BENEFIT-RISK FRAMEWORK FOR THE ASSESSMENT OF MEDICINES:
Maximising the value of PBRERs: Company approaches to post-approval benefit-risk assessment

12 DECEMBER 2013
PHILADELPHIA, USA

TECHNICAL FORUM REPORT
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### Workshop Programme

**12 December 2013**

#### SESSION 1: DOCUMENTING BENEFIT-RISK ASSESSMENTS IN THE POST-APPROVAL SETTING: WHAT ARE COMPANIES DOING AND ARE THESE APPROACHES FIT-FOR-PURPOSE?

<table>
<thead>
<tr>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chairman's welcome and introduction</td>
<td>Professor Stuart Walker, Founder, CIRS</td>
</tr>
<tr>
<td>Moving from a risk-based post-approval approach to a new benefit-risk landscape – What are the driving forces and the challenges?</td>
<td>Prof Sir Alasdair Breckenridge, Former Chairman, Medicines and Healthcare products Regulatory Agency, UK</td>
</tr>
<tr>
<td>Focus on PBRERS - How have companies prepared for the introduction of PBRERS? What have been the experiences and challenges? Case Studies</td>
<td></td>
</tr>
<tr>
<td>Company Experience - 1 - Bayer</td>
<td>Dr Jutta Pospíšil, Head TA Primary Care, Global Pharmacovigilance, Bayer Healthcare Pharmaceuticals, Germany</td>
</tr>
<tr>
<td>Company Experience - 2 Roche</td>
<td>Valerie Murer, F.Hoffmann-La Roche, Switzerland</td>
</tr>
</tbody>
</table>

#### SESSION 2: POST-APPROVAL – MEASURING BENEFIT-RISK: WHAT ARE THE CHALLENGES?

<table>
<thead>
<tr>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are the current issues in measuring benefit-risk in the post-approval period?</td>
<td>Dr Bennett Levitan, Director, Quantitative Safety Research, Janssen Research Foundation, USA</td>
</tr>
<tr>
<td>The traditional methodology of observational studies – What are the challenges for regulatory agency acceptance?</td>
<td>Dr James Rhys Williams, Associate Director, Epidemiology, Biogen Idec, USA</td>
</tr>
<tr>
<td>New approaches/technologies to capture Benefits and Risks in the post-approval Phase – What are the practical and regulatory challenges?</td>
<td>Dr Marilyn Metcalf, Senior Director, Benefit Risk Evaluation, GlaxoSmithKine, USA</td>
</tr>
<tr>
<td>Roundtable discussion and feedback: Methodologies for measuring post-approval benefit-risk - what needs to be considered?</td>
<td></td>
</tr>
<tr>
<td>Chairman’s summary</td>
<td></td>
</tr>
</tbody>
</table>
BACKGROUND TO THE WORKSHOP

Agencies and companies are increasingly focusing on the post-approval period in the development of medicines for its ability to provide a better understanding both of their benefits and harms. Indeed, the recent ICH E2 guideline now requires companies to provide continually updated information on the benefit-risk balance – a process, that should also include a structured benefit-risk evaluation, not just when new information becomes available but also when medicines are being periodically re-evaluated. Any benefit-risk framework for the evaluation of medicines should be flexible enough to incorporate evolving scenarios, particularly as knowledge increases about new medicines.

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. However, whilst the ICH guideline articulates the need for a structured benefit-risk evaluation, it does not specify detailed agency requirements. As a result, companies have designed formats for their Periodic Benefit-Risk Evaluation Reports (PBRERs) which they believe will satisfy requirements.

CIRS has established a programme to examine benefit-risk in the post-approval stage. The June 2014 CIRS Benefit-Risk Workshop was designed to focus specifically on this topic and addressed current challenges and future expectations that surround this issue. To inform the Workshop, this Technical Forum was held to discuss and examine the challenges and experiences of companies as they comply with the requirements of the PBRER. This meeting will also provide a forum for company discussions of the anticipated future requirements as well as the development of appropriate methodologies for providing evidence of benefits and risks in the post-approval stage.

Workshop Objectives

- Discuss structured approaches to evaluating the evidence in balancing benefit-risk in the post-approval period, including the challenges, hopes and expectations
- Develop proposals for applying a benefit-risk framework in the post-approval setting and determine how this framework can help drive evidence generation and the presentation of the evidence and the appropriate methodologies for providing post-approval benefit-risk evaluations
- Share company experiences in implementing PBRERs and how agencies have responded to their submissions

PRESENTATION SUMMARIES

*Forum Chair and CIRS Founder, Professor Stuart Walker* initiated the meeting by outlining recent CIRS activities in the area of benefit-risk including the work of the four regulatory agencies comprising the Consortium for Benefit-Risk Assessment (COBRA) in evaluating the Universal Methodology for Benefit-Risk Assessment (UMBRA) benefit-risk template and that of the more recently formed group of agencies with emerging pharmaceutical markets who are piloting the International Summary Approach to Benefit-Risk Evaluation (ISABRE). In addition, he detailed recent CIRS visits to the EMA, PMDA and US FDA and provided a list of recently and soon-to-be published benefit-risk journal articles and book chapters authored by CIRS staff. Professor Walker also announced that in collaboration with Dr Bennett Levitan of Johnson and Johnson and colleagues CIRS has developed an updated version of the CIRS-Benefit-Risk Action Team (BRAT) software tool which also includes a working case study example of the use of software in the evaluation of a hypothetical triptan. This tool is now available for free download at http://www.cirs-brat.org/

KEY POINTS FROM PRESENTATIONS

SESSION: DOCUMENTING BENEFIT-RISK ASSESSMENTS IN THE POST-APPROVAL SETTING: WHAT ARE COMPANIES DOING AND ARE THESE APPROACHES FIT-FOR-PURPOSE?

By the time a new drug is first marketed, much is known regarding its pharmacology as well as its safety and efficacy albeit in a limited population. These data, however, provide an incomplete and potentially misleading record of the drug’s effectiveness in the population at large and even greater knowledge gaps can occur with respect to its safety, underscoring the need for an ongoing assessment of drugs’ effectiveness and safety in the post-marketing phase. *Prof Sir Alasdair Breckenridge.*
Benjamin R. Pratt and David A. Street, University of Washington, Seattle, USA

Challenges to the implementation of PBRERs include the need to ensure that the processes for generating and updating PBRERs are robust and efficient. Dr. Jutta Pospíšil, Head TA Primary Care, Global Pharmacovigilance, Bayer Healthcare Pharmaceuticals, Germany explained that there are benefits to the use of the reports including the fact that Bayer is able to integrate PBRER creation into other processes wherever possible, with other common data locks and document updates for Investigator Brochures, DSURs, Risk Management Plans and Clinical Overview addenda. In addition PBRER summary tabulations represent an improvement over the line listings used in PSURs and PBRERs represent an opportunity to evaluate the benefits of new medicines, which puts risk evaluation into the proper context and to assess to impact of safety signals that emerge from multiple reports rather than individual cases.

Roche has achieved significant and pioneering accomplishments in the area of Periodic Benefit-Risk Evaluation Reports over the period of 18 months, including the implementation of a cross-functional PBRER governance platform. Valerie Murer, F. Hoffmann-La Roche, Switzerland reported that gaps that were identified by the Roche PBRER pilot team included the need for efficacy literature searches, a process for updating standard operating procedures, the need to formalise the methodology for post-marketing and off-label use data collection and advanced reporting requirements. Challenges were faced during implementation such as the need for cross-functional alignment, change management issues and the necessity for oversight of staff training. Key success factors for the project that were identified included organisation awareness and a robust change management programme; an adequately resourced project team that includes dedicated cross-functional resources representing all PBRER process stakeholders, a project manager and resources to support training, development, implementation and oversight; flexibility and a continuous improvement mind set.

SESSION: POST-APPROVAL – MEASURING BENEFIT-RISK: WHAT ARE THE CHALLENGES?

Post-approval benefit-risk assessment poses a variety of challenges that manifest themselves in the steps of a typical benefit-risk framework, in particular, the decision context and the identification and use of outcomes and data sources. Dr. Bennett Levitan, Director, Quantitative Safety Research, Janssen Research Foundation, USA provided examples of these challenges, such as the fact that after approval, the evaluation of a drug’s benefit and harms might take place at the compound level when there may be multiple doses, formulations and combination products to evaluate. In addition, experiences in certain patient subgroups are more likely to have a greater impact after approval than during drug development, resulting in a much lengthier and more complex decision context. Also, the definition of desired endpoints can vary and they are not always captured in each data source and there are typically many more data sources to manage in the post-approval period. Surmounting these hurdles is aided by the use of a benefit-risk framework but ultimately, evaluations are a case-by-case exercise that benefits from the use of a toolkit approach.
Dr James Rhys Williams, Associate Director, Epidemiology, Biogen Idec, USA listed the challenges for regulatory acceptance of post-marketing observational studies: these included the regulatory prioritisation of benefit-risk data collection, the definition of non-interventional research in the European Union, the role of an active comparator cohort and the timing and reconciliation of feedback from multiple regulatory agencies. Practical steps to overcoming these barriers include continuing the dialogue about operational challenges in the conduct of these trials and the merits of active comparator cohorts under appropriate conditions. Regulatory agencies should be encouraged to specifically include assessments of both benefits and risks in post-market safety study guidance documents and to adopt more flexible and clear definitions of non-interventional research. Finally stakeholders should engage with regulatory agencies, industry organisations and others to include an assessment of post-market requirement feedback in ongoing evaluations of FDA/CDER’s 21st Century Review Process conducted as part of the fifth iteration of the Prescription Drug User Fee Act (PDUFA V).

GlaxoSmithKline has evaluated the approach for the regulatory assessment of the benefits and risks of OTC medicines proposed by Eric Brass and colleagues. Dr Marilyn Metcalf, Senior Director, Benefit Risk Evaluation, GlaxoSmithKline, USA said that in this model, which is similar to that of Universal Methodology for Benefit-Risk Assessment (UMBRA) and others that have been used in the evaluation of prescription medicines, benefit and risk attributes are identified using a value-tree framework. This decision tool is designed as a two-factor, two-stage instrument, with each attribute independently assessed on both the frequency of occurrence and clinical impact of the attribute. GSK found congruence with this model and the EU Guidance for risk management plans and the recommendations of the Innovative Medicines Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (IMI PROTECT). As there are many different report formats for the evaluation of benefit-risk for OTC products with the same goals, it may be feasible to consider the application of the “Brass approach” (after Dr Eric Brass and colleagues) as a standard framework. GSK will next prepare case studies of the use of the Brass model in the benefit-risk evaluation of different types of products and solicit internal feedback to assist in the preparation of proposals for wider implementation.
Section 2: Roundtable Discussions

Participants were organised into roundtables each tasked with discussing what needs to be considered when developing methodologies for measuring and reporting post-approval benefit-risk assessments. The discussion touched on a number of important topics, which all companies should consider addressing as they formulate their approaches to creating PBRERs.

A checklist of considerations when implementing PBRERs

- What are the internal and external challenges facing the pharmaceutical industry as a result of the requirement for PBRERs?
- What other challenges are facing the pharmaceutical industry as a result of the requirement for PBRERs? Are they internal or external and involving old or new products?
- What skills, tools and people are needed to best implement PBRERs? Are these in place in your organisation?
- Does your company have a standard approach to documenting some or all of the data required?
- Who are the owners/drivers for PBRERs within your company?
- Do you believe that the development of PBRERs is beneficial to your company and if so in what way?
- How should quantitative and descriptive approaches be used in PBRERs?
- Does the PBRER necessitate having a structured approach to benefit-risk assessment before approval?
- Has your company’s approach to the collection of benefit data changed following the introduction of PBRERs?
- What are the major issues in measuring benefits in the post-marketing period?
- Does a structured (formal) benefit-risk assessment need to be undertaken for every PBRER submitted?
- From what sources should companies collect benefit data?
- What role do social media have in the future for collection of benefit and harm information?
- What are your submission strategies for the ICH regions of the EU, USA and Japan?
- Are regulatory agencies suggesting new approaches that should be investigated and if so, what is being suggested?
Chairman’s introduction: CIRS benefit-risk activities

Prof Stuart Walker
Founder, CIRS

COBRA
Professor Walker initiated his discussion of CIRS benefit-risk activities by reviewing the progress of the Consortium for Benefit-Risk Assessment (COBRA). Consisting of the Therapeutic Goods Administration (TGA), Australia; Health Canada, Swissmedic and the Health Sciences Authority (HSA) of Singapore, COBRA was formed for the purpose of facilitating joint or shared reviews among these four mid-sized agencies. To that end, the group participated in the CIRS development of the Universal Methodology for Benefit-Risk Assessment (UMBRA) an eight-step framework that represents a systematic standardised approach to benefit-risk assessment. A feasibility study of the use of a documentation template for the framework was performed in 2011 and a retrospective study of one product reviewed by all of the agencies was held in the following year. After some resulting modifications to the template and the creation of a user manual with the assistance of Dr James Leong, TGA, Health Canada and HSA conducted a prospective trial in 2013. Moving forward, each of the agencies will investigate the individual incorporation of the template elements into their own clinical assessment models.

ISABRE
The work that has been carried out by COBRA has now become the basis for consideration by other international agencies and review divisions, including those in the Philippines, Malaysia, South Korea, China, Chinese Taipei and Singapore as well other countries with emerging pharmaceutical markets, working as the International Summary Approach to Benefit-Risk Evaluation (ISABRE) initiative.

These jurisdictions were asked to evaluate the feasibility and applicability of the framework within agencies in the emerging markets through the conduct of a retrospective study of one or two products evaluated by each agency. The objective of the study was to determine whether the electronic version of the summary portion of the template would be an appropriate mechanism for facilitating and documenting benefit-risk decisions.

Following these assessments, CIRS met with the reviewers who had undertaken the evaluations and with the senior heads of the review divisions to determine areas within the template that worked well as well as those that might need to be changed and to discuss how the template could ultimately best be used. Almost all the agencies had completed or were working on two carefully selected, retrospective case studies of oncology or cardiovascular medicines or antibiotics that had received either positive or negative regulatory decisions, for which local issues or ethnic factors were key in those decisions.

All of the agencies made positive comments regarding both the structure and content of the template and identified how, with some modifications, it could improve documentation and internal and external communications. The majority of the agencies believed that steps 1-3 and 8 of the framework were being currently undertaken within their organisation. In addition, they indicated that most of the information requested in the template was already in their assessment reports, although not in a structured format. Step 4, 5 and 7 of the framework, namely, assessing relative importance, scoring the options and visualisation, however, were not undertaken explicitly at any of the agencies. The agencies suggested a reordering of some of the template sections as well as the addition of new sections that would include issues of local context and clinically relevant ethnic issues that influence the benefit-risk balance for the country and more explicit instructions for certain areas in the user manual as well as translation of the
template into the local language.

All the agencies saw that a systematic structured approach to documenting benefit-risk, whether incorporated into their existing clinical assessment template or used in association with this document had value within their agency. It was specified that the approach could be used in communicating with registration or key decision committees, expert clinical consultants and review divisions as well as for difficult case discussions both internally and with the sponsor. All agencies indicated their interest in continuing to the next stage of review and several jurisdictions are setting up internal working parties.

**PMDA and EMA**

A representative from the Japanese PMDA visited CIRS in February 2013 followed by a CIRS visit to Japan in April to discuss benefit-risk in the post-approval period.

The UMBRA template was at least partially based on a 2008 EMA guidance document and a CIRS visit to the EMA was scheduled to take place in February 2014 to review the final comments from Health Canada, HSA and TGA regarding their use of the template as well as to provide the agency with the current status of other CIRS benefit-risk activities.

**FDA**

At a recent CIRS meeting at the FDA, it was learned that the FDA recognises that the UMBRA framework incorporates the five-step FDA framework (Figure 1). Other learnings included the fact that the pilot study for the use of the FDA five-step benefit-risk framework for the evaluation of six products from six different therapeutic areas was regarded as an internal study to formulate the right questions to be associated with use of the framework rather than for publication. The Center for Drug Evaluation and Research (CDER) is also working on a series of worked examples of benefit-risk assessment by therapeutic area. It was also mentioned that the recently published medical reviews providing the summary basis of approval in the five-step template format are not the result of the pilot study but follow an efficacy-safety approach rather than what might be considered a true benefit-risk assessment.

There are plans to incorporate benefit-risk assessment and relevant clinical questions into an appendix within the clinical assessment template by late in 2014; however, reviewer training and implementation of the use of the framework may not be rolled out until 2015. Currently, there is no intention of making the five-step approach to benefit-risk assessment mandatory for PhRMA companies in their submissions and the FDA regards international regulatory alignment with regard to the electronic common technical document (eCTD) as ultimately the responsibility of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH). Finally, an FDA meeting was planned for 12-13 February under the auspices of the Institutes of Medicine as part of the commitments contained within the fifth iteration of the Prescription Drug User Fee Act (PDUFA 5) agreement to organise two benefit-risk workshops.

Professor Walker recommended that forum participants read the FDA Guidance for Industry and Food and Drug Administration staff, *Factors to consider when making benefit-risk determinations in medical device premarket approval and de novo classifications*, which was issued by the Center for Devices and Radiological Health (CDRH) and Center for Biologics Evaluation and Research (CBER) 28 March 2012. In addition to the consideration of the benefits and risks associated with a device, the guidance specifies additional factors for assessment including uncertainty, characterisation of the disease, patient tolerance for risk and perspective on benefit, the severity and chronicity of the disease or condition, the availability of alternative treatments or diagnostics, the mitigation of risk,
post-market data, a medicine’s potential status as a novel technology addressing unmet medical need.

CIRS 2014 benefit-risk Workshops and publications.* include The assessment of benefits and harms and their relative importance to patients, industry and agencies: How should they be captured? which took place 1-2 April 2014 in Surrey, UK and Benefit-risk assessment in the post-approval period: How to ensure a life cycle approach to evaluating the benefits and harms of medicines, on 12-13 June, 2014 in Washington, DC USA.


Finally, Professor Walker announced that in collaboration with Dr Bennett Levitan of Johnson and Johnson and colleagues CIRS has developed an updated version of the CIRS-Benefit-Risk Action Team (BRAT) software tool which also includes a working case study example of the use of software in the evaluation of a hypothetical triptan. This tool is available for free download at http://www.cirs-brat.org/

*List updated August 2014.

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**Moving from a risk-based post-approval approach to a new benefit-risk landscape – What are the driving forces and the challenges?**

Prof Sir Alasdair Breckenridge

*Former Chairman, Medicines and Healthcare products Regulatory Agency, UK*

**The need for pharmacovigilance**

Critical alterations in the regulation of medicine have followed in the wake of tragedies such as the contamination of sulphanilamide with ethylene glycol in 1938, which led to the 1938 Food, Drugs and Cosmetics Act in the United States, the use of thalidomide by pregnant women in 1962, which led to international regulations requiring the testing of the teratogenicity of new medicines and the serious adverse events experienced by patients in the UK studies of TGN1412 in 2006, which led to changes in the regulation of phase 1 testing of drugs.

By the time a new drug is first marketed, much is known regarding its pharmacology as well as its safety and efficacy albeit in a limited population. These data, however, provide an incomplete and potentially misleading record of the drug’s effectiveness in the population at large and even greater knowledge gaps can occur with respect to its safety, underscoring the need for an ongoing assessment of drugs’ effectiveness and safety in the post-marketing phase.

Despite the public obsession with safety, the value of new drugs is primarily based on their benefit-risk profile. In fact, medicines used to treat serious diseases such as cancer or human immunodeficiency virus (HIV) often have extremely unfavourable safety profiles, which are balanced in the real world by their effectiveness in diseases of unmet medical need. In addition, the benefit-risk profile of new drugs, which may be optimal at the time of registration, may change with clinical use in larger populations that may contain patients
in higher risk groups, those with concomitant illnesses, those using multiple medicines or those with poor adherence behaviours (Figure 2). Pharmacovigilance throughout a medicine’s lifecycle can be maintained, however, through the efforts of healthcare professionals, regulatory and the pharmaceutical industry.

Healthcare professional responsibilities
Pharmacovigilance is practiced through the discovery of evidence of harm and the extension of the knowledge of safety. Descriptive methods of passive surveillance are used to find evidence of harm including the spontaneous reporting and intensive monitoring techniques. Spontaneous reports are events associated with the use of a medicine that are documented by patients and healthcare professionals and subsequently reported by industry to regulators. The World Health Organization defines these signals of drug safety as “reported information on a possible causal relationship between an adverse event and a drug, the relationship being either previously unknown or incompletely documented.”

Extending knowledge of drug safety involves testing hypotheses using the techniques of active surveillance with observational studies or clinical trials. The ICH Harmonised Tripartite Guideline for Pharmacovigilance Planning defines active surveillance as “a systematic approach to population based drug safety surveillance which seeks to ascertain completely the number of adverse events by means of a continuous pre-organised process.” Active surveillance depends on the collection of clinical data in several ways. Data regarding specific drugs, classes of drugs or specific conditions can be collected through clinical trials, patient registers and patient medical records, which can be accessed through a single database, a record-linked database or even through healthcare professionals and prescriptions. There are limitations on patient registries and databases however, as these provide data on dispensed drugs that are not randomly prescribed and typically do not provide information on patient exposure, concomitant over-the-counter drugs and socioeconomic, smoking and weight data and other potentially confounding factors.

Regulator responsibilities
In 2007, at the invitation of the US Food and Drug Administration, the Institutes of Medicine (IOM) issued recommendations for the enhancement of drug safety in the United States, which specified that the FDA should establish a more systematic evaluation of safety over the lifecycle of medicines. Passed at around the same time, the FDA Amendments Act substantially strengthened the authority of the FDA in the post-marketing period, specifying the circumstances under which post-marketing requirements and commitments for adverse event surveillance, observational studies and clinical trials could be made and empowered the agency to require risk evaluation and mitigation strategies (REMS) for selected drugs. The amendment also required the FDA to develop and monitor an active surveillance system for drug safety. REMS remain one of the pillars of the US regulatory safety system, minimising known risks while preserving benefits. There are no set rules for the imposition of REMS and they can apply, as needed, to all new drugs and biologicals. Possible requirements might include a medication guide, patient package insert, communication plan, prescription limitations and monitoring of patients through such methods of registry enrolment.

REMS became an important issue in the lifecycle of the diabetes therapy Avandia (rosiglitazone), which was licensed in 1999 using surrogate
endpoints of fasting blood sugar and HbA1c levels. After a 2007 meta-analysis of Avandia, which also causes increases in low-density lipoprotein cholesterol and in weight suggested an increase, not decrease in myocardial infarctions, the product was removed from the market in Europe. It remained on the market in the United States but the FDA required a strict risk minimisation programme for its continued use.

In 2012, the IOM published 23 further recommendations including one that specified that the FDA require a benefit-risk action management plan (BRAMP) be implemented during the lifecycle of a new medicine. BRAMPs are meant to resolve public health questions posed by a new drug through a formal assessment of its benefits and risks, providing a rationale for any post-market study of effectiveness or safety. The IOM recommended that BRAMPs be part of the regulatory submission that is initiated by the sponsor of the new drug and be discussed with and approved by the FDA and updated over the medicine’s life cycle.

Meanwhile, new regulations on pharmacovigilance were also enacted in Europe in 2012. These regulations established the importance of risk management plans for all newly approved products, improved the legal basis for post-authorisation studies of safety and effectiveness and sought to improve the transparency of and access to safety data. The definition of risk management plan as established in the EMA Guideline on Good Pharmacovigilance Practices is “a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products in relation to the effectiveness of these interventions.” The components of these plans are risk detection (safety specification), risk assessment (pharmacovigilance plan), risk minimisation and risk communication.

Industry responsibilities
In addition to the required reporting of passive surveillance, industry is responsible for other cumulative reports of drug safety, namely, Periodic Safety Update Reports (PSURs), Periodic Adverse Drug Experience Reports (PADERs) and Periodic Benefit-Risk Evaluation Reports (PBRERs). PADERs in Europe and PBRERs in the United States are intended to harmonise the periodic safety reporting requirements to regulatory authorities in a common format. They provide data reviews of safety for one entity at fixed intervals, consisting of an analysis of adverse drug reactions and lack-of-efficacy reports and safety data from studies. In the EU they are followed with risk management plans and potential label changes. PBRERs represent an evolution from PSURs, reviewing product risk in the context of benefit and seriousness of condition. They consist of analytical interval and cumulative data submitted at a frequency that is at the discretion of the national regulatory authority. PSURs came into effect in the EU in January 2013. These newer risk management plans are all associated with certain challenges, including variability in their worldwide acceptance. Moreover, their place in the formal qualitative and quantitative assessment of benefit and risk and the timing with which these ideas will progress globally remains to be established.

How have companies prepared for the introduction of PBRERs?

Company experience – Bayer

Dr Jutta Pospíšil
Head TA Primary Care, Global Pharmacovigilance, Bayer Healthcare Pharmaceuticals, Germany

Bayer Healthcare Pharmaceuticals began their initiative for the use of Periodic Benefit-Risk Evaluation Reports (PBRERs) around the time of the new EU Pharmacovigilance (PV) Legislation in March 2012, with the embedding of Periodic Safety Update Reports (PSURs)/PBRERs in the Bayer “Project for Implementation of the New EU PV Legislation.”

The main interface work streams for PSURs/PBRERs in this project were Signal Management, Risk Management and Post-Approval Safety Studies. To implement PBRERs, the company built upon its ongoing pharmacovigilance efforts, including the existence of a PSUR Coordination group and Development Safety Update Reports.
Figure 3. Bayer integrates the process of PBRER development into other processes wherever possible.

Integration of PBRER process into other processes

- Harmonized Data Lock Points for various types of documents, whenever possible
- Common contributions that can be used for different documents
- Modular Approach for Documents covering different time periods

[other benefits of PBRERs] are the opportunity to evaluate benefits, which puts risk evaluation into the proper context . . .

Evaluation into the proper context and to assess safety signals that can emerge from multiple sources rather than individual cases. In addition, summary tabulations represent an improvement over the line listings used in PSURs.

There were challenges to the implementation of PBRERs. There is no synchronicity between the Pharmacovigilance Risk Assessment Committee (PRAC) review of PBRERs and other PRAC activities. Additionally, the benefit-risk framework for PBRERs is not yet fully aligned with other benefit-risk frameworks and the different international timing requirements for PBRER/PSUR submissions and non-ICH countries’ requests for additional appendices to PBRERs can represent an administrative burden. The lexicon for the reports would also benefit from global harmonisation: US PBRERs are PSURs in Europe and in Module VII, ICH uses the terms, New Signal, Ongoing Signal, Closed Signal and Refuted Signal and in Module IX, Validated Signal and Confirmed Signal.

Learnings from the implementation included the need for a change management system, ongoing training and scheduled kick-off meetings to accommodate the many products, contributing functions and need for updated information. Outsourcing was necessary to solve resourcing issues and to take advantage of external expertise.
How have companies prepared for the introduction of PBRERs?

Company experience – F. Hoffmann-La Roche

Valerie Murer
F. Hoffmann-La Roche, Switzerland

All ICH countries have accepted the Periodic Benefit Risk Evaluation Report (PBRER) format, which is expected to become the global standard for periodic reporting of the benefits and risks of new medicines. In 2013, Roche shifted from the Periodic Safety Update Report (PSUR) to the PBRER and benefit-risk processes. The objectives for the initiative to implement PBRERs within the company were the documentation and optimisation of PBRER and benefit-risk processes and the development of relevant training to support teams in their preparation of quality PBRER documents. The approach employed for the programme involved processing feedback from pilot PBRER teams and implementing the resulting process improvements and defined best practices as well as identifying and documenting global medical affairs key data deliverables and the benefit-risk evaluation process and methodology for marketed products. There was one PBRER Team tasked with aligning PSUR and benefit-risk process activities.

The key external challenges to PBRER implementation at Roche were a lack of clarity and understanding of new regulations, which led in turn to over- and under-engineering of processes and created the general potential for misinterpretation. In some areas of the PBRER guidance, for example, interpretation could be better supported by providing more scenarios and practical examples. Additionally, there was misalignment with ICH in terms of the timing of updates and a duplication of efforts and inefficiencies occurred due to the initial limited PBRER acceptance. Key internal challenges to PBRER implementation at Roche were a lack of awareness and acknowledgement of the impact of the change, the need for new collaboration models between company functions, new accountabilities and requirements for affiliates, new processes and systems for post-marketing data tracking and storage and the resources and infrastructure to support new processes.

Roche initiated a campaign of early awareness and communication to develop a company-wide understanding of the challenges and changes in mind set and cross-functional commitments that would be required to comply with new legislation. A very high-level guidance and SOP were then developed for the first teams that would go through the PBRER process, with the plan of collecting their feedback to further optimise and update the guidance before its rollout to the entire organisation.

Feedback was collected from these pilots in 2012-2013 and the resulting recommendations fell into three categories. Recommendations for targeted training specified that PBRER awareness information should be concise and convey positive messages; that detailed hands-on training should be provided that is tailored to specific deliverables of functions and that PBRER “champions” should guide company functions through a standardised procedure and data delivery plan before a kick-off meeting.

Recommendations for guidance in model documents specified that these documents be expanded to include all guidance organised by deliverables, including methodology for comparative benefit-risk methodology; that best practice PBRER examples be provided to teams and that standardised PBRER language be developed. Recommendations for the project management plan template specified that the template include roles, responsibilities, timelines, major considerations, information sources, milestones and a detailed kick-off agenda; that communication and support be assigned as
specific roles and that comparative benefit-risk evaluation be considered as part of the PBRER, rather than as a separate process.

Overall PBRER accountability at Roche resides within the global development product team as a cross-functional activity, including responsibilities for regulatory, safety, medical and clinical science members to deliver information for the PBRER documentation. PBRER timelines were developed that identified the required timing for specific deliverables from team members after strategic preparatory meetings (Figure 4). Dedicated clinical project managers were also added to staff who are responsible for support during all phases of PBRER development.

Two types of PBRER training are conducted at Roche, high-level process overview training delivered through a learning management system and function-specific hands-on training, delivered in quarterly workshops.

The Roche PBRER Knowledge Portal website provides users with all relevant PBRER information, including supporting materials and process optimisation information (Figure 5). This and other resources help staff answer PBRER-related questions they may have such as “Where do I get more information, What do I have to write where, When do I have to do what? What responsibilities do I have? What is my contribution to section X and How should I structure a comparative benefit-risk evaluation?”

The implementation of PBRERs requires constant learning and process optimisation.

Summary
Roche has achieved significant and pioneering accomplishments in the area of Periodic Benefit-Risk Evaluation Reports over the past 18 months, with implementation of a cross-functional PBRER governance platform. However, although there are solutions in place, implementation is not yet complete because of the need to adapt interim solutions to long-term more optimised solutions. Additionally, new, updated EMA pharmacovigilance guidance was expected at the time of this Workshop and new formats and mandates are being developed.

Gaps that were identified by the Roche PBRER pilot team included the need for efficacy literature searches, a process for updating standard operating procedures, methodology for post-marketing and off-label use data collection and advanced reporting requirements. Challenges were faced during implementation such as the need for cross-functional alignment, change management issues and the necessity for oversight of staff training. Key success factors for the project that were identified were:

- detailed and timely impact assessment and planning for change;
- organisation awareness and change management;
- an adequately resourced project team that includes dedicated cross-functional resources representing all PBRER process stakeholders, a project manager and resources to support training, development, implementation and oversight;
- process and data delivery alignment;
- PBRER and benefit risk cross-functionally;
- project management for entire PBRER process and
- flexibility and continuous improvement mind set.

The implementation of PBRERs requires constant learning and process optimisation - with the ultimate goal for companies of maintaining the license to operate. Stakeholders are advised, therefore, to be proactive, stay informed and share best practices.
Current issues in measuring benefit-risk in the post-approval period

Dr Bennett Levitan
Director, Epidemiology, Janssen Research Foundation, USA

Post-approval benefit-risk assessment
The benefit-risk assessments within Periodic Benefit-Risk Evaluation Reports (PBRERs) differ from other benefit-risk evaluations because of both the constraints imposed by regulatory requirements and the wide variety and heterogeneous nature of post-approval data sources.

In addition to the fulfillment of standard regulatory requirements, the need for the conduct of PBRERs can be triggered by

- Changes in the rate of previously known benefits or harms
- The discovery of new harms (or potentially a new benefit)
- Changes in the clinical impact, or weight, of a benefit or harm (such as from changes in treatment paradigms or in a risk management plan)
- The launch of a new comparator or the loss of an existing comparator
- The identification of a new patient subgroup or biomarker
- A specific health authority request

The key challenges in the conduct of a PBRER's benefit-risk evaluation lie in three steps of a typical benefit-risk framework: the establishment of decision context, the identification of clinically relevant outcomes and identification and integration of appropriate data sources.

Challenges in post-approval decision context
Characteristics that form the context of a decision regarding the assessment of benefits and risk include the study drug, dose, formulation, Indication, treatment population, comparator(s), the epidemiology of the disease to be treated and the nature of its symptoms, the time horizon for outcomes, key subgroups and the perspective of decision makers. Because the benefit-risk evaluation is performed on a compound level for PBRERs and there is a separate analysis for each approved indication, greater resources are expended than is typical of most benefit-risk evaluations. A side effect of compound level evaluation, however, is that product teams may pool safety data over multiple indications if those indications have similar pathophysiology, if the treatment has a similar mechanism of action for each indication and if there is no evidence that any adverse events merit special consideration for any of the indications.

Other decision context challenges involve the evaluation of a drug at the compound level when there may be multiple doses and formulations and combination products to evaluate. There may not be a single "study drug" but rather several, each of which could potentially require its own analysis. Additionally, it must be decided what the appropriate comparator is for evaluation. In typical benefit-risk assessments, there are only one or two comparators. For PBRERs, there could be many comparators based on current standards or care. Clinical trial data may become less relevant if the comparator used in the trials is no longer a standard.

It must also be determined if the effects of the drug will be evaluated only for the intent-to-treat patient population or for an actual-practice patient population and whether the study drug will be used with or without concomitant treatments, whether it will be used as specified in the label or as used in real-life practice or as described in individual data sources. Finally, patient subgroups are more likely to assume a greater role in the post-approval period than during drug development and data for those groups is more likely to be available, resulting in a much lengthier and more complex decision
Post-approval benefit-risk assessment poses a variety of challenges that manifest themselves in many steps of a typical benefit-risk framework. Surmounting these challenges is aided by the use of a benefit-risk framework but the evaluations are ultimately a case-by-case exercise that benefit from the use of a toolkit approach.

context than typically used for benefit-risk evaluation in development.

Post-approval outcome identification challenges

In post-approval benefit-risk assessment, potential and identified risks are both included and potential endpoints can be more difficult to analyse because confirmatory evidence may not be available. Although PBRER guidelines specify the use of “important” or “key” endpoints, it is not always clear how to distinguish these from other endpoints or how to defend that distinction. The definition of desired endpoints can vary and they are not always captured in each data source. For example, major adverse coronary events (MACE) have variable definition and has been defined as “cardiovascular death plus myocardial infarction plus stroke” or “cardiovascular death plus myocardial infarction plus stroke” or “all-call death plus myocardial infarction” or other ways. Combining endpoints by name may lead to misleading results.

Observational databases often do not have the endpoint granularity used in full development. For example, in a typical value tree of endpoints for anticoagulant treatment of atrial fibrillation, there are often separate endpoints of disabling and non-disabling stroke and for major and non-major bleeding. These distinctions can be important in benefit-risk discussions conducted with regulators. However, these differentiations are unlikely to be available in post-approval databases. In addition, because new endpoints gradually replace older ones, comparing or combining data from old and new datasets may not be possible.

A wide variety of events are observed in real-world use and the evaluator needs to be clear about what is not being included in the value tree and why. It may be necessary to trim the level of detail in the value tree for many sources and it is often necessary to find the right balance between detailed and broad endpoints; for example, whether to group all malignancies together or report particular cancers separately.

In summary, post-approval data sources may not always have the ideal endpoints for a benefit-risk assessment, and it will often be necessary to compromise the level of detail in the analysis due to data availability.

Challenges in post-approval data source identification and use

There are typically many more data sources to consider in the post-approval period including original clinical trials, long-term extensions, phase 3b/4 studies, registries, epidemiology studies, pharmacovigilance activities, company databases and large, simple safety studies. Moreover, conditions surrounding these data are far less controlled. Sources may not match the clinical study inclusion and exclusion criteria and patients using the drug under real-world conditions may have comorbidities and be using concomitant medications under conditions in which there is far less monitoring, potentially resulting in non-adherence and overdose.

As a consequence, defending the quality of data often takes on a greater role than required for benefit-risk evaluation in development. Potential issues for defence include the relevance of the database (e.g., whether the population is matched to the clinical trial data), study retention, open-label use, confounding by indication (i.e., patients are channelled to different treatments according to their degree of illness).

Additionally, it can be challenging or even impossible to integrate information from multiple sources, especially when varying measures such as relative risk, overall risk and hazard ratios are used, although it may be sufficient to show consistency over multiple sources. It also can be difficult to disentangle the risks themselves from the consequences of real-world risk management. There also rarely is current clinical trial comparator data available once a product is several years from approval.

Potential solutions to these challenges are to compare current safety data to original clinical results or to database results, to conduct formal epidemiologic studies, to compare data from patients before and after treatment or to show the stability of response since approval or since a prior PBRER.

Preparing for a post-approval benefit-risk evaluation

Teams preparing a PBRER should compile basic information about the drug to be evaluated, such as a list of approved indications, the evolution of the product since approval such as changes in indication or current signals, and the current treatment alternatives. They must
also consider which comparator(s) should be used for the benefit-risk evaluation and for which of those comparators data are available. A list of benefit measures from clinical trials, registries, epidemiology studies and of potential and identified risks from these sources and a risk management plan (if available) should also be prepared. In preparation for conducting the PBRER benefit-risk exercise, the team should also be familiar with available data including short- and long-term studies, registries, observational studies and meta-analyses and subgroups of importance. Issues in project management should be resolved including the determination of timelines for submission and available resources such as statisticians and medical writers.

Teams should also be aware of the differences between a first-time PBRER and an update. For a first time PBRER, teams should bear in mind that the benefit-risk analysis must be based on data cumulative from approval. It is also important at this time to reconsider the selection of endpoints, deciding which efficacy endpoints are sufficient to characterise benefit and how to count events. Data sources should be revisited and ideally, comparator data for both efficacy and safety should be available over the full course of use since approval. An updated PBRER, however, could build an incremental analysis from a prior report, or potentially be just a safety update. As is stated in ICH and EMA PBRER guidelines, “Where little new information has become available during the reporting interval, the primary focus of the benefit-risk evaluation might consist of an evaluation of updated interval safety data.”

Conclusions

Post-approval benefit-risk assessment poses a variety of challenges that manifest themselves in many steps of a typical benefit-risk framework, in particular, the decision context and the identification and use of outcomes and data sources. Surmounting these challenges is aided by the use of a benefit-risk framework but the evaluations are ultimately a case-by-case exercise that benefit from the use of a toolkit approach.

The traditional methodology of observational studies – What are the challenges for regulatory agency acceptance?

Dr James Rhys Williams

Associate Director, Epidemiology, Biogen Idec, USA

Traditionally, observational studies to monitor the benefit and risk outcomes of medicines in the post-market setting are prospective studies that are integrated with routine clinical care or retrospective studies that are conducted for example, through the use of administrative health claims or electronic medical record systems. The challenges for regulatory acceptance of these studies centre on their design and include the regulatory prioritisation of benefit-risk data collection, the definition of non-interventional research, enrolling an active comparator cohort and the timing and reconciliation of feedback from multiple regulatory agencies.

Regulatory prioritisation of risk data collection

Regulatory agency requests for post-market studies are often motivated by safety concerns and as such, specify risk outcomes but are silent on endpoints that concern benefit. The resulting trials are framed as safety studies rather than benefit-risk studies and benefit outcomes are included as secondary or exploratory endpoints, if at all. In fact, the FDA Guidance for Industry Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug and Cosmetic Act specifies that “postmarketing studies and clinical trials may be required to assess a known serious risk related to the use of the drug, to assess signals of serious risk related to the use of the drug or to identify an unexpected serious risk when available data indicates the potential for a serious risk.”

Likewise, the EMA Guideline on good pharmacovigilance practices (GVP): Module VIII – Post-authorisation safety studies (Rev 1) states that a post-authorisation safety study is defined as “any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.”
In accordance with its guideline for post-marketing studies, which does not relate to the assessment of benefit, the FDA post-market requirement for Tecfidera (dimethyl fumarate), the Biogen Idec treatment for relapsing multiple sclerosis (MS), called for a “large, long-term, prospective observational study in adult patients with relapsing multiple sclerosis, with the primary objective of determining the nature and incidence of serious infections including opportunistic infections, leiomyoma, malignancies including renal cell cancers and other serious adverse events including serious renal and hepatic events and other medically significant events occurring with marketed use of Tecfidera (dimethyl fumarate). The study should include characterization of the finding of urinary ketones. A minimum of 5000 multiple sclerosis patients treated with Tecfidera (dimethyl fumarate) should be enrolled and followed for a minimum of 5 years.”

Biogen Idec, however, felt that it was important to collect both benefit and risk data in order to make a comprehensive evaluation of any safety issue. Accordingly, the Biogen Idec ESTEEM study, a multicenter, global, observational study to collect information on safety and to document the drug utilisation of Tecfidera (dimethyl fumarate) when used in routine medical practice in the treatment of multiple sclerosis was conducted to better characterise the long-term benefit-risk profile of Tecfidera in patients with multiple sclerosis who are prescribed the drug under routine clinical care. The primary objective of the trial was to determine the incidence, type and pattern of serious adverse events, including infections, hepatic events, malignancies and renal events and of AEs leading to treatment discontinuation. The secondary objectives of the study were to determine Tecfidera prescription and utilisation patterns in routine clinical practice in patients with MS; to assess the effectiveness of Tecfidera on MS disease activity and disability progression in routine clinical practice and MS relapse information and to assess the effect of Tecfidera on health-related quality of life, healthcare resource consumption and work productivity.

The key rationale for using external data as the comparator in the ESTEEM study was that prior to launch the possibility of any channelling bias that influences a physician's choice to prescribe Tecfidera versus another multiple sclerosis treatment could not be accurately predicted. In addition, it was likely that treatment algorithms would likely evolve over the study period, making it difficult to pre-speak appropriate active comparator groups. Given these challenges, it was likely that more informative comparisons could be made from cohorts derived from external databases rather than an active comparator cohort and there was an increased probability of having a sufficient sample size to match important demographic and clinical characteristics.

Data from post-market observational studies were also included as a supportive evidence for the positive benefit-risk profile of the Biogen Idec drug for multiple sclerosis, Tysabri (natalizumab) in its EMA 5-year marketing authorisation renewal. In the Tysabri Observational Program in 2150 patients receiving Tysabri, the mean annualized relapse rate (ARR) decreased from 1.98 at baseline to 0.26 on Tysabri. In patients with 1 relapse in the year prior to starting Tysabri treatment, mean ARR decreased from 1.00 to 0.21. The National Italian Tysabri Registry was another source of post-marketing data, showing that in 285 MS patients receiving Tysabri, the ARR decreased from 2.13 in the year prior to Tysabri to 0.26 after 1 year of Tysabri therapy.

**Definition for non-interventional studies**

According to Article 2c of the Directive 2001/20/EC, non-interventional studies require the use of a medicinal product according to marketing authorisation, no assignment to therapeutic strategy other than current practice and no additional diagnostic or monitoring procedures. However, The Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (Rev 1) allows that (in) non-interventional studies . . . interviews, questionnaires and blood samples may be performed as part of normal clinical practice.

Inconsistencies exist in the interpretation of a non-interventional trial by ethics councils in the EU Member States and studies have been delayed or not conducted at all due to differences in interpretation of the definition. This lack of clarity has led to hesitation in including clinical scales and patient-reported outcomes to measure a product’s benefit-risk profile in post-market studies in order to prevent
being classified as interventional by a European ethics council. The limited ability to collect biospecimens or suggest laboratory measures in observational studies also results in missed opportunities to explore biomarkers related to benefit-risk profiles.

Seeking to define the scope of prospective, non-interventional research, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) proposed the following determinants to define current practice. A diagnostic, monitoring or therapeutic procedure can be considered current practice if at least one of the following is fulfilled:

- Routinely performed by a proportion of healthcare professionals
- Not deemed obsolete
- Performed according to evidence-based medicine criteria
- Defined in guidelines issued by a relevant medical body
- Mandated by regulatory and/or medical authorities
- Reimbursed by the national or private health insurance

The ENCePP proposed interpretation of current legislation and guidance also stated that observing the use of a drug in real life (as opposed to the rigid settings of clinical trials) could include incorporate the evaluation of use, including capturing off-label use and could even be conducted with this specific aim because this research is purely observational, as there is no experimentation involved.

**Active comparator arms in post-market observational studies**

Active comparator arms are often requested in post-market observational studies although there may be unclear feasibility for their use in prospective studies, where there may be competing trials within a therapeutic area, potential biases related to differential ascertainment due to differences in recommended monitoring and a lack of practicality for reimbursement of off-label monitoring. It must also be recognised that pharmacovigilance is not intended to test hypotheses for comparative effectiveness. It is more appropriate to collect data for one cohort and to use new secondary external data sources to form comparisons.

**Timing and reconciliation of feedback from multiple regulatory agencies**

Another hurdle in post-marketing observational studies is the disparate timelines between agencies for requesting and reviewing post-market observational studies. The EMA requires concept protocol or full protocol on day 80, with feedback provided on day 120 and day 180 and resolution prior to marketing authorisation. The US FDA requires the receipt of a post-marketing description during the last four weeks of the review cycle, with initial feedback usually provided six months post-approval and resolution occurring up to twelve or months post-approval. The impact of these timing differences includes an increased likelihood of submitting an amendment for comment to an agency after obtaining agreement, a delayed study launch, operational pieces such as database builds that remain incomplete until the protocol is finalised and missed recruitment opportunities, especially for products with rapid market uptake or with competitor products launching near the same time.

**The way forward**

Practical next steps to overcome potential barriers in post-marketing observational studies include continuing the dialogue about operational challenges in the conduct of these trials and the merits of active comparator cohorts under appropriate conditions. Regulatory agencies should be encouraged to specifically include assessments of both benefits and risks in post-market safety study guidance documents and to adopt more flexible and clear definitions of non-interventional research in European Union laws. Finally stakeholders should engage with regulatory agencies, industry organisations and others to include an assessment of post-market requirement feedback in ongoing evaluations of FDA/CDER’s 21st Century Review Process conducted as part of the fifth iteration of the Prescription Drug User Fee Act (PDUFA V).

**References**

Capturing benefits and risks in the post-approval phase – What are the practical and regulatory challenges?

Dr Marilyn Metcalf
Senior Director, Benefit Risk Evaluation, GlaxoSmithKline, USA

Benefit-risk and over-the-counter drugs

There are more than 80 therapeutic over-the-counter (OTC) product categories in the US, ranging from acne to weight control. Generally, characteristics of OTC drugs include the fact that their benefits outweigh their risks, the potential for misuse and abuse is low, a consumer can use them for self-diagnosed conditions, they can be adequately labelled and health practitioners are not needed for their safe and effective use. As with prescription drugs, the US Food and Drug Administration Center for Drug Evaluation and Research (FDA CDER) oversees OTC drugs to ensure that they are properly labelled and that their benefits outweigh their risks.

Periodic Benefit-Risk Evaluation Report (PBRER) implementation may be the first instance of benefit-risk assessments of OTC medicines that are formally documented. In addition, general regulatory guidance for benefit-risk assessment is intended for new chemical entities (NCEs) and more interpretation is needed for its use with mature products such as those that are being switched from prescription to non-prescription status and risk assessment tools suitable for NCEs may not be as useful or applicable. In the development of an OTC PBRER, information sources need to be considered since they vary with age and type of product. Full use must be made of data generated for other purposes including the core data sheet for identification of risks, claims data, treatment guidelines, review articles, information for the product class and health records.

The Brass model

GlaxoSmithKline has evaluated the approach for the regulatory assessment of the benefits and risks of OTC medicines proposed by Eric Brass and colleagues. In this model, which is similar to that of Universal Methodology for Benefit-Risk Assessment (UMBRA) and others that have been used in the evaluation of prescription medicines, benefit and risk attributes are identified using a value-tree framework. This decision tool is designed as a two-factor, two-stage instrument, with each attribute independently assessed on both the frequency of occurrence and clinical impact of the attribute. These two factors are scored on a 0–3 scale (0 score = no occurrence or no clinical impact; 3 = high frequency of occurrence or high clinical impact.) In the first stage, the tool is initially used early in drug development to facilitate communication amongst stakeholders and to identify important data gaps and then in the second stage, is updated after new data are generated during the development programme. This approach allows regulators to maintain flexibility with respect to how final decisions are made, yet allows specificity and transparency during the evaluation and further modifications can be incorporated to address drug-specific requirements or regulatory preferences. The utility of the Brass model could also be further increased by use of a Group-Delphi technique.

GSK identified broader potential uses for the principles proposed by Brass such as the retrospective review of current OTC products to support the benefit-risk conclusions in regulatory documents including PBRERs, the benefit-risk assessment of existing OTC products and the prospective assessment of the potential for switching relevant prescription-only products for OTC use. Longer-term, the Brass model could be used to work with identified internal stakeholder groups to embed suitable benefit-risk assessments for OTC and switched products, to develop materials to support teams with these assessment and to identify and align risks from key sources to streamline documentation.

Similar to prescription drug PBRERs, OTC PBRERs
can be used to construct an overall benefit-risk profile. Sections of the PBRER correspond to those of Development Safety Update Report and the safety specifications of a risk management plan can be identical in content for increased efficiency. OTC PBRERs allow teams to summarise relevant new safety information that could have an impact on the benefit-risk profile of the medicinal product and any important new efficacy or effectiveness information that has become available during the reporting interval. It can be noted whether new data are in accord with a previous benefit-risk profile and where important new safety information has emerged, it facilitates the conduct of an integrated benefit-risk evaluation for approved indications, including proposed action(s) to optimise the benefit-risk profile when appropriate, while taking care that urgent safety information and new safety information is reported through the appropriate mechanisms.

The Brass model for benefit-risk evaluation corresponds to other approaches. EU Guidance on the format of the risk management plan (RMP) part II, module VIII, summary of the safety concerns states that a summary should be provided of the safety concerns identified in previous RMP Modules. A safety concern may be an important identified or potential risk or missing information, newly identified safety concerns, recent study reports with implications for safety concerns, details of identified and potential risks from clinical development and post-authorisation experience, identified and potential interactions and pharmacological class effects.

Other similarities to the Brass approach can be found in recommendations from Work Package 5 of the Innovative Medicines Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (IMI PROTECT) which characterise the benefit-risk model as a communication channel amongst different audiences. The arrival of new comparators onto the market and safety signals or other emerging data require the revisiting of a product’s benefit-risk assessment in order to include additional outcomes and may require some remodelling of the value tree as any preference weights used in a quantitative analysis may no longer be valid in the presence of new outcomes and therefore will need to be re-elicited.

A standard approach

As there are many different report formats for the evaluation of benefit-risk for OTC products with the same goals, it may be feasible to consider the application of the Brass approach as a standard framework. However, industry considerations for this action include the necessity for the separation of the patient and population domains where applicable and the need to assess which effects are common to most OTC or switch products to enable a focus on the most important effects that are specific to the product under evaluation. The benefit domains of the Brass approach are those of all OTCs: improved access to effective drugs, improved clinical outcomes, improved public health, enhanced involvement by consumers in their healthcare and the economic benefits of non-prescription medicine availability. The risk domains are unintended misuse, intentional misuse with therapeutic intent, accidental ingestion, intentional overdose and worsened outcomes due to self-management. Figure 7 shows the mapping of these domains to the EU RMP risk tables and Figure 8 shows Brass benefit domains mapped to the CIRS UMBRA Benefit-Risk Action Team (BRAT) value tree and separated into patient and population effects.

An example of the EMA evaluation of the benefits and risks of a medicine being switched from prescription to OTC status can be found in the EPAR for an application for approval for the short-term use of esomeprazole orally in...
the strength of 20 mg to treat gastric reflux symptoms as a non-prescription medicine. The application was reviewed against the criteria as laid down in the 2006 revision of the Commission Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use. The first criterion was the existence of direct or indirect danger, even when used correctly, if utilised without medical supervision; the second criterion was known incorrect use; and the third criterion was activity or side-effects which require further investigation.

In addition to also evaluating safety concerns and risk minimisation measures, the EPAR detailed the evaluation of the benefits and risks of esomeprazole through the examination of its beneficial and unfavourable effects, the importance of those effects and the uncertainty in the knowledge about them.

GSK intends to prepare case studies of the use of the Brass model in the benefit-risk evaluation of different types of products and to solicit internal feedback and meet with key stakeholders to assess their views about this approach as well as their needs and the challenges in this area to assist in the preparation of proposals for wider implementation.

Reference
### Appendix: Workshop Attendees

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<tr>
<th>Name</th>
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<tr>
<td>Dr Hesham Aboshady</td>
<td>Boehringer Ingelheim</td>
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<td>Diane Barnes-Glait</td>
<td>Takeda Pharmaceuticals</td>
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<td>Mark Bokelman</td>
<td>EMD Serono Inc</td>
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<td>Dr Carmen Bozic</td>
<td>Biogen Idec</td>
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<td>Professor Sir Alasdair Breckenridge</td>
<td>MHRA</td>
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<td>Sheila Dickinson</td>
<td>Novartis Pharma AG</td>
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<td>Dr Steven Gao</td>
<td>Daiichi Sankyo</td>
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<td>Dr Tarek Hammad</td>
<td>Merck Research</td>
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<td>Dr Diana Hughes</td>
<td>Pfizer Inc</td>
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<td>Haley Kaplowitz</td>
<td>Allergan</td>
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<td>Dr Bennett Levitan</td>
<td>Janssen</td>
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<td>Anders Lindholm</td>
<td>Shire Pharmaceuticals</td>
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<td>Marilyn Metcalf</td>
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<td>Steven Miller</td>
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<td>Jane Møll Pedersen</td>
<td>Novo Nordisk A/S</td>
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<td>Dr Valerie Murer</td>
<td>F.Hoffmann-La Roche</td>
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<td>Dr Becky Noel</td>
<td>Eli Lilly and Company</td>
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<td>Jane Porter</td>
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<td>Dr Jutta Pospisil</td>
<td>Bayer Health Care</td>
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<td>Dr Susan Rosen</td>
<td>Shire Pharmaceuticals</td>
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<td>Dr Linda Scarazzini</td>
<td>AbbVie Inc</td>
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<td>Leslie Williams</td>
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<td>Centre for Innovation in Regulatory Science</td>
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<td>Patricia Connelly</td>
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<td>Art Gertel</td>
<td>Senior Research Fellow</td>
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<td>Lawrence Liberti</td>
<td>Executive Director</td>
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<td>Dr Neil McAuslane</td>
<td>Director</td>
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<td>Professor Stuart Walker</td>
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