. Regulatory guidance in this area is lacking and as of yet there is no clear role for

Figure 28. Required weight loss and time to preserve that lost for obese patients to accept a 1/200 chance of death from the implantation of a device to treat obesity.



preference studies in a new drug application or dossier. Furthermore, there is a perception that preference studies are subject to uncontrolled bias.

Additionally, the need for preference studies must be determined individually. Many benefit-risk assessments can be conducted solely with the use of clinical judgement and it can be a challenge for industry to determine whether to invest the resources for a patient-focused study. The optimal timing for the conduct of a patient preference study must also be identified. The potential harms of a new medicine cannot be known with certainty until after study results are unblinded; however, once unblinding occurs, there is only limited time for conducting analyses and the potential for bias is increased. Moreover, industry is wary of pre-approval interaction with patients, which can be regarded as off-label marketing, especially when research instruments often associated with marketing are used for that interaction.

Other considerations include the wide variety of methods for patient preference studies, which differ in time, cost, scientific rigour, complexity and transparency and the limited guidance on the choice of appropriate methodology. Obtaining patients for a preference study can also be challenging. Using patient panels raises concerns that include limited alignment between the panel population and a clinical trial population, reporting and verification of self-reported diagnoses, potential bias due to self-selection or the use of an Internet-

based population, recall bias and the lack of understanding of the alignment between panel populations in different countries. Finally, there is growing recognition of the need to examine more than the average set of preferences. Generally, sponsors have been unwilling to invest the resources need to obtain a sample size large enough to explore heterogeneity and spanning the gap between population-based and individual patient decisions remains a critical issue.

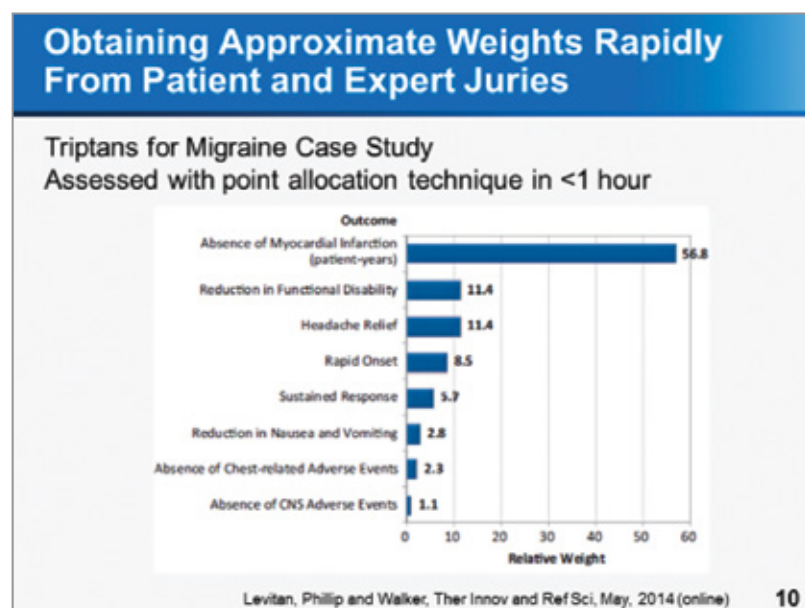
Recommendations

Although not all benefit-risk evaluations may require patient preference studies, several scenarios suggest value such as

- Cases in which the timing or relative frequency of benefits and harms impose a natural tradeoff such as for those medicines with clear benefit but rare, serious harms, those in which benefits occur early and harms occur much later or harms occur early and benefits much later;
- Cases in which the clinical impact of benefits and harms are best assessed by those experiencing them and for which clinical experience of key endpoints is highly subjective, such as pain, nausea or skin disease or cases for which benefits could be characterized as “lifestyle” such as baldness or impotence; or diseases that are rare with effects that are therefore less familiar to reviewers and
- Cases in which there is a suggestion that patients or subgroups of patients are willing to accept more risk than caregivers may believe.

Several possible organisational entities could address the use of patient preference studies in clinical development. First, a public-private partnership could devise initial guidance on the collection and use of patient perspectives and preferences for regulatory review. Promising starts in this direction have been made by organisations such as the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the Patient Centered Outcomes Research Institute (PCORI), Medical Device Innovation Consortium (MDIC) and the Society of Medical Decision Making (SMDM) and others. Second, health authorities and industry could jointly consider a mechanism for adding preference studies to submissions, continue to develop in-house expertise in the use and evaluation of preference studies and set up

Figure 29. Rapid, approximate weights in triptan therapy for migraine



advisory groups. Third, a consortium for patient perspective and preference assessment could be established, to include members from regulatory, academic, industry and patient advocacy groups. This could provide a central site for unbiased, high-quality assessments. Such a consortium could pool resources from multiple stakeholders, partner with the best key opinion leaders, use untapped resources in patient advocacy groups, standardise methods and reduce concerns about bias.

Several organisations such as ISPOR, PCORI, MDIC, SMDM and Cochrane have developed guidelines for decision aids and shared decision-making tools. Standards already developed should be exploited, such as those contained in the reports from the ISPOR Taskforces on Good Research Practices Conjoint Analysis and Experimental Design Good Research Practices, the Cochrane Collaboration Review on Decision Aids and the International Patient Decision Aid Standards Collaboration Patient Decision Aids Checklist.

Patients could be identified for preference studies through probabilistic sampling from patient panels, physician selection or from existing clinical trials. Although there are some complex operational issues, using trial

participants would have the advantages of 100% alignment between the clinical trial and preference study, exploiting existing trial infrastructure, allowing confirmation of diagnosis and history, providing large patient populations, making it possible to analyse all trial data in preference subgroup analyses and relating patients' treatment experiences to preference results. However, not all trials easily lend themselves to preference studies.

There is a bright future for understanding the relative importance of the benefits and risks of new medicines to patients and many stakeholders have a strong interest in this subject, such as patients themselves, regulators, industry and academics. Numerous ongoing initiatives are addressing technical, operational and regulatory issues and despite these current challenges, benefits have already been realised.

Reference

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Understanding the benefits and risks and their relative importance to patients:

Challenges and recommendations – A patient viewpoint

Dr Durhane Wong-Rieger

President, Canadian Organisation for Rare Disorders, Canada

Scientific benefit-risk assessment

Benefit-risk assessment is a complex decision-making process with quantitative and qualitative dimensions that are affected by context. Scientific methodologies incorporating expert deliberation and stakeholder perspectives can improve certainty of forecasts, place the known and the unknown in a practical context and address uncertainties in the context of patient preferences but can also reveal new

uncertainties.

Eliciting values for risk choices combines technical and scientific information about alternatives and value-based preferences. Learning over time and flexibility to adapt are key; one should consider robust and resilient alternatives over a wide range of uncertainties. Decisions must be made before all uncertainties are resolved and “surprises” are a potential part of any risk decision process.

Patient input into benefit-risk assessment

Before soliciting patient input into benefit-risk decision making, certain determinations must be made.

- Do we know how the patient perspectives will be integrated with other perspectives?
- How much value is accorded to patient values and to individual patient preferences and judgements?
- How should essentially qualitative perspectives be represented?

- Do validated quantitative measures adequately capture the patient perspective?

Multiple challenges are associated with the determination of these issues.

Heterogeneity and the effect of perspective on therapy choice

It should be recognised that a patient population is not a homogeneous group and the greater the variability in the group, the greater the challenge of eliciting a representative patient view. In the post-approval period; patient variation can be even greater and even more challenging to capture and individual patient preferences and actions may wreak havoc with the best scientific methods.

Patients with the same disease experienced in different contexts may weigh factors differently and perceptions of benefits and harms can have varying impacts across a patient population. A patient's personal weighting of the risks of harms caused by progressive disease versus the potential benefits of a therapy may greatly influence their healthcare choices. For example, in one real-world case, a university professor who had both cardiovascular and Parkinson's diseases strongly resisted all therapies until his illnesses progressed to the point at which they interfered with his ability to function normally in his profession. This type of patient value cannot be effectively assessed in a clinical trial and requires another approach.

Blood transfusion offers another example of individual perception of benefits and harms: Thirty years after the identification of human immunodeficiency virus (HIV) and 20 years after the introduction of effective blood screening tests, there is still a common belief that the use of donated blood poses a significant risk of contracting HIV, causing many patients to prefer synthetic and autologous blood to donated blood. This risk avoidance endangers maintaining an adequate blood supply and methods must be identified to address such emotional responses to scientific evidence.

In another case demonstrating a therapy decision based on individual benefit and risk perceptions, the family of a 5-year-old boy with neonatal onset multisystem inflammatory disease decided not to switch to a new

Ultimately, the ways in which therapy will affect quality of life may be more important to patients than the consideration of benefits and risks.

medication that could be administered once every 8 weeks from one that required a daily injection, as the benefits and risks of the original drug were well known to the family and the child had accepted the daily injections as part of his normal routine.

Comparison theory holds that some patients may be satisfied with a therapy not because of its benefits and harms but because they perceive it to be better than their previous experience. This theory also maintains that patients will adhere to an "ineffective" therapy if they perceive no better alternatives but they will leave an "effective" therapy if a "better" alternative arises.

Uncertainty may play a smaller role in patient decision making, with patients choosing a therapy based on the personal value they place on a possible benefit or harm rather than uncertainty about its likelihood of occurrence. That is, if that potential benefit is perceived to be valuable enough, patients may choose the therapy even if the likelihood of actually achieving the benefit is very small. Likewise, patients may reject a therapy if the potential harm would exert an impact that is personally very important to them, even if the likelihood of that harm is very small.

Benefit-risk versus quality of life

Ultimately, the ways in which therapy will affect quality of life may be more important to patients than the consideration of benefits and risks. It is also important to recognise that most patients are not scientists and may make decisions based on emotional impact and intuition rather than on evidence-based probabilities. This results in the major challenge of determining how to integrate what may be personal, intuitive, quality-of-life oriented, value- and emotion-laden judgements with objective, evidence-based, outcomes-oriented, cost-effective evaluations.

Communicating benefit risk decisions to stakeholders

Professor Stuart Walker

Founder, Centre for Innovation in Regulatory Science

Documenting benefit-risk decisions

Major regulatory agencies have acknowledged the need to communicate benefit-risk decisions for medicines to their stakeholders; however, there is currently no universal format to communicate this information. The overarching CIRS Universal Methodology for Benefit-Risk Assessment (UMBRA) 8-step benefit-risk framework incorporates the principles of methodologies that have been developed for the assessment of medicines, such as the five-step US Food and Drug Administration (FDA) framework, the 8-step European Medicines Agency (EMA) framework and the 6-step CIRS Benefit Risk Action Team (BRAT) framework. Use of the UMBRA framework is facilitated by the CIRS Benefit-Risk Template and User Manual, which has been evaluated in its full or summary format by twelve international regulatory agencies for use in documenting benefit-risk decisions under different review models.

Dr James Leong and colleagues recently conducted a case study that compared the elements of CIRS Benefit-Risk template and existing publicly available summary assessment

... regulatory authorities might consider revising their publicly available communication documents and listing the benefits and risks that were evaluated with justification for their roles in assessing the benefit-risk balance and the reasons for their inclusion or exclusion

reports used by the US FDA, EMA and Australia's Therapeutic Goods Administration (TGA) to communicate benefit-risk decisions for ziv-aflibercept (Zaltrap; Sanofi) a treatment for metastatic colorectal cancer administered with chemotherapy (Figures 30, 31).¹

Issues that were considered in the study included the lack of a universal format for benefit-risk evaluation; different expectations and requirements among stakeholders; differences among countries, cultures and practices; the regulatory requirements of different jurisdictions some of which do not include the publication of summary bases of approval and the lack of collaborative efforts.

Study findings

The study findings showed that the existing summary assessment report formats examined are generally similar and that this should facilitate the future use of a universal template. Generally, however, a listing of the benefits reviewed and subsequently included or not included was not available. Also missing was information on the risks or harms that were reviewed but not included and the assignment of relative importance and details of values for options. Furthermore, visualisation and the evidence of a guided, structured, systematic approach were not always apparent from the publicly available documents produced by the agencies.

Recommendations for future communication of benefit-risk

In light of these missing elements, regulatory authorities might consider revising their publicly available communication documents by listing the benefits and risks that were evaluated with justification for their roles in assessing the benefit-risk balance and the reasons for their inclusion or exclusion; valuing the identified benefits and risks of the various treatment options; examining the relative importance of the identified parameters; potentially providing

Figure 30. A general comparison of the UMBRA Benefit-Risk Summary Template with publicly available benefit-risk information from four regulatory agencies.

BR Summary Template	US FDA	EMA	Health Canada	TGA
Content	Benefit-risk framework	EPAR – Executive Summary	SBD	AusPAR
1.1 Background (Decision context)				
1.1.1 Specify proposed therapeutic indication	Analysis of condition	Not available	Not available	Section 1
1.1.2 Treatment modalities evaluated	Current treatment options	Not available	Not available	Section 1
1.1.3 Medical need	Analysis of condition	Not available	Section 2	Section 1
2.1 Overall summaries		Not available		
2.1.1 Quality conclusions	Not available	Not available	Section 7 - Quality	Section 6
2.1.2 Non-clinical conclusions	Not available	Not available	Section 7 - Non-clinical	Section 6
2.1.3 Human pharmacology conclusions	Not available	Not available	Section 7 - Clinical	Section 6
2.1.4 Clinical conclusions	Benefit, Risk	Not available	Section 7 - Clinical	Section 6
3.1 Identified benefits and risks				
3.1.1 Listing of all benefits, and justification for inclusion and exclusion	Not available	Not available	Not available	Not available
3.1.2 Listing of all risks, and justification for inclusion and exclusion	Not available	Not available	Not available	Not available
4.1 Clinical study summary	Benefit	Not available	Section 7 - Clinical	Section 4
5.1 Risks: Overall summary	Risk	Not available	Section 7 - Clinical	Section 4
6.1 Weighting and valuing of benefits and risks	Not available	Not available	Not available	Not available

BR Summary Template	US FDA	EMA	TGA
Content	Risk Benefit Assessment	EPAR – Executive Summary	AusPAR – Overall Conclusion
1.1 Background (Decision context)			
1.1.1 Specify proposed therapeutic indication	✓	✓	✓
1.1.2 Treatment modalities evaluated	✓	✓	✓
1.1.3 Medical need	✓	✓	✓
2.1 Overall summaries			
2.1.1 Quality conclusions	Not available	Not available	✓
2.1.2 Non-clinical conclusions	Not available	Not available	✓
2.1.3 Human pharmacology conclusions	Not available	Not available	✓
2.1.4 Clinical conclusions	✓	✓	✓
3.1 Identified benefits and risks			
3.1.1 Listing of all benefits, and justification for inclusion and exclusion	Not available	Not available	Not available
3.1.2 Listing of all risks, and justification for inclusion and exclusion	Not available	Not available	Not available
4.1 Clinical study summary	✓	✓	✓
5.1 Risks: Overall summary	Not available	Not available	✓
6.1 Weighting and valuing of benefits and risks	Not available	Not available	Not available
7.1 Conclusion			

Figure 31. Figure. A comparison of the use of the UMBRA Benefit-Risk Summary Template with publicly available information from three regulatory agencies for the benefit-risk evaluation of ziv-aflibercept.

visualisations to aid in the communication of the evaluation and a guided discussion and structured questions to illustrate key discussion points.

Participants in the April 2014 CIRS Workshop in Surrey, UK identified the needs and requirements of healthcare stakeholders in benefit and risk. Patients' primary concern is whether a product meets their needs and whether it is effective and comparatively safe. Physicians want to know the details of benefit-risk decisions to make a better informed decision for their patients. Pharmaceutical companies need to understand the basis of the decision and the rationale for inclusion of benefits and risks. HTA agencies, in evaluating the product for pricing or reimbursement want to understand the rationale and details for regulatory decisions. Maturing agencies need to know the details of the decision-making process outcome because they rely on the decisions of reference agencies in their reviews.

On the basis of those recognised needs and on the comparison of the publicly available regulatory documents for benefit-risk, Professor Walker listed four recommendations:

- First, the current structure of patient information should be analysed to better reflect the benefits, harms, consequences and uncertainties of taking medications in language that is easy to understand.
- Second, a survey should be carried out to ascertain the expectations of patients, physicians, pharmaceutical companies, maturing regulatory authorities and HTA agencies as to what should be included in publicly available benefit-risk documents.
- Third, a standardised template should be developed for public assessment reports by a consortium of agencies, to include the key elements of a benefit-risk assessment.
- Fourth, regulatory agencies should evaluate the UMBRA Framework and Benefit-Risk Template for utility as a basis for developing new or revised publicly available documents to meet the needs of all stakeholders.

Reference

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Appendix: Workshop Attendees

Regulatory agencies		
Prof Sir Alasdair Breckenridge	Former Chairman	Medicines and Healthcare Products Regulatory Agency, UK
Dr Gerald Dal Pan	Director, Office of Surveillance and Epidemiology	Food and Drug Administration, USA
Dr Petra Doerr	Head of Communication and Networking, Deputy Director	Swissmedic, Switzerland
Sara Eggers	Operations Research Analyst, Office of Program and Strategic Analysis	Food and Drug Administration, USA
Patrick Frey	Director, Office of Program and Strategic analysis, CDER	Food and Drug Administration, USA
Dr Akiko Hori	Director, Office of Safety II	Pharmaceuticals and Medical Devices Agency, Japan
James Leong	Senior Regulatory Specialist	Health Sciences Authority, Singapore
Dr Theresa Mullin	Director, Office of Strategic Programs, CDER	Food and Drug Administration, USA
Prof Robert Peterson	Executive Director, Drug Safety Effectiveness Network	Canadian Institute of Health Research
Dr Co Pham	Senior Scientific Advisor, Marketed Health Products Directorate	Health Canada
Dr Francesco Pignatti	Head of Section, Oncology, Haematology & Diagnostics	European Medicines Agency
Jalene Poh	Director, Therapeutic Products Branch, Health Products Registration Group	Health Sciences Authority, Singapore
Barbara Sabourin	Director General	Therapeutic Products Directorate, Health Canada
Prof Tomas Salmonson	Chair	CHMP, EMA
Dr Sinan Sarac	Senior Medical Officer	Danish Health and Medicines Authority
Daisuke Sato	Reviewer	Pharmaceuticals and Medical Devices Agency, Japan
Dr Mark Walderhaug	Associate Office Director for Risk Assessment, CBER	Food and Drug Administration, USA
Dr Kimberly Witzmann	Medical Officer, Division of Pulmonary, Allergy and Rheumatology Products, Office of New Drugs	Food and Drug Administration, USA
Pharmaceutical companies and organisations		
Isma Benattia	Vice President, Global Safety	Amgen, USA
Dr Mondira Bhattacharya	Therapeutic Area Head, Infectious Diseases	AbbVie, USA
Dr Carmen Bozic	Senior Vice President, Clinical and Safety Sciences	Biogen Idec, USA
Mladen Bozic	Senior Director, Regulatory Policy and Intelligence	Shire, USA
Frances Duffy-Warren	Vice President, Head of US Regulatory Affairs	Actelion Clinical Research Inc, USA
Karen M. Hauda	Sr. Director, Regulatory Policy Clinical Development, Medical, & Regulatory Affairs	Novo Nordisk, USA
Dr Rick Hermann	Safety Science Physician	AstraZeneca, USA
Dr Paul Huckle	Chief Regulatory Officer	GlaxoSmithKline, USA
Dr Diana Hughes	Vice President, WSS Primary Care	Pfizer, USA
Dr David Jefferys	Senior Vice President	Eisai Europe Ltd, UK
Dr Eva Katz	Manager	Johnson & Johnson, USA

Dr Stephen Knowles	Senior Director, Global Patient Safety	Eli Lilly and Company, USA
Gabriella Lavezzari	AVP, Scientific and Regulatory Affairs	PhRMA, USA
Dr Inge Lefevre	Director, Clinical and Labelling (Regulatory)	GlaxoSmithKline Vaccines, Belgium
Dr Bennett Levitan	Director	Janssen, USA
Dr Stephen Lin	Vice President, Global Safety Surveillance & Risk Management	Sanofi, USA
Anders Lindholm	Pharmacovigilance and Risk Management TA Head	Shire Pharmaceuticals, USA
Dr Thomas Lonngren	Independent strategy Advisor	Pharma Executive Consulting, Sweden
Jorgen Matz	Head of Risk Management, Global Pharmacovigilance	H. Lundbeck A/S, Denmark
Brian Mayhew	Director, Regulatory Policy and FDA Liaison	Novartis Pharmaceuticals, USA
Dr Meni Melek	Senior Director, Global Head Hematology, Global Regulatory Affairs	Bayer HealthCare, USA
Dr Marilyn Metcalf	Senior Director, Benefit Risk Evaluation	GlaxoSmithKline, USA
Steve Miller	Vice President, Cardiovascular and Metabolism, Global Regulatory Affairs	Janssen Research and Development, USA
Jesús Muñiz	Senior Director, Global Regulatory Policy & Intelligence	Shire, USA
Dr Filip Mussen	Head of Regional Regulatory Affairs	Janssen Research & Development, Belgium
Dr Becky Noel	Director	Eli Lilly and Company, USA
Dr Leo Plouffe	Vice President, Head of Risk Management Global Pharmacovigilance	Bayer HealthCare Pharmaceuticals, USA
Mary Jo Pritza	Director, Regulatory Affairs	Astellas Pharma, USA
Eddie Reilly	Vice President, Global Regulatory Affairs	GlaxoSmithKline, Belgium
Monika Richter	Vice President, Regulatory Regions, Labelling Operations	Boehringer Ingelheim Pharmaceutical, USA
Frank Rockhold	Senior Vice President, Global Clinical Safety and Pharmacovigilance	GlaxoSmithKline, USA
Tracy Rockney	RA, Vice President, Global Labelling, Advertising & Promotion, Regulatory Policy and Intelligence	AbbVie, USA
Dr Alain Romero	Vice President, Medical Affairs	Actelion Pharmaceuticals Inc, USA
Dr Susan Rosen	Senior Vice President, Global Pharmacovigilance and Risk Management	Shire Pharmaceuticals, USA
Paula Sandler	Vice President, Regulatory Affairs	Biogen Idec, USA
Dr Linda Scarazzini	Vice President, Medical Safety Evaluation – PPS	AbbVie Inc, USA
Helen Sile	Medical officer, Office of New Drugs Guidance and Policy Team	Food and Drug Administration, USA
Dr Priya Singhal	Vice President, Global Head, Safety and Benefit Risk Management	Biogen Idec, USA
Dr Meredith Smith	Director, US Drug Safety Science and Strategy	EMD Serono Inc, USA
Dr Nia Tatsis	Associate Vice President, Regulatory Affairs	Sanofi, USA
Dr Kristin Van Goor	Assistant Vice President	PhRMA, USA

Mostafa Wali	Senior Director, Risk Management Center of Excellence	Takeda, USA
Judith Xu	Principal Statistician, Analytical Science	Takeda Pharmaceuticals, USA
Academic institutions and patient organisations		
Prof Deborah Ashby	Co-Director of Imperial Clinical Trials Unit and Deputy Head School of Public Health	Imperial College London, UK
Dr John Bridges	Associate Professor	Johns Hopkins Bloomberg School of Public Health, USA
Prof Bruno Flamion	Professor of Pharmacology	University of Namur, Belgium
Dr Mamoru Narukawa	Associate Professor	Kitasato University Graduate School of Pharmaceutical Sciences, Japan
Dr Durhane Wong-Riegner	President	Canadian Organization for Rare Disorders
Centre for Innovation in Regulatory Science (CIRS)		
Patricia Connelly	Manager, Communications	
Art Gertel	Senior Research Fellow	
Lawrence Liberti	Executive Director	
Dr Neil McAuslane	Director	
Prisha Patel	Portfolio Manager	
Professor Stuart Walker	Founder	