DEVELOPMENT OF A UNIVERSAL BENEFIT-RISK ASSESSMENT FRAMEWORK AND ITS APPLICATION FOR REGULATORY AGENCIES

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ABSTRACT

The assessment of medicines has moved from efficacy and safety to that of a benefit-risk balance and regulatory agencies and pharmaceutical companies are improving their processes in order to achieve greater consistency and transparency in decision-making. However, their efforts are largely independent and do not address the lack of consistency in decisions by different countries, albeit for the same medicine, resulting in the potential inaccessibility of important medicines. The aim of this study was the development and validation of a universal benefit-risk framework for use by regulatory authorities.

A questionnaire, specifically developed for this study, was used to evaluate the current approaches to benefit-risk assessment of medicines by 14 regulatory agencies and 24 pharmaceutical companies. None of the 11 agencies (79%) and 20 companies (83%) that responded used a fully quantitative approach, but the majority used a qualitative system for benefit-risk assessment. The development of a universal benefit-risk framework for use by both regulators and industry, with the involvement of all stakeholders, was supported by the study participants.

A comparison of the existing benefit-risk assessment frameworks used by agencies and companies identified the common elements. As no major differences were observed, an 8-step universal framework was developed which incorporated the other frameworks. To support the framework in the assessment of benefits and risks, a template for documenting the benefit-risk decision together with a user manual was also developed. Four regulatory agencies conducted a retrospective pilot study to investigate the feasibility of this framework, the benefit-risk template and user manual.

Subsequently, a prospective study was conducted by TGA of Australia, Health Canada and HSA of Singapore. The agencies found the benefit-risk template was ‘fit for purpose’ in terms of the relevance of information supporting the benefit-risk decision, the documentation and communication and the relative importance and values of the benefits and risks. The results showed that the benefit-risk summary template was adequate to document benefits and risks, relevant summaries and

conclusions for the emerging markets. The applicability and validity of the summary component of the benefit-risk template was evaluated by sixteen HSA clinical reviewers in a retrospective study. They found that the BR Summary Template was adequate to document benefits, risks, relevant summaries and conclusions. However, a revision of the BR Summary Template should include technical improvements and more details of safety information. The BR Summary Template was thought to be a useful tool for communicating benefit-risk decisions to a variety of stakeholders.

The formats of publicly available reports from major regulatory agencies were compared and found to be generally similar**.** When compared to the BR Template, the listing of benefits and risks, assigning of weights and values, visualisation and a more detailed, systematic standardised structure were found to be absent**.** This research has demonstrated that the 8-step universal framework is of value for the assessment of benefits and risks of medicines by regulatory agencies and the template was found to be useful for documenting and communicating benefit-risk decisions.

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List of Abbreviations

AUSPAR: Australian Public Assessment Report (of TGA)

BR: Benefit-Risk

CHMP: Committee for Medicinal Products for Human Use

CIOMS: Council for International Organizations for Medical Sciences

CIRS: Centre for Innovation in Regulatory Science

EMA: European Medicines Agency

EPAR: European Public Assessment Report

EU: European Union

FDA: Food and Drug Administration

HSA: Health Sciences Authority, of Singapore

ICH: International Conference on Harmonisation

MCDA: Multi Criteria Decision Analysis

NNH: Numbers Needed to Harm

NNT: Numbers Needed to Treat

SBD: Summary Basis of Decision (of Health Canada)

TGA: Therapeutic Goods Administration of Australia

WHO: World Health Organisation

Glossary of terms

Adverse event	Also known as adverse experience, it is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
Adverse reaction/effect	In the pre-approval setting when the therapeutic dose(s) may not be established, it is all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. For marketed medicinal products, it refers to a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.
Benefit	A potential favourable effect seen to be promoting or enhancing the current state of health, resulting from the treatment using the product
Benefit-risk assessment	Also referred to as assessment and known as benefit-risk evaluation, it is the review of scientific data in support of the proposed indication of the product, conducted by a reviewer/assessor
Benefit-risk balance	Also known to as benefit-risk profile or outcome, it is the expert opinion cumulative of the consideration of the benefits and risks - weighing the relative contribution and the uncertainties of the evidence provided, incorporating the current medical knowledge and experience - and recommending a positive or negative outcome
Benefit-Risk Summary	Part of the Benefit-Risk Template; consist of the conclusions of various aspects of assessment, and the final benefit-risk balance
Benefit-Risk Template	A product of this research which documents and communications the assessment findings supporting the benefit-risk balance and decision; includes the Benefit-risk Summary and proforma

Benefit-Risk Summary Template	A product of this research which documents and communications the assessment findings supporting the benefit-risk balance and decision, extracted from the main Benefit-Risk Template
Company/Sponsor	Refers to the owner of the product, and whom initiates the submission
Comparator	An investigational or marketed product (i.e. active control) used as a reference in a clinical trial
Effect size	The quantum of difference arising from the comparison between treatment outcomes of the product with the comparator; it contributes to the overall interpretation of effectiveness and clinical relevance
Investigated product	Also referred to as the product, it is the entity on which the submission of an application for market authorization is based, and for which the clinical studies are conducted
Medicines	Refers to pharmacological products for use in human with the intention of medical intervention
Methodology	A tool, concept or set of principles that guides the assessment of benefits and risks
Multi criteria decision analysis (MCDA)	A decision analysis technique which disaggregates a complex problem, measures the extent to which the options achieve its objectives, applies weights to the objectives and finally reassembles these information to contribute to the decision
Patient reported outcomes	Observations as part of a study related to the results obtained directly from the patients, which may include patients' satisfaction, tolerability, symptoms, patient preferences, quality of life and interruptions to daily living

Proforma	Part of the Benefit-Risk Template; consist of various sections providing the details of the basis on benefit-risk balance decisions
Reviewer	Also known as evaluator or assessor, personnel trained in the scientific evaluation of data, and using clinical judgment to provide a recommendation on the benefit-risk balance of the product
Risk	Also known as harm, an unfavourable effect or adverse reactions/effects on patients' health, public health or the environment resulting from exposure to the product
Scoring	The process of assessing the performance of each option against a relevant criteria by assigning a numerical value
Seriousness (of adverse event/reaction/effect)*	A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: • results in death, • is life-threatening (at risk of death at the time of the event) • requires inpatient hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability/incapacity, or • is a congenital anomaly/birth defect.
Severity (of adverse event/reaction/effect)*	The intensity of a specific adverse event which may or may not be of medical significance or seriousness, which is defined by a set of criteria.
Submission	An application sent for review to the regulatory authorities by the company, for the market authorization of the proposed indications of the product
Value tree	A methodology used in multi-criteria decision analysis for incorporating and organising the different criteria in the model structure. It clusters the criteria in a hierarchical way

Valuing	An exercise of providing qualitative or quantitative figure (values) reflecting of the effect observed from the studies; this assist in the interpretation of effect size and relevance of treatment
Weighting	An exercise of expert judgment indicating the relative importance of the available options, commonly done through a logical system of rank assignment (weights)

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CHAPTER 1

General introduction

The regulation of medicines is essentially conducted to ensure patients' accessibility to medicines that fulfil the criteria of quality, safety and efficacy. As patients are not equipped to make a scientific assessment, regulators play an important role in controlling the access to safe and effective medicines. Two of the key elements highlighted by the World Health Organisation (WHO, 2003) for effective regulation of medicines included strong cooperation and collaboration between stakeholders and transparency and accountability. The latter is deemed critical for the communication of the basis of decisions and building public confidence. In the WHO's strategic directions for medicines (WHO, 2010), new policy and guidance was developed to ensure transparency and good governance in pricing, procurement and regulation.

The review of medicines by regulatory agencies is largely based on the submission of clinical data collected from clinical trials phases I to IV. The US FDA may occasionally be involved in the developmental phases of a product through investigational new drug (IND) applications, where the trial data generated will subsequently feed into the new drug application (NDA) for a marketing authorization. The assessment of clinical efficacy of a medicine is supported by studies which are statistically designed to provide a reliable and robust conclusion through the scientific investigation of suitable endpoints. It is expected that these measured endpoints would be translated to meaningful benefits to the patients intended for the treatment. However, due to practical reasons to conduct and complete a trial in a timely manner for generating the required clinical data, these measured endpoints may be surrogates of the actual clinical benefits on the basis of the observed effect on these endpoints. These types of endpoints include parameters like blood pressure, cholesterol levels or microbial eradication which may not translate to reduced cardiovascular events or a faster recovery from an infection. To establish the utility of a medicine, some trials are required to produce clinical endpoints that could directly benefit a patient, such as overall survival, reduction in hospital stay or an improved quality of life from a chronic debilitating disease. However, a clinical trial is limited by its scientific robustness in taking into account the many other factors that would constitute a benefit to a patient. Indeed the definition of a benefit may differ among physicians, patients and between diseases. This may be due to differences in severity of the disease itself and the subjective perception of the expectations arising from the treatment. Moreover, a benefit should also take into account the trade-off

incurred from the potential adverse effects of the treatment. As a result, the endpoints from a well-designed clinical trial may not always produce a meaningful beneficial treatment for the patient. A proven clinical efficacy in a study therefore may not always translate into a benefit for the patient.

In the assessment of risk or harm, safety data are collected alongside the conduct of the clinical studies which are primarily designed for the purpose of proving clinical efficacy. As such, there could be more subjectivity in the perception and conclusion of risks to the patients and how the safety information may be rationalised into objective outcomes (Slovic et al., 2004). In a study conducted by the EMA as part of the benefit-risk methodology project, the variability in the individual risk perception of regulators was reviewed (EMA, 2011a). The differences appeared to be related to gender, years of regulatory experience, the medicine itself and specific benefit and risk dimensions. It was recommended that a tool be included as part of a benefit-risk assessment framework to increase the awareness of this subjective component in decision-making and therefore introduce transparency and consistency into the process. Moreover, the number of patients in a clinical trial could not always elucidate the rare adverse effects which could be medically severe and significant. At the point of a product approval for market authorisation, there is only limited information on the potential risks. This is mitigated by post-market risk management plans and pharmacovigilance activities to further monitor the safe use of the product, so as not to further impede the timely access of a potentially useful medicine.

In a discussion of the changing role of clinical pharmacology on drug development (Zineh et al., 2013), it was commented that given the review staff at US FDA had a different preference for strategies, a robust framework is now needed to help them understand if their review strategy is appropriate for the medicine. This is to help reduce the uncertainties relating to their decisions that may have contributed to an observed excessive aversion to risks. This may also contribute to an understanding and addressing the current issue of the huge financial investment in drug development and an unexpected high failure rate during development.

Given the limitations and uncertainties in confirming the individual benefits and risks to patients, it will be a challenging task to justify the likely outcomes to a patient. In

making any decision, it should always entail the perspectives of expected advantages and the potential disadvantages that may be incurred. Likewise, for exploring options in managing the medical condition, the treatment should be viewed in terms of the benefits, risks and the uncertainties involved. The traditional method of assessing efficacy and safety separately could not be logically collated to provide a balanced view. It can be assumed that agencies would have gone through much deliberation on the trade-offs between the benefits and risks, but these are generally not documented or made known to the public.

Breckenridge (2010) shared his views on the challenges in the assessment of benefits and risks of medicines, where the shift is mainly to review the overall balance between the benefits of a drug and the associated risks rather than the individual impact. This balance could be expressed in a transparent manner using a structured framework which aids in the communication of the differences in opinions between regulators and the drug developers. Indeed, for the regulatory challenges to be adequately addressed there must be further integration among the stakeholders.

This shift in paradigm had already been observed much earlier, when there was a movement from safety, efficacy and quality to relative safety, comparative efficacy and relative quality. In moving from a risk-centric approach, the risk management strategy assesses the identified potential safety issue in the light of an overall change in the benefit-risk balance, as well as exploring new benefits in addition to managing the risks (CMR, 2002). The EMA (2008) realised the importance of reviewing both benefits and risks as an overall balance in their regulatory decision-making and therefore produced a reflection paper on the benefit-risk assessment of medicines. This movement added to the ICH final concept paper (ICH, 2010) to review the current periodic safety update reports (PSUR) and focus on benefit-risk evaluation, leading to the current periodic benefit-risk evaluation report (PBRER). It is however noted that the benefit-risk evaluation can be carried out qualitatively without the need for a formal mathematical or quantitative tool. In early 2013, EMA put the PBRER into effect (EMA, 2013a), supporting this initiative as there is now greater emphasis on risk management planning and recognising that new safety information can only be meaningfully assessed in the context of the medicine’s benefits.

A study of clinical practice guidelines, to assess how well patient preferences are incorporated showed that current practice guidelines did not integrate patient preferences (Chong et al., 2009). Given the differences in the understanding of scientific evidence and values in decision-making, there is an expected variability in the contribution (Umschied, 2009). Yet we know that the regulation of medicines is moving towards being patient-centric, so that decisions are made in the view of the wide-ranging needs of patients which can only be obtained if communications with stakeholders is part of the process (Walker et al., 2006). Indeed the increasing importance of patients' perspectives in the form of patient reported outcomes in clinical trials can complement the traditional efficacy endpoints (Hareendran et al., 2012). With various examples of how patient decisions had influenced the availability of some medicines including HIV drugs and monoclonal antibodies, it is only prudent to include the views of the patients in expressing the benefit-risk balance (Breckenridge, 2011).

Both EMA and US FDA have indicated their plans to incorporate stakeholders' views into their benefit-risk assessment and decision-making process. In a workshop conducted to review the patient's role in benefit-risk assessment (CIRS, 2012a), it was proposed that patients' preferences and their values be brought into the regulatory decision-making system through public hearings, patient representation or incorporation of such measures into clinical trials. In another workshop on framework development, patient inputs were identified as important when the medical condition involves subjective benefits and risks (CIRS, 2011). The US FDA alluded to the agency's plans, as part of the Prescription Drug User Fee Act (PDUFA) V (FDA, 2012a and 2013), to obtain patient perspectives on disease severity and unmet medical needs. Therefore, it is expected that a framework for the assessment of benefits and risks should be able to reflect the contribution of patients' perspectives in the benefit-risk balance and the final regulatory decision.

In a study on the effect of format on understanding the benefits and risks of clinical trials, it was found that pictographs are superior in providing an adequate overall understanding (Tait et al., 2010). The use of graphics and other visual displays are being used more often and also as an adjunct to verbal and numerical communications of risks (Lipkus, 2007). In a workshop to discuss the development of

a framework that informs stakeholder perspective and clarity of decision-making (CIRS, 2011), it was agreed that visualisation tools could provide a focus for benefit-risk discussions on critical issues, identifying gaps and exposing overlapping benefits and harms and providing a succinct summary of the information needed to make benefit risk decisions. Hence it would be appropriate, that a framework for the assessment of benefits and risks, to incorporate visualisation of the outcomes to facilitate the communication to stakeholders.

Recent significant contributions by various stakeholders

Academia

Mussen et al. (2007a; 2009), in the course of their published works for developing a systematic approach to decision-making during the assessment of medicines, reviewed benefit and risk criteria through identifying these from the ICH's Common Technical Documents (CTD), EMA's European Product Assessment Report (EPAR) and US FDA's Medical Review. The identified criteria were subsequently verified through a survey, refined in a workshop conducted by CMR (CMR, 2008) and produced recommendations for a future framework. The following efficacy parameters should be included in a benefit-risk framework:

- Magnitude of treatment effect as observed in the pivotal studies
- Clinical relevance of the observed magnitude
- Statistical significance
- Relevance of primary endpoints and studied population of the pivotal studies
- Discussions on dose and comparators
- Methodology and study design issues
- Validation of scales and outcome measures
- Evidence of efficacy in relevant subgroups
- Confirmation of efficacy by secondary endpoints and supporting studies
- Patient reported outcomes
- Patient compliance

The framework should also include the following safety parameters:

- Overall incidence of serious side effects
- Discontinuation rates due to adverse effects
- Incidence, seriousness and duration of specific adverse effects
- Extrapolation of safety profile to intended population for the indication
- Adverse effects of the pharmacological class and other related classes
- Safety in subgroups
- Concerns arising from non-clinical evaluation
- Overall incidence of adverse effects by categories
- Drug-drug and drug-food interactions
- Potential for off-label use and safety concerns
- Risk mitigation plans and strategies

In constructing a benefit-risk balance, Mussen et al. (2009) recommended the following parameters as part of the framework:

- Description of alternative therapies or interventions
- Calculation of uncertainties on benefits and risks
- Direct comparison of gains versus harms in terms of lives saved or lost or clinical events
- Evaluation of acceptable risk with regards to the clinical benefit in the specified context
- Evolution of the benefit-risk balance over time
- Evaluation of benefit-risk in major subgroups
- Identification of outstanding issues and potential post-market commitments
- Consideration of different regulatory options for approval

In a review of the benefit-risk assessment models, Mussen et al. (2009) reviewed three general models, namely “Principle of Threes” (Edwards et al., 1996), evidence-based model (Beckmann, 1999) and Transparent Uniform Risk Benefit Overview (TURBO) (CIOMS, 1998). They were found unable to balance the benefits and risks and did not meet his criteria for a framework to assess benefits and risks. These

models did not define clearly the type, quality and relative importance of the data required. The models were simple, could not account for different attributing factors and were not validated in practice. However, these models would collate the thoughts and considerations of the assessment and hence contribute to decision-making. Mussen et al. proceeded to develop a new framework which would function as a model for decision analysis. The MCDA (Belton V et al., 2001) formed the foundation of this framework, as it allowed the balancing of multiple criteria, namely the different benefits and risks of treatment with the medicine being assessed. This is a process described in the Multi-criteria analysis (MCA) manual (Dodgson et al., 2009) which aimed at exploring the individual contributing aspects of the decision-making process before collating the outcomes to form the basis of the decision. There are three key phases of the MCDA process. The problem is first identified and structured, secondly the decision-maker's preferences are taken into account and lastly, action plans are developed.

A final 7-step framework based on the MCDA principles was eventually developed (CMR, 2010). The assessment of the benefit-risk balance was recommended to be carried out as follows:

1. Establish the background and context of the decision
2. Identify the options to be considered (treatment, placebo or active comparator)
3. Identify the criteria (benefits and risks) and arrange these into a value tree
4. Establish scales for the criteria and score the options on the criteria
5. Assign weights for each criterion
6. Normalise the weights, calculate the weighted scores and overall preference score for each option
7. Examine the results and conduct sensitivity analysis by varying the weights of the criteria

A framework uses a set of underlying principles to provide an overarching structure in which essential processes can be carried out to achieve its objectives. Therefore, despite the use of values and weights, both the MCDA and the above 7-step approach should be considered as frameworks rather than quantitative methodologies, in recognition of the underlying MCA principles described above.

Part of the framework development involved participants in two CMR workshops (CMR, 2004 and 2005) who applied the framework in two clinical settings. The first involved the use of a new recombinant necrosis factor receptor inhibitor compared against methotrexate in managing rheumatoid arthritis, and the other a hypothetical drug with cardiovascular safety concerns for treating schizophrenia. One utility of the framework was the provision of a platform for structured conversation and decision conferencing, which allowed an agreement despite a divergence in the opinions of the data. In addition, the workshops demonstrated that use of values and weights are required to provide a complete judgment on the benefits and risks. The framework was also applied to various other clinical scenarios (Mussen et al., 2007b). The final conceptual framework was adopted by CIRS (2009, 2010) and further refined through future workshops.

As part of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Risk-Benefit Management Working Group, Guo et al. (2010) conducted a literature review on quantitative methodologies for the assessment of benefits and risks of medicines. The search was not limited to a single stakeholder's perspective and thus included tools used by regulatory agencies, pharmaceutical companies and academia. They identified and reviewed 12 quantitative benefit-risk assessment models, which included the Quality-adjusted Time Without Symptoms and Toxicity (Q-TWiST) (Gelber et al., 1993; Cole et al., 2004), number need to treat (NNT)/ number needed to harm (NNH) (Holden et al., 2003a, 2003b; Laupacis et al., 1988; Cook et al., 1995), incremental net health benefit (INHB) (Garrison et al., 2007; Lynd 2010), probabilistic simulation methods (PSM) and Monte Carlo simulation (Lynd et al., 2004; Shaffer et al., 2006), multi-criteria decision analysis (MCDA) and stated preference method (SPM) (Ryan et al., 1998; Gan et al., 2004). Some models like the NNT used subjective weighting and allow a non-statistical or qualitative assessment and others like the MCDA and SPM were useful in allowing joint assessment of both benefits and risks. Simple methods like the NNT and NNH are widely used, but it could not account for the quantum or value of the benefits and harms, or allow the contribution of several relevant benefits and harms into the same context for decision-making. In addition MCDA was found to be capable of handling missing data and uncertainties through use of relevant modelling tools and

application of weights, as well as exploring the robustness of the outcomes through sensitivity analyses. While MCDA could account for the various factors contributing to the decision-making, it is nonetheless a relatively new and intensive tool that may be limited to more complex evaluations. The SPM is a theoretical tool that could incorporate patients' preferences and the evaluation of benefit-risk trade-offs. This method would require the collection of patients' treatment preferences, for which the current best practice to achieve this is still being developed. However, the SPM may be considered by healthcare professionals as it involves the opinions of the patients. Overall, it appeared that the reviewed methodologies were not adopted by the agencies and companies and were primarily for research purposes. Guo et al. (2010) concluded that some of these methodologies would be helpful to lessen concerns over the subjective component of assessment and provide the required transparency, but all have their own set of limitations. None was found to be able to function across all scenarios and it was recommended that various tools be used to appropriately profile the benefit-risk balance. Due to the limited published information for net clinical benefit analysis, the principle of threes and net-benefit-adjusted for-utility analysis, these methods were not reviewed.

Regulatory agencies

As expectations of stakeholders change with the rapid advancement of science, regulatory agencies make plans to adapt and meet these changing needs. In EMA's roadmap to 2015, they identified one of the strategic areas to be facilitating the access of medicines through reinforcing the benefit-risk balance assessment model, to be achieved through a set of priority activities (EMA, 2011b). These included looking at appropriate quantitative tools, improving the quality and consistency of the outcomes, reviewing the EPAR's to improve communication of benefit-risk decisions to stakeholders and increasing the involvement of patients, academia and healthcare professionals in the assessment of medicines to ensure their views are taken into consideration. A CHMP working group was formed in 2006 to look into methods to improve the transparency, consistency and communication of benefit-risk assessment. A preliminary review of NNT/ NNH, "Principles of Three", Transparent Uniform Risk Benefit Overview (TURBO) and MCDA was conducted and the advantages and limitations of each were discussed. In their report, they emphasised that qualitative evaluation and expert judgment are not to be replaced by quantitative

benefit-risk assessment. They recommended that a model for benefit-risk assessment should be structured and of a qualitative approach, be able to describe explicitly the importance of benefits and risks in the context of the decision and the impact of the uncertainties on the benefit-risk assessment (EMA, 2007). This led to the reflection paper for benefit-risk assessment of medicines as mentioned above and also the benefit-risk methodology project.

The benefit-risk methodology project was aimed at looking at tools and processes that provide aid to regulatory decision-making, training of assessors and communicating benefit-risk decisions to stakeholders (EMA 2009), through a series of five work packages. The first work package (EMA, 2011c) was to describe the practices of benefit-risk assessment within the EU for the centralised procedure. The key findings steered the movement of the remaining work packages and these findings appeared to be reflective of the global environment. Among the key findings were:

1. Variability in the understanding and definitions of “benefit” and “risk”
2. The benefit-risk balance is assessed mainly intuitively and by matter of expert judgment or extensive discussion
3. Importance of consistency in decisions and the process of decision-making
4. There is no system or model currently used by any agency and many felt there could be improvement made for the existing processes

In addition, the EMA produced a set of five criteria to verify a model’s applicability for benefit-risk assessment. These include logical soundness, comprehensiveness, acceptability of results, practicality and generativeness.

As part of their benefit-risk methodology project, twenty-one approaches were reviewed, including three qualitative frameworks (BRAT, CMR framework and US FDA’s benefit-risk framework) and 18 quantitative models in the second work package (EMA, 2010). This was conducted with the above five criteria for a benefit-risk assessment model. In response to the observation in the first work package, they attempted to redefine benefits as favourable effects, harms or risks as unfavourable effects and uncertainties as variations, bias, flaws and deficiencies of the above types of effects. With regards to the qualitative frameworks, these were still under

development at the time of the review and hence limited comments were made. It was highlighted however, that the uncertainties of benefits and risks, being of concern to regulators, should be addressed by these frameworks. The quantitative approaches were reviewed according to four broad categories based on their functions, namely simulation, models, statistics and measurements. Some of the approaches reviewed included the Markov processes (Sonnenberg et al., 1993), TURBO, Principles of Three, QALYs/ Disability adjusted life years (DALYs), Kaplan-Meier estimators (Kaplan et al., 1958) and conjoint analysis (Johnson, 2006). They concluded that four approaches, namely the qualitative framework, MCDA, Bayesian statistics (O'Hagan et al., 2006; Ashby et al., 2000) and decision trees (Goodwin et al., 2009; Stonebraker et al., 2002), would be useful to regulators and can comprehensively quantify a benefit-risk balance. A qualitative framework would be required to support any quantitative model and may be used for simple decision-making. Again, it was recommended that a combination of tools would be useful in selected situations involving magnitude, seriousness and uncertainty of the effects. With the findings and understanding of the potential of the MCDA in this area, EMA proposed their own benefit-risk framework which consists of eight steps, the PrOACT-URL (Table 1.1). This is meant to be a flexible framework that can accommodate the various scientific methodologies for assessing benefits and risks, as well as a graphical representation of the outcomes of assessment.

The PrOACT-URL was subsequently applied to the third and fourth work packages. In the third work package (EMA, 2011d), the framework guided the review of selected quantitative approaches conducted retrospectively using the European Public Assessment Reports (EPAR). The products reviewed were Accomplia® (rimonabant), Cimzia® (certolizumab), Sutent® (sunitinib) and Tykerb® (lapatinib) using a combination of MCDA, probabilistic simulation (PSM), Markov model and decision tree. The use of the framework and the quantitative approaches allowed for different perspectives to be tested, reviewed the impact of uncertainties, as well as provided a structure to the review and communicated explicitly the objectives and trade-offs. However, this current method would be labour intensive and require the availability of suitable software to conduct the various analyses. Moreover, justifications for clinical judgment were not accounted for as the outcomes were to be quantified.

Table 1.1 The proposed qualitative framework from EMA – PrOACT-URL

	Steps	Actions
1	**Problem**	• Determine the nature of the problem and its context • Frame the problem
2	**Objectives**	• Establish objectives that indicate the overall purposes to be achieved • Identify criteria of favourable and unfavourable effects
3	**Alternatives**	• Identify the options to be evaluated against the criteria
4	**Consequences**	• Describe how the alternatives perform for each of the criteria, that is, the magnitudes of all effects and their desirability or severity and the incidence of all effects
5	**Trade-offs**	• Assess the balance between favourable and unfavourable effects
6	**Uncertainty**	• Assess the uncertainty associated with the favourable and unfavourable effects • Consider how the balance between favourable and unfavourable effects is affected by uncertainty
7	**Risk tolerance**	• Judge the relative importance of the decision makers' risk attitude for this product and indicate how this affected the balance
8	**Linked decisions**	• Consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions

The ability of the PrOACT-URL to accommodate a quantitative aspect of benefit-risk assessment shown in this work package was reported and published by Phillips (2011). The fourth work package (EMA, 2012) continued to support the findings in the third work package, the use of PrOACT-URL framework and the value of graphical displays. It was recommended that the effects table be used for simpler cases and a full MCDA approach be employed for contentious cases. The last work package would be the development of training materials which have not been published at the time of this research. On top of the work to identify benefit-risk methodologies, EMA has also extended its transparency movement to include publication and public access to clinical trial data (EMA, 2013b).

Since 2009 the US FDA have taken initiatives to explore systematic approaches to assess and communicate benefits and risks, in tandem with the efforts taken at the

EU. The initiatives included the development of a framework to characterise and provide a structure for the benefit-risk assessment already existing in their decision-making processes, as well as communicate the reasoning behind the decision to all stakeholders (FDA, 2012a). This led to the current 5–step benefit-risk framework which was put together after a pilot project in 2012. The five steps are related to the five key areas to be discussed in the assessment of the medicine, namely the analysis of the condition, the medical need for the product, clinical benefit, risk and risk management (FDA, 2013a). The strength of the evidence and its uncertainties would be considered during the assessment, with the reasons provided for the conclusion of each of the five areas. The outcomes of these five areas would then be cumulatively discussed leading to the overall benefit-risk conclusion. The framework would also look into current treatment options, a summary of the submitted evidence for the benefits and risks and risk management plans. With the development of this initial framework, the US FDA embarked on the five-year plan, starting 2013 till 2017, for a structured approach to benefit-risk assessment, which was part of the larger PDUFA V program. During this period they will further refine the framework and how this might be worked into their current clinical reviews to facilitate communication. Mullin of the US FDA, during a workshop conducted by CIRS (2011), commented that this structured framework had the potential to improve the predictability and consistency of decision-making as it is capable of clearly outlining both the available evidence and the uncertainties. It would also articulate the consideration and clinical judgement taken for the benefit-risk decision and hence improve the transparency of the decision-making process.

The US FDA acknowledged that the existing programmes to facilitate patient representation may be inadequate and thus they are committed to a new initiative, Patient-Focused Drug Development. This aims to obtain the patients' perspective on the medical condition and the currently available therapies for a set of disease areas and runs till 2017. For each disease area, FDA conducts a public meeting and invites participation from FDA staff, the relevant patient advocates and other interested stakeholders. Diseases covered thus far include chronic fatigue syndrome and myalgic encephalomyelitis (FDA, 2013b), human immunodeficiency virus (HIV) (FDA, 2013c), lung cancer (FDA, 2013d) and narcolepsy (FDA, 2013e). Other diseases planned for 2014 and 2015 includes fibromyalgia and sickle cell disease. The US

FDA has also published its own user's guide on communicating benefits and risks (FDA, 2011), which provides the expectations and standards of communicating risks.

In the MHRA's corporate plan for 2013-2018 (MHRA, 2013a), it was indicated that benefit-risk decisions should be made more informed by the experiences and perspectives of patients and views from other stakeholders. This is to be achieved through initiatives like more stakeholder partnerships to increase the understanding of benefits and risks of medicines and a better representation of patient and public views in regulatory decisions.

Through their new initiatives for the next three years, TGA will be focusing on increasing transparency and engaging stakeholders with a new framework for communications which is committed to relaying the benefits versus risks approach in their regulation of medicines (TGA, 2013). This is to be achieved through information that is easily understood by patients and consumers and received and shared by healthcare professionals. TGA aims to provide accessible, clear and consistent relevant information through various multimedia platforms. In addition, consumers would be consulted for the labelling changes. The stakeholder engagement is also extended to the healthcare professionals, in improving the awareness and accessibility to relevant information.

Pharmaceutical companies

To a similar extent, the pharmaceutical industry has been also taking an initiative to address the need for an improved benefit–risk assessment by developing a structured, systematic, and transparent framework. Led by the Pharmaceutical Research and Manufacturers of America (PhRMA), the Benefit Risk Action Team (BRAT) Framework sought to incorporate all relevant aspects of benefits and risks and focused on both qualitative and quantitative analysis, for the purpose of communication between the companies and regulatory agencies. The framework aimed to advance the reproducibility, transparency and communication of the basis of the benefit–risk decisions (Coplan et al., 2011). This six-step framework (Table 1.2) is a flexible structure which allows the use of appropriate scientific tools to analyse the outcomes.

In a workshop organised by CIRS (2011), Hughes from Pfizer reviewed the steps of the BRAT framework and the history of its development. The process of BRAT framework starts with defining the decision context (including the formulation, indication, patient population, comparators and decision perspective). Next, the benefit and risk outcomes are identified and selected, followed by the creation of an initial value tree which determines the preliminary set of outcome measures. In step three, source data are extracted to support outcome measures and input into summary tables. The framework is then customised and the value tree re-examined and revised to incorporate any additional clinical context. In step five, the outcome is assessed for its importance, with informal or formal weighting methodologies being employed to determine the relative importance of all outcomes. Finally, the key measures and data are summarised in a visual format to aid the interpretation and decision, information gaps are filled in and sensitivity analyses are conducted.

Table 1.2 The Benefit-Risk Action Team (BRAT) Framework

	Steps
1	**Define the decision context**
2	**Identify outcomes**
3	**Identify and extract source data**
4	**Customise the framework**
5	**Assess outcome importance**
6	**Display and interpret key benefit-risk metrics**

In developing the framework, BRAT conducted interviews with 16 companies to build a baseline of industry perspectives on benefit-risk and benefit-risk assessment. These interviews showed that most companies engage with regulatory agencies in discussions of benefit-risk profiles, but only some do so consistently throughout the development of a medicine and few companies used explicit benefit-risk frameworks during US FDA and EMA approval discussions. With the challenges of interacting with regulatory agencies as well as internally, a common benefit-risk language and approach was proposed. The BRAT framework is designed to supplement rather than substitute for expert judgement and to facilitate a balanced approach. The triptans were used as an example to illustrate the applicability of the framework

(Levitan, 2011). The utility of BRAT was also studied in the background of the various frameworks by the regulatory agencies (Levitan B, 2012). The experience of using the BRAT framework as a retrospective review of Tysabri® (IMI PROTECT, 2012a and 2012b) illustrated the potential in benefit-risk assessment.

To obtain real-world experience with the use of the BRAT framework, PhRMA commissioned the Soft Pilot programme. The goals for this programme were to gain PhRMA member companies' experience with the framework process and tools. These experiences were used to further refine and develop the framework and to help facilitate increased use across the other member companies. To date, ten companies have enrolled and the pilot is currently in the implementation phase. The main aim of the programme is to refine the framework and also to gather additional information regarding the effectiveness and use of the framework and this is now the responsibility of CIRS since 2012.

Regulatory collaborations

The Innovative Medicines Initiative (IMI) commenced a project in September 2009, the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) (IMI PROTECT, 2010 and 2011a). This is a collaborative effort between public bodies (including the EMA, MHRA, regulatory agencies of Denmark and Spain), academia and the pharmaceutical industry (collectively represented by the European Union and the European Federation of Pharmaceutical industries and Associations (EFPIA) which includes major companies such as GlaxoSmithKline, Bayer, AstraZeneca, Novartis and Pfizer). This consortium is led by the EMA and is to extend over a period of five years to achieve the objectives and is funded by the IMI and EFPIA among others. While PROTECT is primarily aimed at strengthening the safety and benefit-risk monitoring of medicinal products in Europe, the conduct of this project will also review and develop tools to improve the evaluation and communication of a product's benefit-risk balance. This is to be achieved by various work packages, through the enhancement to the early detection of safety data and enabling of the integration and presentation of benefits and risks. Three work packages (second to fourth) focused on the safety signal detection and evaluation, as well as the opinions of users of traditional methods of data capturing, that would contribute to improving the profiling of epidemiological

risks. The assessment and communication of benefits and risks was studied in the fifth work package, while the sixth package looked into the validation of the methodologies identified in the fifth package. To complete the entire project, the last work package will be looking into training and education to ensure the successful implementation of the findings from PROTECT.

The fifth work package related to the integration and communication of benefits and risks and was investigated in five separate steps (IMI PROTECT, 2011b and 2011c), including identification of framework, review of assessment methods and graphical representations, case studies and application across databases. A literature search was conducted to identify approaches and was inclusive of other existing reviews, both qualitative and quantitative methods and use in pharmacoepidemiology, clinical trials and health technology assessment (IMI PROTECT, 2013a). The approaches were reviewed and broadly classified into benefit-risk frameworks, metric indices (for threshold, trade-off and health utility), estimation techniques and utility survey techniques. To appraise these approaches, criteria used in the EMA's Benefit-risk project were referenced. A final set of appraisal criteria was developed around four key dimensions, namely fundamental principle, features of respective approaches, visual presentation of models and lastly, assessibility and accessibility. These were meant to gauge the theoretical reasoning, capacity to deal with uncertainty, ease of use and availability of visualisation respectively.

A framework for the evaluation of benefits and risks was required and the PROTECT project found that there were fundamentally two types, namely the non-quantitative or descriptive type and the quantitative or comprehensive type. The former group included the PrOACT-URL and BRAT, both of which were considered suitable for further testing. The PrOACT-URL was found to promote a systematic consideration of critical elements in decision-making and hence improves the transparency of the process. However it may not provide substantial value for communication. While BRAT could aid in the communications (including visualisation) of benefits and risks between regulators and companies, the recommended use of odds ratios may not be acceptable by the different stakeholders. Other descriptive frameworks were still under development among the various agencies and hence appraisal was not conducted for these. The UMBRA (CIRS) was noted to be a collative development

for international use. Among the descriptive frameworks appraised, it was assessed that both the PrOACT-URL and UMBRA could accommodate a wider scope of perspectives including the pharmaceutical companies, healthcare providers and regulatory agencies. Quantitative frameworks deemed appropriate for further study were the MCDA and its variant, the Stochastic Multi-criteria Acceptability Analysis (SMAA) (Tervonen et al., 2008; 2011). MCDA may be limited when preference information or consensus are not available and could not account for uncertainties, while the SMAA accounts for this through simulation. However, it was highlighted that MCDA is the only approach capable of incorporating multiple objectives simultaneously. The potential limitation to the use of SMAA is the requirement of extensive mathematical and computational knowledge which may not be widely available across the stakeholders. Both MCDA and SMAA were found to be able to accommodate the wide scope of perspectives from various stakeholders.

The quantitative methodologies consisting of metric indices, estimation techniques and utility survey techniques were separately appraised. These tools were expected to be capable of estimating the magnitude and incidence of events related to the benefits and risks, from both patients' and regulators' perspective. These values should then be combined into a single quantitative measure for interpretation. It was believed that metric indices may be used under a framework or with other techniques, but not solely for benefit-risk decision-making as they lack the transparency and possess variable subjective issues. PROTECT recommended five metric indices for further studies, namely NNT/NNH, impact numbers (Attia et al., 2002; Heller et al., 2002), QALY (Weinstein et al., 2009), Q-TWiST, INHB and Benefit-risk ratio (BRR) (Chuang-Stein et al., 2008; Korting et al., 1999). While many statistical concerns can be addressed by estimation techniques, the satisfactory contribution to decision-making may be dependent on concurrent use of various techniques and would require compliance to these techniques across regulatory practices to effectively increase transparency. PROTECT recommended probabilistic simulation method (PSM) and mixed treatment comparison (MTC) (Lumley, 2002; Lu et al., 2004) for further study. Utility survey techniques were included for review of benefit-risk assessment as they can afford robust value judgments. The discrete choice experiment (DCE) (Ryan et al., 2008) was proposed for further study.

Case studies were carried out in a retrospective manner as part of the fifth work package to review the application and integration of the selected 13 methodologies above. The information for case studies was obtained from clinical trials and publicly available assessment reports and these were used to document the benefits, risks and uncertainties together with the value judgments and assessment. Two waves of case studies were conducted. The first wave of case studies used Tysabri® (natalizumab)(IMI PROTECT, 2013b), Acomplia® (rimonabant)(2011d), Ketek® (telithromycin)(2012c) and Raptiva® (efalizumab)(2013c) for the above recommended tools. The second wave included rimonabant (IMI PROTECT, 2012d), rosiglitazone (2013d), natalizumab (2012e) and warfarin (2013e). It was meant to compare and benchmark the frameworks and quantitative tools through these retrospective exercises.

Given the emphasis on graphical representation (or visualisation techniques) and communication of the outcomes of benefit-risk assessment, visualisation techniques were assessed for their suitability in achieving this goal for the 13 methodologies identified, with recommendations for each specific methodology. Each potential visualisation technique was appraised against a common set of criteria, namely the representation type, display design and elements of communication. The outcomes of the first part of the review (IMI PROTECT, 2013f) led PROTECT to recommend various techniques for the 13 methodologies, specifically the effects table for PrOACT-URL and forest plot and bar graph for BRAT. For both MCDA and SMAA, bar graph and forest plot were recommended. PROTECT commented that recommendations of visualisation techniques were limited to those typically already accompanying the methodologies as a result of the review and they were not able to explore potential innovations that may improve or be customised for the eventual user. Simpler tools may be preferred if complex visual presentations offer no clear advantages for the benefit-risk outcomes. For the second part of the review (IMI PROTECT, 2013g), PROTECT provided 17 high-level recommendations for the use of visualisations in benefit-risk assessment of medicines. These are meant to address the concerns regarding the general principles for visualisation, use in the different key stages of assessment and common benefit-risk questions. The Wicken's Principles of Display Design (Wickens et al., 2004) was recommended to help facilitate user's understanding, while the GSK Graphic Principles (CTSpedia, 2012a,

2012b) should be used to enhance data communication. Various recommendations were provided specifically for each process in the benefit-risk evaluation process, namely context and structuring the issue, data gathering and preparation, data analysis and exploration (statistical robustness and uncertainties). A second wave of case studies was conducted to refine the methodologies as well as the application of visualisation techniques.

The sixth work package of PROTECT (IMI PROTECT, 2012f) aimed to validate the transferability and feasibility of the identified tools in the preceding work packages to other data sources and patient population groups, in addition to using other data to investigate specific aspects of a safety or benefit-risk concern. It could be seen as an extension of the previous two waves of case studies in the fifth work package. Data sources used in this work package included national databases (General Practice Research Database, UK, GPRD), patient registries (Danish Psychiatric, Somatic Hospital Discharge & Mortality Registers, DKMA; Utrecht Patient Oriented Database, Netherlands, UPOD) and research databases (Pharmacoepidemiology General Research Extension, PGRx). The research goals were to address reproducibility with the same data source, external validity, impact of uncertainties, sensitivity and specificity, validation by clinical records and controlling for confounders. This work package started in September 2010, but a report on the findings was not available at the time of this research.

The Centre for Innovation in Regulatory Science (CIRS) is an independent, not-for-profit organisation with a focus on furthering regulatory sciences. It provides a common and non-binding platform for various stakeholders such as the regulatory agencies and pharmaceutical companies to discuss and convene the development and future direction of regulatory science. Since the 2002, CIRS has been involved in the development of a framework for the assessment of benefits and risks of medicines, as well as including the role of patients in these processes.

More than a decade ago, in two workshops attended by both regulatory agencies and pharmaceutical companies, the need to manage and communicate risks in the development of new medicines was discussed (CMR, 2002 and 2003). Methods for communicative risk information should consider the society's changing views on

risks, so that regulatory science would not hinder the evolution of innovation. It was also identified that physicians, patients and consumers should be involved earlier in a communication strategy and not just the final marketing phase. The industry commented on the need for greater transparency among internal and external customers' expectations and best practices for decision-making as some approaches to minimise the attrition of potential candidates for drug development. As shared from the European regulator's viewpoint, the goals of communication should allow open and transparent information on the benefit and risk balance to be presented in a concise manner. Interactions within and among stakeholders, namely the industry, academia and regulators, had to be optimised as it was recognised that the various stakeholders held different skillsets essential for the development of successful strategies in risk management and communication. It was agreed that risk management plans should extend from discovery to the end of the product life cycle. The stakeholders also agreed that the communication tools should be improved and scientific discussion could be conducted between the agencies and companies earlier in the development of a medicine. Taskforces and workshops were deemed useful in pursuing the key goals above. Importantly, during these workshops, the stakeholders agreed that the information on risk should always be discussed in the context of the management of the medical condition to allow a balanced perspective. The risks of use should be interpreted in relation to the expected benefits. In facilitating this new perspective that involved assessing the balance between benefits and risks, CIRS studied the potential of the MCDA framework for this purpose (CRM, 2004 and 2005). The framework was well received and it was proposed that it should be further validated through the various stakeholders, especially the incorporation of the views of patients. If the agencies would believe that the framework could improve communication, the companies would support its use and incorporation into the CTD dossier for regulatory submission.

CIRS continued to investigate the potential use of a global benefit-risk framework through engaging both regulators and companies to provide the critical factors used in determining a benefit-risk balance and opinions on the future direction forward for the framework (CMR, 2008). A framework, to be used globally, should contain the elements considered by both regulators and companies in assessing the benefit-risk balance. While quantitative methodologies might have its merits in ensuring

consistency, accountability and communication but it should not replace clinical judgment. A benefit-risk framework should be used as an aid in the process of decision-making. Emerging markets should be engaged early in the development of such frameworks so that the acceptance would be timely across agencies and companies around the world. The use of the framework should be applied at all stages of the product life cycle, including post-market risk management plans. To ensure the correct understanding of terms used in a framework and to put users on a common platform for discussion, a lexicon was proposed to be developed. In the subsequent workshop by CMR (2009), the lack of common definitions was believed to be a barrier to the communication of benefits and risks. Indeed it becomes necessary to acknowledge the differences and commonalities among the stakeholders and provide a common understanding of terms used through a lexicon if a universal framework is to be developed (CIRS, 2012b). It was also agreed among the regulators and companies that a benefit-risk framework would provide a structure for discussion and lead to greater transparency, a desired element in communication. Walker (CMR, 2009) presented a preliminary framework consisting of five steps, in which after data on the product's safety and efficacy are identified, summary tables are constructed, a value tree of benefits and risks is developed, a prioritisation of the those values is made, a weight is assigned to the prioritised values and the benefit-risk assessment is finalised using expert judgment. However, it was noted that the acceptance of weighting of benefit-risk parameters varied widely among agencies, which could be due to the differences in regional regulatory and cultural viewpoints (CIRS, 2012b). This framework was later refined to the 7-step process (CMR, 2010), based on further collaborative work (Mussen et al., 2009).

During one of the workshops conducted to refine the benefit-risk framework, it was agreed among the regulatory agencies and pharmaceutical companies that tools such as a value tree and supportive data tables are necessary for a structured benefit-risk debate (CMR, 2010). Eichler from the EMA also commented that as methodology and presentation evolve from providing implicit to explicit value judgements and from being a reflection of regulators' values to those of patients, the development of a toolkit for benefit-risk assessment will further enhance the predictability and auditability of regulatory decisions (CIRS, 2011). However, in order for the best practices to emerge and thus identify the appropriate tools, time should

be allowed for these to be developed, refined and validated for use. This would require commitment, resources and time from the stakeholders to establish the processes for the management and the archiving of information to support iterative improvements in techniques for benefit-risk assessments (CIRS, 2012b).

In communicating benefit-risk decisions, visualisation tools help to focus the discussions on critical issues, identifying gaps and congruence of opinions for benefits and harms and providing a concise summary of the information needed to make the benefit-risk decision. MCDA may provide a framework that achieves the communication of a decision rationale. However, stakeholders like physicians, may require assistance to understand the underlying principles and methodology, while patients may benefit from a simplified set of results through the use of graphically displayed quantification of trade-offs (CIRS, 2011). Stakeholders should thus be introduced to novel visualisation tools in a methodical and educational manner, to allow them to familiarise themselves with the strengths and weaknesses of each approach. The familiar Forest plot was agreed by the agencies and companies to be a simple way to represent and visualise the results of a benefit-risk assessment (CMR, 2010).

In a workshop that focused on developing a framework to improve the clarity of decision-making, it was agreed among the stakeholders who participated that for conditions involving subjective benefits and harms, patient input is invaluable in informing the thinking of decision makers such as regulators and researchers (CIRS, 2011). Following this another workshop (CIRS, 2012b) was conducted to look into the patient's role in benefit-risk assessment, during which Breckenridge from the MHRA commented that while there was significant progress in the work on the benefit-risk assessment of medicines over the past decade, much less attention was given to the contribution of the patient, who is the primary stakeholder. It should be highlighted that the views of patients and their caregivers on the potential risks and benefits may differ from those of the regulator, companies and healthcare technology agencies. Eichler from the EMA added that in order to bring patients and their preferences and values into the regulatory system, the EMA engaged patients in the regulation of medicine in Europe through the public hearing and representation on committees. Another method would be the systematic exploration of the input of

patients enrolled in clinical trials. Similarly, the US FDA through the PDUFA V initiatives started a series of patient meetings to understand medical needs and patients' opinions in various medical conditions. Among the recommendations that surfaced from the 2012 workshop included the development of guidelines for the engagement of patients and their involvement throughout the life cycle of medicines. There is much to learn from the patients' input from other sectors such as over-the-counter medications or experiences on drugs that failed during development, both which are areas neglected for information collection. There should also be efforts to engage legislative bodies to review and eliminate potential legal barriers to patient involvement in benefit-risk decisions.

Another recent CIRS workshop (CIRS, 2013a) conducted to assess the potential contribution of patients in the assessment of benefits and risks highlighted the various consortia involving patient organisations that were required to achieve the long-term goal of accelerating patients' excess to innovative medicines through active participation and input of clinical data. Rockhold from GSK recommended a non-competitive approach to obtaining information about medicines and the perspectives of patients living with disease, as all stakeholders would benefit from the alignment of these inputs and methodologies. With the current approaches, benefit-risk decisions are made by clinicians and regulators who might not be trained specifically to investigate the impact of patients' inputs. Johnson, Principal Economist from Research Triangle Institute, commented that patients rather than physicians or regulators are the best judge of their own welfare. He also reviewed the potential of three different methods for eliciting patients' values and preferences: analytic hierarchy process, best-worst scaling and discrete-choice experiments, also known as conjoint analysis.

McAuslane (2013a) presented the pharmaceutical companies' hurdles to patient participation, which included the varying perspectives on the different methodologies and the uncertainty regarding how the input would be used and accepted. These may be solved by developing patient engagement guidelines and alignment on flexible methodologies for benefit-risk assessment. From the agencies' perspective, the hurdles were finding representative, informed patients without unresolved conflicts of interest and methodological issues on how to accurately represent and extrapolate

the findings from the entire cohort to the population. Solutions proposed included guidelines to resolve potential conflict of interest and the direct engagement with patient groups. From the patient's perspective, the major hurdle is the lack of understanding arising from the language and statistical methods used. Proposed solutions include the expansion of patient involvement and education. In addition, further recommendations were highlighted to improve the involvement of patients. These included using inputs from interviews to be conducted in Phase I and II studies to develop appropriate methodologies for confirmatory trials, incorporating the use of media technology to obtain and communicate information and conducting a wider reaching survey to ascertain the barriers to including patient information.

An earlier workshop in 2012 revealed that companies' involvement with patients may be construed as marketing influence and product advocacy (CIRS, 2012a). Thus rules of engagement must be established to avoid misunderstandings, which further support the need for such guidelines. The clinical development frequently relies on well-established efficacy endpoints (which may include traditional patient-reported outcomes), but these might not necessarily address the needs of the patients given the evolving context of medical care. By having patients' input into the development and regulation of medicines, it will connect the use of the most clinically relevant patient-reported outcomes as part of clinical trial design. Patients should also be informed of the results of their input as they have contributed much time and effort to the research programmes and would benefit from an education regarding the inherent nature of uncertainty in such benefit-risk decisions. While the value of patient input appears implicit, it has to be demonstrated to a wider audience through further research and communication.

Certain principles were consistently mentioned through these workshops in a continued effort to development a framework for the assessment and communication of benefits and risks. This included the need to communicate the balance between benefits and risks, as the unopposed communication of risk without the benefits would not represent the appropriate context of the decision-making process (CMR, 2009). The assessment of benefits and risks should involve all stakeholders and conducted throughout the product life cycle, as the updated information on evolving benefits and risks becomes available over time and use. As stakeholders approach

the benefit-risk assessment from various perspectives, differing opinions are expected and these should form the basis of discussion in addressing the multiple factors affecting the balance (CIRS, 2011). In developing a global framework, it was proposed that the framework should start as a qualitative one and eventually refined to be quantitative. This is in recognition of various quantitative tools which should be accommodated within a standard framework and aid in both the assessment and communication of benefits and risks (CMR, 2010). Uncertainty must be formally incorporated into a benefit-risk framework and applied across the entire decision-making process and not be limited to statistical uncertainty or to a single step of the assessment (CIRS, 2012b). Regulatory decision-making should consider four crucial aspects, namely transparency, consistency, communication and definition of the treatment populations (CIRS, 2011). One of the challenges identified in making quality decisions include internal organisation processes such as the difficulty in applying valuing and weighting, communicating the problem statements and explaining uncertainties. Another challenge would be to apply the global framework to their current workflow, regardless of the individual jurisdictions and contexts. Participants at the workshop, however, agreed that the validated framework would accommodate individual circumstances and the various stages of the medicine's life cycle (CIRS, 2012b).

In the recent workshop to look into the role of frameworks in facilitating the provision of quality decisions, stakeholders again agreed that a decision framework is a "structured, flexible, systematic and scientific approach to organising, evaluating, quality assuring, summarising and re-assessing over time both the known and the unknown information and the subjective values and judgements that form the basis of the decision" (CIRS, 2013b). This will help provide quality and transparent decisions to be documented and communicated. Such frameworks should be applied at common time-points in the regulatory review process, namely at submission, all stages of evaluation, during the communication of deficiencies, responses, expert opinions, benefit-risk balances and the final regulatory decision for the product.

The need for a universal benefit-risk assessment framework

Leufkens et al., (2011) commenting on innovations in regulatory science, suggested that there are three dimensions in this area. Firstly, regulators should keep current

their understanding of the science and technologies and help in drug development and the advancement in innovation. Secondly, new standards and tools should be developed to evaluate and assess benefit-risk balance of medicines to facilitate a sound and transparent decision-making process. Lastly, the entire system should be monitored for its impact on patient safety, public health and meeting medical needs. Therefore it is likely that a new overarching framework would be required to encompass these new initiatives.

From the above activities of the major regulatory agencies US FDA and EMA and the pharmaceutical industry, a framework is required to provide a systematic and structured approach to the assessment of benefits and risks with the greater involvement of the stakeholders for decision-making. The outcomes of this approach should support a transparent and consistent basis of decision-making and facilitate the communication of the benefit-risk decisions. It does however appear that effective communication is the focus of these initiatives, as ultimately a sound framework should enable the communication of the final benefit-risk decision. Indeed the failure to communicate will compromise all efforts to improve consistency, transparency and accountability to stakeholders. In a workshop to identify strategies for communicating benefits and risks, it was agreed that appropriate communication should be accommodated and made a feature within benefit-risk assessment frameworks (CMR, 2009). In fact, it was discussed more than a decade ago in a workshop for developing effective stakeholder communication the importance of involving physicians and patients early in the development of a new medicine and not wait until the product is approved for marketing (CMR, 2002). The interpretation of safety information needs to be made more transparent and information held by industry and regulators needs to be shared. Ideally this could be based on information used for the preparation of a submission document and provide information that is complete and understandable for the relevant benefit-risk decisions (Schmid E F et al, 2007).

It can be deduced that though the stakeholders' acknowledge that a framework will provide a structure and consistency in decision-making, their efforts in achieving this have largely been independent. As observed by EMA within the EU, there is no common framework being utilised and this would compromise the consistency of the assessment of benefits and risks and decision-making. Echoing this sentiment, there

is now a need to identify a common framework that can be used by both regulatory agencies and pharmaceutical companies to fulfil their pursuit in improving communication to stakeholders. These are in line with the discussions from a workshop on strategies for the benefit-risk assessment of medicines, where it was agreed that a framework should address the difficulty faced by agencies and companies in explaining the outcomes of the assessment (CMR, 2008).

Mussen et al. (2009) had identified the use of MCDA in regulatory decision-making and this approach has been the principle foundation for existing frameworks, namely the EMA's PrOACT-URL, the BRAT framework and the 7-step CIRS framework. While IMI PROTECT might have classified MCDA as a qualitative method, the steps of executing MCDA were based on the MCA, which are the qualitative and logical steps in decision-making. As such, it would be the tools used in MCDA that would confer a quantitative nature. By itself MCDA is a qualitative illustration of the thought processes that went into a decision. As evident in the journey of framework development thus far, a qualitative framework is seen as more desirable now as its flexibility can accommodate various benefit-risk assessment tools and visualisation techniques.

While the MCDA approach has been embraced by many, in particular CIRS, the investigated use during its development was largely retrospectively based on selected case studies however its full utility and impact on regulatory processes could not be fully understood at that time. The EMA's PrOACT-URL is now being implemented and also further supported by the IMI PROTECT initiatives, but its functionality is only being validated within the EU regions. Similarly, the US FDA's 5-step benefit-risk framework is still under development and largely within the context of the USA. The BRAT framework is piloted among the companies and hence its usefulness to regulators may not be fully illustrated. As observed above, the activities of developing and validating a benefit-risk framework is limited to individual jurisdictions and purposes. There is currently no single framework that is proposed for use by all stakeholders in making and communicating benefit-risk decisions. It is also apparent that the smaller agencies and emerging markets have largely been left out in these activities. For a framework that is designed for universal use, it would have to be applied and accepted by agencies, companies and other stakeholders in

all parts of the world. The current activities are exclusive and will not contribute to addressing this need.

There are currently on-going projects utilising different scientific tools to find those best suited for benefit-risk assessment and for visualisation. The immediate need is to first identify a universal benefit-risk framework that can be used by all regulatory agencies and pharmaceutical companies based on the principles of benefit-risk assessment and enable the communication of the basis of the decision. By encompassing a qualitative and overarching character, it should accommodate the future tools required by individual stakeholders to conduct the benefit-risk assessment specific to each product and medical context.

Study aim

This research aims to develop a universal framework for the assessment of benefits and risks of medicines by regulatory agencies and its role in communicating the benefit-risk decisions.

Objectives

The objectives for this research are to:

- Review the current practices in benefit-risk assessment by agencies and companies and the needs and perception for a common framework
- Review existing frameworks and propose a universal framework that would encompass the current frameworks and meet the needs of stakeholders
- Validate the applicability of the universal framework by regulatory agencies in benefit-risk assessment which would increase the effectiveness and transparency of communication.
- Explore the applicability of the universal framework in documenting and communicating benefit-risk decisions in the emerging markets
- Explore the applicability of the universal framework in communicating benefit-risk decisions in comparison with current publicly available assessment reports from major regulatory agencies

CHAPTER 2

Study rationale and methodological framework

STUDY RATIONALE

With the evolution of the assessment of efficacy and safety towards systematic explicit benefit-risk balance, both regulatory agencies and pharmaceutical companies have developed frameworks albeit each for their own jurisdiction and purpose. Given the individual efforts, this will perpetuate the problem of inconsistency in regulatory decision-making and the perceived lack of transparency in the processes. Hence, there is now a need to provide a universal framework that is able to meet the needs of the various stakeholders. Based on the background information reviewed thus far, it appears that a universal benefit-risk assessment framework should:

- Encompass the existing frameworks used by the regulatory agencies and pharmaceutical companies
- Align and support the current principles of the assessment of benefits and risks
- Be flexible and accommodate the various scientific tools to assess different benefits and risks
- Reflect the contribution of other stakeholders e.g. that of patients to the overall decision
- Enhance transparency of the decision-making process
- Aid communication of the benefit-risk balance and the basis of regulatory decision to stakeholders
- Include visualisation or other graphic representation of the assessment outcomes

METHODOLOGICAL FRAMEWORK

Research design

Research can be broadly classified into qualitative and quantitative designs. The latter are commonly employed in clinical studies, where the goal is likely singular. Analysis of the data will be conducted through predefined statistical methods to minimise the bias in interpretation of the outcomes. This is possible as the measures of the data are objective and quantifiable, allowing the application of statistical testing on the numerical outcomes. The purpose of quantitative design is usually to prove the acceptance of a hypothesis through the generation of statistical evidence to support the conclusion. For qualitative studies, the scope is wider and is likely used to generate collective opinions and directions for future quantitative studies. While basic descriptive statistics may be generated, the overall conclusion is obtained

through expert interpretation rather than statistical outcomes. However, the absence of statistical outcomes should not be seen as a limitation in the use of qualitative designs. Both quantitative and qualitative studies are conducted in a systematic manner to collect predefined data that is relevant to the study goals. In settings where opinions, comments and experience are explored to generate concepts that would guide future developments (Pope, 1995), qualitative designs should be considered. Pope illustrated the differences between quantitative and qualitative research (Figure 2.1).

Figure 2.1 Differences between qualitative and quantitative research design*

	Qualitative	Quantitative
Social theory:	Action	Structure
Methods:	Observation, interview	Experiment, survey
Question:	What is X? (classification)	How many Xs? (enumeration)
Reasoning:	Inductive	Deductive
Sampling method:	Theoretical	Statistical
Strength:	Validity	Reliability

**adopted from Pope, 2005*

For the purpose of achieving the objectives for this research, it appears that qualitative designs would be more appropriate.

Data source

Literature searches strategy

To provide a good overview of the current environment in regulatory assessment of benefits and risks, published literature should be systematically searched. Two established repository of reputable publications will be used, namely PubMed and ScienceDirect. The following keywords and terms are considered relevant in searching the literature:

- Benefit
- Risk
- Benefit assessment
- Risk assessment

- Benefit risk assessment
- Benefit risk balance
- Assessment framework

To optimise the validity of the opinions from the publication, the period of search should be confined to within the last five years. However, it is expected that some older literature would provide vital fundamentals to the history relevant to this research and these should be included for reference.

Main regulatory authorities' websites

Guidance documents for benefit-risk assessment from major regulatory agencies and international bodies should be reviewed to understand the underlying principles in the evaluation of medicines. This is important as any framework proposed should not deviate or challenge these fundamentals, but rather support the execution of the processes. The major reference regulatory agencies should include the EMA, US FDA and TGA while relevant international bodies would include the ICH and WHO. Likewise, the search for existing frameworks and publicly available assessment reports by these recognised bodies should be conducted, either through publications or their respective websites.

DATA COLLECTION TECHNIQUES AND ANALYSIS

Comparing existing frameworks

The key goals of the comparison of the frameworks are to identify the similarities and differences. Similarities will be carried over to the universal framework as these would facilitate the adoption of the new framework by the owners of the reference frameworks. The similarities will also be reviewed for their functionality and how these can be harmonised across the frameworks. The differences may potentially challenge the use of a universal framework and these will be assessed for the contribution to the overall decision-making process. Differences that are deemed relevant to benefit-risk assessment will be considered for the universal framework, while those differences found to be related for the purpose of fulfilling specific jurisdiction requirements may be omitted. Beyond the content of the framework, the flow of processes will also be compared. The ideal flow should correlate closely to the processes undertaken by a reviewer.

Validating the proposed universal framework and templates

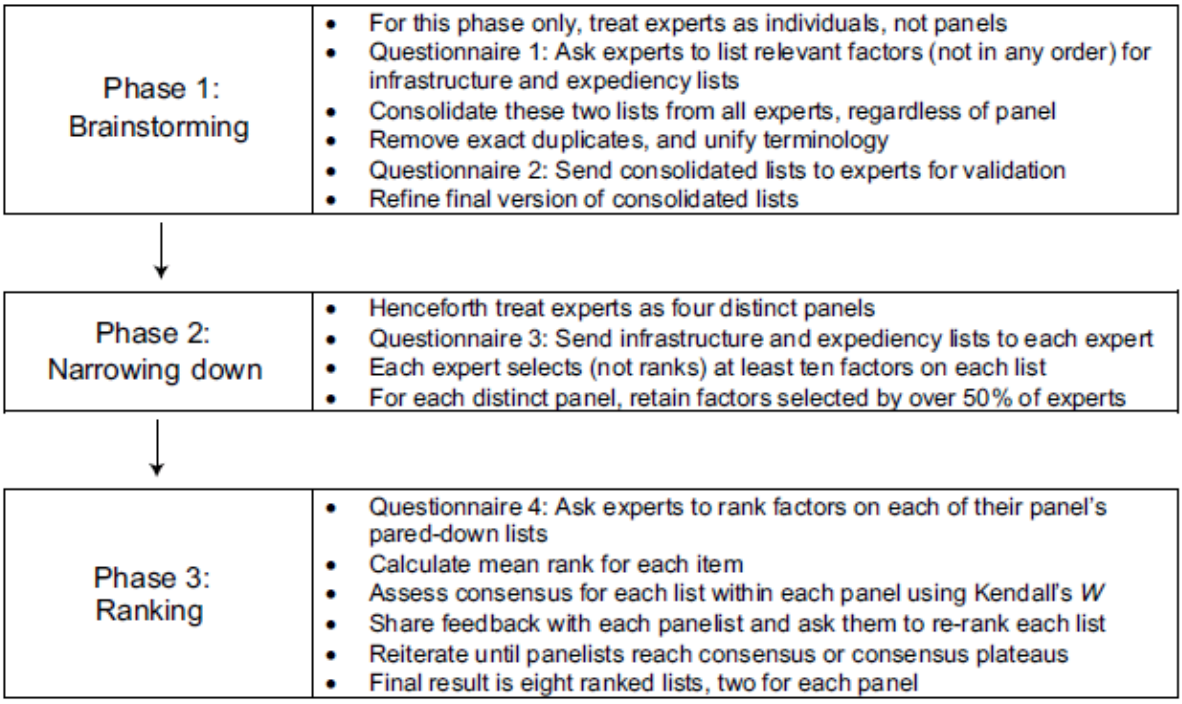
To carry out the systematic collection of opinions and comments, study tools will be developed. Questionnaires, surveys and decision conferencing are common tools employed for such purpose. One established approach to develop a survey is the use of the Delphi method for structuring group communication process to ensure the effectiveness in allowing a group of individuals to solve a complex problem (Linstone et al., 2002). This will be further explored here.

Delphi Technique

Linstone et al expounded on the application of the Delphi process, which can be carried out either using the traditional "Delphi Exercise" or the newer “Delphi Conference” manner. The traditional approach requires the draft questionnaire to be sent via hardcopy documents to the respondent group for feedback on the proposed contents. With the inputs returned from the respondents, the questionnaire is revised and the group is again sought to review their original answers based on the new questionnaire. This approach is similar to a combination of a poll and a process to shift the need for a large communication to the smaller team developing the questionnaire. The newer "Delphi Conference" replaces the hardcopy exchanges with real-time communications afforded by the current technology and thus reduces the time to obtain the responses. Regardless of the approaches, there are four distinct phases. The first phase determines the subject for discussion and provides the initial content deemed relevant for the questionnaire. The second phase aims to understand of how and where the group agrees or disagrees on the contents. Disagreements are then explored in the third phase to find out the underlying reasons for the differences and review them. The final phase includes the final review by the group when all previous responses are reviewed and the outcomes have been fed back for consideration. Okoli et al (2004) showed an alternative but similar way for executing the Delphi method (Figure 2.2) and also further explained on the process of selecting the panel of experts forming the respondent group. Simple statistical analysis of the responses can be carried out to assist in the analysis of the outcomes.

The use of the Delphi method is frequently employed for postgraduate and higher learning degrees (Skulmoski et al., 2007). It has been utilised widely in social sciences (Landeta, 2006) as well as in healthcare systems, such as the identification of characteristics for injury surveillance and long term prevention (Mitchell et al., 2009) and a consensus statement among respiratory specialists on the health effect of asbestos (Banks et al., 2009). It is also considered a versatile tool and can be used in selecting and defining a further research topic (Okoli et al., 2004).

Figure 2.2 One approach of carrying out the Delphi method*



**adapted from Okoli, 2004*

Comparison of the Delphi Technique with other questionnaire techniques

Okali et al (2004) also provided differences between a traditional survey against a questionnaire constructed via the Delphi method. Some surveys may require statistical tools to power the findings and thus require an appropriate sample size, the Delphi method does not require a statistical number of participants. However, the ideal number of members in a panel has been recommended to be 10 to 18. While a survey tends to extrapolate a conclusion based on a select group of individuals, the Delphi method can draw out expert opinions that are superior to the views of the individuals. As per the Delphi method, there is a follow-up to the data collected during

the process, leading to a richer amount of relevant data. This however is limited when conducting a traditional survey.

Linstone et al (2002) also shared on the limitations of the Delphi method. One of these is discounting the future, since the subjective nature of the inputs tends to change over time and the applicability of the questionnaire would be affected. With the multiple of contributing opinions, there is a tendency to select a few and fit them into a familiar context. This behaviour is called the “simplification urge”. As such, the final questionnaire may not also represent holistically or entirely the actual situations. Another limitation is the illusory expertise, where the group, typically a panel of experts in the field, may not be the best at predicting the relevance of the contents. This may be due to the panel members being too specialised in a niche area, leading to a failure to understand the interactions of the entire system at large. Therefore, it is important that the panel selection is carried out effectively to best optimise the Delphi method, as the entire process is dependent on their inputs. Bolger et al (2011) investigated the impact of various factors related to the panel, including degree of confidence, expertise and majority positioning. It was found that majority opinion is the strongest influence and the conduct of Delphi method should aim to reduce this along the process. A recent more scientific method of weighing and pooling scientific advice, the Cooke method may be considered (Aspinall, 2010). Its goal is to quantify uncertainty and not eliminate this unavoidable concern from the decision-making process.

Validity of questionnaire techniques

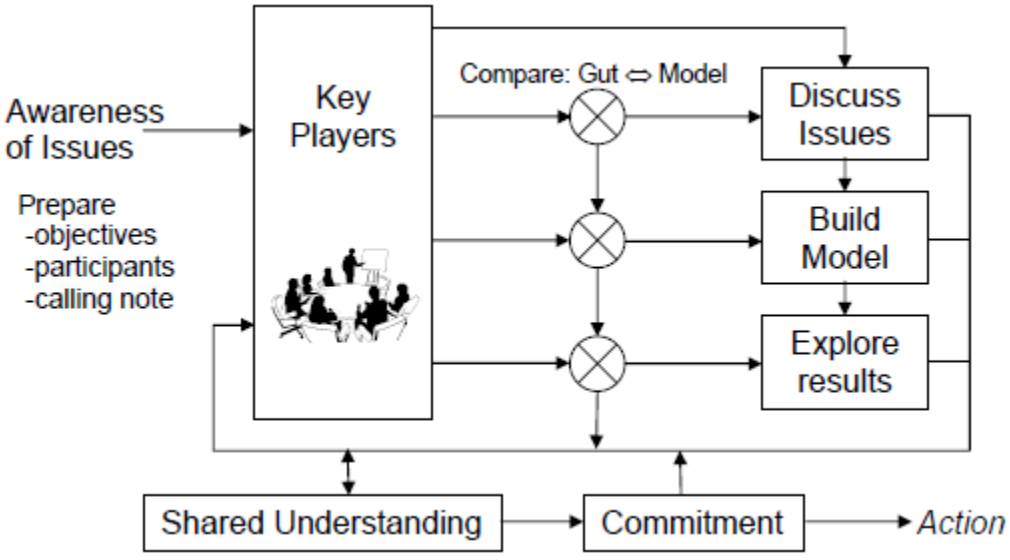
The validity of the questionnaire will determine the robustness of the outcomes. A basic way of looking at validity would be the content validity, which is how well the item on the questionnaire can measure what it is intended to measure and possesses the appropriate level of emphasis and focus (Nunnally and Bernstein, 1994). The importance of content validity should be emphasised as it forms the foundation of accurate measurement of the outcomes (Yaghmaie, 2003). It should be noted that in order to achieve content validity, there must be face validity. Face validity has been defined as the appropriateness of the items in relating to the goals of the questionnaire (Nunnally and Bernstein, 1994; Anastasi, 1988; Nevo, 1985). As for most research, the conclusions are generalised and extrapolated beyond the

original research. It is important that such claims are supported by causal relationships between the observations i.e. internal validity (Johnson, 1997). Indeed, the ultimate aim of a questionnaire is to achieve construct validity, where the logical relationship between the outcomes and the outcomes with the system is being established (Guyatt et al. 1993).

Design conferencing

Another method of systemically reviewing a group's input is to conduct a decision conference (Phillips, 2006). The process starts with a discussion on the objectives (Figure 2.3). To achieve these objectives, the model that captures the key elements is required to resolve the issues. Discussions would involve personal judgments, intuitive opinions and feelings of unease. Exploring the observed difference may identify new insights that feed into improving the model. With the new inputs, the process is repeated again until the model reflects the new perspectives. Decision conferences help to generate a shared understanding of the issues, without requiring consensus about all issues. It can also develop a sense of common purpose, and find the best way forward in the midst of disagreements. Decision conferencing can be frequently employed during workshops in which many new initiatives can be generated.

Figure 2.3 A decision conference process*



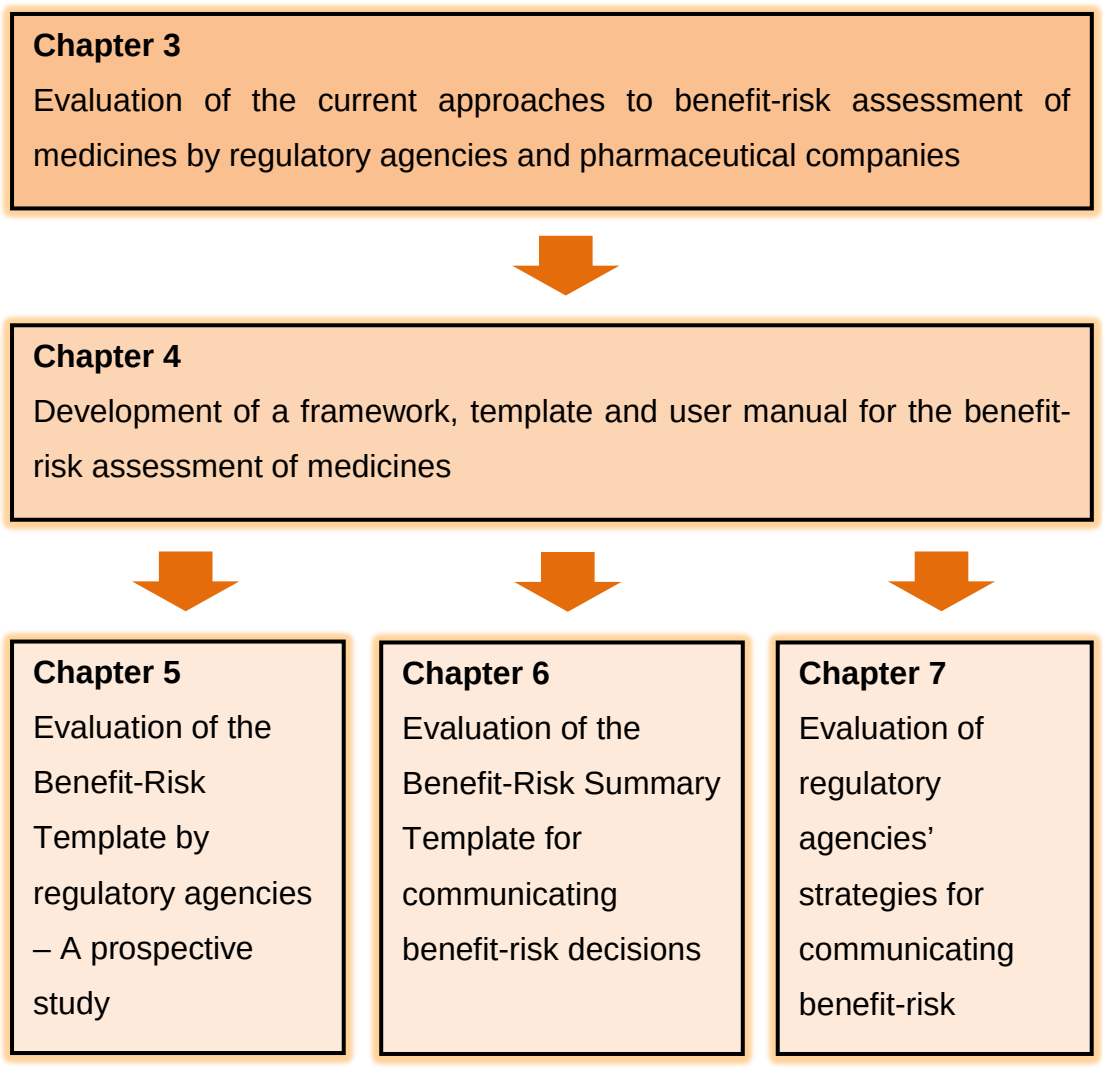
**adopted from Phillips, 2006*

The choice of methods for carrying out a study would be dependent on the availability of both time and experts. It is expected that both questionnaire techniques and decision conferencing will be the main tools employed for this study to achieve the objectives.

STUDY PLAN AND DATA COLLECTION

The conduct of this research will begin with a review of the current approaches used by the major stakeholders for benefit-risk assessment and regulatory decision-making. The outcomes will provide inputs for the development of a universal framework and benefit-risk assessment template, which these would be tested out in various settings (Figure 2.4).

Figure 2.4 The study flowchart



Evaluation of the current approaches to benefit-risk assessment of medicines by regulatory agencies and pharmaceutical companies

This will be carried out by the administration of an assessment tool to regulatory agencies and pharmaceutical companies. The scope of this review is limited to these two main stakeholders. The introduction of other stakeholders at this stage may compromise the review as too many opinions and perspectives have to be accommodated. The assessment tool is expected to be a combination of a tick-box checklist and a free-text comments box. The Delphi method is not suitable as critical issues need to be identified through a general qualitative review first.

Development of a framework, template and user manual for the benefit-risk assessment of medicines

A comparison of the existing frameworks, especially among the major regulatory agencies, will be carried out to identify the common items and the difference. A universal framework will be proposed based on the findings of the comparison. It is expected that a documentation tool or template should be available for the implementation of such a framework. Guidance on the assessment of benefits and risks will be referenced to form the basis of this template. A pilot exercise to review its feasibility will be conducted among selected regulatory agencies. A retrospective study using an application of the agency's choice on the proposed template should suffice for this preliminary investigation. Solicited comments on improving the template will contribute to the revision of the template. To aid the use of the template, a user manual will be developed to provide guidance and clarification.

Evaluation of the Benefit-Risk Template by regulatory agencies – A prospective study

The revised template from the pilot study will be further validated through the prospective application of the template for chosen submissions by the selected agencies. A study evaluation tool will be developed, as a tick-box checklist and free-text comments box. The feedback will provide information on improving the template.

Evaluation of the Benefit-Risk Summary Template for communicating benefit-risk decisions

A simplified version of the template will be studied using a regulatory agency from the emerging market. This is to examine the feasibility of extending the use of the framework and template to the rest of the emerging markets, who are earlier identified as stakeholders pursuing the regulatory trends led by the major agencies. A study evaluation tool similar to the one used for the prospective study of the template will be administered, given that the similar study goals are applicable to both template and the summary template.

Evaluation of regulatory agencies' strategies for communicating benefit-risk decisions

A comparison of the existing publicly available assessment reports will be conducted against the developed template. This is to assess the potential applicability of the template in communicating benefit-risk decisions.

CHAPTER 3

Evaluation of the current approaches to benefit-risk assessment of medicines by regulatory authorities and pharmaceutical companies

INTRODUCTION

The benefit-risk assessment of medicines is a critical process in regulatory decisions, resulting in their approval or rejection. Regulatory authorities bear the responsibility to ensure that the approved products demonstrate the efficacy and safety as shown in the clinical trial data submitted. However, such regulatory decisions are largely based on clinical judgment and the local medical context in each country. In a bid to minimise subjectivity for such important decisions, there have been attempts to utilise quantitative approaches in assessing benefits and risks of a medicine (EMA, 2009). As a result, pharmaceutical companies have also initiated the use of quantitative approaches in developing their products for submission to the regulatory authorities (Levitan et al, 2011).

Guo et al (2010) reviewed the methodologies and identified 12 quantitative approaches such as multi-criteria decision analysis (MCDA), probabilistic simulation methods (PSM), Monte Carlo simulation (MCS), incremental net health benefit (INHB), minimum clinical efficacy (MCE), number needed to treat (NNT), number needed to harm (NNH), and quality-adjusted time without symptoms and toxicity (Q-TWIST). They concluded that these quantitative methodologies should serve as supplementary tools, but not replace the decision-making process of clinicians or regulators. In the absence of a consensus among the agencies for a standard methodology, they recommended the use of multiple approaches across different clinical settings.

During 2010, the European Medicines Agency (EMA, 2010) completed the second phase of their research into benefit-risk assessment, with the main objective of identifying suitable approaches that can be utilised within member states. Based on their first phase and experience, a list of criteria (logical soundness, comprehensiveness, acceptability of results, practicality and generativeness) for reviewing the methodologies was constructed. A list of qualitative and quantitative techniques, identified through literature search and experience, was reviewed against the criteria. When reviewing, these methodologies were also subjected to evaluators' opinion of relevance. The conclusions of the second phase were that a combination of approaches may be useful in different clinical settings and an overarching qualitative framework will be required to effectively develop any quantitative

methodologies. Structured processes should be in place to improve transparency, audit trail, communication as well as the quality and speed of decision-making.

The aims of this study were to solicit opinions from the major stakeholders (agencies and companies) regarding their knowledge and use of different qualitative and quantitative techniques in order to put the findings by Guo et al (2010) and EMA (2010) into an international context, as well as to elucidate any potential differences between agencies' and companies' expectations.

OBJECTIVES

The objectives of the study were to:

- Identify agencies' and companies' current approaches to benefit-risk assessment
- Establish the criteria for including a framework/model for benefit-risk assessment
- Investigate agencies'/companies' current views of the advantages and disadvantages of the various models/frameworks available or being developed
- Identify both the internal and external barriers and possible solutions to incorporate a framework/model into medicines development and their regulatory review

METHODS

Development of the assessment tool

Current knowledge suggested that regulatory agencies and pharmaceutical companies had in place a framework for the assessment of the benefits and risks of medicines. These frameworks can be broadly classified into 3 types, as seen in the Table 3.1. Of note, all final decisions incorporated expert judgment, thus emphasizing the role of the framework as a supporting tool and not as a replacement for decision-making.

In addition, current opinions on the advantages and barriers to implementing a universal framework were sought, and relevant factors for the review of a framework were investigated. Seven factors (Table 3.2) were proposed for this study and these had been identified from those utilised by the EMA (2010) study.

Table 3.1 Definitions of systems

System	Definition
Qualitative	The system is a purely qualitative framework based on internal experts or management making a "gut decision" on the benefit-risk profile of each product and providing a conclusion. The final decision will be exercised based on Expert Judgment.
Semi-quantitative	The system is semi quantitative in that it has a structured (written) framework or standard operating procedure for data collection and analysis. The conclusion is based on the result of the outcomes of the internal system, as well as contributing opinions. The final decision will be exercised based on Expert Judgment.
Quantitative	The system is a fully quantitative model which includes a benefit-risk balance for a new medicine, and is applied across study data and contributing opinions. The conclusion is based on the cumulative outcome from this single system. The final decision will be exercised based on Expert Judgment.

Table 3.2 Definition of factors for reviewing of frameworks

1. Logical soundness	Provides an approach that is sound and allows decisions that are coherent and aids rational thinking
2. Comprehensiveness	Provides an approach that handles all forms of data (including qualitative and quantitative, subjective and objective information) and allows for multiple criteria
3. Acceptability of results	Provides an approach that checks for inconsistencies in data and judgment and a realistic approach to the evaluation of benefits and risks
4. Practicality	Provides an approach with minimum burden on resources and ease of use
5. Specificity and sensitivity	Provides a statistical perspective underpinning the reliability of the decision
6. Presentation (visualisation)	Provides outcomes in an easily understandable format such as charts and plots
7. Scope	Provides a consistent approach throughout drug development and post-approval monitoring

It was presumed that agencies and companies would have different opinions and experiences and it would be meaningful to study these differences and their potential impact on the development and implementation of a universal framework. Therefore, the study decided to stratify the data pertaining to agencies and companies.

Study participants

The participants were those holding senior positions and involved in benefit-risk assessment and decision-making. To improve the representation, participants from various sized organisations and geographical locales were invited.

Data collection

The assessment tool was finalised into a questionnaire consisting of 13 questions. Out of these, the following 4 questions required the participant to rate or rank a list of statements found within each question:

- Perceived advantages of the benefit-risk framework
- Barriers to implementing a formal benefit-risk framework
- Perception of the need for an appropriate benefit-risk framework
- Factors for reviewing benefit-risk frameworks

Eight questions were included using checkboxes for information collection:

- The current system employed by the organisation for the benefit-risk assessment of a new medicine during review (qualitative, semi-quantitative, or quantitative)
- The use of values, weights, and selected parameters during assessment of benefits and risks
- Satisfaction with current system
- Reasons for not using a semi-quantitative or quantitative system
- Plans to implement a semi-quantitative or quantitative system
- Construction of the benefit-risk framework
- Opinions of various models and approaches
- Development of visualisation tools for communicating benefit-risk balance

An open ended question was also used to solicit the potential hurdles and solutions, to be provided in a free-text manner. Most of the questions had an open field for

comments, allowing the participants to provide any issues of concern or relevant points that were not addressed by the questionnaire. The study tool can be seen in Figure 3.1.

All participants were required to indicate if they were from regulatory authorities ("agencies") or pharmaceutical companies ("companies"). The questionnaires were sent via email directly to the participants. Completed responses were received via email, as instructed to the participants.

Data processing and analysis

All responses were stratified into 2 groups, the agencies and the companies, allowing comparisons between these two stakeholders.

Some items that required categorical inputs in the questionnaire received very low responses. To allow meaningful interpretation of the results, these low responses were combined with others into logical categories. Variables of similar opinions were also grouped, as seen in the table below.

Table 3.3 Grouping of categorical variables

Categorical variables	Logical groups for interpretation	
Yes, No, Sometimes	Yes, Sometimes	No
Strongly agree, agree, indifferent, disagree, strongly disagree	Strongly agree, agree	Indifferent, disagree, strongly disagree
High, Medium, Low, Not applicable	High	Medium, Low, Not applicable

All other data were expressed as percentage over number of responders for that item, and ranking was applied when necessary. Free-text comments were collated and presented in appropriate categories.

This was designed as an exploratory study and the outcomes were interpreted to provide qualitative inferences relating to the objectives. No statistical analyses were planned or conducted.

Figure 3.1 Study tool

Please tick the appropriate box throughout the questionnaire

1) Which statement would best describe your agency system for assessing the benefit-risk (BR) of a new medicine during review?

A) Qualitative system	
Our internal system is a purely qualitative framework based on internal experts or management making a "gut decision" on the BR profile of each product and providing a conclusion. The final decision will be exercised based on Expert Judgment.	
B) Semi-quantitative system	
Our internal system is semi quantitative in that it has a structured (written) framework or standard operating procedure for data collection and analysis. The conclusion is based on the result of the outcomes of the internal system, as well as contributing opinions. The final decision will be exercised based on Expert Judgment.	
C) Quantitative system	
Our internal system is a fully quantitative model which includes a benefit-risk balance for a new medicine, and is applied across study data and contributing opinions. The conclusion is based on the cumulative outcome from this single system. The final decision will be exercised based on Expert Judgment.	

Semi-quantitative and quantitative systems (options B and C) may be described as "formal". Qualitative system (option A) would be "informal".

- **If you have selected option B or C i.e. formal systems, please proceed to questions 2 and 3.**
- **If you have selected option A i.e. informal system, go directly to questions 4 and 5.**

*The following questions 2 and 3 are for those who **use** a semi-quantitative or quantitative (formal) system.*

2) Regarding the formal system used in your agency:

2.1) Do you put a value on each of the benefit/efficacy parameters? Yes ❑ No ❑ Sometimes ❑

2.2) Do you put a value on each of the risk/harms parameters? Yes ❑ No ❑ Sometimes ❑

2.3) Are these parameters weighted? Yes ❑ No ❑ Sometimes ❑

2.4) Do you include any other parameters in your internal model such as:

- Incremental Net Benefit Yes ❑ No ❑ Sometimes ❑
- Quality Adjusted life years Yes ❑ No ❑ Sometimes ❑
- Patient preferences Yes ❑ No ❑ Sometimes ❑
- Numbers needed to treat Yes ❑ No ❑ Sometimes ❑
- Numbers needed to harm Yes ❑ No ❑ Sometimes ❑

Others: Please specify: .....

.....

3) Are you satisfied with your existing BR framework?

Yes ❑ No ❑

If **No**, please select reason(s) that best describes your situation.

- ❑ Too time consuming to utilize the system
- ❑ Requires additional training to understand and learn to use the system
- ❑ Poor acceptance by staff
- ❑ System is not validated
- ❑ Benefits of the system are not apparent so far
- ❑ Others (please provide details): _____

Please proceed to question 6.

*The following questions 4 and 5 are for those who **do not use** a semi-quantitative or quantitative (formal) system.*

4) From the list below, choose reason(s) that best describe why a formal system is not used:

- ❑ Not required for current product regulatory processes
- ❑ Lack of knowledge of BR frameworks in general
- ❑ Lack of a scientifically validated BR framework
- ❑ Lack of a common BR framework among peers and/or stakeholders
- ❑ Benefits of a BR framework not apparent
- ❑ Resource limitations
- ❑ Administrative limitations
- ❑ Others (please provide details): _____

5) Kindly indicate if you have any plans to implement a formal system.

- ❑ Yes, within the next 3 years
- ❑ Yes, within the next 5 years
- ❑ No plans as yet

Please proceed to question 6.

6) Perceived advantages of Benefit-Risk framework

It is believed that the implementation of a benefit-risk framework should confer certain advantages to the organization.
From the list below, please rate the following advantages as high, medium, low, or not applicable.

Advantages	High	Medium	Low	Not applicable
6.1) Acts as a tool for communication among peers within organization				
6.2) Acts as a tool for communication between organization and stakeholders (including companies)				
6.3) Provides documentation for structured discussion				
6.4) Ensures consistency in quality of assessment				
6.5) Acts as a training tool for new evaluators				
6.6) Aligns the scientific direction internally in BR assessment				
6.7) Inspires confidence in customers (agency to companies, and to the public)				
6.8) Streamlines evaluation work				
6.9) Enhances transparency and accountability				
6.10) Others: Please specify:				

7) Barriers to implementing a formal Benefit-Risk framework

It is believed that the successful implementation of a benefit-risk framework may be impeded by certain barriers.
From the list below, please rate the following barriers as high, medium, low or not applicable.
If you have rated more than one barrier as "High", please rank them, with 1 being the most significant.

Barriers	High	Ranking*	Medium	Low	Not applicable
7.1) Resource limitation e.g. manpower, finances					
7.2) Lack of knowledge/expertise to execute framework					
7.3) Resistant to change (culture documentation or methodology)					
7.4) Significant change to work processes					
7.5) Significant retraining of staff required					
7.6) Support from senior management required					
7.7) Lack of a scientifically validated framework					
7.8) Lack of a framework accepted and/or recognised by stakeholders (both within and outside agency)					
7.9) Others: Please specify:					

*For barriers rated as "High" only

8. Constructing the Benefit-Risk Balance:

Consider the following criteria in producing an acceptable benefit-risk framework for use in your agency, and put a tick in the boxes that best describe your situation.

Criteria	Already included in our agency model	Should be included in any formal BR framework	Not relevant
8.1) Description of the alternative therapies or interventions (where relevant), i.e. clear description of the medical need			
8.2) Calculation of the uncertainties on benefit and risk.			
8.3) Direct comparison of the absolute gains (efficacy) or harms (safety) in terms of lives saved or lost, or in terms of specific clinical events			
8.4) Calculation of the level of risk that would be acceptable with regards to the level of clinical benefit in the specific context			
8.5) Evolution of the BR balance over time and its sensitivity to various assumptions			
8.6) Calculation of a BR balance for each major patient subpopulation			
8.7) Identification of any outstanding issues and potential post-marketing commitments in this regard			
8.8) Consideration of the different regulatory options for approval (e.g. standard marketing authorisation, conditional/priority marketing authorisation).			
8.9) Other Please Specify:			

9. Perception of the need for an appropriate Benefit risk framework

Regarding the need for an appropriate BR framework, please read the following statements and mark one of the given options: **Strongly agree / Agree / Indifferent / Disagree / Strongly disagree.** If you would like to modify the statement or have additional comments, please add these in the footnote.

	Strongly Agree	Agree	Indifferent	Disagree	Strongly disagree	Tick here if you have added comments or modify the statements – explain in a footnote
9.1) There is a need for a BR framework to be developed that can be used by <u>both</u> agencies and companies						
9.2) This BR framework should also be applicable to health technology assessment groups						
9.3) For the registration of new medicinal products it will be possible to develop an overarching BR framework.						
9.4) For the registration of new medicinal products it will be necessary to develop therapeutic area specific BR frameworks						
9.5) Our agency preference would be a quantitative approach to BR assessment rather than a purely qualitative approach						
9.6) The purpose of establishing an appropriate BR framework is to improve:						
A) The consistency of decision making						
B) The transparency of decision making						
C) Communication of the decision						
9.7) The purpose of an appropriate BR framework is to define a number that translates the BR balance in absolute terms and can be used to measure its sensitivity to various parameters						
9.8) It is important that any BR framework, if developed for registration purposes, is utilized across regulatory divisions <u>within an agency</u>						

(continued)

	Strongly Agree	Agree	Indifferent	Disagree	Strongly disagree	Tick here if you have added comments or modify the statements – explain in a footnote
9.9) It is important that any BR framework, if developed for registration purposes, is utilized across agencies <u>worldwide</u>						
9.10) An appropriate BR framework for registration should also enable assessment of benefit-risk management plans.						
9.11) An appropriate BR framework for registration should also apply to all stages of drug development from drug development to post-approval changes						
9.12) It is important that all stakeholders (agencies, companies, doctors and patients) are part of the development and validation of an appropriate Benefit Risk framework						
9.13) There is a need for a coordinating group including representatives from agencies academia, pharmaceutical companies and other relevant stakeholders to ensure the appropriate direction and application of a benefit-risk systematic standardized framework						

Footnotes: *Any modifications to the statements or comments on the statements please detail here with appropriate comment number.*

10. Factors for reviewing benefit-risk frameworks

In the latest report on benefit-risk assessment by the European Medicines Agency [a] (EMA) led by Dr Lawrence Phillips and the project team, various quantitative models and approaches were reviewed. Several criteria were collated from the previous work package, and these were used to assess the models and approaches.

The list below features those criteria employed in reviewing those models, as well as a few additional criteria. Please rate these criteria as highly significant, less significant, or not relevant, by putting a tick in the corresponding boxes.

Factors for review	Highly Significant	Less Significant	Not relevant *
10.1) Logical soundness Gives an approach that is sound and allows decisions that are coherent, and aids rational thinking without changing when alternatives are amended.			
10.2) Comprehensiveness Gives an approach that handles all forms of data (including quality and quantitative, subjective and objective information) and allows for multiple objectives.			
10.3) Acceptability of results Gives an approach that checks for inconsistencies in data and judgment, and provide a realistic approach to the evaluation of benefits and risks.			
10.4) Practicality Gives an approach whose implementation is economical, with ease of teaching and use.			
10.5) Specificity and sensitivity Gives a statistical perspective in providing reliability of the decision, by employing statistical tools at various points in the evaluation.			
10.6) Presentation (Visualisation) Gives an approach that provides the outcome in an easily understandable format such as, like charts and plots.			
10.7) Scope Gives a consistent approach from drug development to post-approval monitoring.			

Factors for review *(continued)*	Highly Significant	Less Significant	Not relevant*
10.8) Others: Please specify:			

a. Benefit-risk methodology project: Work package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment. 31 August 2010. EMA/549682/2010.

*For factors deemed not relevant, kindly provide reasons or details for explanation:

11. In the report by EMA[a] led by Dr Lawrence Phillips and the project team, various models and approaches were selected to be further explored, based on its relevance and usefulness to regulators.

The list below features the models and approaches reviewed by his team. Please put a tick in the boxes that best describe your situation.

Models / Approaches	I have no experience with this model / approach	My organization utilises this method for BR assessment	I find this model / approach useful and relevant in benefit-risk assessment
11.1 Qualitative Approach			
11.2 Discrete event simulation			
11.3 Probabilistic simulation			
11.4 System dynamics			
11.5 Bayesian belief networks			
11.6 Bayesian statistics			
11.7 Decision trees and influence/relevance diagrams			
11.8 Evidence-based benefit and risk model			
11.9 Incremental net health benefit			
11.10 Markov processes			
11.11 Multi-criteria analysis, including MCDA			
11.12 QALYs/DALYs			
11.13 Kaplan-Meier estimator			
11.14 NNT/NNH			
11.15 Conjoint analysis			
11.16 Contingent valuation			
11.17 Stated preferences			

a. Benefit-risk methodology project: Work package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment. 31 August 2010. EMA/549682/2010. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500097750.pdf

12. In working towards an internationally acceptable BR framework, what would be the 3 major hurdles to be addressed, and how would these be overcome?

Major hurdles	**Possible Solutions**
1)	
2)	
3)	

13. Has your agency developed an effective visualization tool (eg forest/tornado plots, for communicating benefit risk balance to:

Communicating internally Yes ❑ No ❑

Healthcare professionals Yes ❑ No ❑

Patients: Yes ❑ No ❑

If yes please comment or provide an example:

Before returning the completed questionnaire, kindly sign and date the box below.

Signature:	Position:
Name:	Location:
Date:	Company:

RESULTS

For the purpose of clarity the results will be presented in three parts:

- Part I - Current systems for benefit-risk assessment during development and review;
- Part II - Criteria identified for the development of a universal benefit-risk assessment framework; and
- Part III – Barriers and solutions to implementing benefit-risk assessment frameworks

Demographic Characteristics of the Study Participants

A total of 38 questionnaires were sent out to 24 pharmaceutical companies and 14 regulatory agencies. Eleven out of 14 (79%) agencies responded. These agencies included the European Medicines Agency (EMA), national agencies from the European member states, Medicines and Healthcare products Regulatory Agency of UK (MHRA), the US Food and Drug Administration of (US FDA), Therapeutic Goods Administration of Australia (TGA), Health Canada, SwissMedic and the Health Sciences Authority of Singapore (HSA). Among the companies, 20 out of 24 (83%) responded. These companies comprised of both small and large organisations. The overall responders formed a diverse group with representation from developed and developing nations.

Part I – Current Systems of Benefit-risk Assessment during Development and Review

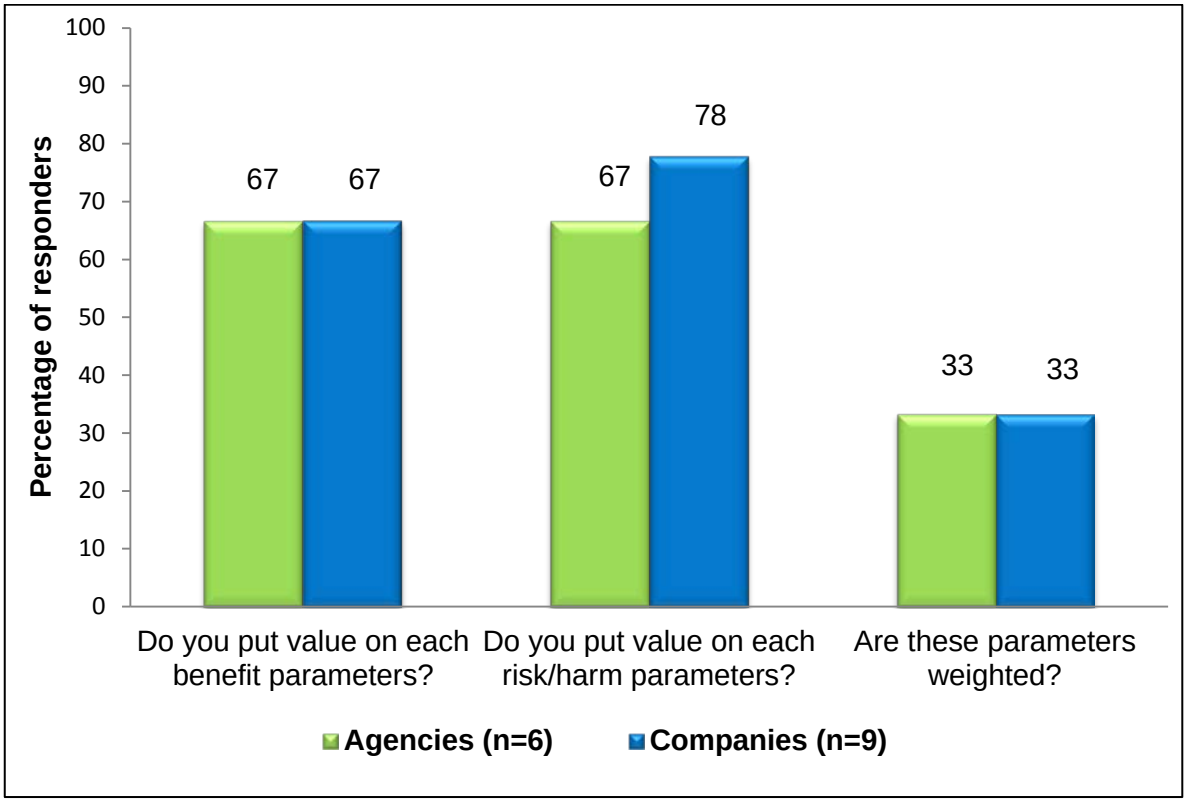
Usage of qualitative and semi-quantitative systems

No responders indicated that they used a fully quantitative system. Among the agencies, there were similar numbers using qualitative and semi-quantitative systems (five versus six agencies respectively). A similar trend was observed among the companies when making a decision to submit an application, with ten companies using qualitative systems and nine using semi-quantitative systems. However, during the companies' development of a medicine, more used qualitative systems than semi-quantitative systems (13 versus seven companies respectively). Generally, it was observed that the companies utilised qualitative systems more frequently than the agencies.

Use of values, weights and selected assessment parameters

Six agencies and nine companies who were currently using semi-quantitative systems responded and similar trends were observed between the two. Combining the two response options of “Yes” and “Sometimes”, it demonstrated that two thirds of responders assigned values and one third assigned weights for benefit and risk parameters (Figure 3.2). There was no observed correlation between responders who provided value inputs and those who applied weighting. This suggests weighting of parameters was not commonly utilised in the assessment of benefits and risks.

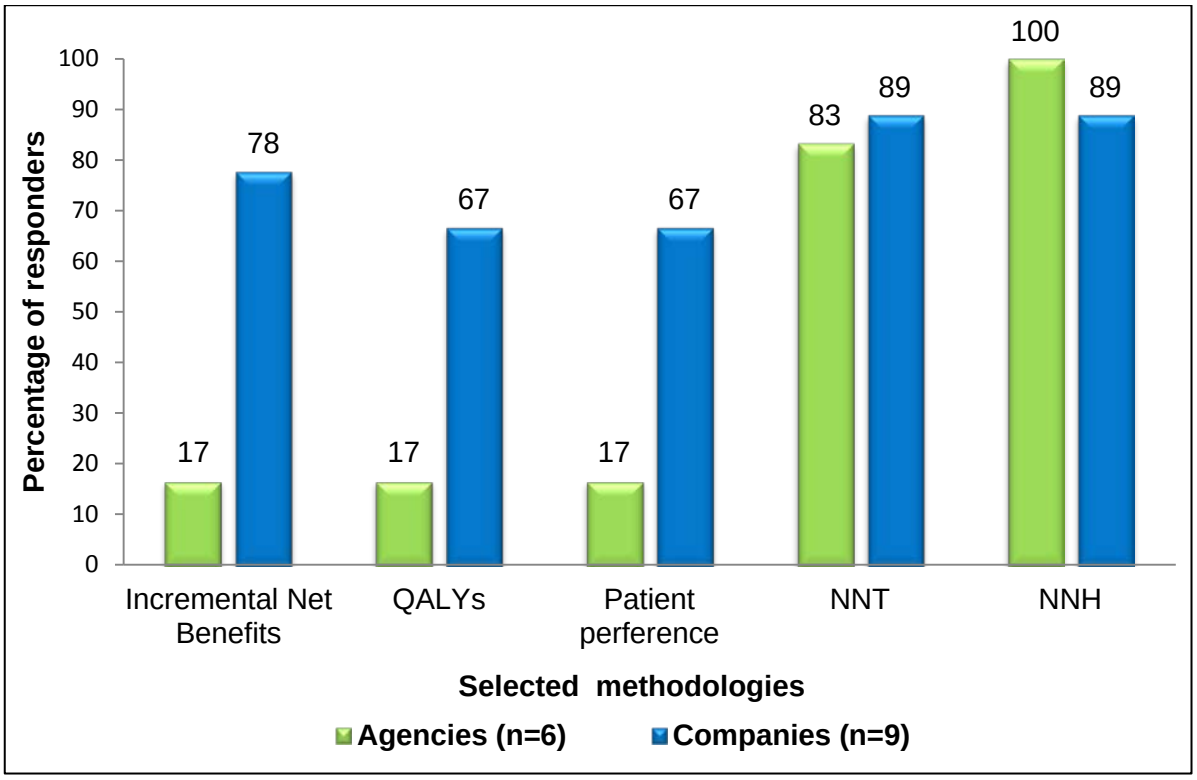
Figure 3.2 Percentage of responders applying values and weights to benefit and risk parameters



Among these agencies, the majority used number-needed-to-treat (NNT) and number-needed-to-harm (NNH), while the companies tended to include other parameters (Figure 3.3). Nonetheless, NNT and NNH were the commonly utilised parameters in semi-quantitative systems for assessing benefits and risks between the agencies and companies.

Other parameters indicated by responders were Markov modelling, Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team (PhRMA BRAT) framework, probabilistic sensitivity analysis and sales statistics.

Figure 3.3 Percentage of responders applying selected methodologies



Experiences with various systems and approaches

To obtain the participants' experience with some commonly used systems and approaches (collectively known as methodologies), a list of 17 methodologies (Table 3.4) was presented to the participants in the study. Ten agencies and 19 companies responded.

The most common methodologies used by the agencies included the qualitative approach and NNT/NNH (Table 3.5). The agencies had minimal or no experience with a discrete event approach, system dynamics, stated preferences, conjoint analysis, Bayesian belief network and contingent valuation. In comparison, companies showed a similar trend to the agencies for the methodologies frequently used. However, the companies had more experience with a wider variety of methodologies, with responses provided across all the presented systems and approaches. Major differences in experience were observed for stated preferences

(agencies 11% versus companies 56%) and conjoint analysis (agencies 10% versus companies 61%); companies had markedly more experience with these two methodologies.

Table 3.4 List of 17 methodologies presented in study

Qualitative approach	Decision trees and influence/relevance diagrams	KM estimators
Discrete event approach	Evidence based benefit-risk model	NNT/NNH
Probabilistic simulation	Incremental net health benefits	Conjoint analysis
System dynamics	Markov processes	Contingent valuation
Bayesian belief networks	MCDA	Stated preferences
Bayesian statistics	QALY/DALY	

Table 3.5 Top five methodologies currently used by agencies and companies

Ranking	Percentage of responders			
	Agencies	%	Companies	%
1	Qualitative approach	67	Qualitative approach	83
2	NNT/NNH	67	KM estimators	56
3	Evidence based benefit-risk model	56	Decision trees and influence/relevance diagrams	53
4	Decision trees and influence/relevance diagrams	50	Evidence based benefit-risk model	47
5	KM estimators	40	NNT/NNH	44

The top methodologies considered useful and relevant for agencies and companies are Bayesian statistics and MCDA. It was observed that the three main methodologies used by agencies, namely qualitative approach, NNT/NNH and evidence based benefit-risk model, did not rank highly for usefulness and relevance (Table 3.5 and 3.6). The companies' responses were more evenly distributed across the methodologies compared with the agencies. Although Bayesian statistics and MCDA were ranked top methodologies by agencies and companies in terms of usefulness and relevance; their current usage was low to none.

Table 3.6 Comparison of rankings between top methodologies considered useful and relevant with those currently used

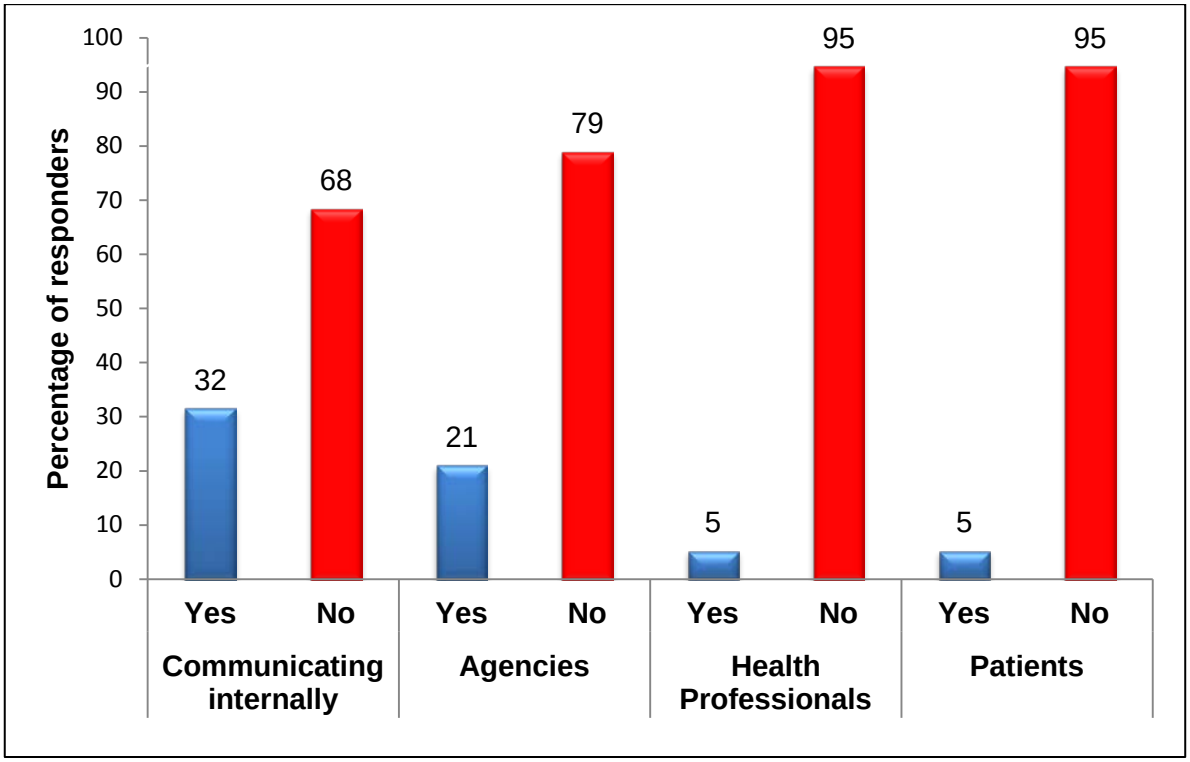
Agencies					Companies				
Methodology	Useful and relevant		Currently in use		Methodology	Useful and relevant		Currently in use	
	% of responders	Rank	% of responders	Rank		% of responders	Rank	% of responders	Rank
Bayesian statistics	40	**1**	30	**7**	MCDA	47	**1**	12	**13**
MCDA	40	**1**	0	**15**	Bayesian Statistics	44	**2**	28	**8**
Probabilistic simulation	30	**2**	10	**10**	Qualitative approach	44	**2**	83	**1**
Decision trees and influence/ relevance diagrams	30	**2**	50	**4**	NNT/NNH	44	**2**	44	**5**
Markov processes	30	**2**	0	**14**	QALY/DALY	44	**2**	33	**6**
					Incremental net health benefits	44	**2**	28	**7**
					Conjoint analysis	44	**2**	28	**9**

In general, both agencies and companies had most experience with and usage of the qualitative approach, but viewed this methodology not as relevant and useful. In contrast, Bayesian statistics and MCDA were not widely used but deemed to be the most useful and relevant. Hence, future frameworks should consider the inclusion of these two methodologies.

Development of visualisation tools for communication of benefit-risk balance

None of the nine agencies who responded had developed any visualization tools for such purposes. It was observed that for the 19 companies who responded and developed visualization tools, it was more for internal communication, and infrequently for communications to health professionals and patients (Figure 3.4).

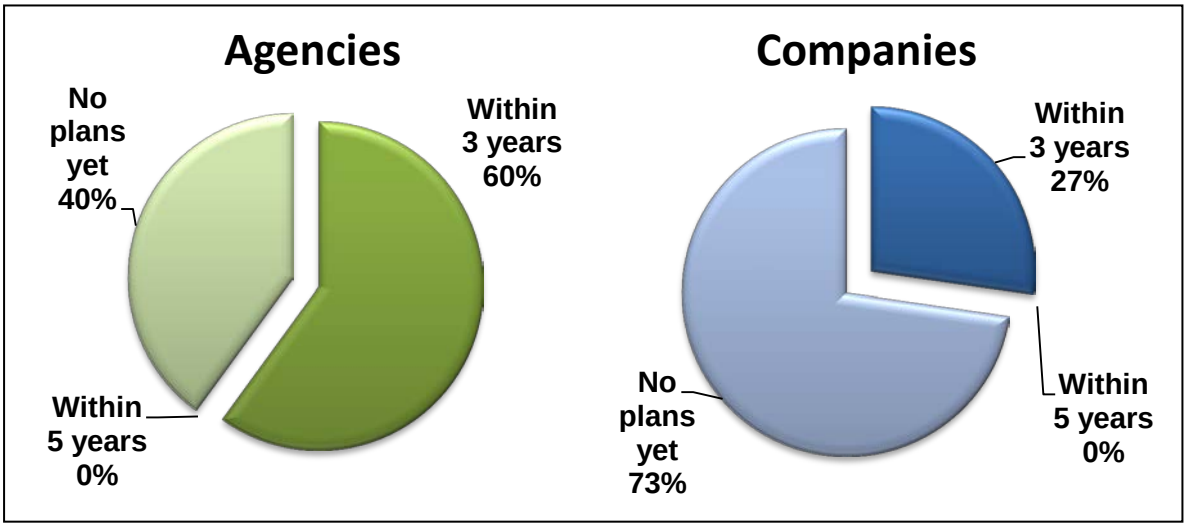
Figure 3.4 Companies' responses to the use of visualization tools to communicate benefit-risk balance



Plans for implementing a semi-quantitative or quantitative system

Five agencies and 11 companies responded, and no responders indicated plans to implement a semi-quantitative or quantitative system within 5 years. Three out of the five agencies indicated their plans to implement within 3 years, compared to 27% of the companies (Figure 3.5).

Figure 3.5 Indication of plans to implement a semi-quantitative or quantitative system



Part II – Criteria Identified for Development of a Universal Benefit-risk Assessment Framework

Perception of the need for an appropriate benefit-risk framework

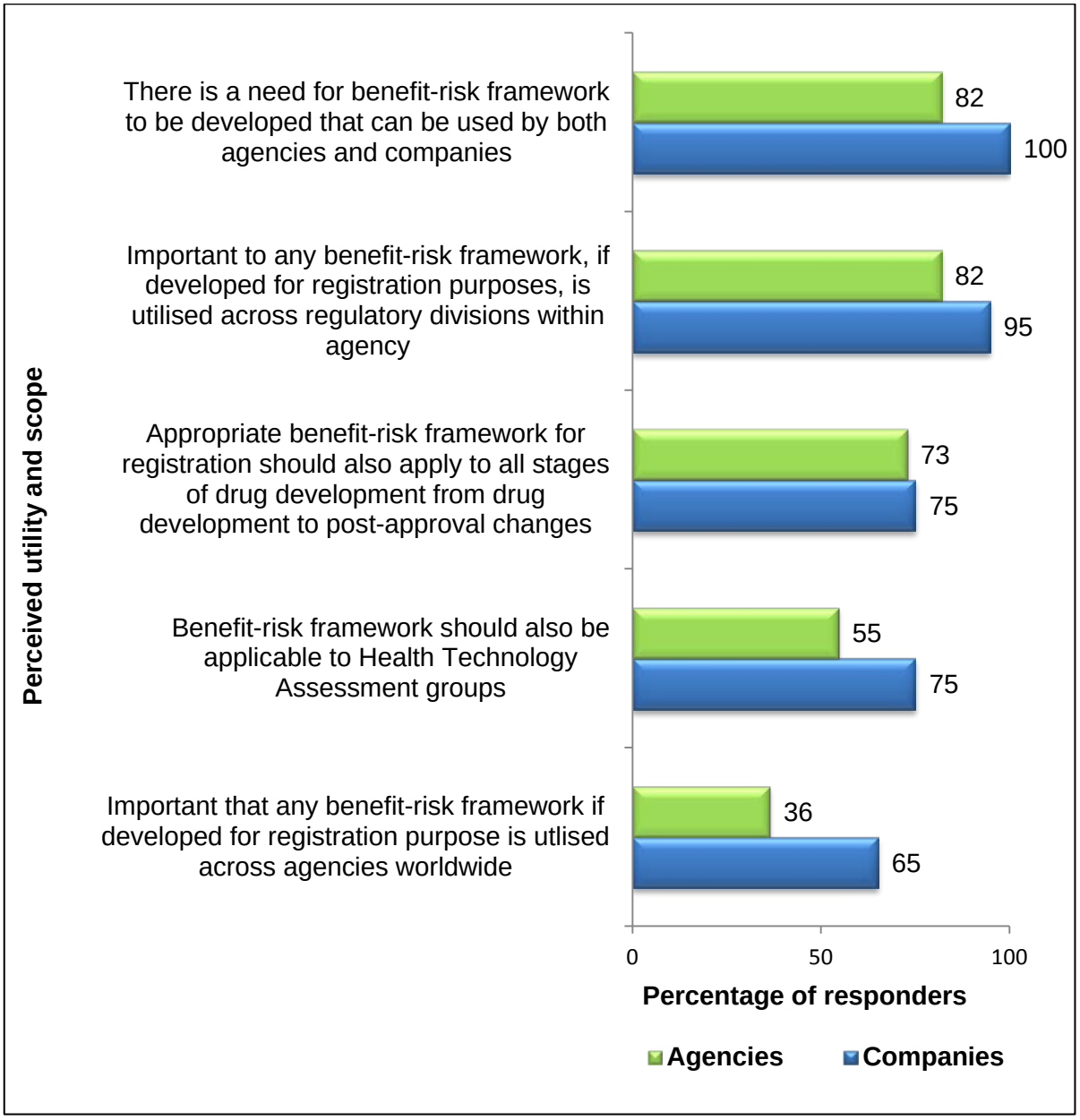
The results were collated from the responses to 13 statements in the study regarding the perception of the need for an appropriate framework. Eleven agencies and 20 companies responded and these responses were reviewed and presented as three categories namely utility and scope, purpose and direction for developing a benefit-risk framework.

Utility and Scope of a benefit-risk framework

Most agencies felt that a benefit-risk framework should be used by both agencies and companies, across divisions of a regulatory agency, and be applied from drug development to post-approval changes (Figure 3.6). Responses from the companies had a similar trend.

Fewer agencies believed that the framework, if developed for registration of medicines, should be utilised across agencies worldwide. However, the majority of companies would prefer this to be so. It was also observed that more companies than agencies wanted the framework to be applicable to heath technologies agencies (HTA).

Figure 3.6 Responses to perceived utility and scope of a benefit-risk framework



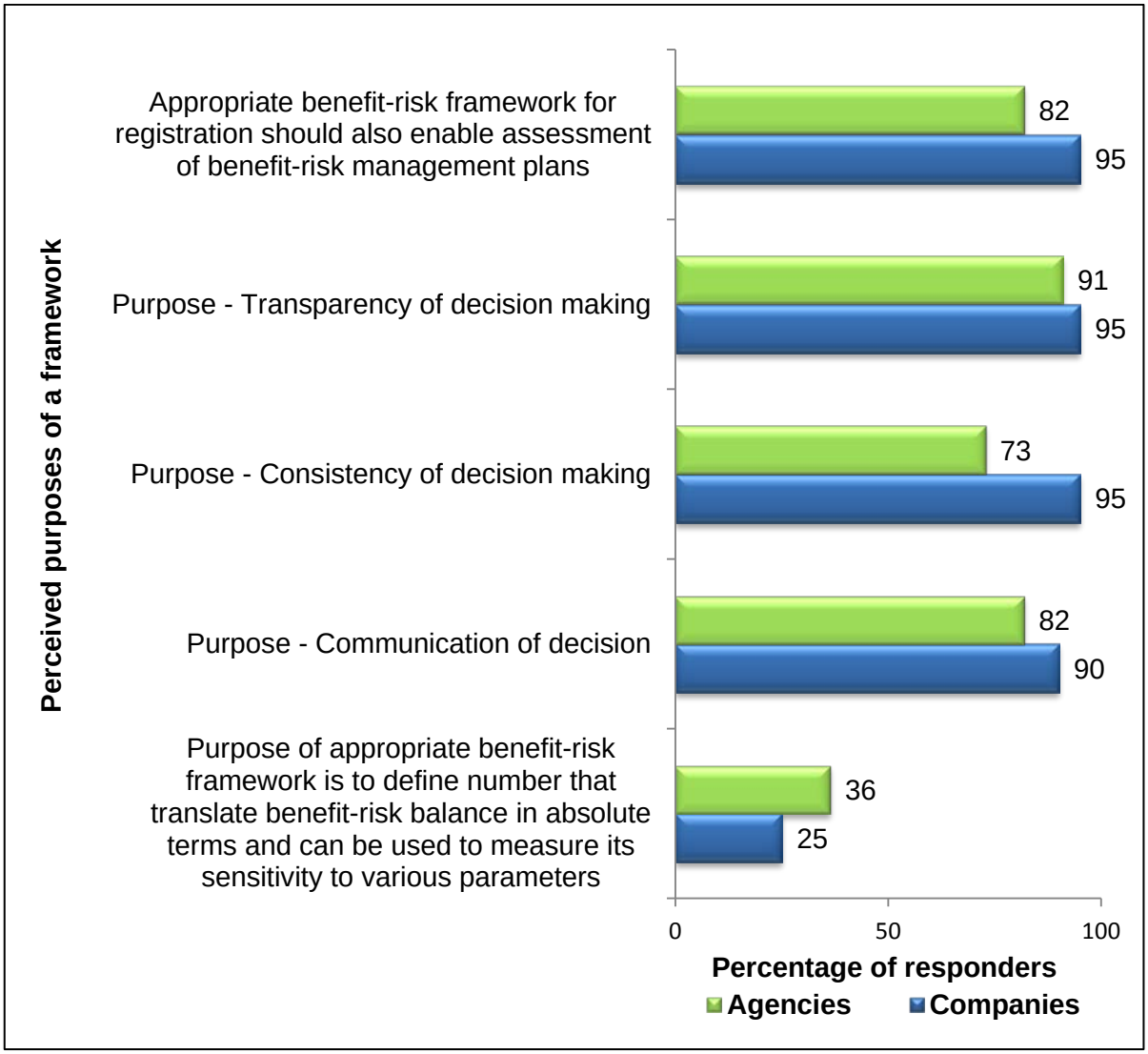
The general consensus was for a benefit-risk framework to be utilised by both agencies and companies and for the entire life cycle of a medicine.

Purpose of a benefit-risk framework

There was a good level of agreement between the agencies and companies for the purposes of a framework. Both groups felt that a benefit-risk framework would enhance the quality of communication and enable the assessment of benefit-risk management plans (Figure 3.7).

Similarly, both agencies and companies did not feel the need to have a framework that translates benefit-risk balance into absolute numeric terms and measures sensitivity to various other parameters. This closely mirrored the observations that no responders currently utilise a fully quantitative system and the inconsistent use of values and weights for benefit-risk parameters.

Figure 3.7 Responses to perceived purposes of a benefit-risk framework



Direction for developing a benefit-risk framework

A high proportion of the agencies would prefer a quantitative approach in assessing benefits and risks and have an overarching framework (Figure 3.8). Majority of the companies would prefer to have a coordinating group (consisting of representatives

from agencies, companies, academia and other stakeholders) to guide the direction and application of the framework and to involve these relevant stakeholders in developing and validating the framework. These outcomes were agreed by both agencies and companies. Differences in opinions could be observed in the preference for a quantitative approach, and the need to develop specific frameworks for different therapeutic areas.

Perceived advantages of benefit-risk framework

This study evaluated the perceived advantages of a framework through nine statements. All responders, 11 agencies and 20 companies, provided responses to this section. The main advantages of a benefit-risk framework, as perceived by agencies, were in providing documentation for a structured discussion, acting as a tool for communication among peers within the organization and communicating between the organization and stakeholders (Figure 3.9). The main advantages, indicated by companies, were to enhance transparency and accountability and communicate between the organization and stakeholders.

A major discrepancy between the agencies' and companies' responses was in having the framework as a training tool with more than half of the agencies believing this advantage was significant, but not with the companies. Among the responders, all the listed advantages were considered significant. Between agencies and companies, there was a general agreement that the advantages of a framework included proper documentation and enhancement of communications (including transparency and accountabililty of decisions). The advantage of streamlining of current work did not appear to be a high priority. Additional comments received from these responders included the advantages of focusing on both benefits and risks of a medicine as well as providing a tool for decision-making in urgent situations.

Figure 3.8 Responses to the perceived directions in developing a benefit-risk framework

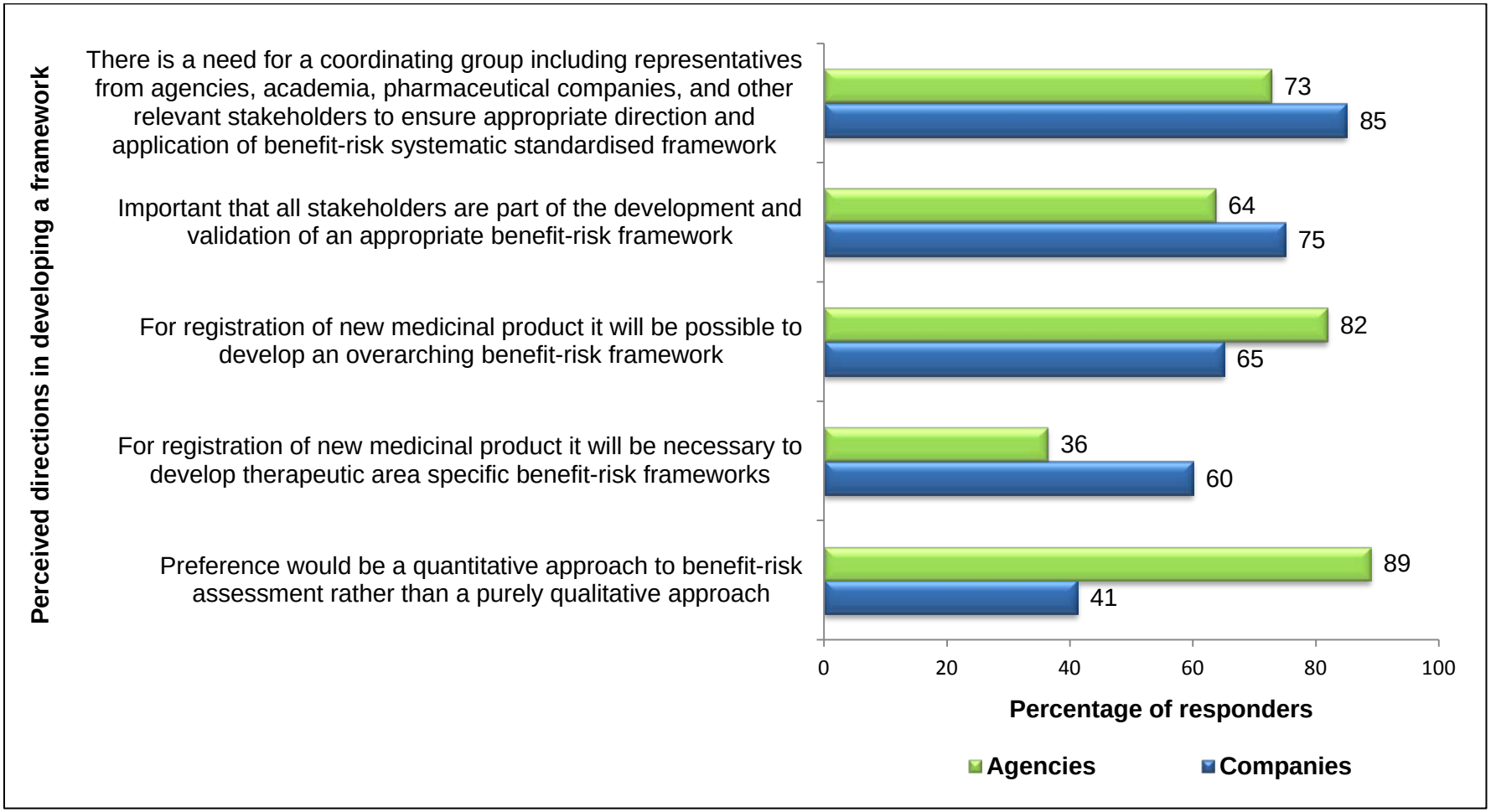
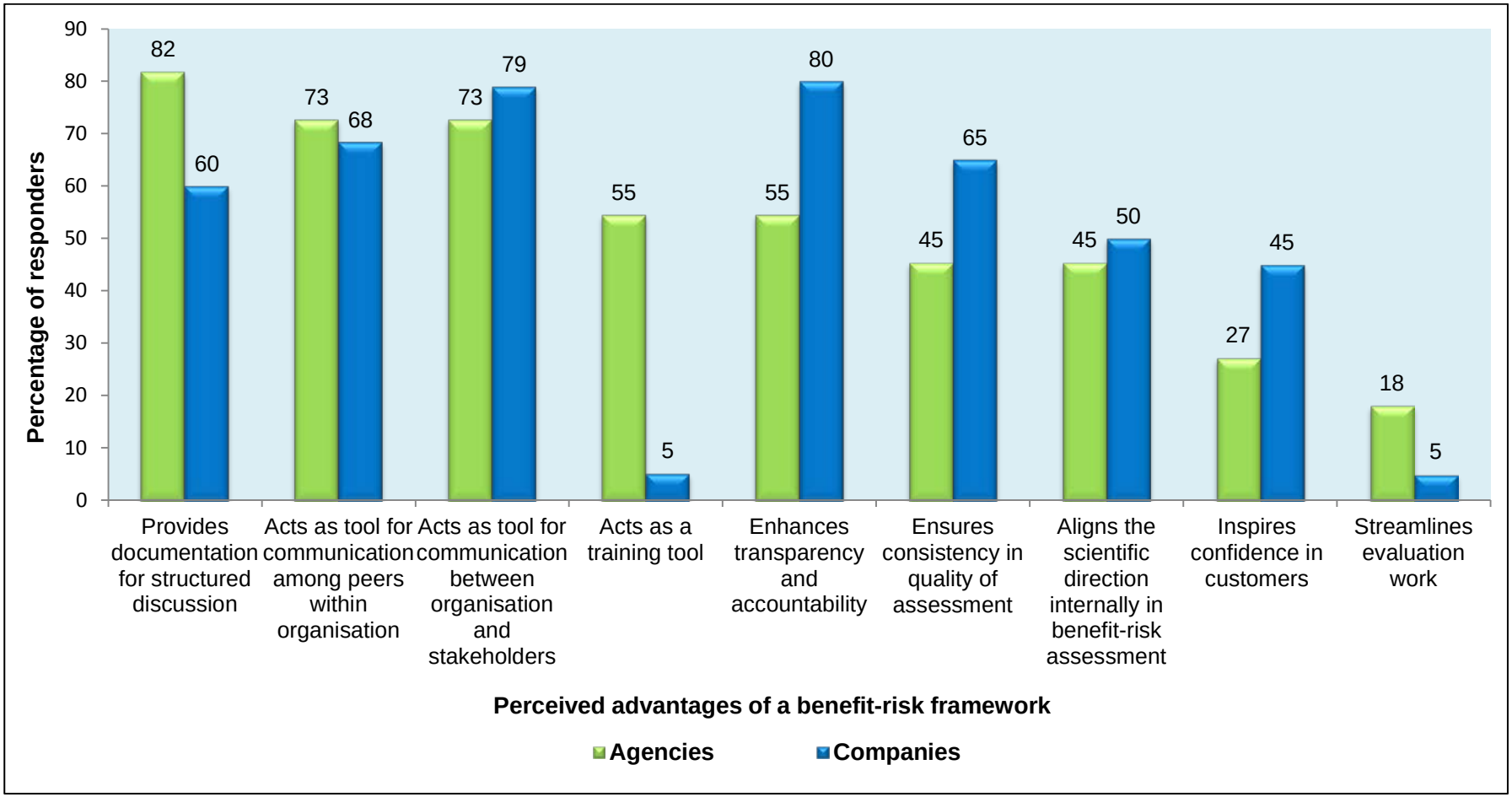


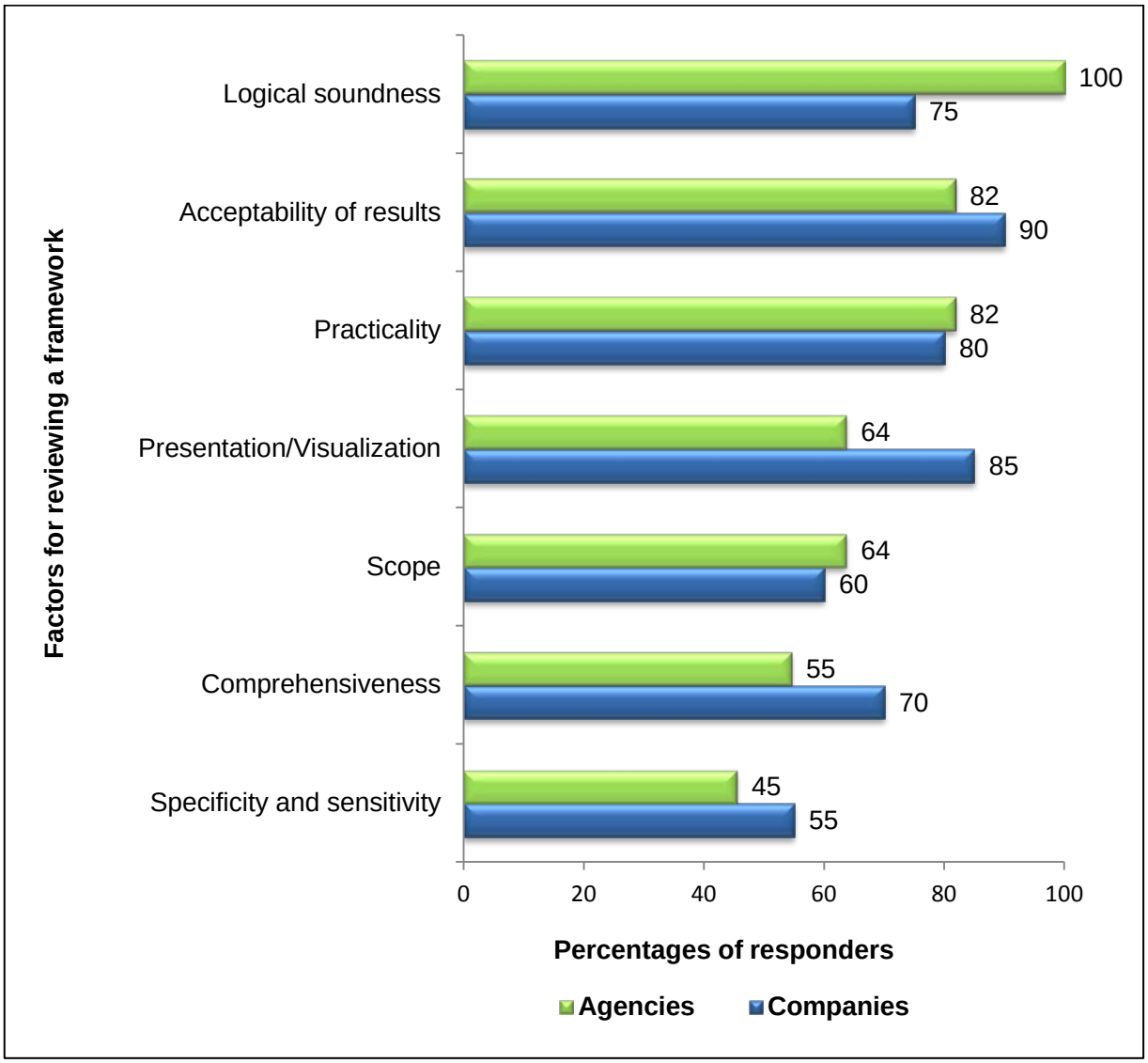
Figure 3.9 Responses indicating the perceived advantages of a benefit-risk framework



Factors for reviewing benefit-risk frameworks

The major factors for reviewing a benefit-risk framework were logical soundness, acceptability of results and practicality. These results were similar for both agencies and companies (Figure 3.10).

Figure 3.10 Responses indicating the relevance of factors for reviewing a benefit-risk framework



In general, all the listed factors could be considered relevant in reviewing a benefit-risk framework for appropriateness. Additional comments provided by responders were to include factors like transparency of the methodology and provision of an audit trail from evaluation to decision.

Criteria in constructing benefit-risk balance

The criteria used for constructing a benefit-risk balance were similar between the agencies and companies. The more frequently used criteria were the description of alternative therapies or interventions, the identification of outstanding issues and potential post-market commitments (Figure 3.11). In addition, other criteria included the direct comparisons of the absolute gains or harms in terms of lives saved, lost, or specific clinical events. Five out of 11 agencies (45%) and three out of 20 companies (15%) calculated the benefit-risk balance for each major subpopulation. Similarly there was a difference with respect to the acceptable level of risk with regards to clinical benefit (36% of agencies compared with 16% of companies) and the evolution of benefit-risk balance over time (36% of agencies compared with versus 20% of companies). The remaining criteria, namely consideration for different regulatory options for approval and calculation of the uncertainties for benefit and risk were used in similar frequencies by agencies and companies.

In considering criteria important to construct a benefit-risk balance, there was agreement between the agencies and companies to include the calculation of uncertainties on benefits and risks, direct comparison of absolute gains or harms, calculation of acceptable risk with regards to clinical benefits, the description of alternative therapies or interventions and the identification of outstanding issues and potential post-market commitments (Figure 3.12). With the exception of the calculation of acceptable risk with regards to clinical benefits, the rest were currently used in similar frequencies by agencies and companies. In general, these five criteria should be considered in the development of a benefit-risk framework.

Figure 3.11 Comparison between agencies and companies for criteria currently used in constructing benefit-risk balance

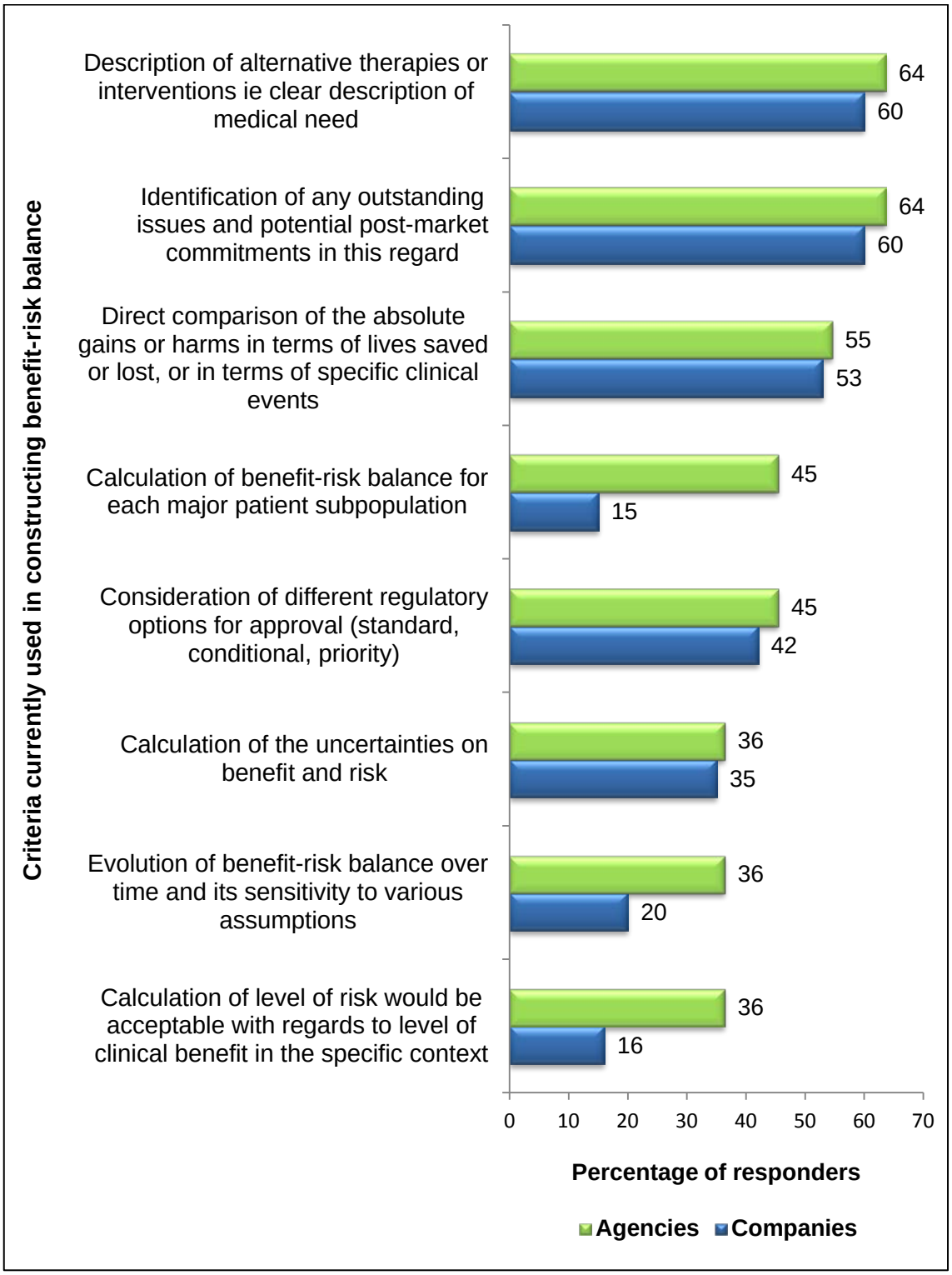
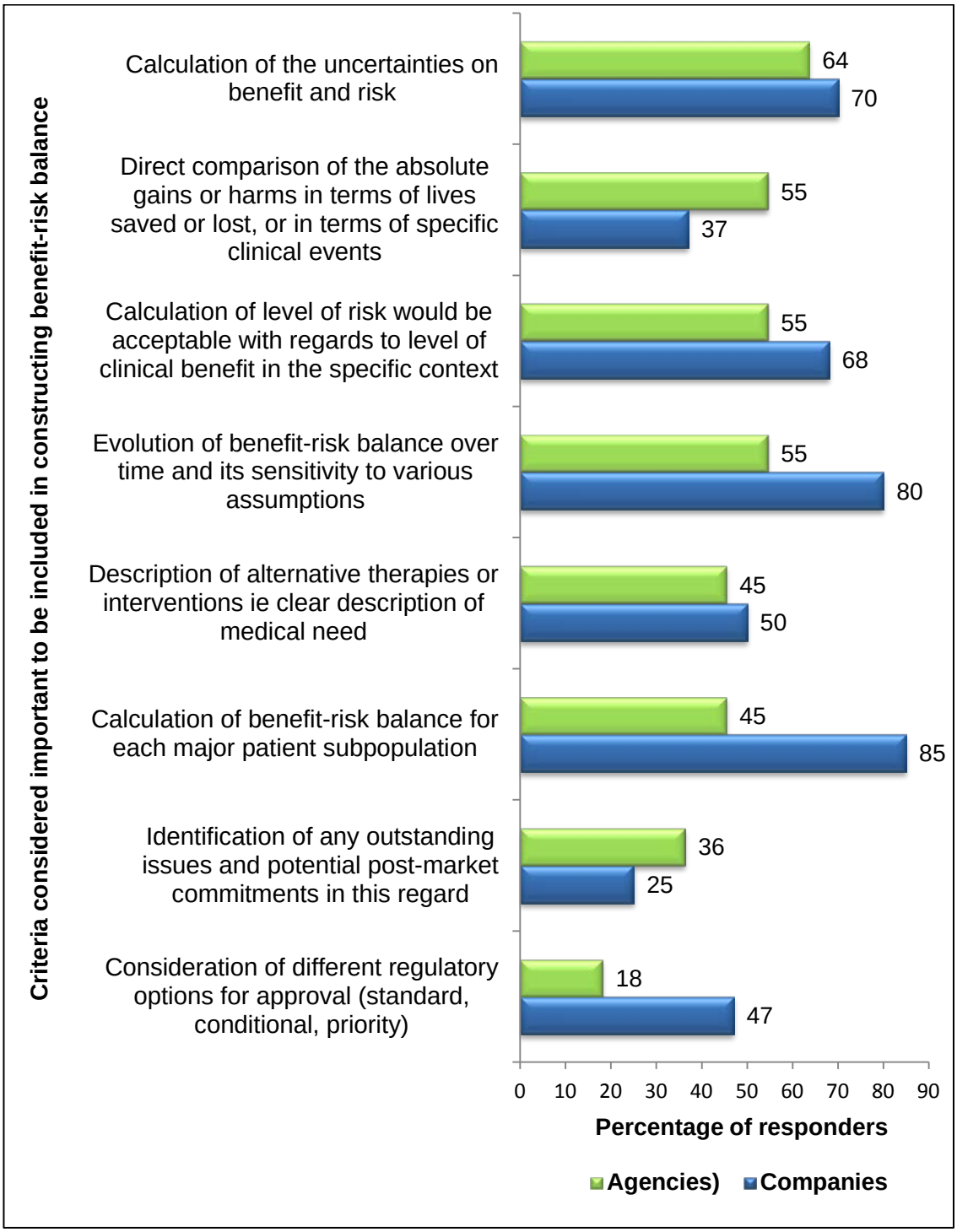


Figure 3.12 Comparison between agencies and companies for criteria considered important to be included in constructing benefit-risk balance



There was a difference between agencies and companies with respect to the criteria as to whether the benefit-risk framework could be of value for regulatory approval options. Half the companies reported that this criterion was important, whereas in contrast the agencies considered it to be of no value. Other differences were also

observed for two other criteria namely evolution and sensitivity of benefit-risk balance over time and calculation of benefit-risk balance for each major patient subpopulation, with more companies considering them important to be included.

Part III – Barriers and Solutions to Implementing Benefit-risk Assessment Frameworks

Agencies' and companies' satisfaction with existing benefit-risk assessment system

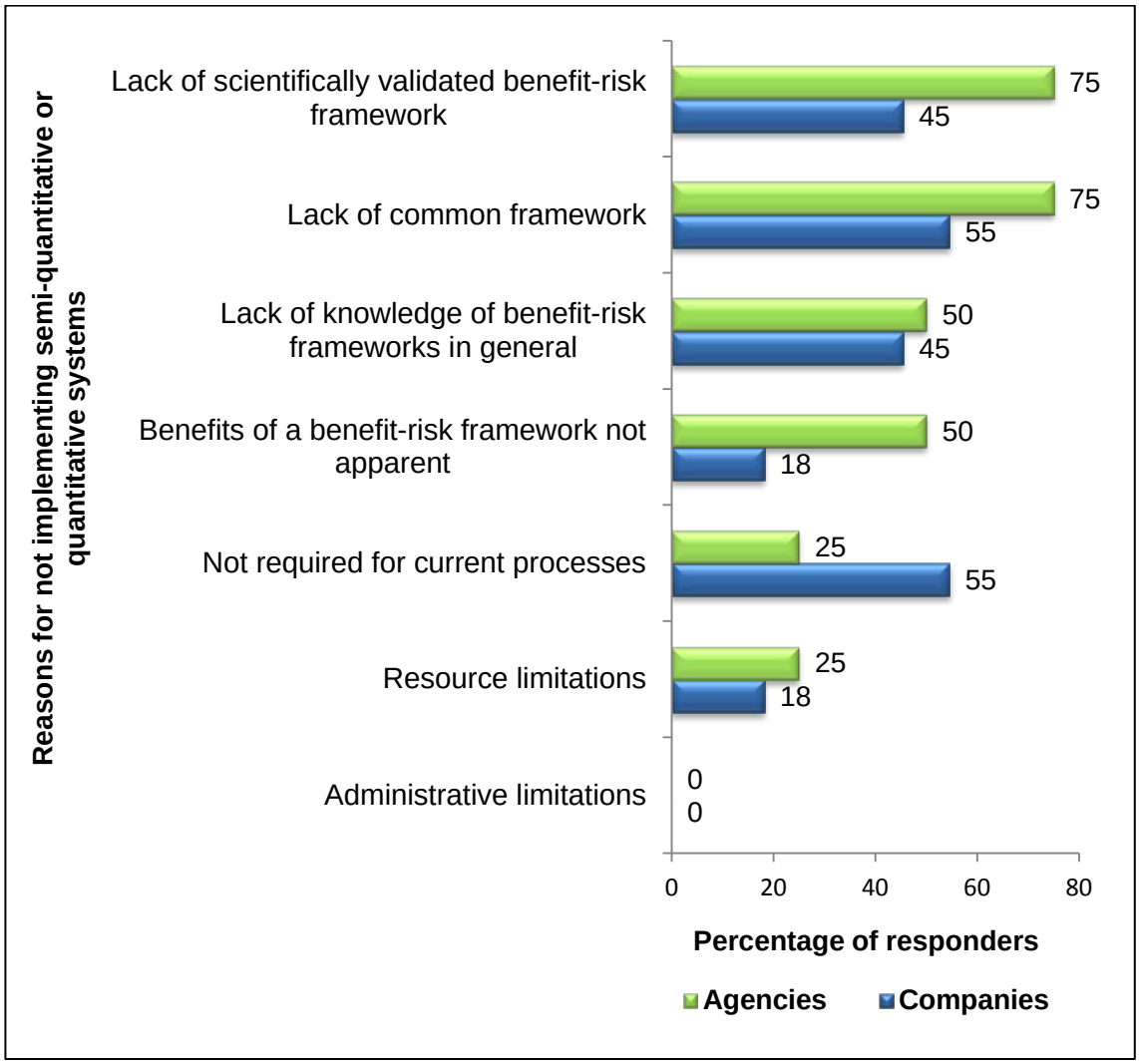
The majority of the agencies and companies (10 out of 15) who were currently using semi-quantitative systems were not satisfied. The reasons for this were that their current semi-quantitative systems required additional training, had poor acceptance by staff and were not validated. In addition, there were concerns about the uptake of certain methodologies by the stakeholders with some agencies preferring different models and some not requesting any formal approaches at all. The methodology should be structured and standardised and be applied through product development to submission for registration.

Reasons for not using semi-quantitative or quantitative systems

Four agencies and eleven companies who were currently using qualitative systems responded. The major reasons, among the agencies, were the lack of a scientifically validated framework and a universal framework (Figure 3.13). However, for the companies, the lack of a universal framework and the semi-quantitative or quantitative system not being required for current processes in the organizations, were the reasons given.

For six of the seven reasons for not implementing semi-quantitative or quantitative systems, there was a consistent trend by both agencies and companies with the agencies attaching more importance with the exception of one reason, namely "not being required for current processes" in the organizations (Figure 3.13). The most important reasons indicated by both agencies and companies were the lack of a common framework and a scientifically validated framework. Further, the area of closest agreement was in respect of the lack of knowledge of benefit-risk framework.

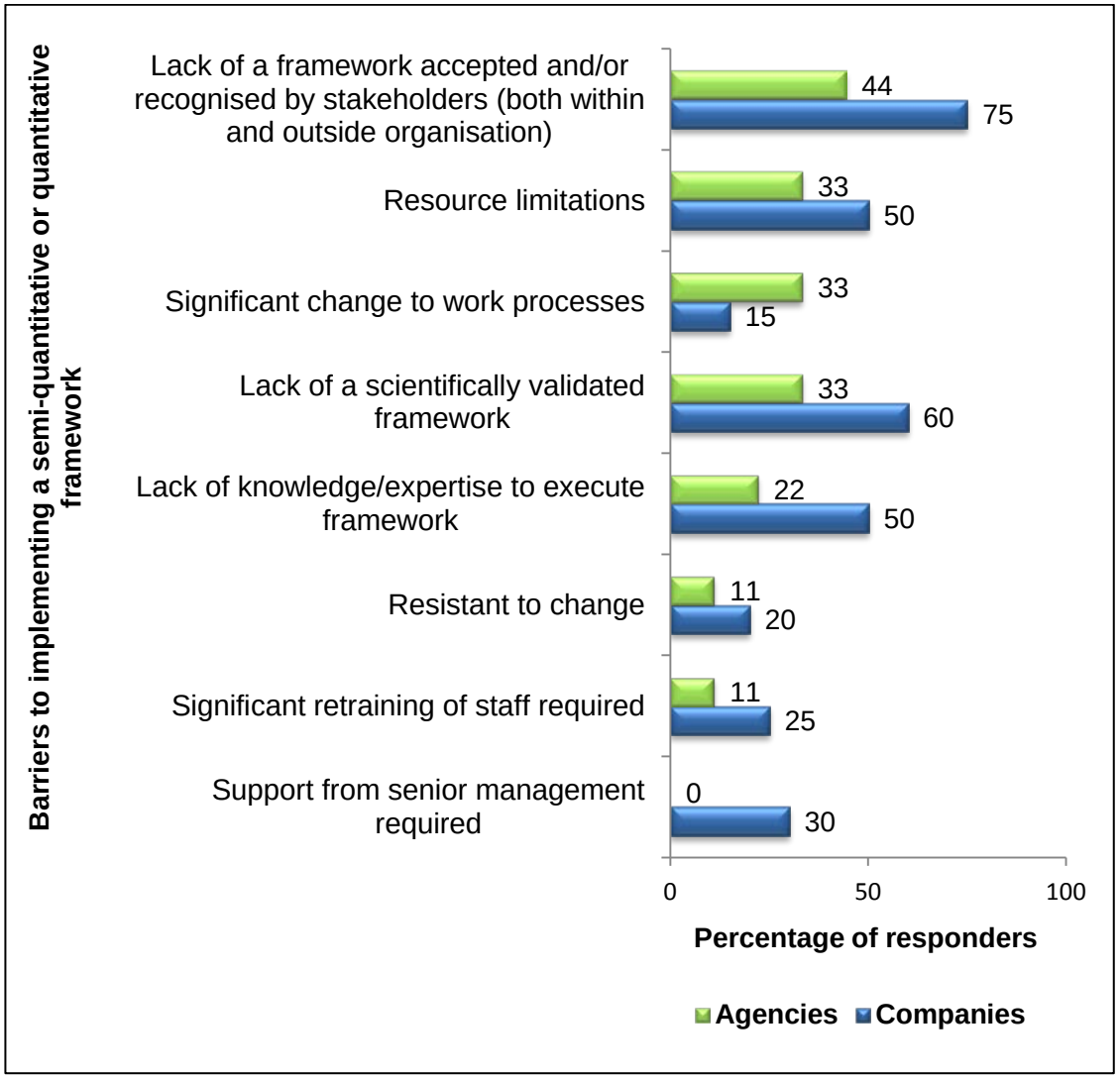
Figure 3.13 Comparison between agencies and companies for not implementing semi-quantitative and quantitative systems



Barriers to implementing a semi-quantitative or quantitative benefit-risk framework

The barriers that were most commonly observed among the agencies included the lack of an accepted framework, resource limitations, change in work processes and the lack of a scientifically validated framework (Figure 3.14). For the companies, the major barriers were the lack of an accepted and scientifically validated framework. The lack of an accepted and validated framework expressed by both agencies and companies as significant barriers to implementing a framework correlated with the findings for reasons for not using a semi-quantitative or quantitative framework. Close to half of the agencies and companies rated support from senior management as low in significance or not applicable.

Figure 3.14 Comparison between agencies and companies for barriers to implementing a semi-quantitative or quantitative benefit-risk framework



Hurdles and possible solutions to implementing a benefit-risk framework

Ten agencies and 20 companies provided free-text comments regarding potential hurdles to implementing a benefit-risk framework and the possible solutions. These comments were reviewed and categorised accordingly.

The major potential hurdles were the lack of consensus and various considerations for implementing and developing a common framework (Table 3.7). These results correlated with the reasons for not implementing a semi-quantitative and quantitative framework and barriers to implementation (Figure 3.13 and 3.14).

Table 3.7 Major hurdles to implementing a benefit-risk framework

1. Lack of consensus
• Absence of a global and common framework meeting the needs of both agencies and companies • Absence of clear directions on the purpose and utility of a common framework in assessing benefits and risks • Absence of buy-in from major regulatory agencies for a single common framework
2. Considerations before implementing a common framework
• Need to account for differences in legal, cultural and medical practices • Need to consider the requirements for manpower, skills, training and changes in work processes • Need to consider the communication of relevance and the need for a common framework, involving a change management within an organisation
3. Considerations in developing a common framework
• Need for validation using real-world examples, accounting for uncertainty, consistency and communication of decisions • Need for a flexible framework, incorporating various methods • Need for framework to be comprehensive, quickly usable and easily understood

The majority of the proposed solutions pertained to coordination of activities related to the development and implementation, as well as the communication of these activities (Table 3.8). The comments also reported on the need to provide a toolbox of methodologies for use under this framework. The proposed solutions aligned well with the main perceived directions in developing a framework (Figure 3.8).

The proposal to form a committee to oversee the progress of the development and implementation will help to obtain consensus across the stakeholders, communicate the purpose and utility of the common framework and initiate validation studies. The toolbox will provide flexibility to account for the differences in legal, cultural and medical practices, as well as preferences for selected methodologies. Guidance on the use of the common framework will alleviate the strain on training and changes in work processes. In general, the proposed solutions appeared effective in resolving the identified hurdles.

Table 3.8 Main proposed solutions to overcome hurdles

1. Coordination and communication
• Form a committee or working group comprising stakeholders to oversee the development and implementation of the framework • Put up a guidance at international level e.g. International Conference on Harmonisation (ICH) • Advise change management of organisations, ensure and promote the continued use of the framework • Initiate pilot studies for validation, setting of standards and lead scientific discussions
2. Toolbox of benefit-risk methodologies
• Obtain consensus for toolbox of methodologies for assessing benefits and risks, (including at least one for testing sensitivity), allowing flexible for different situations and with the option to add relevant methodologies along the way
3. Resources for implementing a common framework
• Provide training via workshops and simple protocol/guidance

DISCUSSION

Benefit-risk assessments and decisions for approving medicines rely on scientific capabilities and clinical judgment. These decisions should be monitored during the life cycle of a medicine from drug development to post-marketing. Many stakeholders are involved in the management of the life cycle of a medicine including pharmaceutical companies, regulatory agencies, health technology assessment agencies, physicians and patients. Information should be flowing effectively from one stakeholder to another and from one phase to another, emphasizing the importance of appropriate communication. Effective communication is facilitated by appropriate documentation and the information to be transferred in a manner that can be accurately understood by stakeholders (EMA, 2008).

The study showed that qualitative systems were employed by both agencies and companies, which may undermine communication as there is unlikely to be an appropriate structure for documentation and communication on the basis of the decisions. Among those using semi-quantitative systems, values and weightings

were generally not applied. Valuing the options can be used to highlight the relative differences between investigated product and comparator, and hence assist in deciding the clinical relevance of the medicine in managing the condition. Placing weights on the different benefits and risks to allow a clarification of relative importance of each parameter in the context of the decision to be made is critical. Without the use of values and weights it may be difficult to articulate the basis of the decision. A well-documented and logical flow of thought processes will form a platform for transparent discussion amongst stakeholders especially in situations of differing opinions.

Visualisation tools display the outcomes of benefits and risks in a clear and simple manner for ease of interpretation and understanding. This may be significant for physicians and patients who do not have access or the expertise to evaluate the vast amount of data in clinical study reports. However, this study revealed that only companies develop these tools and this was mainly for internal communication. It appears that more initiatives can be taken to enhance the appropriate flow of critical information at a level that can be easily interpreted by different stakeholders.

In the absence of fully quantitative systems, values, weights and visualisation tools, it remains a significant challenge to optimise the communication of benefit-risk decisions to all stakeholders. This current situation places a burden on regulatory authorities to provide transparent and consistent decisions that other stakeholders are seeking to determine their accountability. The proposed framework should provide a formal structure for documenting logical thought processes leading to the final decision and thereby fulfilling the need for transparency. Thus, communication will be clear and effective. This is important in the healthcare context whereby appropriate communication across stakeholders is pivotal to making informed decisions.

The robustness of benefit-risk assessment lies in the scientific capabilities and clinical judgment and it is fundamental that the science used to back the decisions should be optimised. It is apparent that both agencies and companies are aware of better scientific methodologies that may improve the quality of their assessment of benefits and risks, as revealed by the disparity between those methodologies

currently used and those considered relevant. Therefore, current methodologies employed by agencies and companies may not be able to provide the best assessment of benefits and risks of medicines. This may have led to inconsistent assessments for the same medicine. Consequently, the intention to be transparent about the processes of decision-making may be hampered by this deficiency not being rectified. As healthcare sciences advance rapidly, there must be an alignment to develop tools that are capable of assessing the benefits and risks correctly. Further studies should be conducted in this area to identify the required methodologies for inclusion into the proposed overarching framework.

The outcome of benefit-risk assessment should contribute to the availability and utility of a medicine. Patients are the eventual recipients of this decision on benefits and risks, but their views are often not incorporated in the development (Hareendran et al, 2012) and review of the medicine. Though there are current tools like patient reported outcomes, there is currently no recommended approach to this. In the absence of patients' perspectives, a medicine may be approved but poorly utilised or is not made available in ignorance of what ultimately matters most to the patients.

Health technology assessment agencies (HTA) play a key role in deciding the availability of the medicine. They may consider other factors like cost effectiveness, value and the availability of other therapeutic options in making their decisions. However, there is little information on their requirements and methods of assessment. In view of these potential differences (Eichler, 2012a), regulatory agencies, pharmaceutical companies and HTAs should focus on communication, which enables them to emphasize contentious issues. In this way, the potential differences in expectations can be better managed and a consistent message can be available to the patients. A universal framework will help to achieve this. The lack of communication may result in the delay of a medicine being made available or the lack of payor coverage leading to fewer therapeutic options for patients. Future studies should consider collecting information on the current status of how assessments are carried out by the HTAs, and how these differences can be resolved across the various stakeholders.

Regulatory agencies are charged with approving medicines that are shown to be safe, efficacious and meeting the medical needs of the intended population. They are accountable for their decisions backed by the assessment of scientific evidence. The agencies have a tendency to focus on scientific aspects, as evidenced in their preference to adopt semi-quantitative systems. It is also justified that each agency makes decisions suitable for their own jurisdiction, as determined by individual legislation, disease demographics, medical practices and culture. The agencies are expected to then account to the public for their decisions through appropriate communication, while taking caution not to impose additional liabilities on themselves. Therefore, the main concerns for agencies appear to be enhancing scientific capabilities. It is observed that agencies have little experience with the various tools currently available in assessing benefits and risks and effectively communicating these decisions to their local population. It is thus observed that fewer agencies felt the need to have a framework to be used internationally.

Pharmaceutical companies are driven by the objective to market a medicine by demonstrating to the agencies and HTAs that the medicine is proven to be safe and effective. Their challenge is to provide a similar set of clinical data to meet the varying regulatory requirements of different countries. Despite similar clinical data, companies could receive diverse opinions and regulatory decisions from the different countries resulting in a lack of predictability for the companies. To address this need, the companies would be seeking a universal framework for transparent communication between the agency and the company which would ease the sharing of information across agencies and reduce the resources required to meet varying regulatory requirements.

Patients' perspectives have already been identified as a fundamental consideration in assessing the benefits and risks of medicines (EMA, 2008). However, approaches to represent and collect objective information are still being explored. The US FDA is embarking on PDUFA V (FDA, 2012a) and identifying diseases whereby patients' perspectives would have a significant impact on regulatory decision-making.

There are currently many available methodologies to assess medicines though none have been established as a standard as there are varying perspectives in assessing

the benefits and risks. To reach a consensus for standard tools, it requires them to be validated across different users and situations. This can take a considerable time and is unlikely to be fruitful, given that the science behind the tools continues to advance as we validate their use. Hence, to facilitate identifying the methodologies for use under the proposed framework, it would be prudent to understand the characteristics of an acceptable universal framework. These can be found from the factors for reviewing a framework namely logical soundness, acceptability of results, practicality, presentation/visualisation, scope, comprehensiveness, sensitivity and specificity. Any methodologies for inclusion into a framework should enhance the quality of the above factors which have been agreed by both agencies and companies.

There seems to be conflicting approaches regarding the speed with which to bring about changes to the current benefit-risk assessment systems within the agencies and the companies. Therefore there is an urgent need for the stakeholders concerned to come together to agree on the way forward for a universal benefit-risk framework and the timetable for its implementation.

SUMMARY

- Evidence to date showed that there is no consensus for a universal benefit-risk assessment framework.
- This study aimed to explore the current views, potential differences and future directions in benefit-risk assessment between agencies and companies.
- Eleven agencies (79% response rate) and 20 companies (83% response rate) responded and was found that none uses a full quantitative system while among the companies, more were using a qualitative system.
- There were discrepancies between the methodologies currently in use by the responders and those that were deemed useful and relevant.
- From the results, it appears that a benefit-risk framework, if implemented, should be able to be utilised by both agencies and companies, through relevant divisions of a regulatory agency, and its scope to include the entire life cycle of a product.
- It was reported by both agencies and companies that there is a common need for the provision of a framework that can be used for benefit-risk management plans throughout the life cycle of a product.
- There is a need to involve relevant stakeholders in the development, validation and application of an appropriate benefit-risk framework.
- Major barriers, as expressed by both stakeholders, are resource limitations, the lack of knowledge/expertise, a scientifically validated and accepted/recognised framework.
- It is reported that while the stakeholders are looking forward to a change, the system is likely to be an overarching, semi-quantitative framework that incorporates a toolbox of various assessment methodologies.

CHAPTER 4

Development of benefit-risk assessment support system (BRASS) - a framework, template and user manual for the benefit-risk assessment of medicines

INTRODUCTION

Currently there is a need to understand why different regulatory agencies come to different outcomes despite having the same data submitted for their assessment. This has led to an increasing pressure on agencies to improve transparency and accountability and establish appropriate document governance for their decision-making processes. A universal framework (CMR, 2008) would be of value and should be applicable to both pharmaceutical companies and regulatory agencies resulting in a standardised framework for benefit-risk assessment to support transparency in decision-making.

A survey conducted within pharmaceutical companies and regulatory agencies showed that the main hurdle to establishing a universal framework was the lack of an accepted, validated and international model. It is therefore vital to establish a universal framework with the participation of major regulatory agencies to ensure the possible uptake of the same framework by other regulators across the world. One of the challenges is to harmonize the different requirements of such a framework for the assessment of benefits and risks of medicines which could be applied across different jurisdictions and scenarios.

At a time of constrained resources, shared and joint reviews are a possible way forward and this led to the formation of the Consortium, consisting of four similar-sized agencies (SwissMedic, Therapeutic Goods Administration (TGA), Singapore's Health Sciences Authority (HSA) and Health Canada). The four agencies had a plan to initiate work sharing whereby a harmonised benefit-risk assessment template would be required. In order to achieve this, it was important to review the existing frameworks and select one for further development.

OBJECTIVES

This study had the following objectives, namely to develop:

1. A universal framework for benefit-risk assessment of medicines to achieve a systematic approach to benefit-risk decision-making
2. A benefit-risk template to document benefit-risk decision-making using the benefit-risk framework principles

3. A user manual for regulatory assessors to guide the use of the benefit-risk template

METHODS

In order to develop and propose a universal framework that facilitated decision-making, the expectations and requirements of such a framework were obtained through a review of published literature and reports from relevant workshops. Opinions were then collated and organised to provide a list of requirements for a universal framework for the benefit-risk assessment of medicines.

Existing frameworks for the assessment of benefits and risks of medicines were reviewed. The selected frameworks were assessed against the list of criteria which included logical soundness, comprehensiveness, acceptability of results, practicality, specificity and sensitivity, presentation (visualisation) and scope. Finally, the selected framework was evaluated by comparing the components with those of existing frameworks to determine if it included the essential elements for a universal framework.

Benefit-risk decisions need to be communicated in an effective and systematic manner, allowing appropriate understanding of the information by the stakeholders. A template should be an aid for documenting the processes leading to the construction of a benefit-risk balance and the eventual basis that would support the decision. A search was conducted for guidances used by regulatory agencies in order to identify those elements considered essential to the assessment of benefits and risks of a medicine. The EMA guidance document of 2008 was utilised in developing an appropriate BR template. These elements were then transformed into a template that allowed documentation and editing. This initial developmental template was then reviewed against the universal framework so that it could support the principles outlined in the overarching universal framework.

The initial template was assessed by the Consortium who evaluated its use in a feasibility study and the template was amended and finalised based on the feedback from the Consortium. Comments from the reviewers of the template highlighted the need for a user manual. It was found that the usefulness of the template would be

dependent on an understanding of the terms and requirements of the input fields and compliance in completing the template. The Consortium identified areas in the template that would require clarification or additional explanation. These provided the critical elements in producing the user manual to guide users in completing the template. The initial user manual was further revised by the Consortium resulting in the final version.

RESULTS

The results are presented in three parts, namely:

- Part I – Development of the universal framework
- Part II – Development of the benefit-risk template
- Part III – Development of the user manual

Part I – Development of the universal framework

Requirements of a universal framework

The EMA Benefit-Risk Methodology Project (EMA, 2009) was aimed at the development and testing of tools and processes for balancing multiple benefits and risks, which could be used as an aid to informed, science-based regulatory decisions about medicinal products. This project consisted of five consecutive work packages. The second work package (EMA, 2010) examined the applicability of three qualitative frameworks, namely the Pharmaceutical Research and Manufacturers of America (PhRMA) benefit-risk assessment team framework (BRAT framework), the seven-step framework developed by the Centre for Innovation in Regulatory Science (CIRS), and the benefit-risk framework developed by the US FDA, and the 18 quantitative approaches for assessing the benefit-risk balance.

It was found that clinical judgment remained a critical role in regulatory decision-making and models could assist but not replace the complex process of constructing a benefit-risk balance and incorporating uncertainties into the final decision. In the EMA's evaluation of quantitative approaches, it was concluded that any quantitative method or approach would require a qualitative framework within which the model could be effectively developed. Combinations of approaches could prove useful in situations that required a review of the contributions by the magnitude of favourable effects, seriousness of unfavourable effects, uncertainties, transitions in health states

and the time spent in each state and trade-offs between effects. Therefore, an overarching benefit-risk assessment framework with the capacity to incorporate various quantitative methods would be ideal.

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Risk-benefit Management Working Group conducted a study (Guo et al., 2010) to review and compare published quantitative benefit-risk assessment methodologies employed by regulatory agencies and/or the pharmaceutical industry in the hope that comparisons may help disclose unique characteristics of the techniques that may be more applicable to a specific drug evaluation scenario or a specific therapeutic indication. It was found that each quantitative method had its unique advantages and disadvantages based on data requirements and statistical properties. Numerous methodologies have been proposed, but there were a limited number of empirical applications of these techniques and there was no consensus among regulators for defining a clear gold standard. When evaluating any new health-care technology, Guo et al (2010) recommended the use of multiple benefit-risk assessment approaches across different therapeutic indications and treatment populations to construct the risk–benefit profile. This was similar to the EMA opinion regarding the need to vary the tools available for effective benefit-risk assessment, which should be governed under an overarching framework.

In the report of methods for benefit and harm assessment in systematic reviews by the Agency for Healthcare Research and Quality (Boyd et al, 2012), some principles for a review protocol development were highlighted. Firstly, the key potential benefits and harms should be identified. Then the approaches used in the reporting of the benefit and harm outcomes should be indicated, including the assumptions undertaken for the approaches described e.g. number needed to treat (NNT) and number needed to harm (NNH). This would help to understand the appropriateness and rationale for the approaches selected. Preferences (including patients' preferences) should also be considered in the assessment and sensitivity analyses conducted to determine the impact of varying preferences. In delivering the overall benefit harm assessment, a qualitative or quantitative approach should be clearly stated.

Mussen et al (2009) conducted a literature review of tools for the assessment of medicines and argued that the development of a new model ought to achieve the following objectives:

1. Framework should match current practices of regulatory agencies for benefit-risk assessment, in order that the framework can be used in the scope of those practices
2. Framework should be able to take into account the data in a marketing authorisation application and the scientific data otherwise available to regulatory agencies
3. Framework should not require additional analyses or re-analyses of source clinical data, or additional clinical meta-analyses
4. Use of framework for initial registration and post-approval re-assessment of existing medicines
5. Framework should be applicable to all kinds of medicines, including vaccines and non-prescription medicines
6. Framework should be considered a tool for regulatory agencies and pharmaceutical companies for assessing benefit-risk balance of medicines, but not substitute decision-making
7. Framework should be validated

A study was conducted to explore the current status and the need for a universal benefit-risk framework for medicines in regulatory agencies and pharmaceutical companies (Chapter 3). It was found that for the utility and scope of a universal benefit-risk assessment framework, most agencies and companies believed that a benefit-risk framework should be applied throughout the life cycle of the medicine with the emphasis on applicability to product registration, health technology assessment agencies and across the life cycle of a product (Table 4.1). The general consensus was that a benefit-risk framework should be utilised by both agencies and companies. Both agencies and companies also believed that a universal framework would enhance the quality of communication and enable the assessment of benefit-risk management plans. The advantages of a universal framework were that it would provide documentation for a structured discussion, act as a tool for communication among peers within the organization and enable communication between the organization and stakeholders. There was a general agreement that these

advantages would include appropriate documentation and enhancement of communication together with transparency and accountabililty of decisions.

Table 4.1 Requirements of a universal benefit-risk framework

Utility and Scope of a universal framework
• Need for a universal benefit-risk assessment framework • Importance of a universal benefit-risk framework developed for registration purposes • Importance of a universal benefit-risk framework applied throughout life cycle of a medicine • Applicability of a universal benefit-risk framework to health technology assessment agencies • Utility of a universal benefit-risk assessment framework
Purposes of a universal framework
• Application of a universal benefit-risk framework to benefit-risk management plans • Transparency and consistency of decision-making • Communication of decision

Chapter 3 also identified the criteria from both agencies and companies for reviewing a benefit-risk framework (Table 4.2). These would be used to assess the suitability of frameworks in consideration for further development into a universal framework. The findings from EMA and Guo et al (2010) for an overarching framework allowing various assessment tools can be subsumed under the criterion "Comprehensiveness".

Identification of a suitable framework

There were five frameworks identified that are currently used for the assessment of the benefits and risks of medicines (Table 4.3). Of these, two were used by regulatory agencies and another two by pharmaceutical companies. The 7-step framework by CIRS had been reviewed by both the major stakeholders, namely regulatory agencies and pharmaceutical companies. None were currently used as a universal framework.

Table 4.2 Criteria influencing the quality of a universal benefit-risk framework

1. Logical soundness	Provides an approach that is sound and allows decisions that are coherent and aids rational thinking
2. Comprehensiveness	Provides an approach that handles all forms of data (including qualitative and quantitative, subjective and objective information) and allows for multiple criteria
3. Acceptability of results	Provides an approach that checks for inconsistencies in data and judgment and a realistic approach to the evaluation of benefits and risks
4. Practicality	Provides an approach with minimum burden on resources and ease of use
5. Specificity and sensitivity	Provides a statistical perspective underpinning the reliability of the decision
6. Presentation (visualisation)	Provides outcomes in an easily understandable format such as charts and plots
7. Scope	Provides a consistent approach throughout drug development and post-approval monitoring

Table 4.3 Frameworks currently used for the assessment of benefits and risks of medicines

Source	CIRS	EMA	US FDA	PhRMA	Novo Nordisk
Name of framework	7-step framework	8-step PrOACT-URL	5-step Benefit-risk Framework	6-step BRAT framework	8-step BRAIN framework
Basis of framework	MCDA	MCDA		MCDA	MCDA
Reviewed by	Regulatory agencies and pharmaceutical companies	EU regulatory agencies	US regulatory agency	Pharmaceutical companies	Pharmaceutical companies

Multi-criteria decision analysis (MCDA) was the platform on which other frameworks were based and it was also confirmed as a useful relevant methodology (Chapter 3). MCDA is a process described in the Multi-Criteria Analysis (MCA) manual (Dodgson et al, 2009) which aims to explore the individual contributing aspects of the decision-making process before collating the outcomes to form the basis of the decision. There are three key phases of the MCDA process. The problem is first identified and structured and secondly the decision-maker's preferences are taken into account. Lastly, action plans are developed. The steps in executing these three key phases can be found in Table 4.4.

An important feature of the MCDA model is the ability to carry out sensitivity analyses on the results by varying any of the weights and scores to assess the impact on the overall benefit-risk balance. The MCDA model generates two assessments of the data, with the first being the overall value (cumulative outcomes after scoring and weighting) and the second a sensitivity analysis (through adjusting the scores and weights). The criteria to be taken into account in determining the outcome for the assessment were grouped as 'benefits' and 'risks'. The criteria for risks included not only the incidence of adverse events and drug-related reactions, but also unobserved and potential risks based on knowledge of factors including related products and the mechanism of action.

Each criterion would then be assigned a score and given a weight according to its relative importance to the benefit-risk decision. Weighted scores were then calculated at each level in the hierarchy which enabled an overall weighted score to be calculated for each of the options. The process of 'scoring' would be based predominantly on measurable data such as the clinical trial endpoints and incidence of adverse events, measured as percentages. The process of 'weighting' the criteria was where experience and judgement were built into the methodology. The assignment of weight to a criterion was normally based on a combination of factors on which a value judgement would be made.

Table 4.4 Steps in Multi-criteria Decision Analysis (MCDA)

	Steps	Actions
1	**Establish the decision context**	• Establish aims of the MCDA; identify decision makers and other key players • Design the socio-technical system for conducting the MCDA • Consider the context of the appraisal
2	**Identify the options to be appraised**	
3	**Identify objectives and criteria**	• Identify criteria for assessing the consequences of each option • Organise the criteria by clustering them under high-level and lower-level objectives in a hierarchy
4	**Scoring – Assess the expected performance of each option against the criteria, then assess the value associated with the consequences of each option for each criterion**	• Describe the consequences of the options • Score the options on the criteria • Check the consistency of the scores on each criterion
5	**Weighting – Assign weights for each of the criteria to reflect their relative importance to the decision**	
6	**Combine the weights and scores for each option to derive an overall value**	• Calculate the overall weighted scores at each level in the hierarchy • Calculate the overall weighted scores
7	**Examine the results**	
8	**Sensitivity analysis**	• Conduct a sensitivity analysis: do other preferences or weights affect the overall ordering of the options? • Look at the advantage and disadvantage of the selected options, and compare pairs of options • Create possible new options that might be better than those originally considered • Repeat the above steps until a “requisite” model is obtained

MCDA is believed to have the following advantages as it:

- Takes explicit account of multiple and conflicting criteria
- Helps to structure the problem
- Helps decision-makers learn about the problem, their own and others' values and judgment and through structuring and presenting the information, identifies a preferred course of action
- Serves to complement and challenge intuition, but does not seek to replace intuitive judgment or experience
- Leads to better considered, justified and explainable decisions and provides an audit trail
- Demonstrates that decisions are conceptually simple and transparent

In addition in support of a universal benefit-risk framework, the MCDA model is not limited by type of data and is used for approval or post-marketing and with all types of medicines. It makes use of available data without the need to conduct further analyses and does not aim to replace decision-making, but provides clarity with respect to the basis of the decision made. Scoring, weighting and sensitivity analyses fulfil the requirements for a universal framework that could check for inconsistencies in the data (acceptability of results) as well as specificity and sensitivity.

MCDA, in providing a structured flow of information leading to a decision, is a tool for communicating a transparent and consistent decision. It also appears not be limited in its scope and can be applied to benefit-risk management plans and be used by health technology assessment agencies.

The factors influencing the quality of a universal benefit-risk framework were reviewed against the MCDA approach and the steps in executing this model. The structure of MCDA, in presenting and organising information, provides logical soundness and since it uses available data, it would be a comprehensive and practical framework not limited by the scope of application in approval and post-marketing scenarios. However MCDA does not provide any form of visualisation that could enhance the ease of understanding the outcomes. It could help enhance the consistency, objectivity and transparency of the decision-making process for benefit-

risk assessments by providing a structured and systematic approach and appropriate documentation for tracking the process and providing greater accountability. It also facilitates the reviewing of past decisions and experiences to ensure the consistency of regulatory decisions on marketing authorisation applications. Through this, a better understanding could be achieved of the contexts as to why different agencies could reach different conclusions on the basis of the same data as well as imparting objectivity to the regulatory process.

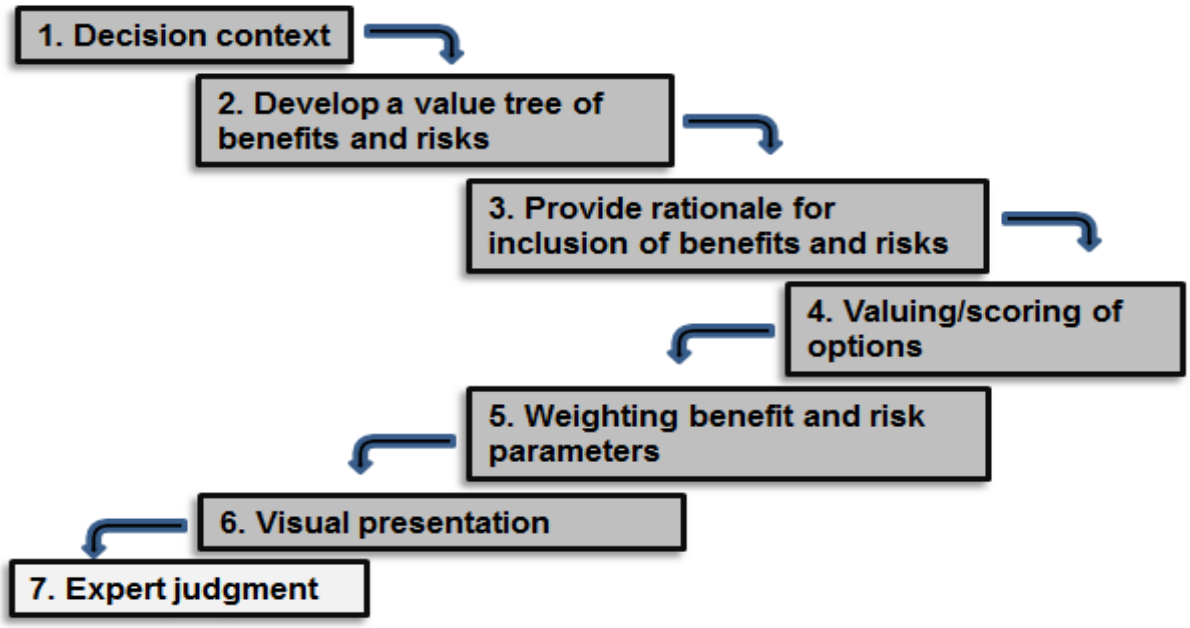
It thus appeared that frameworks using the MCDA approach could be considered appropriate for further development into a universal framework. The CIRS 7-step framework was chosen as the model for further development into a universal framework due to its independent development and its exposure to both regulatory agencies and pharmaceutical companies.

Development of the Framework

The CIRS 7-step framework, based on the 3 key phases of MCDA, was reviewed to identify areas of improvement. The processes of this 7-step framework are described in Figure 4.1. Step 1, namely “decision context”, is the identification and structuring of the problem, while steps 2 to 5 are the development of decision-maker preferences i.e. criteria for benefits and risks. Step 7 is “Expert judgment” and correlated to the final key phase of MCDA, in providing an action plan leading to a decision. It should be noted that Step 6 “Visual presentation” was added to fulfil the requirements as identified earlier for a universal framework.

Although the CIRS 7-step framework had been reviewed by both major stakeholders, it had not been applied in the real world situation. Noting that groups of the four other frameworks were currently used individually by the respective developers harmonisation of the essential elements was conducted to impart a character of universal utility to the CIRS framework. This would help incorporate the existing work processes of the various stakeholders around the world and make the potential uptake of the universal framework more appropriate.

Figure 4.1 The initial 7-step Framework for the assessment of benefits and risks of medicines



The US FDA used a framework (Table 4.5) that would accurately and concisely describe benefit and risk considerations to help assessors apply a structured approach in regulatory decision-making (CIRS, 2011). An important consideration is the context of the decision, an understanding of the condition treated and the unmet medical need. A more systematic and open discussion with informed patients could provide valuable insights in a given disease and the potential gaps or limitations in available therapies. There are now ongoing projects to develop and implement a plan to integrate a benefit-risk framework in the drug review process during PDUFA V (FDA, 2012a).

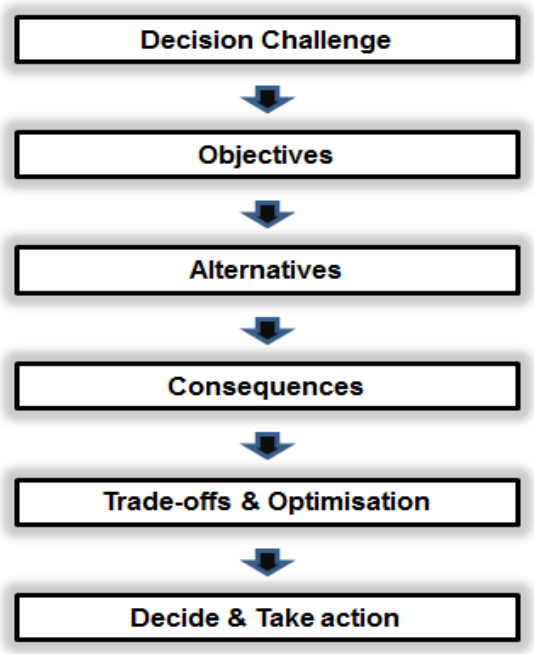
The European Medicines Agency (EMA) used a set of guiding principles (Figure 4.2) in decision-making for medicines (EMA, 2011d, 2012). It commenced by examining the challenge or decision to be made and the objectives, considering the options, alternatives and trade-offs before a decision or action would be decided.

Table 4.5 US FDA's 5-step approach to assessment of benefits and risks

Consideration	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Summary of evidence:	Conclusions (implications for decision):
Unmet Medical Need	Summary of evidence:	Conclusions (implications for decision):
Clinical 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):

Mullin T (CDER): 16-7June2011 CIRS Workshop, Visualising benefit-risk: The key to developing a framework that informs stakeholder perspective and clarity of decision-making Washington DC.

Figure 4.2 The guiding principles used by EMA in assessment of benefits and risks of medicines



The PrOACT-URL (Table 4.6) was developed on the basis of the above guiding principles to further illustrate the considerations undertaken in making the decision on the benefits and risks of the medicines. This 8-step framework shown was based on a generic framework for decision-making (Hammond et al, 1999).

Table 4.6 EMA's Approach: 8-step PrOACT-URL

	Steps	Actions	
1	**Problem**	• Determine the nature of the problem and its context • Frame the problem	At this point, only issues concerning the favourable and unfavourable effects, and their balance, have been considered
2	**Objectives**	• Establish objectives that indicate the overall purposes to be achieved • Identify criteria of favourable and unfavourable effects	
3	**Alternatives**	• Identify the options to be evaluated against the criteria	
4	**Consequences**	• Describe how the alternative perform for each of the criteria, that is, the magnitudes of all effects and their desirability or severity and the incidence of all effects	
5	**Trade-offs**	• Assess the balance between favourable and unfavourable effects	
6	**Uncertainty**	• Assess the uncertainty associated with the favourable and unfavourable effects • Consider how the balance between favourable and unfavourable effects is affected by uncertainty	These three steps are relevant in considering how the benefit-risk balance is affected by taking account of uncertainties
7	**Risk tolerance**	• Judge the relative importance of the decision makers' risk attitude for this product and indicate how this affected the balance reported in step 5	
8	**Linked decisions**	• Consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions	

The Benefit Risk Action Team (BRAT) under the auspices of the Pharmaceutical Research and Manufacturers of America (PhRMA) developed a 6-step framework (Noel et al, 2012; Coplan et al, 2011). The BRAT Framework (Table 4.7) is a set of flexible processes and tools that provides a structured approach to pharmaceutical benefit–risk decision-making in drug development and in the post-approval setting. It consists of six steps that produce representations of key trade-offs, with appropriate

documentation of the rationale for decisions and the assumptions made in their development.

Table 4.7 PhRMA's Benefit-risk Action Team (BRAT) Framework

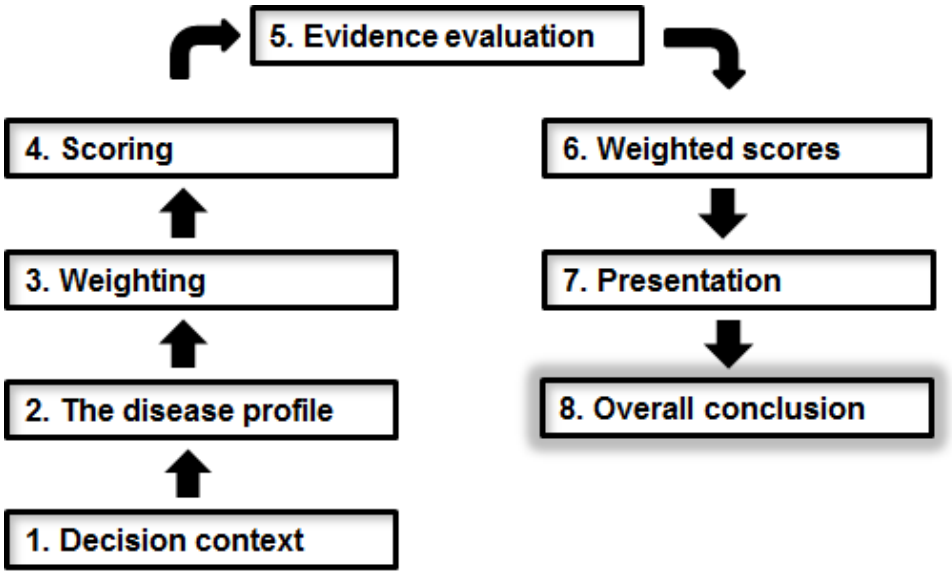
	Steps	Actions
1	**Define the decision context**	• Define drug, dose, formulation, indication, patient population, comparator(s), time horizon for outcomes, perspective of the decision makers (regulator, sponsor, patient, or physician)
2	**Identify outcomes**	• Select all important outcomes and create the initial value tree • Define a preliminary set of outcomes measures/endpoints for each outcome • Document rationale for outcomes included/excluded
3	**Identify and extract source data**	• Determine and document all data sources (e.g. clinical trials, observational studies) • Extract all relevant data for the data source table, including detailed references and any annotations, to help the subsequent interpretations create summary measures
4	**Customise the framework**	• Modify the value tree on the basis of further review of the data and clinical expertise • Refine the outcomes measures/endpoints • May include tuning of outcomes not considered relevant to a particular benefit-risk assessment or that vary in relevance by stakeholder
5	**Assess outcome importance**	• Apply or assess any ranking or weighting of outcome importance to decision makers or other stakeholders
6	**Display and interpret key benefit-risk metrics**	• Summarise source data in tabular and graphical displays to aid review and interpretation • Challenge summary metrics, review source data and identify and fill any information gaps • Interpret summary information

This framework was developed to address the differences in information on benefits and risks between regulatory agencies and companies to communicate these views to patients and healthcare professionals and results in the transparency of the decision-making process. The BRAT Framework is guided by a number of principles: a systematic approach to defining the decision context and outcomes needed, the

documentation of all key underlying assumptions, including the rationale for the exclusion of particular outcomes or data sources from the assessment, the transparency of the sources/information underlying all the measures appearing in the summary, the flexibility to accommodate differing technical benefit–risk methodologies and perspectives and the use of clear and flexible visual displays to simplify understanding and communicate complex trade-offs.

The last framework reviewed was developed by Novo Nordisk and is an interactive process based on the experience gained from working with several different medicines. This process can extract information from clinical trials, which are otherwise not captured by statistics. The method, called the Benefit Risk Assessment in New and old drugs (BRAIN, Figure 4.3), consists of eight steps (CMR, 2010).

Figure 4.3 The BRAIN framework by Novo Nordisk



In profiling the decision context, the aims, goals, expectations and relevant information to support the benefit-risk assessment are identified. For defining the disease profile, this includes the identification of benefit and risk criteria that characterise the disease. For the most important criteria selected within the given decision context, justifications are provided and the decisions can be tracked. Weighting and scoring are then applied to these criteria and an evaluation of the

evidence is conducted by assessing the strength of the evidence. Weighted scores are computed by multiplying the weights and scores and these are visualised through a Tornado-like diagram. An overall conclusion and recommendation is then provided with any uncertainties and its impact described. Unexpected issues are included and strategies for further studies are also presented.

The steps of the various frameworks are tabulated and common process elements identified. It was found that at a higher level of categorisation of the tasks involved, four common core elements (Table 4.8) were identified:

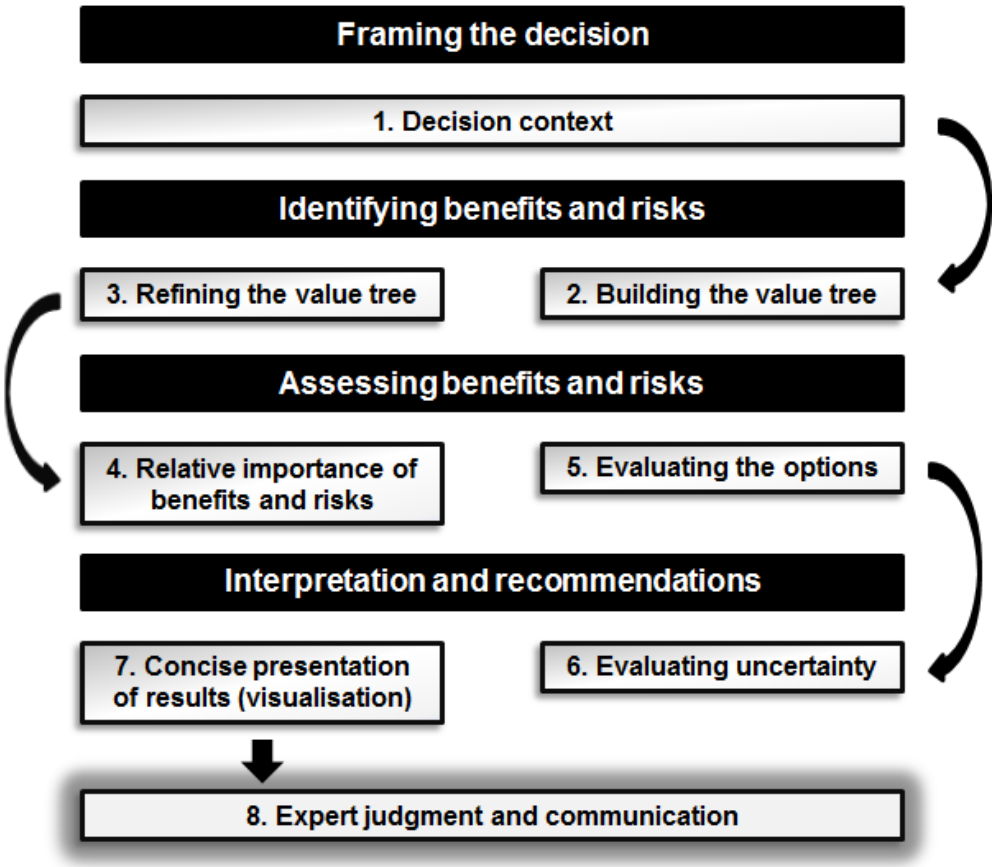
a. Framing the decision
b. Identifying benefits and risks
c. Assessing the benefits and risks
d. Interpretation and recommendation

As there were no observed differences among the frameworks, a harmonised framework could possibly be constructed to incorporate all the elements included in the other frameworks. It appeared that the CIRS 7-step framework closely represented the common essential activities and this was selected for revision. It was thus amended to reflect the core elements above and provide a unified standardised framework that would meet the requirements of the US FDA, EMA, the two frameworks developed by the industry (BRAT and BRAIN). The final universal benefit-risk framework (Figure 4.4) consisted of eight steps and the processes were essentially unchanged, with the addition of “Evaluating uncertainty” now as a specific step in the process.

Table 4.8 Comparisons of existing benefit-risk assessment frameworks

Frameworks reviewed	Core elements							
	Framing the decision	**Identifying benefits and risks**		**Assessing benefits and risks**		**Interpretation and outcome**		
US FDA	Analysis of conditions and unmet medical needs	Clinical benefits, risks		Evidence and uncertainties				Conclusions and reasons, risk management plans
EMA PrOACT-URL	Nature and framing of the problem	Objectives, favourable and unfavourable effects		Alternatives regarding options to be evaluated and the consequences	Trade-offs and benefit-risk balance	Evaluating uncertainty	Effects table and risk tolerance	Consistency of decisions (linked decisions)
The BRAT framework	Define decision context	Identify outcomes, extract source data: build value tree	Customise framework: refine value tree	Assess relative importance of different outcomes: weighting or ranking, other stakeholders		Evaluating uncertainty	Display and interpret key benefit-risk metrics and validate results	Decision and communication of benefit-risk assessment
Novo Nordisk BRAIN	Decision context	Disease profile	Weighting	Scoring	Evidence evaluation	Weighted scores	Presentation	Overall conclusion
CIRS 7-step framework	Decision context	Building the value tree for all benefits and risks	Rational for which benefits and risks to be included for benefit-risk assessment	Weighting of benefits and risks	Valuing or scoring of options		Visualisation	Expert judgment and risk management
Universal benefit-risk framework	**Step 1**	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**	**Step 7**	**Step 8**
	Decision context	Building the value tree	Customising the value tree	Weighting of benefits and risks	Scoring the options	Evaluating uncertainties	Concise presentation of results (visualisation)	Expert judgment

Figure 4.4 The final 8-step universal benefit-risk framework for the assessment of benefits and risks of medicines



This final universal benefit-risk assessment framework was developed with elements common to other existing frameworks and used by the two major regulatory agencies and the pharmaceutical companies. It is an overarching, internationally acceptable and standardised benefit-risk framework that will serve as the on-going platform for discussions around the development of novel, dynamic methodological tools to address the diverse needs of benefit-risk assessment throughout a product's lifecycle by diverse stakeholders.

The development of this version of the universal benefit-risk framework enhances the objectivity and transparency of the decision-making process by providing a structured and systematic approach that could be adopted by both regulatory agencies and

pharmaceutical companies. The process of decision-making would also now be both auditable and provide greater accountability.

Part II - Development of the Benefit-Risk Template

The importance of communication between companies and agencies is frequently highlighted. There is also a need for a better understanding of why different agencies come to different conclusions when faced with essentially the same application data. Improved transparency is required as both companies and agencies hold different skillsets and interpret efficacy and safety information differently. There is further pressure on agencies to increase transparency and accountability and to establish an appropriate documentation system for the basis of their decisions. It was therefore important to have a document that enables the effective communication of benefit-risk information amongst stakeholders in addition to having a universal framework for the assessment of benefits and risks. The communication of risks without the communication of benefits may serve to undermine public discourse and for this purpose, a template was proposed to be used in accordance with the principles outlined in the universal framework.

The Centre for Innovation in Regulatory Science had identified the need for a template to be used in conjunction with their 7-step framework for the assessment of benefits and risks. They searched for a guidance document for the assessment of benefits and risks of medicines, which led to the identification of the published reflection paper by EMA (EMA, 2008). In the absence of the principles and methodologies for benefit-risk assessment from other major regulatory authorities, there would be issues of consistency, transparency and communication of the outcomes of assessment and the basis of decisions. Hence EMA undertook the task of revising the CHMP assessment report templates and incorporating a structured list of benefit and risk criteria.

In order to recognise demonstrated benefits, important results should be critically assessed and the unresolved issues or uncertainties be identified (Table 4.9). For the assessment of safety (Table 4.10), important non-clinical and clinical findings should be discussed with the background of potential pharmacokinetic and pharmaco

dynamic interactions, the potential for overdose or for abuse, as well as the misuse and off-label use of the medicine. The extent of the contribution to the risk should also be stated.

Table 4.9 EMA criteria for assessing efficacy

1. Efficacy (primary endpoint) versus comparator and its clinical relevance
2. Magnitude of treatment effect
3. Clinical relevance of the primary endpoints
4. Statistical significance of the efficacy results
5. Representiveness of the studied population for the population targeted in the label
6. Discussion of dose
7. Evidence for the efficacy in relative subgroups
8. Design conduct and statistical adequacy of the trial
9. Confirmation of treatment effect by results of non-primary endpoints
10. Validation of scales and outcome measures
11. Patient preferred outcomes
12. Confirmation of efficacy by results of relevant non-pivotal trials and extensions
13. Anticipated patient compliance (and patient convenience)
14. Clustering (consistency) of results of the pivotal trials

Table 4.10 EMA criteria for assessing harms

1. Overall incidence of adverse effects (from clinical trials)
2. Overall incidence of serious adverse effects (from clinical trials
3. Discontinuation rate due to adverse effects (from clinical trials)
4. Incidence, seriousness and duration of specific adverse effects (from clinical trials and post-marketing surveillance)
5. Interaction with other drugs and food
6. Safety in subgroups (e.g. race and sex)
7. Potential for off label use leading to safety hazards
8. Potential for non-demonstrated additional risk due to limitations of clinical trials and/or short market exposure.
9. Potential for non-demonstrated additional risk due to safety issues observed in pre-clinical safety studies but not in humans
10. Potential for non-demonstrated additional risk due to safety issues observed with other medicines of the same pharmacological class

In determining the benefit-risk balance (Table 4.11), EMA decided that this should be put in perspective regarding alternative therapies or interventions (where possible and relevant) and to conclude as to whether the benefit-risk balance is positive in the specified target population. The evaluation of the balance should also take into account the observed benefits and harms as well as the uncertainties and risks. The perspectives of different stakeholders should be taken into account in the assessment of the benefit-risk balance, in particular the perspectives of patients and prescribing physicians.

Table 4.11 Criteria for assessing benefit-risk balance

- Amount of evidence to characterise the benefit-risk balance:
  - Availability of comparative data and their limitations and potential deficiencies
- Interpret key benefits and risks
  - from perspectives of different stakeholders, including patients and treating physicians
- Level of risk acceptability
  - corresponding to the perceived degree of clinical benefit in the specific context
- Relating the benefits to the risks when possible:
  - Using logical comparisons e.g. potential lives saved as a result of treatment compared to potential lives lost as a result of adverse reactions
- Factors affecting the benefit-risk balance:
  - Situations that may alter the current balance e.g. different patient or disease characteristics
- Sensitivity of the benefit-risk balance:
  - Discussion of the potential changes to the balance if the fundamental assumptions are to be amended
- Other appropriate discussions:
  - Effectiveness of proposed treatment compared to available options
  - For negative benefit-risk balance, describe the potential harm incurred upon exposure for the claimed indication
  - Evolution of benefit-risk balance over time
  - Outstanding issues, submission or reports to address identified issues
  - Evaluation of pharmacovigilance plan, risk mitigation plan or other post-marketing commitments including need for further studies
  - Opinions from scientific experts, patients, consumers or advocates and other stakeholders in the benefit-risk assessments
- Conclusion on the benefit-risk being positive or not for every claimed indication.

*adapted from EMA reflection paper

A workshop was conducted by CIRS to seek opinions on the use of the EMA's criteria in the reflection paper and these were deemed appropriate in the absence of other authoritative guidance. Therefore, a developmental version of the template based on the criteria from the EMA reflection paper was produced by CIRS.

The developmental version was in Microsoft Word format and was tested for functionality by the Consortium. This was carried out as a retrospective feasibility study between two pairs of agencies, with each pair testing the template on a

common product. Major amendments to the developmental version included the addition of an overall summary, inclusion of summaries of relevant non-clinical, quality and clinical findings and changes to the presentation of study results. Other changes were made at the suggestion of the Consortium to improve user experiences and included functional tabs at the top of each page and an active content page that linked directly to the corresponding sections of the template.

The second version of the template was again subjected to evaluation by the Consortium. It was in an active PDF format to facilitate the user experience. This phase was conducted as a retrospective exercise using a product submitted for review to all four partner agencies. A new section 6 for visualisation was included at the suggestion of the Consortium, which would further align the template with the universal framework. There were no other major changes, and amendments were made to improve user experience (functional icons to print, email and view the template). Hence the final version of the template consisted of two sections, namely the “Proforma” and “Benefit-risk summary” (Table 4.12). The final template, namely the Benefit-Risk Template or BR Template, is attached as Appendix I.

The potential use of the BR Template was reviewed as to whether this would be able to fulfil the core elements of the universal framework, namely framing the decision (section 1), identifying the benefits and risks (section 2 and 3), assessing benefits and risks (section 4), interpretation (section 5) and recommendations (section 6). In relating to the universal framework, this template fully supports these requirements (Table 4.13).

Part III – Development of the user manual

The need for a user manual and its contents was identified as a result of feedback from the Consortium users who evaluated the BR Template. The user manual consists of two sections, namely a glossary and the instructions for completing the template. Amendments were made (Table 4.14) based on the comments received after the circulation of the draft user manual to the Consortium and the final user manual is attached as Appendix II.

Table 4.12 Components of the Benefit-Risk Template for the assessment of benefits and risks of medicine

Proforma Section
Proforma section 1: Background **Proforma section 2: Overall summaries for** o **Quality** o **Non-clinical** o **Human pharmacology** o **Clinical** **Proforma section 3: Identified benefits and risks together with the main reason for inclusion or exclusion** **Proforma section 4: Benefits and risks – study information** **Proforma section 5: Benefit-risk summary table and expert judgement including weighting and valuing** **Proforma section 6: Visualisation** **Proforma section 7: Benefit-risk conclusions**
Benefit-risk Summary Section
Summary 1: Benefit-risk conclusion **Summary 2: Decision context** **Summary 3: Identified benefits and risks** **Summary 4: Benefit-risk: Weighting and valuing** **Summary 5: Benefit-risk management.**

Table 4.13 The BR Template supporting the universal framework

<table>
<tr><td></td><td colspan="8">Core elements</td></tr>
<tr><td></td><td colspan="2">Framing the decision</td><td colspan="2">Identifying benefits and risks</td><td colspan="3">Assessing benefits and risks</td><td colspan="2">Interpretation and outcome</td></tr>
<tr><td rowspan="2">Universal benefit-risk framework</td><td>Step 1</td><td>Step 2</td><td>Step 3</td><td>Step 4</td><td>Step 5</td><td>Step 6</td><td>Step 7</td><td>Step 8</td></tr>
<tr><td>Decision context</td><td>Building the value tree</td><td>Customising the value tree</td><td>Weighting of benefits and risks</td><td>Scoring the options</td><td>Evaluating uncertainties</td><td>Concise presentation of results (visualisation)</td><td>Expert judgment</td></tr>
<tr><td rowspan="3">Template: Proforma section</td><td>Section 1: Background</td><td colspan="2">Section 3: Identified benefits and risks</td><td colspan="3">Section 4: Benefits and risks – study information</td><td colspan="2">Section 5: Benefit-risk summary table and expert judgment including weighting and valuing</td></tr>
<tr><td rowspan="2">Section 2: Overall summaries</td><td colspan="2" rowspan="2"></td><td colspan="3" rowspan="2">Section 5: Benefit-risk summary table and expert judgment including weighting and valuing</td><td colspan="2">Section 6: Visualisation</td></tr>
<tr><td colspan="2">Section 7: Benefit-risk conclusions</td></tr>
<tr><td>Template: Summary section</td><td></td><td colspan="2"></td><td colspan="3"></td><td colspan="2">Benefit-risk summary section</td></tr>
</table>

Table 4.14 History of changes leading to the final list of definitions for commonly used terms

Term	Draft Definition	Revised Definition	Comments
Adverse event	An effect seen to be disadvantageous or worsening the current state of health, observed during the clinical studies	Also known as Adverse experience, it is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.	Adapted from ICH Harmonised Tripartite Guideline. E2A
Adverse reaction/effect	An effect seen to be disadvantageous or worsening the current state of health, potentially or confirmed to be from the exposure to the Product during the clinical studies	In the pre-approval setting when the therapeutic dose(s) may not be established, it is all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. For marketed medicinal products, it refers to a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.	Adapted from ICH Harmonised Tripartite Guideline. E2A
Comparator	-	An investigational or marketed product (i.e. active control) used as a reference in a clinical trial.	
Risk	Also known as harm, a potential unfavourable effect alluding to adverse reactions/effects resulting from exposure to the Product	Also known as harm, an unfavourable effect or adverse reactions/effects on patients' health, public health or the environment resulting from exposure to the Product	Adapted from European Medicines Agency (EMA).
Seriousness (of adverse event/reaction/effect)	-	A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: • results in death, • is life-threatening (at risk of death at the time of the event) • requires inpatient hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.	Adapted from ICH Harmonised Tripartite Guideline. E2A
Severity (of adverse event/reaction/effect)	-	The intensity of a specific adverse event which may or may not be of medical significance or seriousness, which is defined by a set of criteria.	Adapted from ICH Harmonised Tripartite Guideline. E2A
Submission	An application sent for review to the regulatory authorities by the Company, for the market authorization of the claim indications of the Product	An application sent for review to the regulatory authorities by the Company, for the market authorization of the proposed indications of the Product	

DISCUSSION

The development of the universal framework for the assessment of the benefits and risks of medicines was an outcome of reviewing existing frameworks as used by regulatory agencies and pharmaceutical companies. Through standardisation, the essential components of each framework were preserved and this would facilitate the uptake of the universal framework. Whilst the experience with the existing frameworks was confined to each region or company, this universal framework aims to remove this restriction and be a common global template. As concluded by Noel et al (2012), there is a need for a standardised approach that is broadly accepted and utilised by regulators. The universal framework was developed with the inputs from various regulators and companies, while the use of the template and user manual were reviewed by the four agencies (Consortium) spanning the globe. Thus the Benefit-Risk Assessment Support System (BRASS) now stands as the complete package for the assessment of benefits and risks of medicines during the regulatory review.

The main aim of BRASS is to enhance the transparency of decision-making through comprehensive documentation and a universal framework for assessing medicinal products, allowing the audit of the decision-making process. However, caution must be applied to the degree of transparency. Differing jurisdictions may not allow the same degree of transparency as this is not supported by the individual country's legislation. Such openness may also subject the companies and agencies to immediate public scrutiny of their governance and competence, which therefore must be in place before any attempt to fully publicise their decision-making processes. Indeed, such differences in jurisdictions may also hamper the implementation of a universal framework.

It is ideal to be able to incorporate all stakeholders' perspectives into the framework. However, it should be recognised that due caution is required to retrieve relevant comments that would contribute to the assessment of benefit-risk balance. Patients, advocacies and representatives may be often biased in the interest of their pursuit. Similarly, physicians may only be able to provide a perspective relevant to their practice. The framework and template on their own are not able to discern the intrinsic significance of the values provided and require the regulators to be able to

apply clinical judgment at the conclusion of the assessment. Clinical judgment is a cumulation of education and experience which might not be achieved by BRASS.

This universal framework for the assessment of benefits and risks has yet to address the notion of evolving the model towards a quantitative methodology (Phillips et al, 2011). The exercise of assigning relative importance can be carried out using valuing and weighting, which imparts a fundamental objective and transparent perspective for decision-making (Walker et al, 2011). However, the concept behind this exercise is not apparent to most (Mt-Isa et al, 2011). The BRASS package now consists of a framework that is flexible and is able to accommodate various existing methodologies utilised by companies and agencies. This alludes to the current situation where there is no agreement on the methodologies considered acceptable or commonly applied in assessment. More research is required to further the understanding and application of weightings and identification and consensus of assessment methodologies.

The Consortium thus far has had the most experience in evaluating the template. Though they could understand the potential advantages of implementing BRASS, there are barriers to achieving this. The implementation may result in a major change in work processes and retraining of personnel, which the agencies might not be able to accommodate. It appears that there may be differing opinions between higher management and staff personnel, resulting in a disagreement on the need and approach to implement this framework. As various agencies have diverse agendas and priorities, to implement BRASS globally may be challenged by a long timeline as each make arrangements at different rates to accommodate this framework. The members of the Consortium were also challenged to decide if the template should replace their current report templates or to be incorporated into existing ones.

The BRASS package is only as relevant as the science behind its development. It is essential that continued work be provided to ensure the relevance and currency of the concept and tools as well as meeting the expectations of the stakeholders. This will require the continuous involvement of the stakeholders and efforts must be maintained to retain their on-going contributions. Hence, BRASS should be seen as

the initiation of a universal framework, to which companies and agencies would convene for further development and implementation.

CONCLUSION

The development of the Benefit-Risk Assessment Support System confers a universal applicability and the current package enhances the transparency of decision-making through improving its consistency and objectivity. Greater accountability and governance is also achieved through a structured documentation offered by the benefit-risk template. Finally it facilitates the review of past decisions within an organisation and also among different organisations, helping to understand the rationale for any observed differences in regulatory outcomes.

SUMMARY

- Comparison of the existing benefit-risk assessment frameworks identified common elements and no differences
- A universal framework is now developed to encompass the existing frameworks
- A template for documenting the benefit-risk decision and its accompanying user manual has also been developed.
- A pilot study was conducted with four regulatory agencies to investigate the feasibility of the framework, template and user manual.

CHAPTER 5

Evaluation of the benefit-risk template by regulatory agencies – A prospective study

INTRODUCTION

The current climate in regulatory science seeks transparency of decision-making and communication to stakeholders for accountability. The results from Chapter 3 showed that both regulatory agencies and pharmaceutical companies believe that a benefit–risk framework would enhance the quality (transparency and consistency) of decision-making, provide documentation for a systematic, structured discussion and act as a tool for communication. A tool was thus developed (Chapter 4) with inputs from the Consortium (consisting of TGA, Health Canada, SwissMedic and HSA) and the resulting universal Benefit-Risk (BR) Template was designed to enhance communication and documentation of benefit-risk decisions. This study aims to review the potential value of the BR Template for regulatory agencies.

OBJECTIVES

The objectives are to:

- Examine the value of the BR Template for documenting the benefit-risk assessment decision of new active substances during the review process,
- Evaluate the BR Template as a tool to communicate the benefit-risk decision to other stakeholders in a systematic, structured manner,
- Determine if the BR Summary section of the BR Template is adequate as a stand-alone tool to communicate a benefit-risk decision to stakeholders

METHODS

TGA, Health Canada and HSA agreed to participate in this prospective study which was conducted as non-comparative evaluation. The study package, consisting of the BR Template (which included the Benefit-risk Summary section) and User Manual described in Chapter 4 were sent to the three agencies. The reviewers in the respective agencies selected a product undergoing active evaluation, and completed their own assessment report as well as the BR Template. Following this process, the reviewers were sent a study evaluation tool (Figure 5.1), which they completed and returned.

The study evaluation tool was developed as a questionnaire consisting of 56 questions divided into four sections, namely user-friendliness, documentation, applicability and general comments. There were three systems of rating:

- Excellent, Good, Fair and Poor (comments to be provided for ratings of “Fair” and “Poor”)
- Fit for purpose, Fit for purpose with modifications required, Not fit for purpose (comments to be provided for the latter two choices)
- Yes and No (comments to be provided for rating “No”)

Most of the questions had an open field for comments, allowing the participants to provide any issues of concern or relevant points that were not addressed by the questionnaire. The questionnaires were sent via email directly to the participants. Completed responses were received via email, as instructed to the participants. All responses were collated into a single group and outcomes were presented according to their respective sections in the study evaluation tool. All data were expressed as direct ratings provided by the responders. Free-text comments were collated and presented in appropriate categories.

This was designed as an exploratory study and the outcomes were interpreted to provide qualitative inferences relating to the objectives. No statistical analyses were planned or conducted.

RESULTS

The outcomes will be presented in four parts:

- Part I – User-friendliness of the BR Template
- Part II – Appropriateness (fit for purpose) of the documentation
- Part III – Applicability of the BR Template
- Part IV – Usefulness of the BR Template

None of the agencies used visualisations and hence no outcomes were documented for these items in the survey tools.

Figure 5.1 The study evaluation tool

CONFIDENTIAL

Evaluation of the use of the Benefit-risk Template

Mr James Leong, Cardiff University

Participants:
Dr Jason Ferla - Therapeutic Goods Administration, Australia
Barbara Sabourin - Health Canada, Canada
Jalene Poh - Health Sciences Authority, Singapore
Dr Petra Doerr - Swissmedic, Switzerland

Confidentiality

- All information collected will be kept strictly confidential.
- No data that will identify a participant will be reported, or details made available to a third party.
- External reports or presentations of the data will include only anonymous figures and any appropriate analytical interpretation.
- Data will only be provided to the relevant organization concerned.

Background
Over the past three years, the Centre for Innovation in Regulatory Science (CIRS) in association with Health Canada, the TGA in Australia, HSA in Singapore and SwissMedic (collectively known as the Consortium) have developed a structured systematic standardised approach to the benefit-risk assessment of medicines.

A template based on the EMA guidance document for benefit-risk assessment (March 2008) had been developed to document the benefit-risk decision making process in the regulatory review. The original template had been evaluated in a feasibility study by the Consortium in 2010 and a retrospective pilot study in 2011. As a result of these initiatives, the Consortium had suggested modifications and additions which have now been incorporated into the current electronic version. A user manual has been developed.

An initial seven-step benefit-risk framework proposed and used in both the feasibility and pilot study has now been included in the overarching Unified Methodologies for Benefit-Risk Assessment (UMBRA) eight-step framework, which has been shown to incorporate other frameworks developed and evaluated by various groups including the FDA (five-step framework), the EMA (eight-step PROACT-URL framework) and the PhRMA's BRAT initiative (six-step framework).

CIRS has now put together a Benefit-Risk Assessment Support System (BRASS) which includes the eight-step framework, a benefit-risk template (henceforth referred to as Template) and its user manual. The Consortium is carrying out a prospective study using this package.

Objectives
The objectives are to:

- Evaluate the Template during the review process to see if it is "fit for purpose",
- Assess the value of the Template compared to your existing benefit-risk decision making processes,
- Determine if the Template produces better documentation of information in a systematic, structured manner required for a benefit-risk decision,

Methodology
This tool is been sent to each of the four agencies of the Consortium at the conclusion of the prospective study in order to fulfil the objectives above. An interview may be conducted to provide clarification before reporting the outcomes. All responses should be returned by the middle of May 2013 so that appropriate feedback can be addressed and in anticipation of the CIRS benefit-risk workshop on 20 and 21 June 2013, Washington DC.

Outcomes
A report of the analysed data will be made available to each participant by end of July 2013.

Conclusion
The outcomes of this evaluation will contribute to the role, evolution and further development of the benefit-risk Template.

Instructions for completion of the tool

This tool relates to your recent experience with the following system:

Benefit-risk Assessment Template (Proforma_2012_v1.0.pdf)

There are 4 sections:

A. User-friendliness
B. Documentation
C. Applicability
D. General comments

This tool should be completed as soon as the benefit-risk assessment using the Template is completed.

A structured interview with the participants via face-to-face meetings or teleconferences will be arranged at a convenient dates to provide clarification before reporting the outcomes.

You should relate each statement to your experience of using the Template and tick the box that best describes your opinion.

We would appreciate if you could provide a response to all the items and submit the completed form before the middle of May 2013. Please provide your responses electronically and note that the comment boxes are expandable.

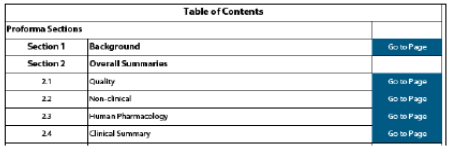
Your comments are extremely valuable, please feel free to use the boxes provided for this purpose.

A. User-friendliness

A practical template should be easy to use and understand.

Having used the Template to document the assessment of benefits and risks, please read through the list of items below and put a tick in the box that best describes your opinion.

Kindly provide comments if your opinion is "Fair" or "Poor".

		Excellent	Good	Fair	Poor	Did not use	Provide comments if opinion is "Fair" or "Poor"
Navigating through the Template							
1	 Navigation to various other sections using the tabs found on top of each page.						
2	 Navigation to required sections using the "Go to Page" button in Table of Contents.						
3	Navigation to required sections using the bookmarks found on the left side of screen display.						
Support functions							
4	 Printing of document via "Quick Links" print function.						
5	Sharing of document via "Quick Links" email function.						

		Excellent	Good	Fair	Poor	Did not use	Provide comments if opinion is "Fair" or "Poor"
6	Viewing of full form or summary via the "Quick Links" view function.						
7	 Auto-population of data into respective fields that requires common inputs.						
Guidance by user manual in completing the Template							
8	Clarity of instructions.						
9	Comprehensiveness of guidance provided.						
10	Applicability of guidance.						

Please comment on how to further improve the user-friendliness, or suggest other functions that might improve the navigation of the Template.

B. Documentation

A functional template should be able to document the processes leading to the final benefit-risk conclusion in a structured and systematic manner.

Having used the Template to assess the benefits, risks and the resulting balance, please read through the list of items below, and put a tick in the box that best describes your opinion.

- "**Fit for purpose**" refers to the Template being able to achieve the item for the majority of the applications.
- "**Fit for purpose with modification**" refers to the Template being able to achieve the item with amendments (kindly specify the changes required).
- "**Not fit for purpose**" refers to the Template not being able to achieve the item at all.

Kindly provide comments as required for your opinion, as indicated in the section.

Section 1 Background (includes section 1.1 to 1.6)		**Fit for purpose**	**Fit for purpose with modification**	**Not fit for purpose**
1	Documents relevant information to support the decision context.		*Specify modification(s) needed:*	*Comment(s):*

Section 2 Overall Summaries		**Fit for purpose**	**Fit for purpose with modification**	**Not fit for purpose**
Section 2.1 Quality Overall Summary				
2	Documents relevant information to support the decision context.		*Specify modification(s) needed:*	*Comment(s):*
Section 2.2 Non-Clinical Overall Summary				
3	Documents relevant information to support the decision context.		*Specify modification(s) needed:*	*Comment(s):*

Section 2 Overall Summaries (continued)		Fit for purpose	Fit for purpose with modification	Not fit for purpose
Section 2.3 Human Pharmacology Overall Summary				
4	Documents relevant information to support the decision context.		*Specify modification(s) needed:*	*Comment(s):*
Section 2.4 Clinical Overall Summary				
5	Documents relevant information to support the decision context.		*Specify modification(s) needed:*	*Comment(s):*

Section 3 Identified Benefits and Risks		Fit for purpose	Fit for purpose with modification	Not fit for purpose
Benefits				
6	Documents the reasons for inclusion or exclusion of all the benefits.		*Specify modification(s) needed:*	*Comment(s):*
7	Documents the relevant benefits as identified by the sponsor.		*Specify modification(s) needed:*	*Comment(s):*
8	Documents your list of benefits to be included in the benefit-risk assessment.		*Specify modification(s) needed:*	*Comment(s):*
Risks				
9	Documents the reasons for inclusion or exclusion of all the risks.		*Specify modification(s) needed:*	*Comment(s):*
10	Documents the relevant risks as identified by the sponsor.		*Specify modification(s) needed:*	*Comment(s):*
11	Documents your list of risks to be included in the benefit-risk assessment.		*Specify modification(s) needed:*	*Comment(s):*

Section 4 Benefit-risk Study Information		Fit for purpose	Fit for purpose with modification	Not fit for purpose
Section 4.1.1 to 4.1.9 Benefits and Risks – Study Information				
12	 Documents the outcomes and conclusions of the studies.		*Specify modification(s) needed:*	*Comment(s):*
Section 4.1.11 to 4.1.15 Benefits and Risks – Study Information				
13	Captures the contribution of other information relevant to the benefits of the product.		*Specify modification(s) needed:*	*Comment(s):*
Section 4.2 Risks: Overall Summary				
14	Documents the overall summary of the incidence of adverse events/effects.		*Specify modification(s) needed:*	*Comment(s):*
Section 4.2.1 to 4.2.4 Risks: Overall Summary				
15	Documents the overall incidences of the adverse effects.		*Specify modification(s) needed:*	*Comment(s):*

Section 4 Benefit-risk Study Information (continued)		Fit for purpose	Fit for purpose with modification	Not fit for purpose
Section 4.3 Adverse Effects				
16	Documents the information relevant to the identified risk.		*Specify modification(s) needed:*	*Comment(s):*
Section 4.4.Uncertainties (Benefits & Risks) for pivotal and non-pivotal studies				
17	Captures the contribution of uncertainties relevant to the benefit and risks of the product.		*Specify modification(s) needed:*	*Comment(s):*

Section 5 Benefit-risk Summary Table & Expert Judgment		Fit for purpose	Fit for purpose with modification	Not fit for purpose
Benefits				
5.1 Benefits Populated from 3.1	Relative Importance (weighting) Using selected relative importance system	Valuing the options: Investigated product	Valuing the options: Comparator	Valuing the options: Placebo / Comment on strength and uncertainty of benefit
For items 28 and 29, please refer to the table above.				
18	Documents the contribution of the weighting/relative importance of the benefits to the final benefit-risk decision.		*Specify modification(s) needed:*	*Comment(s):*
19	Documents the contribution of the values of the benefits from the studies to the final benefit-risk decision.		*Specify modification(s) needed:*	*Comment(s):*
Risks				
5.2 Risks Populated from 3.2	Relative Importance (weighting) Using selected relative importance system	Valuing the options: Investigated product	Valuing the options: Comparator	Valuing the options: Placebo / Comment on strength and uncertainty of each risk / Was the value or weight of this risk altered or mitigated by the ability to control the use of the medicine once on the market?
For items 30 and 31, please refer to the table above.				
20	Documents the contribution of the weighting/relative importance of the risks to the final benefit-risk decision.		*Specify modification(s) needed:*	*Comment(s):*
21	Documents the contribution of the values of the risks from the studies to the final benefit-risk decision.		*Specify modification(s) needed:*	*Comment(s):*

Section 6 Visualisation		Yes	No
22	If you had provided a visualisation, did your previous inputs in other sections help you to create the visualisation? If no, please provide a reason.		*Comment(s):*
23	Did the visualisation provide an appropriate means to support your benefit-risk decision? If no, please provide a reason.		*Comment(s):*

Section 7 Benefit-risk Conclusions		Fit for purpose	Fit for purpose with modification	Not fit for purpose
24	Includes all the relevant information to draw a conclusion regarding the recommendation.		*Specify modification(s) needed:*	*Comment(s):*

The following item refers to the Summary section that is prefilled by the Proforma.

Section 8 Benefit-risk Summary		Yes	No
25	Does this section provide a summary of all the relevant information to be presented in a structured systematic manner that led to the benefit-risk conclusion? If no, please provide a reason.		*Comment(s):*

C. Applicability

The template used to construct the benefit-risk profile should contribute significantly and apply directly to regulatory decision making.

Having used a structured systematic documentation of benefits and risks assessment, kindly indicate if this Template should be part of standard regulatory review practices.

		Excellent	Good	Fair	Poor	Provide comments if opinion is " Fair" or "Poor"
1	The Template's contribution to regulatory decision-making.					
2	The Template's contribution to ensuring consistency in the standard of assessing benefits and risks of medicines.					
3	The Template's contribution to enhancing the transparency of decision-making.					
4	The Template's contribution to promoting effective communication to stakeholders.					
5	The Template's contribution to achieving consistency of decisions between regulatory agencies.					
6	The Template's advantages over the systems I am currently using in my organisation.					

		Yes	No (please provide comments)
Irrespective of the jurisdiction in your country, are you willing to share the entire Template with the following stakeholders? If no, please provide a reason.			
7	• Healthcare professionals		
8	• Health technologies assessment agencies (HTA)		
9	• Patients/patient advocacy groups		
10	• Other regulatory agencies		
11	• Media/public domain		
12	• Academia		
Irrespective of the jurisdiction in your country, is the information in the benefit-risk summary (Section 8) presented sufficient to communicate the basis of decision to the following stakeholders? If no, please provide a reason.			
13	• Healthcare professionals		
14	• Health technologies assessment agencies (HTA)		
15	• Patients/patient advocacy groups		
16	• Other regulatory agencies		
17	• Media/public domain		
18	• Academia		

D. General Comments

The following section should be completed if you are in a decision-making role or management position in your organization.

		Excellent	Good	Fair	Poor	Provide comments if opinion is " Fair" or "Poor"
1	The Template's contribution to improving regulatory memory and enabling documentation of previous decisions to ensure consistency in decision-making.					
2	The Template's contribution as an audit tool.					
3	The Template's potential contribution to post-marketing activities.					

If you have any further comments, kindly use the space below:

Should you have further questions or concerns about this tool, please contact:
Mr James Leong at email: james_leong@hsa.gov.sg

On completion, please send this to the following email:
james_leong@hsa.gov.sg

Participant's Information

Adobe package used in completing the Template: _____

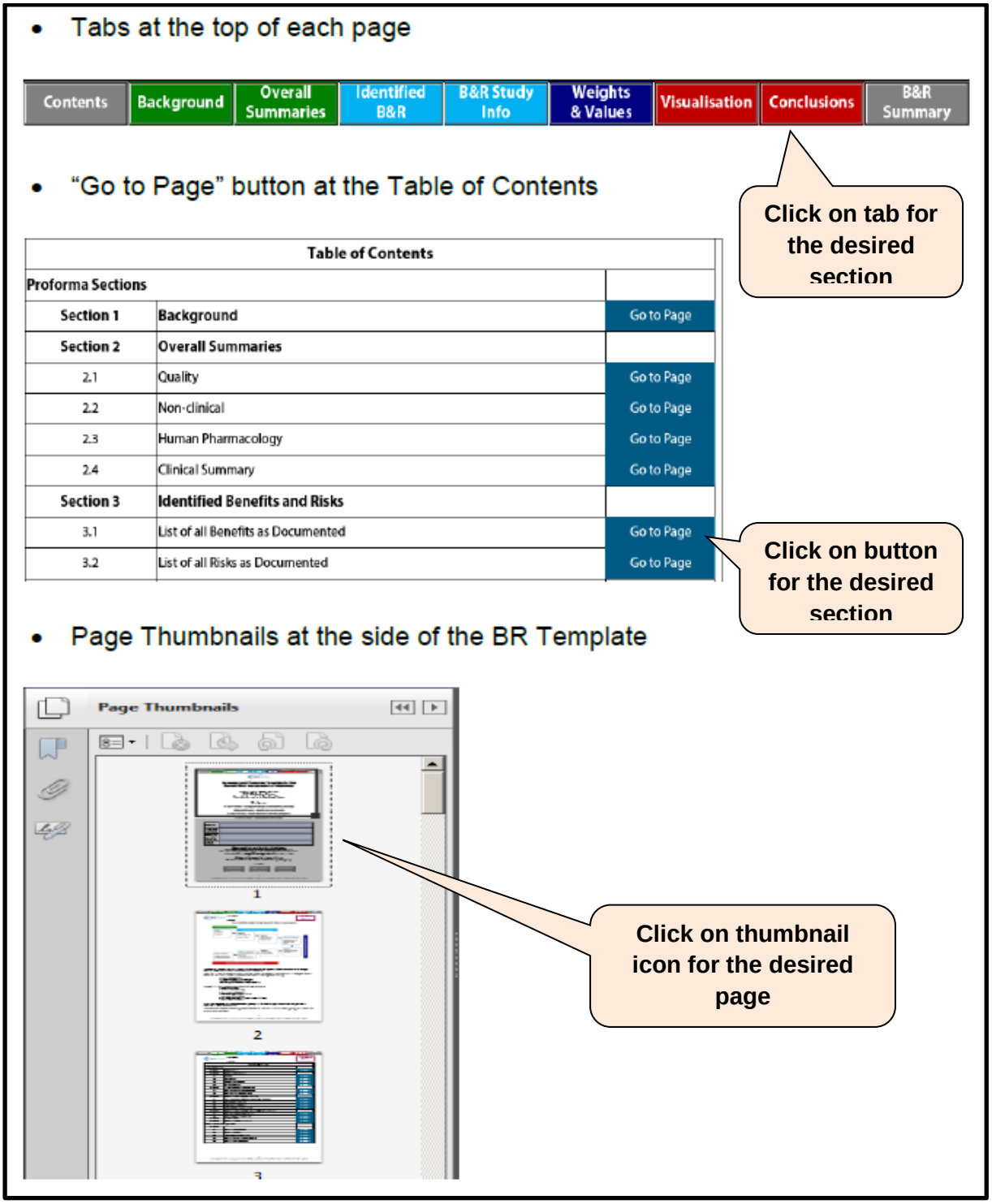
Version of Adobe package used as indicated above: _____

Signature:	**Position:**
Company:	**Location:**
Date:	

Part I – User-friendliness of the BR Template

The BR template has three features that assist the user in locating selected pages within the document, namely the tabs at the top of each page, the "Go to page" button and the page thumbnails (Figure 5.2).

Figure 5.2 Navigation functions of the BR Template



The thumbnails were not used while the tabs and “Go to page” buttons were rated either good or excellent (Table 5.1). The agencies suggested that the use of bookmarks for the sections and subsections would be preferable, as well as a search function for identifying key words within the document.

Table 5.1 Practicality of the navigation functions

Agency	Tabs at top of page	"Go to page" button	page thumbnails
TGA	Excellent	Excellent	Did not use
Health Canada	Good	Good	Did not use
HSA	Good	Good	Did not use

In addition to navigation features, the BR Template incorporates four functions to print, email, view the form (Figure 5.3) and auto-populate information for fields requiring the same inputs (Figure 5.4).

Figure 5.3 Document support functions of the BR Template

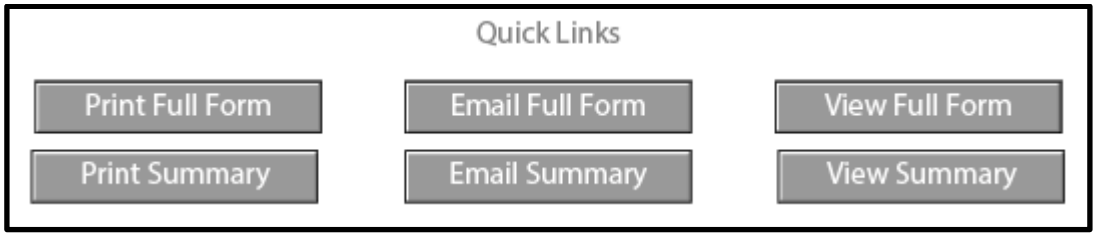
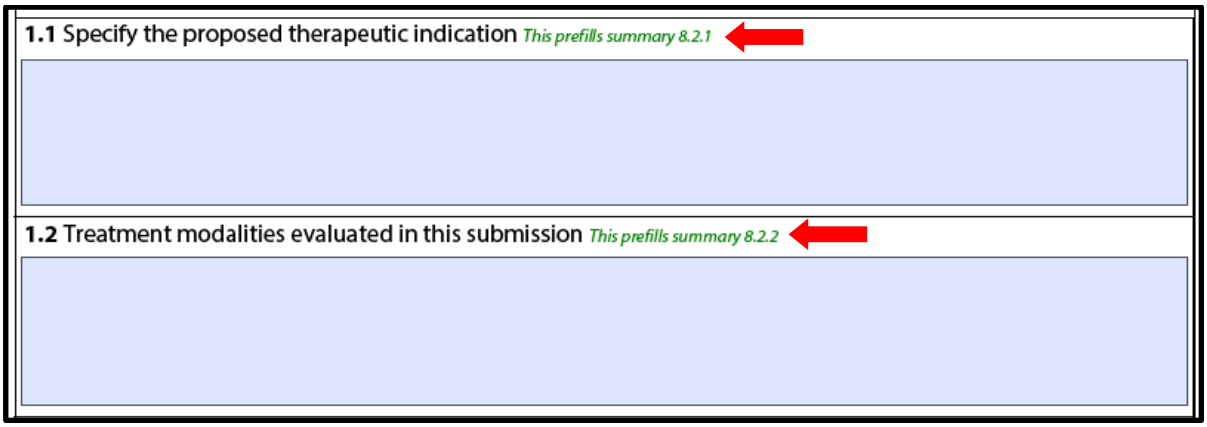


Figure 5.4 Auto-populate function of the BR Template



Conclusion on the usefulness of the print, email and view functions were not provided as TGA did not use the former two functions, Health Canada experienced a technical issue that prevented them from getting back to the document after using these three functions while HSA rated these support functions as good. However, the auto-population function was considered useful by all, being rated as good or fair (Table 5.2).

Table 5.2 Usefulness of the document support functions

Agency	Print function	Email function	View full form function	Auto-populate function
TGA	Did not use	Did not use	Excellent	Good
Health Canada	Poor	Poor	Poor	Fair
HSA	Good	Good	Good	Good

The User Manual was provided as a guide to help the reviewer in completing the BR Template and included a glossary of commonly used terms. TGA and HSA rated the manual as good or fair in terms of clarity, comprehensiveness and applicability (Table 5.3). Overall, the agencies believed more details are needed e.g. case studies and examples to improve the usefulness of the User Manual. Health Canada would like to have more guidance regarding the intention of the BR Template, level of details of the outcomes and the type of information required. HSA commented on the need for examples to show how weighting and valuing may be carried out as this concept is new to the agency.

Table 5.3 Appropriateness of the User Manual

Agency	Clarity of instructions	Comprehensiveness	Applicability
TGA	Good	Fair	Good
Health Canada	Poor	Poor	(Not reported)
HSA	Good	Good	Good

Other comments received on enhancing the technical aspects of the template include:

- Allow changes in fonts (e.g., size, underlining, italicizing), use of bulleted listings within text boxes, use of the tab key within a cell in the tables
- Allow for the use of the tools for commenting and marking-up (highlighting and cross-out functions) in Adobe Acrobat Professional as these would be useful for supervisors or managers recommending revisions to the document
- Ensure that the text copied and pasted from a Word document retains the original formatting (underlining, italicizing, symbols)

Part II – Appropriateness (fit for purpose) of the documentation

The BR Template incorporates five conclusions that are considered important in making a benefit-risk decision, namely the background (decision context) and quality, non-clinical, human pharmacology and clinical conclusions. Of the five, the agencies believed the clinical conclusion is fit for this purpose (Table 5.4). For the remaining four, the template could allow for more details as the actual benefit-risk assessment was carried out in much greater depth and the sections may not accommodate such a level of information.

Table 5.4 Documentation of relevant information supporting the benefit-risk decision

Agency	Background information	Quality conclusion	Non-clinical conclusion	Human pharmacology conclusion	Clinical conclusion
TGA	Fit for purpose	Modifications required	Modifications required	Modifications required	Fit for purpose
Health Canada	Fit for purpose	Modifications required	Modifications required	Modifications required	Fit for purpose
HSA	Modifications required	Fit for purpose	Fit for purpose	Fit for purpose	Fit for purpose

Health Canada commented that these were the only sections to discuss the contributions from quality, non-clinical and human pharmacology in the entire

template whereas the rest of the template is dedicated to clinical benefits and risks. However, Health Canada believed that if the intention of the BR Template was to feature only a high-level summary of the significant findings, then it would suffice. It was mentioned that a considerable amount of evaluation was conducted for those aspects for a new active substance and that this section would not be able to accommodate these findings. Without allowing the reviewer to provide details on the relevant studies, it would be difficult to explain the relevance of the reported issues and concerns. For completeness, TGA recommended the inclusion of sub-headings for pharmacokinetics, pharmacodynamics and drug interactions to further guide the reviewer. HSA preferred the background information to allow a discussion on related applications and products that may contribute to decision-making.

It should be noted that the BR Template was designed to present and communicate only the significant findings that would affect the benefit-risk decision and that the corresponding details would be expected to be available from the original assessment report for the product.

The template was seen by the agencies as being able to document benefits and risks identified by sponsors and the reasons for including or excluding them (Table 5.5).

Table 5.5 Documentation of benefits and risks

	Benefits			Risks		
Agency	**Reasons for inclusion or exclusion of all benefits**	**Relevant benefits as identified by sponsor**	**Selected list of benefits to be included in the benefit-risk assessment**	**Reasons for inclusion or exclusion of all risks**	**Relevant risks as identified by sponsor**	**Selected list of risks to be included in the benefit-risk assessment**
TGA	Fit for purpose	Fit for purpose	Fit for purpose	Fit for purpose	Not fit for purpose	Fit for purpose
Health Canada	Fit for purpose	Modifications required	Not fit	Fit for purpose	Not fit for purpose	Fit for purpose
HSA	Fit for purpose	Fit for purpose	Fit for purpose	Fit for purpose	Fit for purpose	Fit for purpose

However, several concerns were raised for the listing of selected benefits by agencies to be included for benefit-risk assessment although TGA and HSA thought this section fit for purpose. It appeared to Health Canada that only benefits supported by statistics from clinical studies were allowed, as only the selected benefits would be discussed in further details in the template. Health Canada thought that only those benefits that were supported by a primary endpoint of the clinical studies should be considered. Thus, for benefits that were not quantifiable, such as advantages in the route of administration and dosing regimen, these could not be represented although they are taken into account by the reviewer.

While the BR Template mostly accommodates the input of outcomes of clinical studies (which are the basis of the majority of product applications), other relevant benefits, either not quantifiable or intangible, may be further discussed in the template. In documenting the study outcomes, the BR Template allows for the factual representation of the values from the clinical studies with no bias towards positive or negative data.

Although Health Canada stated that it was not clear if negative outcomes should be documented during this listing exercise, it should be clarified that this section was meant to highlight the benefits on which the benefit-risk assessment would be focused. The negative outcomes for these benefits would have been apparent in the section for study outcomes and during further concluding discussions.

With regards to risk, both TGA and Health Canada believed that the template would not be able to effectively document all the risks identified by sponsors (Table 5.5) as they generally play down the risks. Unless the sponsor was specifically requested to provide a list of risks or potential risks, this section would not be reliable and therefore less useful.

As only the selected risks are further discussed in details in the template, Health Canada believe that there are safety concerns that are taken into consideration but may not be documented. The scenarios may include those AEs for which a strong causality was not proved or where there was not a documented incidence of the defined AE in the clinical studies. The current set-up in the BR Template documents

only AEs with incidence rates and hence for those AEs not based on this measurement (for example significant changes in blood components), these could not be captured. In addition, Health Canada also sought for greater clarity in the definition of risks, in terms of nomenclature or categorisation. It was however noted that HSA found the template adequate in all aspects of documenting benefits and risks.

For selected benefits and risks, the BR Template allowed the assignment of weights (relative importance) and values to demonstrate the contributing factors to the benefit-risk balance. Divergent views were received on the effectiveness of such documentation (Table 5.6). TGA believed that as long as the reviewer understood the concept of weighting, the template would fulfil this purpose. Health Canada rated the template as being "not fit" for purpose in this aspect and commented that it was unclear regarding the need to indicate the relative importance of benefits and risks, since those of little significance need not be discussed. Moreover, this exercise of providing values was replicated in another section when presenting study outcomes.

Table 5.6 Documentation of weights and values

Agency	Contribution of weighting/relative importance of benefits	Contribution of values of benefits from the studies	Contribution of weighting/relative importance of risks	Contribution of values of risks from the studies
TGA	Modifications required	Fit for purpose	Modifications required	Fit for purpose
Health Canada	Not fit for purpose	Not fit for purpose	Not fit for purpose	Not fit for purpose
HSA	Fit for purpose	Fit for purpose	Fit for purpose	Fit for purpose

While Health Canada thought this entire section for documenting weights and values was redundant, it should be highlighted that the BR Template referenced the principles of assessing benefits, risks and benefit-risk balance from the published reflection paper by EMA (EMA, 2008). Therefore, it has been designed specifically to document the considerations taken by the reviewer or regulatory agency for the

benefit-risk decision. If there is an explicit listing and the priorities identified for each of the benefits and risks, then there is the possibility of greater transparency in the exchange of information leading to improved communication. However, HSA believed that the BR Template was able to sufficiently document the contribution of both weights and values for benefits and risks.

In documenting study outcomes, both TGA and HSA commented that the template would require modification before it would be fit for this purpose (Table 5.7). Health Canada indicated that since only numerical values are required, the completion of these tables would not effectively document conclusions. In addition, when the reviewer was requested to record the presence of benefits in patients receiving a placebo, Health Canada noted that this would be difficult since there was no opportunity to define when the benefits are present in the placebo group. HSA questioned whether the presence of benefits was dependent on statistical significance, clinical relevance or a combination of both. In addition, for situations where there is only one study, no comparisons can be drawn and hence it cannot be concluded if the benefit is present or absent. For such cases, HSA recommended to include a new option of “Not conclusive”. TGA would like to document the differences in benefits seen when the product is compared to other approved medicines. This would also be meaningful for other stakeholders who can make better informed decisions based on this information. In documenting compliance rates, TGA also suggested that completion rates and withdrawals should be provided.

In documenting information relevant to benefits, Health Canada recommended the inclusion of subgroup analyses, which although often exploratory, can provide supporting information in terms of showing the benefit in relevant subgroups. Similarly, the inclusion of patient reported outcomes might also contribute in a limited way to the overall assessment of benefits. HSA commented that a new option of “Not applicable” be provided for situations where there is only one study and no other contributing information. Overall, the template can adequately document relevant information relating to benefits with the minor amendments as highlighted above by the agencies.

Table 5.7 Documentation of study outcomes, safety information and overall conclusion

	BR Template							**Benefit-risk Summary**
Agency	Outcomes and conclusions of studies	Contribution of other information relevant to benefits	Overall summary of incidence of adverse events/effects	Overall incidence of adverse effects	Information relevant to identified risks	Contribution of uncertainties relevant to the benefits and risks	Relevant information to draw conclusion regarding the recommendation	Benefit-risk summary presented information in a structured systematic manner that led to benefit-risk decision
TGA	Modifications required	Fit	Fit	Modifications required	Fit	Fit	Modifications required	Not fit
Health Canada	Not fit	Modifications required	Not fit	Not fit	Modifications required	Fit	Not fit	Not fit
HSA	Modifications required	Modifications required	Fit	Modifications required	Not fit	Fit	Modifications required	Fit

Health Canada recommended the inclusion of overall summary tables for serious AEs and AEs leading to discontinuation and to allow for the option of summarizing such information as text. HSA preferred the flexibility of being able to upload different common formats in addition to those currently allowed. As the summary was based on the overall safety data, any potential differences that occurred in individual studies would not be documented, but would likely be considered in the overall benefit-risk assessment. Likewise, the input of values of AEs without other relevant information reduced the importance of this documentation, especially for deaths, where a discussion on the causes and temporal relationship would usually be carried out. It also appeared that the BR Template did not clarify the details to be provided, as there would be meaningful and deeper discussion on the comparisons of the type and frequencies of reported AEs, which would also include an evaluation of information at individual patient level. In the BR Template, the term “Adverse events” was used and the general discussion on safety information led Health Canada to the opinion that an examination of the safety impact was irrespective of drug exposure. It would be more meaningful and important to assess adverse reactions for causality and association. HSA felt that amidst the numerous details that would be required in the template, there was a lack of focus and it would be difficult to understand the contribution in justifying the final benefit-risk decision.

All the agencies thought that the BR Template can effectively document uncertainties relating to the benefits and risks, but also agreed that currently the template is not suitable for documenting the relevant information leading to a conclusion or a recommendation. TGA commented on their lack of experience in the weighting and valuing and the assimilation of such outcomes into the benefit-risk conclusion. They thought that a quantitative approach of allocating of score or rank to the final outcome as part of the template would be expected, which may also include affirming these decisions as favourable or unfavourable, or a statement on the evidential strength of the final benefit-risk outcome. HSA, on the other hand, believed that the summary section is suitable for this purpose.

In the development of the BR Template, the current environment and practice of regulatory agencies were taken into consideration. As most were still employing a qualitative or semi-quantitative approach in their assessment of benefits and risks,

the BR Template was designed to accommodate this approach but not the quantitative exercise of allocating a final score to the outcomes.

Health Canada alluded to the fact that there were other factors like practice guidelines, legislation and precedents which should be taken into consideration, but the BR Template appeared not to capture these contributing factors. Other identified factors would include the benefits and risks associated with a proposed route of administration or dosing regimen, judgement calls and decisions from other regulatory agencies. However, the BR Template, in the sections for the concluding discussion, allow for the input of other significant factors otherwise not presented in the earlier parts of the template. Health Canada also highlighted an important point that there was less emphasis on the final recommended indication than the proposed indication and that there was no specific section to discuss the reasons for any amendments to the proposed indication, dosing or critical changes to the package inserts. This opinion was similarly shared by HSA.

Both TGA and Health Canada agreed that the Benefit-risk Summary section was not suitable in presenting information in a structured systematic manner that led to a benefit-risk decision. As for the entire BR Template, TGA noted that a conclusive statement on the outcome of the review of weights and values should be included in the Benefit-risk Summary section which would drive the recommendation to accept or reject the proposed application. No reasons were provided by Health Canada for their negative opinion. These views are aligned to the ratings of both TGA and Health Canada regarding their unwillingness to share the BR Template and Benefit-risk Summary section with other stakeholders.

Part III – Applicability of BR Template

Divergent views were received on the usefulness of the BR Template (Table 5.8). Both TGA and HSA have generally positive opinion of the applicability of the BR Template. TGA believed the template had good utility to document the benefits and risks, but more details would be required to further support the conclusions. Health Canada rated the template as “not fit” for this purpose as it was not able to capture all of the factors in regulatory decision-making. Their reasons that the BR Template was not suitable for documenting relevant information have been discussed above.

Table 5.8 Applicability of the BR Template

Agency	Contributing to regulatory decision-making	Ensuring consistency in standard of assessing benefits and risks of medicines	Enhancing the transparency of decision-making	Promoting effective communication to stakeholders	Achieving consistency of decisions between regulatory agencies	An advantage over the current systems in the organisation
TGA	Fair	Good	Good	Good	Good	Excellent
Health Canada	Poor	Poor	Poor	Poor	Poor	Poor
HSA	Good	Good	Good	Good	Fair	Fair

Therefore, Health Canada could not confirm its contribution to decision-making and standards in assessing benefits, risks and uncertainties. However, Health Canada noted that the BR Template was able to achieve consistency in assessing benefits and risks and was able to document this information.

Regarding the ability of the BR Template to improve transparency and communication, Health Canada stated that the template was neither able to capture critical thinking, nor other significant contributing factors such as the additional analyses that the reviewers requested from sponsors. It is therefore believed that if clarification were to be provided on the existing availability of appropriate sections in the BR Template to discuss these other contributing factors, Health Canada may accept the template as having adequate applicability.

It was also not clear to Health Canada how the template would contribute to achieving consistency in decisions between regulatory agencies, when the decision could be affected by other factors such as the subjective interpretation by a reviewer, precedent decisions made for medicines in the same therapeutic class and clinical practices. Similarly, HSA clarified that, with the understanding that regulatory decisions were dependent on individual jurisdictions, the template would suffice if the intention is to compare the basis of the decision between agencies. Although Health Canada commented that they did not find that the template had an advantage over their current system, they noted the value of the BR Template over their Summary Basis of Decision (SBD) regarding the inclusion of a section dedicated to discussing uncertainties, as this was noted to improve transparency. HSA mentioned that most of the information required was already in the existing evaluation report, leading to duplication of work. Moreover, the BR Template could not replace the existing assessment report as detailed information on the studies would need to be documented.

Both TGA and Health Canada agencies expressed their willingness only to share the completed BR Summary Template under the covering of confidentiality and memorandums of understanding with the receiving stakeholders. As such, their current circumstances do not allow them to share the completed BR Template (Table

5.9). HSA would be willing to share with other stakeholders except patients and the media, as they believed that the contents might be too technical in nature to allow a meaningful and clear understanding.

Table 5.9 Willingness to share the entire BR Template with various stakeholders

Agency	Healthcare professionals	Health technologies assessment agencies (HTA)	Patients/ patient advocacy groups	Other regulatory agencies	Media/ public domain	Academia
TGA	No	No	No	No	No	No
Health Canada	No	Yes	(Not reported)	Yes	(Not reported)	(Not reported)
HSA	Yes	Yes	No	Yes	No	Yes

For the same reason regarding the template, both TGA and Health Canada could not share the completed Benefit-risk Summary section (Table 5.10). Given the correct circumstances, TGA would consider sharing with healthcare professionals, HTA agencies, other regulators and academia if the additional details to support the benefits and risks could be provided in the summary. In addition, they commented that patients and media might benefit from this summary as it would be easier for them to understand. However, HSA again would exclude sharing with patients and the media as the contents might be too technical.

Although, Health Canada believed the current summary would not be suitable for sharing, they commented that the Benefit-risk Summary section was more complete than their current report format (Summary Basis of Decision). Again, they mentioned that the Benefit-risk Summary section did not capture the significant contributing factors which were previously mentioned as the reasons not sharing the BR Template.

Table 5.10 Willingness to share the BR Summary section with various stakeholders

Agency	Healthcare professionals	Health technologies assessment agencies (HTA)	Patients/ patient advocacy groups	Other regulatory agencies	Media/ public domain	Academia
TGA	No	No	No	No	No	No
Health Canada	No	No	No	No	No	No
HSA	Yes	Yes	No	Yes	No	Yes

Part IV – Usefulness of the BR Template

All the agencies rated the BR template as fair or good with regard to ensuring consistency in decision-making through improving regulatory memory. In addition, it can act as an audit tool and contribute to post-marketing activities (Table 5.11).

Table 5.11 Usefulness of BR Template in ensuring consistency, auditing and in post-marketing activities

Agency	Improving regulatory memory and enabling documentation of previous decisions to ensure consistency in decision-making	Contributing as an audit tool	Contributing to post-marketing activities
TGA	Good	Fair	Fair
Health Canada	Fair	Good	Good
HSA	Good	Good	Fair

Health Canada believed that the BR Template could ensure consistency, though their existing documents achieve the same function. If several agencies were to use the same BR Template, it would then be useful in determining the inconsistencies

between these agencies. While the table on benefits, risks and uncertainties might be able to highlight differences, it would allow a discussion of the reasons if relative importance or weights had been applied to enable a benefit-risk decision.

TGA found the BR Template useful for audit as it provided a consistent format although the lack of details about the studies might hamper the auditing process. Health Canada similarly noted that the uniformity of content would be useful for auditing their reviewers if they had consistently used the template appropriately, although again their existing documents might achieve the same purpose.

TGA concluded that while the BR Template had limited information on post-marketing issues, it would be useful for post-licensing reviewers to obtain an overview of the risks of the product. Similarly, Health Canada noted that the tables of risks might be useful for a follow-up post-marketing activity and could also be used as a reference for any risk management plans that were in place for the product. The convenience of quickly accessing this information in the BR Template using the navigation functions was noted.

HSA commented that the template could serve to document the baseline of the benefit-risk assessment of the product at approval. It would be good if the template could be used in the management of the benefit-risk profile of the product throughout the life cycle. However, the template would need to be amended significantly to allow for capture of post-marketing information as such information usually does not come from prospective clinical trials.

DISCUSSION

The outcome of this study has provided many valuable inputs regarding the areas for improvement to the BR Template and User Manual. In examining the value of the template in documenting benefit-risk decisions, it was found that with suitable clarification provided to the agencies, the BR Template should be able to fulfil this role adequately. This is supported by the observation that all the three agencies found the BR Template able to ensure consistency in the decision-making processes through its systematic approach in documentation. The clarifications required, should

consist of a clear objective and the intended functions of the BR Template, which primarily is to document and communicate significant findings and benefit-risk conclusions in a logical systematic manner.

Similarly, with the appropriate modifications suggested by the agencies, the applicability of the BR Template, with its contribution to regulatory decision-making and consistency in the assessment of benefits and risks, would be improved. The template, however, at the time of development, was not intended to replace the existing assessment reports used by the individual agencies but act as a tool for their consideration. This could have led to the views of a negative impact on work processes, increasing workload and worsening timelines.

The approach of using weights and values is new to many stakeholders and not frequently practised explicitly but rather implicitly as part of their current assessment processes. Therefore, adequate academic and scientific support should be provided in order to update and align the understanding and application of this approach. As the use of weights and values is a core component of the BR Template, the failure to understand this approach will directly compromise its effectiveness. It is, however, of interest that TGA was open to this new approach, Health Canada foresees the favourable utility of weights and values in discussing benefit-risk decisions and HSA considers the current template as being suitable for this purpose.

Looking at the outcomes and comments received for increasing transparent and effective communications and the willingness to share the template, it can be concluded that there is a general positive acceptance of these aspects in the light of the required revisions to be made to the BR Template. Although, many of the outcomes appear to be negative, these are supported by constructive inputs to improve the template in achieving its function to facilitate communication. Indeed, all three agencies agreed that the section on discussing uncertainties improves transparency in communication. TGA and HSA believed that the template does present an advantage over their current systems, with both TGA and Health Canada having observed the value of the template as a convenient and accessible source of safety information for post-marketing communication purposes.

It is observed that the reluctance to share the BR Template is largely due to existing legislation and confidentiality clauses for regulatory processes. Hence, it would be a safe assumption, that under relevant memorandums of understanding or future enforcement of legislation for documented transparency, these participating agencies are likely to share both the BR Template and Summary.

Although the rating of the willingness to share the Benefit-risk Summary section were not positive, these opinions were based on TGA's and Health Canada's observations that the BR Template on the whole could not capture some of the relevant information to support the decisions on the benefits, risks and the benefit-risk balance. As the contents of the Benefit-risk Summary section were auto-populated from the main BR Template, it is expected that the changes suggested by the agencies would improve the documentation function of the BR Template. The Benefit-risk Summary section would then be able to fulfil its role adequately. Suitable amendments to the contents may then be carried out to cater for the needs of the stakeholders based on their level of understanding, as suggested by HSA.

Arising from this study, the following clarifications are suggested as it is important to understand that:

- The intention of the BR Template was to highlight significant findings for quality, non-clinical and human pharmacology conclusions and further details could be obtained from the actual assessment report
- The design of the BR Template was to document and communicate the decisions during assessment that lead to the final benefit-risk decision
- How the application of weights and values would contribute to communicating decisions
- The appropriate sections were to document discussion and concerns arising from local clinical practice and guidelines, legislation, precedent decisions for other approved products, advantages of proposed route of administration or dosing regimen, expert opinions and judgement.
- The consistency in regulatory decisions is not a direct goal of the BR Template, but that this is a valuable aspect for emerging markets to benchmark their standards

The User Manual is an essential tool in ensuring the appropriate use of the BR Template and may be used as a vehicle to convey the above clarifications. In addition, the following suggestions were collated from this study, namely to:

- Incorporate bookmarks to facilitate navigation of the document
- Include a search function for keywords to help reviewers identify specific locations within the document
- Investigate the potential technical issues with the document support functions
- Provide case studies and examples to better illustrate the use of the BR Template

This study has also identified some deficiencies of the BR Template which will require attention so that the template can effectively fulfil its objectives which are to:

- Clarify the definitions of AE, risks and the level of details required
- Allow a discussion of the AEs in the section on safety information as well as the causes of SAEs and deaths and their contribution to the benefit-risk decision
- Clarify the definition of benefits in patients who received placebos
- Clarify the intention of the provision of study information if it is to document study details or to show the overall contribution of the identified benefits
- Allow a discussion of the comparison of benefits and benefit-risk balance with other approved products
- Provide a section on reasons for any changes to the proposed indication
- Allow a conclusive statement in the Benefit-risk Summary section on the outcome of weights and values to support the decision and
- Allow the provision of more details to support decisions on benefits and risks in the Benefit-risk Summary section

It is acknowledged that the three participating agencies, given their similarity in capacities and regulatory history, may not always represent other mature, established regulatory agencies or agencies in the emerging markets. Moreover, the opinions provided for this study from the three agencies are not collated from all reviewers and there may be concerns over the bias of a single reviewer representing

their agency. However, the study was completed under the supervision of the management in each agency and hence the outcomes are unlikely to be misrepresented.

With the recommendations provided to enhance the BR Template and User Manual, the next revision is expected to meet the current expectations of these participating agencies. The new BR Template could then be reviewed by other regulatory agencies to assess its potential role as a universal standard for documentation and communication of benefit-risk decisions. With regard to product life cycle management, this BR Template should be evaluated with pharmaceutical companies to assess its role as part of the submission dossier to the regulatory agencies. This should also be carried out with HTA agencies and patient advocacy groups to evaluate the effectiveness of the communication and accuracy of the messaging from the BR Template.

As the BR Template was developed using the criteria for the assessment of benefits, risks and benefit-risk balance as derived from the regulatory authority EMA, the template itself can be seen as guidance to the standards in benefit-risk assessment. There should be further studies to assess the use of the BR Template in helping emerging markets in their pursuit of improving their regulatory standards. In support of the regulatory agencies of the emerging markets, understanding the basis of the decisions of other agencies will be useful as these decisions from major regulatory agencies are often of value to these emerging markets. Although, there may be publicly available assessment reports, these may contain a significant amount of information to review that would require both time and scientific capabilities that are not available. Hence, it is now a suitable opportunity to investigate the use of the Benefit-risk Summary section for smaller agencies, in an effective stand-alone format, so that they can complete, understand and exchange such information with other similar sized agencies.

SUMMARY

- This study has identified changes required to the BR Template and User Manual to help achieve its objective in documenting and communicating benefit-risk decisions
- Most of the clarifications required are relevant to the intention of the BR Template but further guidance in documentation, especially weights and values, is required
- A major deficiency of the BR Template includes more detailed discussion on safety information
- The User Manual should be enhanced to provide the required clarifications and provide examples to illustrate the use of the BR Template
- The potential of the Benefit-risk Summary section should be further investigated

CHAPTER 6

Evaluation of the benefit-risk summary template for communicating benefit-risk decisions

INTRODUCTION

The assessment of benefits and risks of medicinal products for regulatory approval remains largely a qualitative exercise, although there are on-going initiatives to introduce a quantitative approach into the review process. Given the current setting, it is important that both the processes and the benefit-risk decisions are transparent and communicated to stakeholders for accountability. Hence there is a need to find appropriate tools to enhance communication in a manner that it would uphold transparency, consistency and standards.

Previous studies (Chapters 3 and 4) showed that the need for effective communication can be carried out through a benefit-risk framework supported by a documentation tool. The UMBRA Template was designed to enhance the communication of decisions in support of the 8-step framework for the assessment of benefits and risks. However, this template was based on the EMA guidance and the details required may be challenging for emerging regulatory agencies that are currently building up their scientific capabilities and regulatory processes.

The potential use of the BR Summary Template as a stand-alone in the emerging markets was proposed for the purpose of documenting, understanding and exchanging information on benefit-risk decision with other similar sized agencies (Chapter 5). Therefore, this study aims to review the usefulness of the BR Summary Template (a collation of relevant conclusions leading to the final benefit-risk decision) in communicating benefit-risk decisions by the Health Sciences Authority (HSA) of Singapore.

OBJECTIVES

The objectives of this study were to:

- Determine the practicality of documenting benefit-risk assessment for abridged applications in HSA using the BR Summary Template
- Examine the potential of the BR Summary Template for communicating benefit-risk balance and conclusions to stakeholders
- Assess the effectiveness of the User Manual in guiding a reviewer to complete the BR Summary Template

METHODS

This research was conducted as a retrospective and non-comparative study. The study protocol (Appendix III) was made available to all the participants of this study.

The UMBRA BR Template was reviewed and the Benefit-risk Summary section extracted to produce the BR Summary Template (Appendix IV). Both the User Manual and the study evaluation tool (as described in Chapter 5) for the BR Template were changed accordingly to support the BR Summary Template. The study package, namely the study protocol, BR Summary Template, revised User Manual (Appendix V) and the revised study evaluation tool (Appendix VI), were sent to 16 clinical reviewers in HSA (Therapeutic Products Branch) involved in the assessment of benefit-risk balance and the registration of medicines. The reviewers were asked to identify an appropriate product application based on the following criteria:

- New Drug application which requires a benefit-risk evaluation
- An abridged review, applicable to products having obtained a marketing approval in at least one country
- Regulatory decision (having received marketing approval or confirmed benefit-risk decision) obtained within the last three months

The reviewers transferred the relevant information required for the BR Summary Template from the completed clinical assessment reports (as per current processes in HSA) with the support of the User Manual. Following this transfer, the reviewers completed the study evaluation tool.

All responses were collated into a single group and the outcomes were presented according to their respective sections in the study evaluation tool. All data were expressed as percentage over number of responders for that item. Free-text comments were collated and presented in appropriate categories when necessary.

This was designed as an exploratory study and the outcomes were interpreted to provide qualitative inferences relating to the objectives. No statistical analyses were planned or conducted.

RESULTS

A total of twelve responses (75%) were received by August 2013. Of the four who did not respond, one was transferred to another unit, two did not have applications that met the criteria and the remaining one did not respond. Most (75%) of the responders had between one to five years of working experience in the agency, with one having less than a year and two having more than five years. As the reports were written independently, the responses actually represented the evaluation of ten different products reviewed via the abridged route.

The outcomes will be presented in four parts:

- Part I – User-friendliness of the BR Summary Template
- Part II – Appropriateness (fit for purpose) of the documentation
- Part III – Applicability of the BR Summary Template
- Part IV – Suggested amendments to the BR Summary Template

Part I - User-friendliness of the BR Summary Template

The template has two functions to help users navigate the document, namely the “Go to page” button and page thumbnails to locate a specific page (Figure 6.1). These are aimed at reducing the effort required to move between different sections.

The “Go to page” button appeared to be the more useful, as 83% of reviewers rated it either good or excellent (Figure 6.2). For the page thumbnails, 58% indicated it as fair or it was not used as it was commented that the thumbnail icons were too small to decipher the contents and bookmarks might have been more effective, although none rated the BR Summary Template as not user-friendly. There was a suggestion to include a “Back” button to the content page or another primary page.

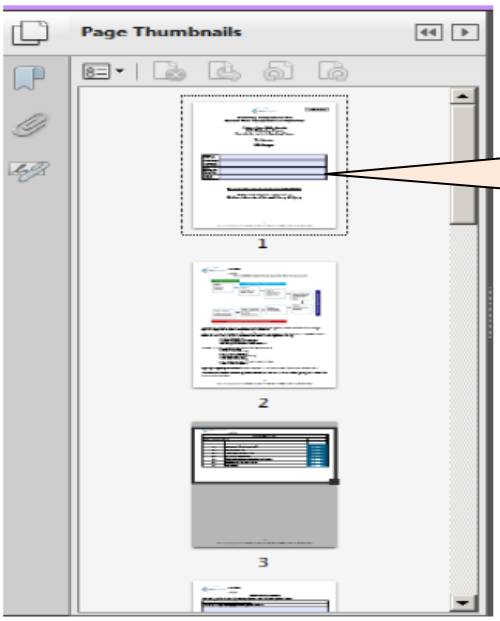
Figure 6.1 Navigation functions of the BR Summary Template

- "Go to Page" button at the Table of Contents

Click on button for the desired section

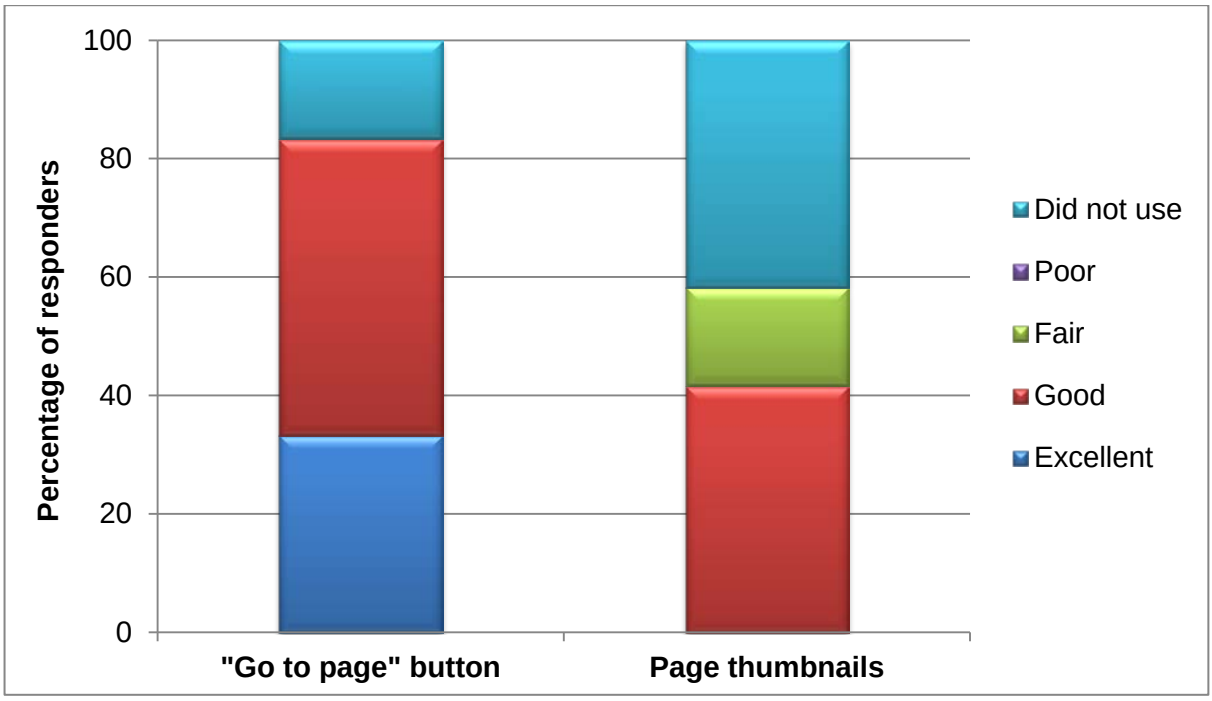
Table of Contents		
Benefit-Risk Summary		
1.1	Background (Decision Context)	Go to Page
2.1	Overall Summaries	Go to Page
3.1	Identified Benefits and Risks	Go to Page
4.1	Clinical Study Summary	Go to Page
5.1	Table of Pooled overall Incidence of events	Go to Page
6.1	Relative Importance and Values	Go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

- Page Thumbnails at the side of the BR Summary Template



Click on thumbnail icon for the desired page

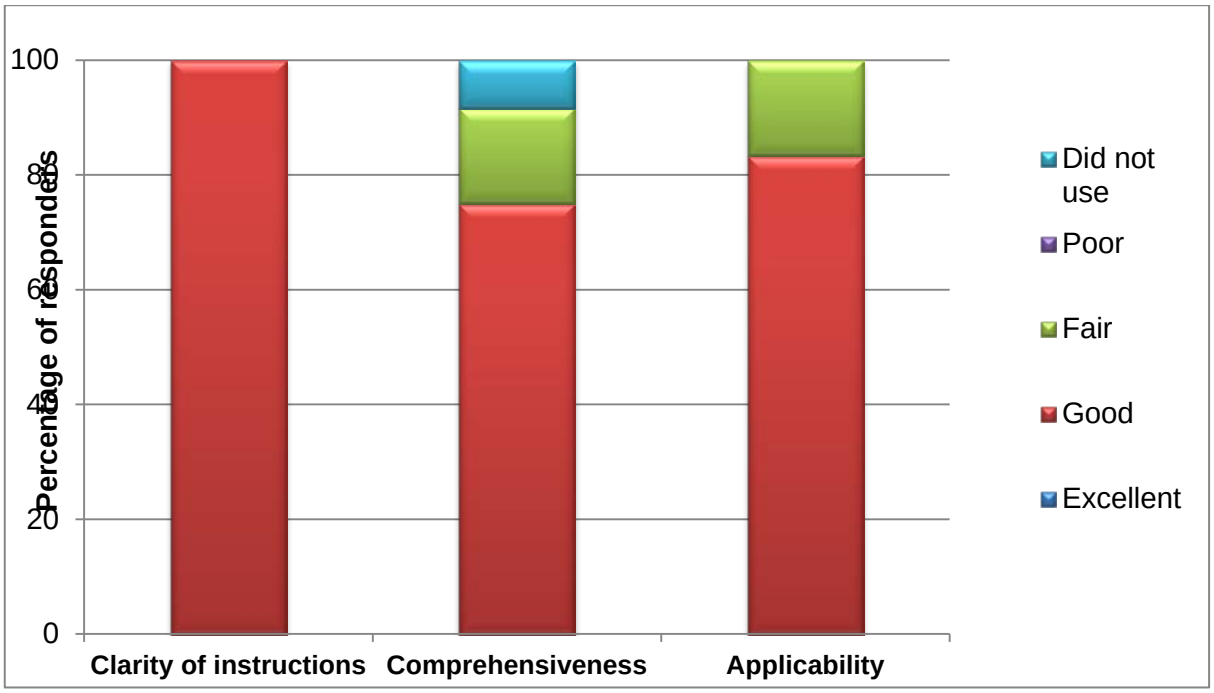
Figure 6.2 Practicality of the navigation functions



The User Manual was provided to guide the reviewer on the steps to complete the template, as well as to clarify the common terms used in the template. The majority of the responders (between 75% and 100%) rated the clarity, comprehensiveness and applicability of the User Manual as “good” (Figure 6.3).

None rated the manual as poor in any of the three parameters. Comments received included the consideration to provide examples or a case study in the manual to better illustrate the use of the template. An inexperienced reviewer might find the manual insufficiently comprehensive. Even though the User Manual provided instructions with regard to assigning relative importance to benefit and risk parameters, the lack of experience by the reviewers prevented them from effectively completing the BR Summary Template in this aspect.

Figure 6.3 Appropriateness of the User Manual

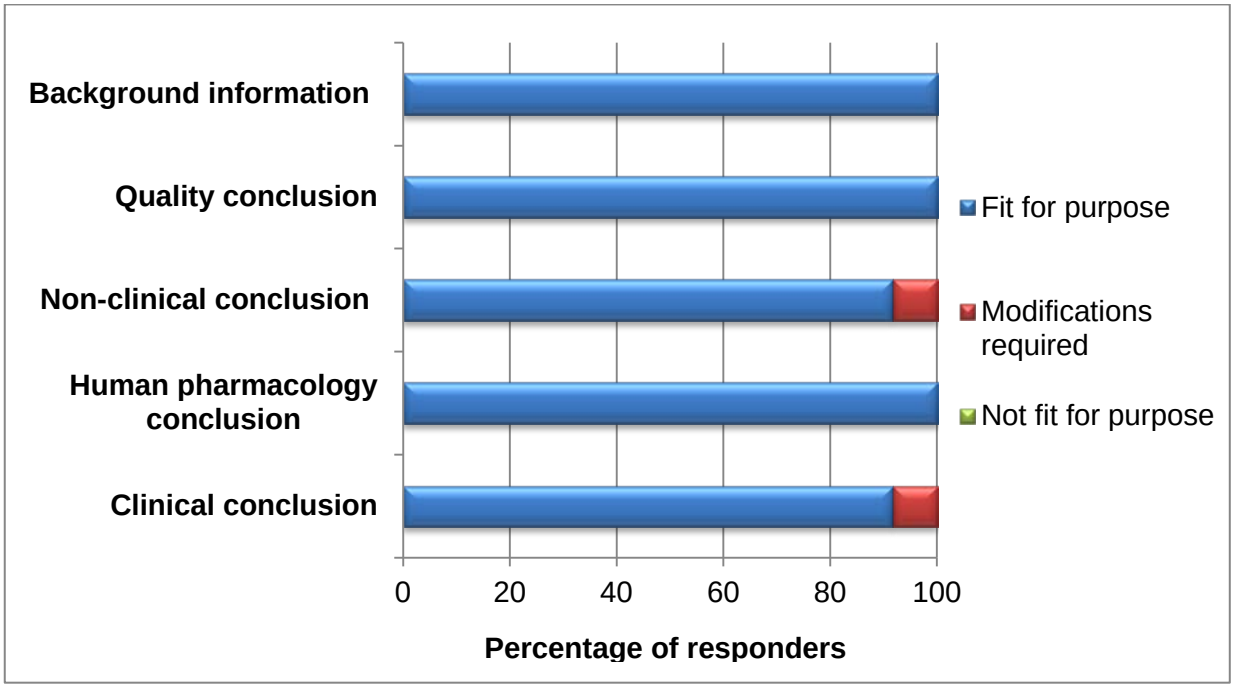


Part II – Appropriateness (fit for purpose) of the documentation

The appropriateness of a template is dependent on its capability to present the processes leading to the final benefit-risk conclusion in a structured and systematic manner. In documenting the various conclusions, the BR Summary Template was largely thought to be fit for purpose (92% to 100%, Figure 6.4).

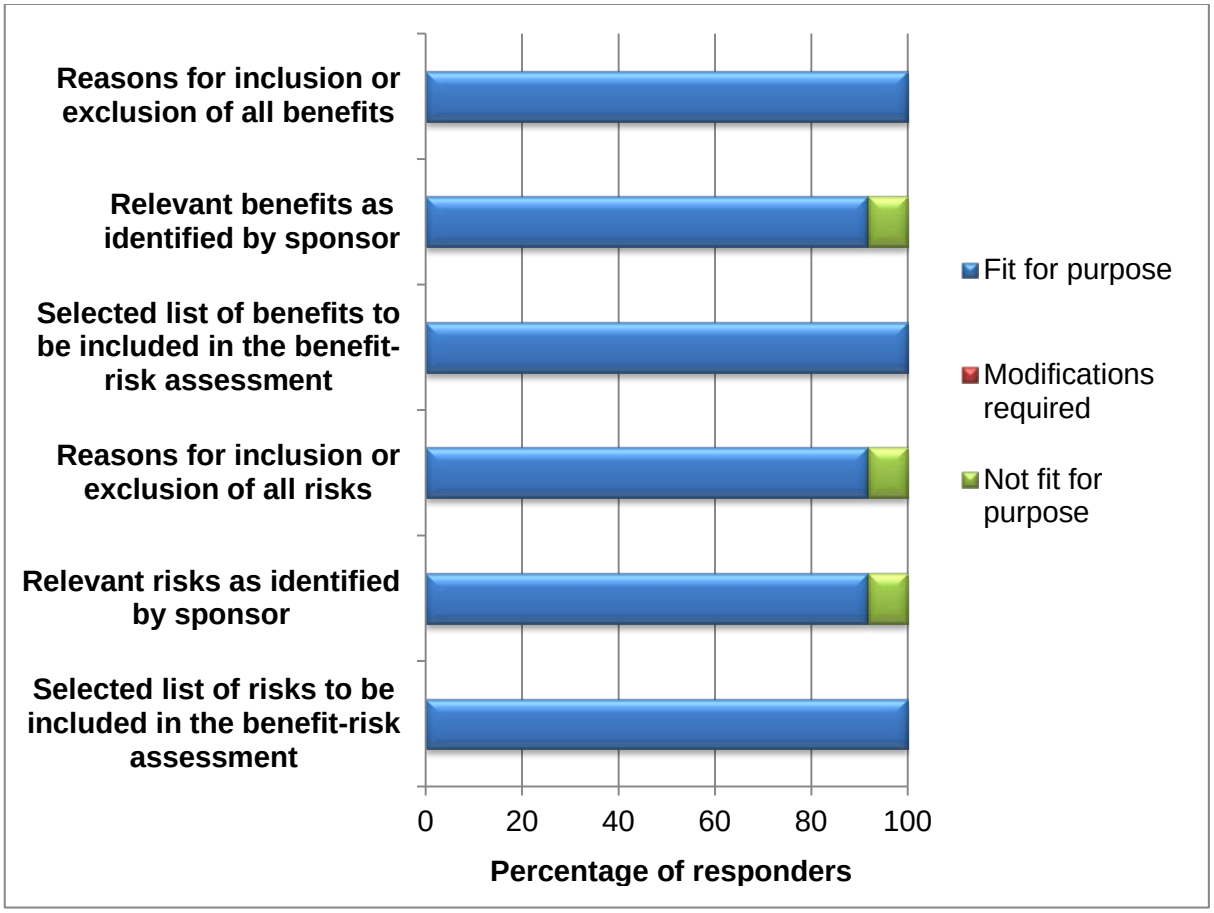
One modification suggested was to clarify the difference between the clinical conclusion section and the overall conclusion for benefit-risk balance, as it might appear redundant if misunderstood. The other modification was to make available more guidance on writing the non-clinical conclusion as some reviewers were not familiar with providing details for this section.

Figure 6.4 Documentation of relevant information supporting the benefit-risk decision



In documenting the benefits and risks for the product being evaluated, 92% to 100% of the responders believed the template is able to achieve the purpose (Figure 6.5). For documenting relevant benefits and risks as identified by the sponsor, one responder was unsure as to the usefulness of this as the reviewer would eventually indicate the benefits and risks that are to be included for assessment and hence rated these two parameters as not fit for purpose. However, the reasons for listing benefits identified by the sponsor and the reasons for inclusion or exclusion by the reviewer is both for transparency and to provide more fully the rationale for the benefit-risk decision. Another responder felt that there must be greater clarity in defining risks in the template as those considered critical to the benefit-risk assessment and as a result rated the documentation of inclusion or exclusion of all risks as being not fit for purpose.

Figure 6.5 Documentation of benefits and risks



The exercise of indicating relative importance and numerical values in the identified benefits and risks is aimed at improving the articulation of the basis of the benefit-risk decision. While the majority of the responders believed it was fit for purpose, 25% to 33% of the responders felt that the template required modifications or was not fit for purpose (Figure 6.6). The reasons and comments are listed in Table 6.1 and can be seen as proposed amendments to the template to improve documentation of weights and values. It can be concluded that the lack of understanding of weighting and valuing in general is the root cause of the above observation.

Figure 6.6 Documentation of weights and values

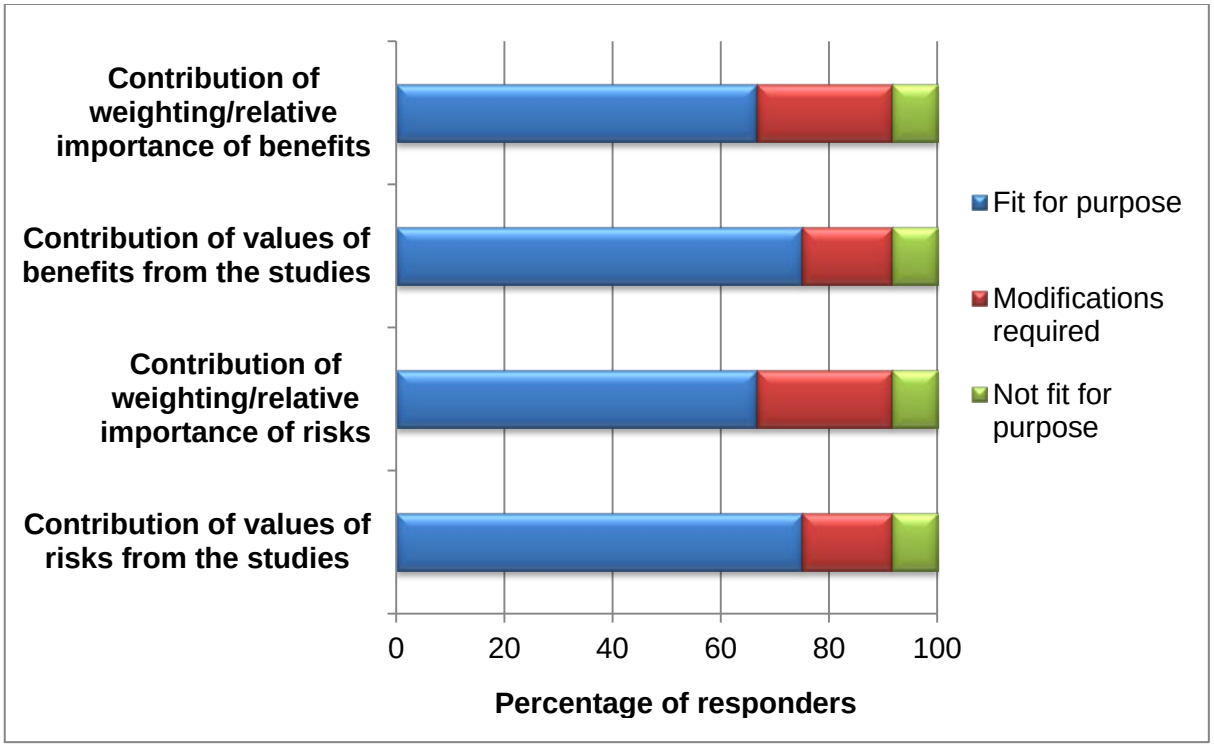
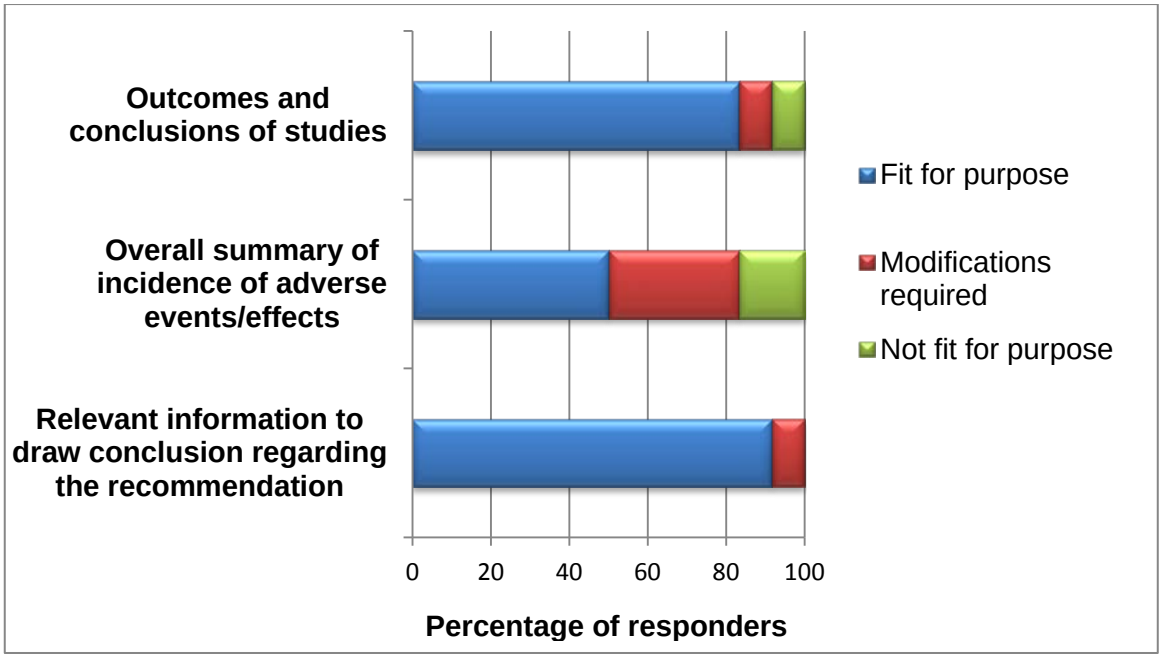


Table 6.1 Amendments required to improve the documentation of weights and values

Modifications required
• Clarification on how to assign weights
• Provide more instructions on how to complete these sections on weighting and valuing
• Recommend a consistent approach for weighting through a drop-down list of either numerical ranking or qualitative descriptors
• Recommend a free text box for cases whereby the weightings are not clear-cut
• Clarify if the weightings are to add up to 100% for both the benefits and risks, or are they to be considered separately for each component
• Provide some examples to illustrate the intention of the sections
Reasons not being fit for purpose
• Not sure how to complete these sections

Overall, the BR Summary Template appeared to be able to document study outcomes and relevant benefit-risk information leading to a regulatory recommendation, with 83% to 92% of responders agreeing on this (Figure 6.7).

Figure 6.7 Documentation of study outcomes, safety information and overall conclusion



With regards to documenting study outcomes, one responder recommended modification to allow for applications based on bibliographic submission or published literature. Another responder who rated the template “not fit” for presenting study outcomes commented that this section did not contribute to the overall benefit-risk assessment. As for the template being useful in presenting information leading to a regulatory recommendation, one responder indicated that more clarification on weighting should be provided in order to achieve this purpose.

As for presenting an overall summary of the adverse events or effects, half of the responders felt that either a modification was required, or the template was “not fit” for this purpose. The amendments required are listed in Table 6.2 and are largely technical in nature to accommodate other formats for uploading safety information.

Table 6.2 Amendments required to improve the documentation of overall summary of adverse events and effects

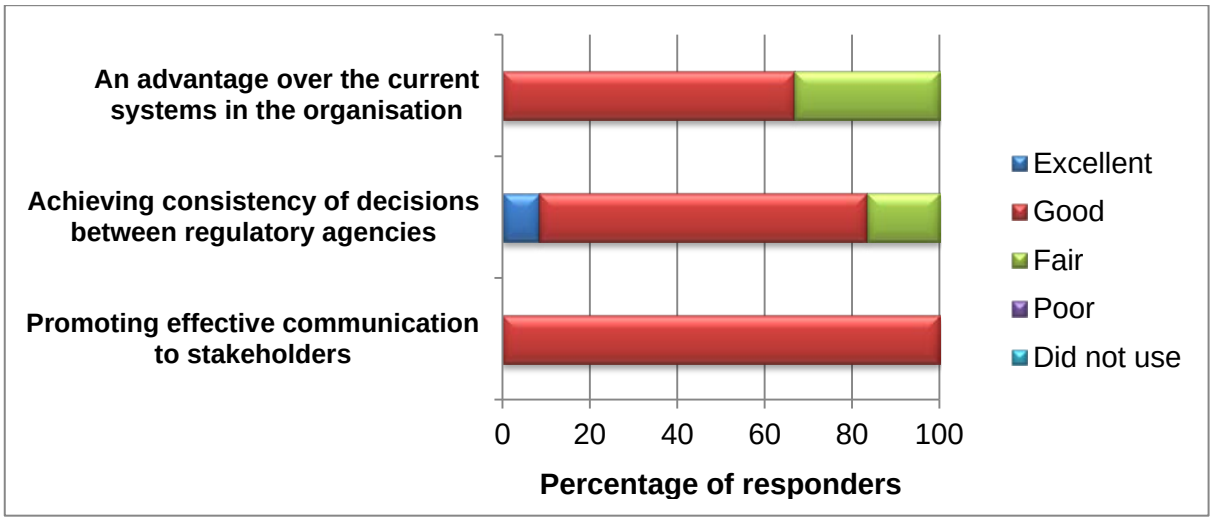
Modifications required	Reasons being not fit for purpose
• Allow text format, PDF snapshots or other common formats besides the picture formats	• This section does not serve the overall benefit-risk assessment
• Further categorisation to listing of common treatment-emergent AEs, serious AEs, death, discontinuations, etc	• Difficulties in attaching the PDF file
	• As the studies had different safety endpoints, there was no pooled summary

Part III - Applicability of the BR Summary Template

The primary goal of the BR Summary Template is to communicate regulatory decision-making either internally or to external stakeholders. All the responders found the template effective in promoting communication to stakeholders (Figure 6.8), and 83% of responders believed it could help achieve consistency of decisions between regulatory agencies. However, one responder commented that with the different weightings applied, consistency in regulatory decisions across agencies cannot be achieved.

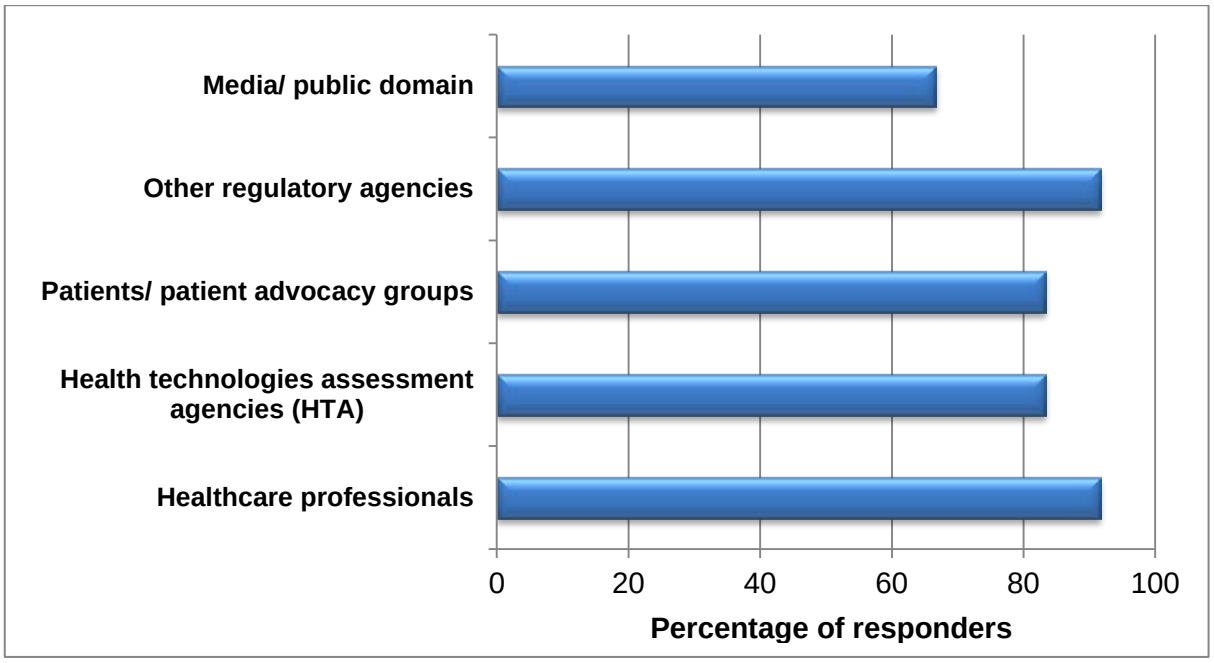
Four responders felt that the template did not confer any additional advantage over the current processes in the organisation. For new users, this approach generally appears more difficult to use than HSA's current report template as the current system is more efficient and reaches the same conclusion. Incidentally, the BR Summary Template is a repeat of a section of the existing HSA's current report template. Moreover, the BR Summary Template was formatted as a PDF which makes the use and uploading of information more tedious compared with the existing Word document.

Figure 6.8 Applicability of BR Summary Template



When the responders were asked if they were willing to share the completed BR Summary Template, 92% were willing to do so with healthcare professionals and other regulatory agencies (Figure 6.9). One responder indicated “Not applicable” for health technologies assessment agencies (HTA) since this jurisdiction is not current in Singapore. One responder commented that the template could not adequately describe the benefit-risk findings. Reservations in sharing with patients, patient advocacy groups, media and in public domains included the use of technical terms and medical jargon being unsuitable for lay persons, which may lead to confusion and misinterpretation. This could invite unnecessary criticism and one responder suggested that only selected sections be made available to such stakeholders.

Figure 6.9 Willingness to share the BR Summary Template with various stakeholders



Part IV – Suggested amendments to the BR Summary Template

One reviewer suggested combining the identification of benefits and risks with the exercise of assigning weights and values to avoid repetition. However, this suggestion could be accommodated by auto-populating the benefits and risks in Section 3 into Section 6. More guidance could be given on listing the reasons for inclusion or exclusion of benefits, like local disease burden (medical need), available alternatives, strength of evidence, clinical relevance and convenience to patients. For completeness, one reviewer recommended adding another section to indicate if the benefit-risk balance is positive or negative, before being asked to provide reasons for a negative benefit-risk balance. While this study was conducted for new active substances, one reviewer recommended that the template could be amended to accommodate clinical variations.

DISCUSSION

The findings of this study showed that the successful implementation of a new process or tool in an established regulatory agency is dependent on the fundamental understanding of the principles behind the template. The concept of weighting or assigning relative importance and valuing is a technique that is relatively new to both

HSA and other regulatory agencies (Chapter 3). However, weighting and valuing is seen as an explicit presentation of the subjective interpretation of a set of clinical information. This exercise aimed to enhance the transparency of decision-making by making it clear that the priorities placed on a set of benefits and risks ultimately affect the resulting benefit-risk balance. Without an understanding of the rationale behind weighting and valuing, some reviewers could not appreciate its contribution to effective documentation and communication.

As for all new initiatives, an implementation strategy or change management programme should be drawn up. This would consist of dialogues with senior management, a dedicated training plan and the use of training tools. It is expected that senior management should be made aware of the potential advantages of the BR Summary Template and are agreeable to implementing this across the relevant departments in the agency. A top-down approach might be required to ensure the appropriate implementation of this template, as this may be helpful in situations where reviewers are unable to comprehend its role and advantages in the entire process. However, the end-users or reviewers should also clearly understand the usefulness of the template, its role in the current processes and the impact on existing workflow so as to ensure maximum compliance. This could be achieved through a standard training programme which would include a driver from senior management. In addition, it should include leaders among the users who would be trained as pioneers for the successful implementation of the BR Summary Template. As is evident from this study, the User Manual proved to be a valuable tool, however amendments would be required to enhance its effectiveness.

The current BR Summary Template would require a revision to the technical capabilities and an improvement for the documentation of safety information and adverse events. The User Manual should be revised to include examples and case studies to better illustrate the use of the template. It appears that the capacity of the BR Summary Template to effectively communicate a benefit-risk decision has been clearly exhibited, as supported by the reviewers who were willing to share this template with stakeholders. However, this should go hand–in–hand with the legal framework to give the agency the mandate to implement it. Without the assurance of

legal protection and support of management, reviewers would be unlikely to release such reports, especially to stakeholders who are lay persons.

The reviewers in this study indicated their willingness to share the completed BR Summary Template for a specific product with other regulatory agencies where there is a memorandum of understanding. It is also appropriate to examine the utility of this template as a means of transferring knowledge and communicating the basis of a decision. For major regulatory agencies it may be a requirement to provide details of the evaluation to achieve a level of transparency stipulated by the jurisdiction. However, this study, even in the absence of these details, has demonstrated that the BR Summary Template is an effective tool to communicate benefit-risk decisions. Therefore it may be considered as a basic report template for agencies that are in transition to build up their evaluation capabilities. Thus this would be an ideal tool for communicating benefit-risk decisions to emerging regulatory agencies, since the components of the template address the basic needs of a sound and scientific discussion.

From another perspective, established agencies may find that the BR Summary Template replicates existing publicly available reports and is thus judged by some to be redundant. Attempts to use IT to auto-populate existing information from current reports should be undertaken to improve on this aspect. Through this study and Chapter 3, it can be seen that weighting and valuing are not consistently applied but the relevance of such an exercise in effective communication is accepted. Again, it is important to educate regulators on the use of weights and values as they form a key component with regard to communicating decisions in a transparent manner. It is only through a global understanding of the need for a common template that consistency in evaluating benefits and risks can be achieved.

The outcome of this case study, involving reviewers within the Health Sciences Authority as representative of the emerging markets in the region, has demonstrated that the principles of the BR Summary Template are applicable to other jurisdictions or similar agencies. This is indeed encouraging in the current climate, where the debate surrounding the benefit-risk assessment of medicines is on the top of many

regulatory agencies' agenda. Thus the promising features of the BR Summary Template will, no doubt, contribute to such on-going discussion.

SUMMARY

- The BR Summary Template is adequate to document benefits, risks, relevant summaries and conclusions
- A revision of the BR Summary Template should include technical improvements and more details for safety information
- The User Manual and navigation functions are useful to guide the reviewer in completing the template
- More guidance should be provided for weighting and valuing, as well as the use of examples and case studies, in the User Manual
- The BR Summary Template can be a useful tool for communicating benefit-risk decisions to a variety of stakeholders
- The principles behind the template may be useful for guiding the benefit-risk assessment of medicines

CHAPTER 7

Evaluation of regulatory agencies' strategies for communicating benefit-risk decisions

INTRODUCTION

The evolution in the requirements for assessing the benefits and risks of medicinal products has resulted in changes in the evaluation processes. Beyond the separate assessment of benefits and risks, the emphasis is now on the balance between the two, having to justify the potential harms in view of the efficacy claims. In a changing society where the demand is for transparency of such decision-making processes, there is a now a major challenge to adequately communicate the relevant information to stakeholders. The articulation of benefit-risk decisions remains both a responsibility as well as an opportunity.

The European Medicines Agency (EMA) and the US FDA have provided guidances on the assessment of medicines. EMA provided a reflection paper on the assessment of benefits and risks of medicines (EMA, 2008), while US FDA (as part of the PDUFA V) has implemented a benefit-risk framework to allow the appropriate discussion on the considerations taken into account for a regulatory decision (FDA, 2012). While these may enhance the benefit-risk evaluation of a product, there is currently no standard template for the documentation and communication of the evaluation outcomes and benefit-risk decisions. Individual agencies have their own internal evaluation report templates and also those for publicly available assessment reports. Consequently, stakeholders seeking information on the assessment of a product may be presented with similar information in different formats.

The results from a study on BR frameworks (Chapter 3) showed that both regulatory agencies and pharmaceutical companies believe that a benefit–risk framework would enhance the quality (transparency and consistency) of communication and should provide documentation for a structured discussion, acting as a tool for communication among peers within the organisation and between the organisation and stakeholders. The 8-step universal benefit-risk framework, UMBRA (Chapter 4), was therefore proposed and this framework encompasses the principles of existing frameworks by other major regulatory agencies such as the US FDA (FDA 2013) and EMA (EMA, 2010) (Table 7.1). A documentation tool was also developed to support this framework and formed part of the Benefit-risk Assessment Support System (BRASS, Chapter 4).

Table 7.1 Comparisons of US FDA and EMA benefit-risk assessment frameworks with the Universal Benefit-Risk Framework

Frameworks reviewed	Core elements							
	Framing the decision	**Identifying benefits and risks**		**Assessing benefits and risks**		**Interpretation and outcome**		
US FDA	Analysis of conditions and unmet medical needs	Clinical benefits, risks		Evidence and uncertainties				Conclusions and reasons, risk management plans
EMA PrOACT-URL	Nature and framing of the problem	Objectives, favourable and unfavourable effects		Alternatives regarding options to be evaluated and the consequences	Trade-offs and benefit-risk balance	Evaluating uncertainty	Effects table and risk tolerance	Consistency of decisions (linked decisions)
Universal Benefit-risk framework	**Step 1**	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**	**Step 7**	**Step 8**
	Decision context	Building the value tree	Customising the value tree	Weighting (relative importance) of benefits and risks	Scoring the options	Evaluating uncertainties	Concise presentation of results (visualisation)	Expert judgment and Communications

This BR Template was designed to enhance effective documentation and communication of decisions and was used as the basis of comparison in this study. The outcomes from three agencies (TGA, Health Canada and HSA) showed that the BR Template is useful for documenting and communicating a benefit-risk decision (Chapter 5), while the BR Summary Template was investigated and similarly found to be adequate for the above purposes (Chapter 6). It is noted that there are currently publicly available assessment reports from the major regulatory agencies. This study aims to review these publicly available assessment reports to see if they adequately fulfil the functions found in the BR Template and BR Summary Template.

OBJECTIVES

The objectives of this study were to:

- Compare the format of the US FDA's, EMA's, HC's and TGA's publicly available assessment reports with the BR Template and BR Summary Template
- Evaluate whether these four regulatory agencies have an effective approach for communicating benefit-risk decisions to all stakeholders
- Examine the utility of the BR Summary Template for communicating benefit-risk decisions by the US FDA and EMA using a case study.

METHODS

In order to establish the utility of the BR Template, four major reference agencies were selected, namely US FDA, EMA, Health Canada, and TGA. The criteria for choosing these reference agencies was based on a positive history of established regulatory processes, global recognition of regulatory standards and the public availability of assessment reports. Therefore, for the purpose of comparison in this study, the following report formats of the four reference agencies were used:

- US FDA – Medical Review and the Risk Benefit Assessment
- EMA – European Public Assessment Report (EPAR) and the Executive Summary
- Health Canada – Summary Basis of Decision (SBD)
- TGA – Australian Public Assessment Report (AusPAR)

The above mentioned report formats were expected to be common in their function to the BR Template, which is to document and communicate the information supporting benefit-risk decisions and regulatory outcomes. Report format templates were retrieved online for each agency. In the absence of an official document that explained the structure of the format, a recent publicly available assessment report would be used to review the contents of the report or support the understanding of the format. Comparison of the report formats from the four reference agencies was conducted by reviewing the section headings of the report against those of the BR Template and BR Summary Template. Where there was a summary in the reference agency's format, this would be directly compared with the BR Summary Template and the findings were tabulated and presented.

Furthermore, to illustrate the use of the BR Summary Template, a case study was conducted using a recent US FDA Medical Review (FDA, 2012b) and EPAR (EMA, 2013c) for the same product. Zaltrap® (aflibercept) was chosen as it was approved around the same time by both agencies (03 August 2012 for US FDA and 01 February 2013 for EMA). Importantly, the US FDA Medical Review was written according to the new 5-step benefit-risk framework that features the Risk Benefit Assessment. These two respective summaries were transferred into the BR Summary Template and the omissions reviewed.

RESULTS

The outcomes will be presented in four parts:

- Part I – Formats of the four reference agencies' publicly available report templates
- Part II – Comparison of the four reference agencies' report templates with the BR Template
- Part III – Comparison of the four reference agencies' report templates with the BR Summary Template
- Part IV – Case study of US FDA's and EMA's summary reports on Zaltrap®

Part I - Formats of reference agencies' publicly available report templates

US FDA's Medical Review

The US FDA Medical Review consists of nine sections (Table 7.2), with the opening section presenting the recommendations and Risk Benefit Assessment (based on the 5-step benefit-risk framework). The remaining sections present the details of the assessment supporting the recommendations. It is known that the public available reports from US FDA are a redacted subset of the complete evaluation data. The original dataset will include discussions of queries and responses by the sponsor with the US FDA.

EMA's EPAR

The EPAR consists of an Executive Summary and four sections (Table 7.3). The publicly available EPAR is extracted from the complete assessment report which would have included responses and justifications to EMA for queries raised. Agency-specific requirements are those relating to submission information and regulatory processes.

Table 7.2 Format of US FDA Medical Review

US FDA's Medical Review	
Section	Content
1	Recommendations/ Risk benefit assessment
2	Introduction and regulatory background
	Product information
	Tables of currently available treatment for proposed indications
	Availability of proposed active ingredient in US
	Important safety issues with consideration to related drugs
	Summary of pre-submission regulatory activity related to submission
	Other relevant background information
3	Ethics and good clinical practices
	Submission quality and integrity
	Compliance with GCP
	Financial disclosures
4	Significant efficacy/safety issues related to other review disciplines
	Chemistry manufacturing and controls
	Clinical microbiology
	Preclinical pharmacology/toxicology
	Clinical pharmacology (mechanism of action, pharmacodynamics, pharmacokinetics)

Section	Content (continued)
5	Sources of clinical data
	Tables of studies/clinical trials
	Review strategy
	Discussion of individual studies/clinical trials
6	Review of efficacy
	Efficacy summary
	Indication (methods, demographics, subject disposition)
	Protocol violations
	Analysis of primary endpoints
	Analysis of secondary endpoints
	Other endpoints
	Subpopulations
	Analysis of clinical information relevant to dosing recommendations
	Additional efficacy issues/analyses

Section	Content (continued)
7	Review of safety
	Safety summary
	Methods (studies, categorisation, pooling of data)
	Adequacy of safety assessment (overall exposure, dose response, special animal and/or in vitro testing, metabolic/clearance/interaction workup, potential AE for similar drugs)
	Major safety results (deaths, non-fatal SAE, dropouts/discontinuation, significant AE, specific primary safety concern
	Supportive safety results (common AE, lab findings, vital signs, ECGs, special safety studies, immunogenicity)
	Other safety explorations (dose dependency, time dependency, drug-demographic/drug-disease/drug-drug interactions
	Additional safety evaluations (human carcinogenicity, human reproduction/pregnancy data, paediatric and effects on growth, overdose/abuse potential/withdrawal/rebound
	Additional submissions/safety issues
8	Post market experience
9	Appendices

Table 7.3 Format of EMA's EPAR

EMA's EPAR	
Section	Content
	Executive summary
1	Background information on the procedure
	Submission of the dossier
	Steps taken for the assessment of the product
2	Scientific discussion
	Introduction
	Quality aspects
	Introduction
	Active substance
	Finished medicinal product
	Discussion on chemical, pharmaceutical and biological aspects
	Conclusions on the chemical, pharmaceutical and biological aspects
	Recommendations for future quality development
	Non-clinical aspects
	Introduction
	Pharmacology
	Pharmacokinetics
	Toxicology
	Ecotoxcitiy/environmental risk assessment
	Discussion on non-clinical aspects
	Conclusion on non-clinical aspects

Section	Content (continued)
2	Clinical aspects
	Introduction
	Pharmacokinetics
	Pharmacodynamics
	Discussion on clinical pharmacology
	Conclusion on clinical pharmacology
	Clinical efficacy
	Dose response studies
	Main studies
	Supportive studies
	Discussion on clinical efficacy
	Conclusion on clinical efficacy
	Clinical safety
	Discussion on clinical safety
	Conclusion on clinical safety
	Pharmacovigilance
	User consultation
3	Benefit-risk balance
4	Recommendations

Health Canada's SBD

The Health Canada's Summary Basis of Decision (SBD) consists of eight sections (Table 7.4). This is a publicly available document that presents the relevant information to support the decision made by Health Canada for the product (Health Canada, 2012a and 2012b). Unlike US FDA Medical Review and EPAR, there is no separate summary portion as the SBD is meant for this purpose. The agency-specific information is related to submission milestones, recent and post-authorisation activities. These disparities are not considered to influence the processes on the assessment of benefits and risks.

Table 7.4 Format of Health Canada's Summary Basis of Decision

Health Canada's Summary Basis of Decision		
Section	Content	Purpose
PAAT	Post-Authorisation Activities Table	List of post-authorisation activities for the approved product
1	What was approved?	Information on approved indication, intended population, contraindications and product presentations
2	Why was <product> approved?	Discussion on basis of benefit-risk balance
3	What steps led to the approval of <product>?	Submission milestones
4	What follow-up measures will the company take?	Information on post-approval commitment
5	What post-authorisation activity has taken place for <product>?	Information provided as link to earlier section on Post-Authorization Activity Table (PAAT)
6	What other information is available about drugs?	Links to other webpages within Health Canada website
7	What was the scientific rationale for Health Canada's decision?	Details on: a) Clinical Basis of Decision i. Clinical pharmacology ii. Clinical efficacy iii. Clinical safety iv. Safety topics of special interest b) Non-clinical Basis of Decision c) Quality Basis of Decision

TGA's AusPAR

The TGA AusPAR consists of six sections (Table 7.5) (TGA, 2012), the format being close to the EPAR but without the Executive Summary. As with the previous formats of the other three agencies, agency-specific information are those related to individual regulatory and submission information. It is known that the AusPAR contains information extracted from the complete, original assessment reports.

Table 7.5 Format of TGA's AusPAR

TGA's AusPAR	
Section	Content
1	Introduction to product submission
	Submission details
	Product background
	Regulatory status
	Product information
	List of abbreviations
2	Quality findings
	Drug substance
	Drug product
	Biopharmaceutics
	Advisory committee considerations
	Quality summary and conclusions
3	Non-clinical findings
	Introduction
	Pharmacology
	Pharmacokinetics
	Toxicology
	Non-clinical summary and conclusions

Section	Content (continued)
4	Clinical findings
	Introduction
	Pharmacodynamics
	Pharmacokinetics
	Dosage selection for pivotal studies
	Efficacy
	Safety
	Clinical summary and conclusions
5	Pharmacovigilance findings
	Risk management plan
6	Overall conclusion and risk/benefit assessment
	Quality
	Non-clinical
	Clinical
	Risk management plan
	Risk-benefit analysis
	Outcome

Part II – Comparison of the four reference agencies' report templates with the BR Template

The outcomes showed that the format of the reference agencies' reports are generally similar and when compared with the BR Template, they were all found to lack the features that list the identified benefits and risks, application of values and weights (relative importance) and visualisation of the assessment outcomes (Table 7.6). In addition, while it is acknowledged that relevant discussions and considerations contributing to the final benefit-risk decision maybe reported in the existing reference agencies' templates, the BR Template allowed for this through a structure of guided questions.

US FDA's Medical Review

There were two comparison made for the Medical Review. Sections 2 to 9 of the US FDA Medical Review format was compared to the BR Template to assess how these sections can accommodate the requirements of the BR Template in presenting the relevant information. Items found specific to US FDA included submission activities and quality, compliance to GCP, financial disclosures and appendices. These were found not to directly influence the decision on benefit-risk balance. The principle between the two templates is found to be similar – the focus is on the contribution of clinical efficacy and safety to the overall benefit-risk balance, with a significant contribution of quality, non-clinical and pharmacology concerns succinctly discussed (Section 4 of Medical Review, Section 2 of BR Template). The second comparison was made between the Risk Benefit Assessment (Section 1 of Medical Review) and the BR Template. It was considered that the former could perform the function of the BR Template, and hence a separate comparison was conducted.

As the BR Template was not designed to present details of the clinical studies, it could not accommodate the US FDA's section on the discussion of studies and clinical trials. In reviewing efficacy, though the BR Template was not structured to discuss the demographics, subject disposition and protocol violations, the essential messages would have been combined into the general considerations. Similarly, this applies to the discussion on the clinical information relevant to dosing recommendation which may not be adequately discussed in the BR Template. It was however noted that the US FDA Medical Review could not fulfil the entire section 3 of the BR Template on listing and justifying the identified benefits. These may be generally discussed in the review but not explicitly stated as in the BR Template. Likewise, there are no features to openly discuss the role of valuing and weighting (relative importance) in their assessment, as in the BR Template, though these may have been achieved throughout the document. There was no visualisation function in the US FDA Medical Review.

Table 7.6 Comparison of sections of reference agencies' publicly available assessment reports with the BR Template

BR Template	US FDA		EMA	Health Canada	TGA
Content	Medical Review	Section 1 (Risk Benefit Assessment)	EPAR	SBD	AusPAR
1 Background					
1.1 Specify proposed therapeutic indication	Section 2	Analysis of condition	Section 1 – Scientific discussion	Not available	Section 1
1.2 Treatment modalities evaluated	Section 2	Analysis of condition	Section 1 – Scientific discussion	Not available	Section 1
1.3 Other current available treatment options not considered or evaluated	Section 2	Current treatment options	Section 1 – Scientific discussion	Not available	Section 1
1.4 Known risks with compounds of same therapeutic class	Section 2	Risk	Section 1 – Scientific discussion	Section 7 - Clinical	Section 1
1.5 Medical need	Section 2	Analysis of condition, Current treatment options	Section 1 – Scientific discussion	Section 2	Section 1
1.6 Aims of treatment and expected treatment size	Section 2	Analysis of condition, Current treatment options	Section 1 – Scientific discussion	Not available	Section 1

Table 7.6 Comparison of sections of reference agencies' publicly available assessment reports with the BR Template (continued)

BR Template	US FDA		EMA	Health Canada	TGA
Content	Medical Review	Section 1 (Risk Benefit Assessment)	EPAR	SBD	AusPAR
2 Overall Summary					
2.1 Quality overall summary	Section 4	Not available	Section 2 – Quality aspects	Section 7 - Quality	Section 6 - Quality
2.2 Non-clinical overall summary	Section 4	Not available	Section 2 – Non-clinical aspects	Section 7 – Non-clinical	Section 6 – Non-clinical
2.2.1 Comments on relevant findings and potential implications/ investigations required	Section 4	Not available	Section 2 – Non-clinical aspects	Section 7 – Non-clinical	Section 3
2.2.2 Conclusions implicating benefit-risk assessment for humans	Section 4	Not available	Section 2 – Non-clinical aspects	Section 7 – Non-clinical	Section 3
2.3.1 Human pharmacology: Overall summary	Section 4	Not available	Section 2 – Clinical aspects	Section 7 – Clinical pharmacology	Section 4
2.3.2 Human pharmacology Conclusions	Section 6	Not available	Section 2 – Clinical aspects	Section 7 – Clinical pharmacology	Section 6 - Clinical
2.4.1 Clinical overall summary	Section 6	Benefit	Section 2 – Clinical efficacy	Section 7 – Clinical	Section 6 - Clinical
2.4.2 Clinical conclusions	Section 6	Benefit	Section 2 – Clinical efficacy	Section 7 – Clinical	Section 6 - Clinical
3 Identified benefits and risks					
3.1 Listing of all benefits, and justification for inclusion and exclusion	Not available	Not available	Not available	Not available	Not available
3.2 Listing of all risks, and justification for inclusion and exclusion	Not available	Not available	Not available	Not available	Not available

Table 7.6 Comparison of sections of reference agencies' publicly available assessment reports with the BR Template (continued)

BR Template	US FDA		EMA	Health Canada	TGA
Content	Medical Review	Section 1 (Risk Benefit Assessment)	EPAR	SBD	AusPAR
4 Benefit and Risk – Study information					
4.1.1 – 4.1.9 Study details of benefit	Section 6	Benefit	Section 2 – Clinical efficacy	Section 7 – Clinical	Section 4
4.1.11 Discussion of consistency across all studies	Section 6	Benefit (Evidence and uncertainties)	Section 2 – Clinical efficacy	Section 7 – Clinical	Section 4
4.1.12 Discussion of evidence in relevant subgroups	Section 6	Benefit (Evidence and uncertainties)	Section 2 – Clinical efficacy	Section 7 – Clinical	Section 4
4.1.13 Discussion of confirmation by results of non-primary endpoint	Section 6	Benefit (Evidence and uncertainties)	Section 2 – Clinical efficacy	Section 7 – Clinical	Section 4
4.1.14 Discussion on patient reported outcomes	Section 6	Benefit (Evidence and uncertainties)	Section 2 – Clinical efficacy	Section 7 – Clinical	Section 4
4.1.15 Overall conclusion	Section 6	Benefit (Conclusions and reasons)	Section 2 – Clinical efficacy	Section 7 – Clinical	Section 4
4.2 Risks: Overall summary					
4.2.1 Overall incidence of adverse effects	Section 7	Risk	Section 2 – Clinical safety	Section 7 – Clinical	Section 4
4.2.2 Overall incidence of serious adverse effects		Risk	Section 2 – Clinical safety	Section 7 – Clinical	Section 4
4.2.3 Discontinuation rate due to AEs	Section 7	Risk	Section 2 – Clinical safety	Section 7 – Clinical	Section 4
4.2.4 Dose reduction rate due to AEs	Section 7	Risk	Section 2 – Clinical safety	Section 7 – Clinical	Section 4
4.3 Adverse effects	Section 7	Risk	Section 2 – Clinical safety	Section 7 – Clinical	Section 4
4.3.1 Details of AE	Section 7	Risk	Section 2 – Clinical safety	Section 7 – Clinical	Section 4

Table 7.6 Comparison of sections of reference agencies' publicly available assessment reports with the BR Template (continued)

BR Template	US FDA		EMA	Health Canada	TGA
Content	Medical Review	Section 1 (Risk Benefit Assessment)	EPAR	SBD	AusPAR
4.4 Uncertainties (benefits and risks)					
4.4.1 Discussion on choice of dose, comparators and endpoints	Section 5	Evidence and uncertainties	Sections 2 & 3	Section 7 – Clinical	Section 6 – Risk-benefit analysis
4.4.2 Discussion on design, conduct and statistics	Section 5	Evidence and uncertainties	Sections 2 & 3	Section 7 – Clinical	Section 6 – Risk-benefit analysis
4.4.3 Discussion on validation of measurements and scales	Section 5	Evidence and uncertainties	Sections 2 & 3	Section 7 – Clinical	Section 6 – Risk-benefit analysis
4.4.4 Discussion on negative studies	Section 5 & 6	Evidence and uncertainties	Sections 2 & 3	Section 2 & 7 – Clinical	Section 6 – Risk-benefit analysis
4.4.5 Discussion of consistency across factors	Section 5 & 6	Evidence and uncertainties	Sections 2 & 3	Section 2 & 7 – Clinical	Section 6 – Risk-benefit analysis
4.4.6 Interactions with food/ drugs	Section 7	Risk	Section 2 – Clinical safety	Section 7 – Clinical	Section 4
4.4.7 Limitations of dataset regarding safety	Section 7	Risk (Evidence and uncertainties)	Section 2 – Clinical safety	Section 2 & 7 – Clinical	Section 6 – Risk-benefit analysis
4.4.8 Potential for off label use, overdose, abuse and misuse	Section 7	Risk (Evidence and uncertainties)	Section 2 – Clinical safety and pharmaco-vigilance	Section 2 & 7 – Clinical	Section 6 – Risk-benefit analysis
4.4.9 Risk with respect to standard of care	Section 7	Risk (Evidence and uncertainties)	Section 2 – Clinical safety	Section 3 – Benefit-risk assessment	Section 6 – Risk-benefit analysis
4.4.10 Comments on any other uncertainties	Section 5, 6 & 7	Evidence and uncertainties	Sections 2 & 3	Section 2	Section 6 – Risk-benefit analysis

Table 7.6 Comparison of sections of reference agencies' publicly available assessment reports with the BR Template (continued)

BR Template	US FDA		EMA	Health Canada	TGA
Content	Medical Review	Section 1 (Risk Benefit Assessment)	EPAR	SBD	AusPAR
5 Benefit-risk Summary Table and Expert Judgment					
5.1 Weighting and valuing of benefits	Not available	Not available	Not available	Not available	Not available
5.2 Weighting and valuing of risks	Not available	Not available	Not available	Not available	Not available
6 Visualisation	Not available	Not available	Not available	Not available	Not available
7 Conclusions					
7.1 Quality conclusions (pre-filled)	Section 4	Conclusions and reasons	Section 2	Section 7 - Quality	Section 6 – Quality
7.2 Non-clinical conclusions (pre-filled)	Section 4	Conclusions and reasons	Section 2	Section 7 – Non-clinical	Section 6 – Non-clinical
7.3 Human pharmacology conclusions (pre-filled)	Section 4	Conclusions and reasons	Section 2	Section 7 - Clinical	Section 6 – Clinical
7.4 Clinical conclusions (pre-filled)	Section 6	Conclusions and reasons	Section 2	Section 7 – Clinical	Section 6 - Clinical
7.4.1 For negative benefit-risk balance, discussion on the harm	Section 1 (Benefit-risk summary assessment)	Risk	Section 2	Section 2	Section 6 – Risk-benefit analysis
7.4.2 Discussion on evolution of the benefit-risk balance	Section 1 (Benefit-risk summary assessment)	Benefit-risk summary assessment	Section 3	Section 2	Section 6 – Risk-benefit analysis

Table 7.6 Comparison of sections of reference agencies' publicly available assessment reports with the BR Template (continued)

BR Template	US FDA		EMA	Health Canada	TGA
Content	Medical Review	Section 1 (Risk Benefit Assessment)	EPAR	SBD	AusPAR
7.4.3 Discussion on outstanding issues and other significant information (hearings, advisories, patients, consumers, stakeholder inputs)	Section 1 (Benefit-risk summary assessment)	Benefit-risk summary assessment	Section 3	Section 2	Section 6 – Risk-benefit analysis
7.4.4 Discussion on pharmacovigilance plans and risk mitigation plans	Section 7, Section 1 (Benefit-risk summary assessment)	Risk management	Section 2 – Pharmaco-vigilance	Section 2 & 4	Section 6 – Risk management plan
7.4.5 Discussion on need for further studies	Section 6, Section 1 (Benefit-risk summary assessment)	Risk management	Sections 2 & 3	Section 2 & 4	Section 6 – Risk-benefit analysis
7.4.6 Any other information relevant to the benefit-risk decision	Section 1 (Benefit-risk summary assessment)	Benefit-risk summary assessment	Section 3	Section 2	Section 6 – Risk-benefit analysis
7.4.7 Conclusion on the benefit-risk balance for proposed indication	Section 1 (Benefit-risk summary assessment)	Benefit-risk summary assessment	Sections 3 & 4	Section 2	Section 6 - Outcome
7.4.8 Recommendation indication	Section 1 (Benefit-risk summary assessment)	Benefit-risk summary assessment	Section 4	Section 1	Section 6 - Outcome

In reviewing safety, it appeared that the US FDA Medical Review's format is very detailed in discussing various safety parameters, including the adequacy of assessment and safety explorations (dose dependency, time dependency, etc). As noted for the assessment of efficacy, there is no function similar to Section 3 of the BR Template to explicitly show the identified risks. Discussion of post-marketing experience was absent in the BR Template. While there is no such dedicated section, this discussion could have been carried out as part of pharmacovigilance review in the BR Template. It is noted that only the US FDA has a specific section on post-market experience which was not found in the other three agencies' formats.

For the second comparison between the section of Recommendations/Risk Benefit Assessment and the BR Template, the discussion on the assessment of benefits, risks, risk management and benefit-risk balance are adequately covered by both documents. Again, it was found that the US FDA's Risk Benefit Assessment did not explicitly present evaluations through weighting, valuing, visualisation or listing of identified benefits and risks. Moreover, the Risk Benefit Assessment did not appear to provide inputs or conclusions on quality, non-clinical and human pharmacology.

Overall, it was observed that the US FDA Medical Review was designed to present details of the evaluation processes including those of the studies and considerations, while the BR Template presents only the information that will directly contribute to the decision on the benefit-risk balance. This can be seen in the detailed structure of the US FDA Medical Review, compared to a more concise benefit-risk documentation template. In terms of utility, the BR Template and BR Summary Template appear to share the US FDA Medical Review's capability to present critical information regarding the benefit-risk decision. The additional details in the US FDA Medical Review format may offer an advantage in transparency, but the more explicit display using the BR Template's sections 3 (identified benefits and risks), 5 and 6 (weighting, valuing and visualisation) may facilitate this outcome better through a more structured format on the discussion for benefit-risk balance and therefore enhance communication.

EMA's EPAR

The EPAR's format allows appropriate discussion of quality, non-clinical and clinical findings, whereas the required details are not accommodated by the BR Template (Table 7.1). Identified benefits and risks (Section 3 of BR Template) are not explicitly listed in the EPAR, unlike the BR Template. A dedicated section on pharmacovigilance is included in the EPAR, but limited information in the BR Template. Similarly, an entire section in the EPAR was given to discussing user consultation, but is only available as a single question in the BR Template.

In assessing the benefit-risk balance, the BR Template provided more structure through the use of guiding questions, while for the EPAR it was a general descriptive write-up. Weighting, valuing and visualisation (Sections 5 and 6 of BR Template) are not featured in the EPAR. Overall, with the exception of details on quality, non-clinical, human pharmacology, pharmacovigilance and user consultation, the utility of the EPAR is found to be similar to the BR Template in presenting relevant information leading to the benefit-risk decision. The BR Template would offer the advantage of presenting outcomes on weighting, valuing and visualisation when deciding on the benefit-risk balance. This may confer improved transparency as well as communicating the basis of the decision.

Health Canada's Summary Basis of Decision (SBD)

All eight sections of the SBD were compared to the BR Template to assess if the former could fulfil the requirements of the BR Template in presenting information on benefit-risk balance. The SBD appears to present quality, non-clinical and clinical assessment with a similar focus, which is different from the BR Template which attempts to focus on the clinical efficacy, safety and the resulting benefit-risk balance. While it may appear that the BR Template lacks details on quality and non-clinical assessment outcomes, it should be noted that the intention with the BR Template is to communicate only the significant quality, non-clinical and human pharmacology issues that contribute to the benefit-risk decision.

In the assessment of efficacy and safety, it appears that the SBD does not provide a detailed structure in presenting this information which may lead to a general

discussion. Of note, identified benefits and risks may not be explicitly displayed (as in Section 3 of the BR Template). This general structure is similarly found in their assessment of the benefit-risk balance and recommendations. While the BR Template provides specific details by using structured questions, the SBD appears to facilitate a general descriptive write-up instead. Weighting, valuing and visualisation of benefit-risk balance (sections 5 and 6 of BR Template) are not presented in the SBD, an observation common to all the agencies considered in this study. Overall, the SBD would require more details than the BR Template for quality, non-clinical and human pharmacology assessment. However, they are comparable for the documentation of clinical efficacy, safety and benefit-risk assessment. In particular, opinions on identified benefits, risks, weighting, valuing and visualisation are only available with the BR Template, and may offer a higher level of quality in communication compared to the SBD.

TGA's AusPAR

All six sections are compared to the BR Template to assess the ability of the AusPAR to fulfil the requirements of the BR Template. The BR Template does not accommodate the details of quality, non-clinical and human pharmacology as per the AusPAR, but presents the relevant and significant findings via the respective conclusions. For the AusPAR, the discussion on the efficacy and safety are not further structured, unlike in BR Template where these are supported with guided questions on identified benefits, risks and uncertainties. There is however a dedicated section for pharmacovigilance findings, which is also included as a single question in the BR Template.

While there is no defined summary for the AusPAR, the section 6 (Overall conclusion and risk/benefit assessment) appears to function similarly to US FDA's Section 1 (Recommendations/risk-benefit assessment) and EPAR's executive summary. Section 7 (Conclusions) of the BR Template is closely aligned to this section of the AusPAR. As with other formats, Sections 5 and 6 (weighting, valuing and visualisation) of the BR Template are not featured in the AusPAR. In particular, the discussion of benefit-risk assessment appears to be better structured in the BR Template. Overall, with the exception of details on quality, non-clinical, human

pharmacology and pharmacovigilance, the AusPAR meets the requirements and utility of the BR Template. As observed with the other agencies, additional features of the BR Template may help increase the effectiveness of discussion and communication.

Part III – Comparison of the four reference agencies' report templates with the BR Summary Template

Two reference agencies have defined summaries within the report. The US FDA Medical Review has the Recommendations/Risk Benefit Assessment which is a discussion based on the benefit-risk framework employed by US FDA (Table 7.7). The Executive Summary of the EMA's EPAR does not have a structure and presents the information in a general discussion. The entire Health Canada's SBD and TGA's AusPAR were compared to the BR Summary, as it is the intent of both to function as summaries of the actual assessment reports.

Table 7.7 US FDA's Benefit-risk framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		
Benefit-Risk Summary Assessment		

As there was no information on the official format for the US FDA's Risk Benefit Assessment, a sample of the Risk Benefit Assessment obtained from the Medical Review of Zaltrap® was used as a reference. In the Risk Benefit Assessment of Zaltrap®, there were six headings:

1. Analysis of condition
2. Unmet medical need (corresponding to "Current treatment options" of the framework)

3. Clinical benefit
4. Risk
5. Risk management
6. Benefit-risk summary assessment

Given that the format appeared to closely reflect the benefit-risk framework, the comparison was conducted using the terms of the US FDA's benefit-risk framework. Although the 5-step benefit-risk framework may appear less comprehensive than other existing frameworks, the US FDA is currently reviewing a list of questions that should be included under each of these steps, in an approach similar to EMA guidance for assessment of benefits and risks. The general findings were similar to those for BR Template, with the exception of EMA's EPAR Executive Summary, as there is no format for comparison (Table 7.8).

US FDA's Risk Benefit Assessment

The Risk Benefit Assessment was comparable to the BR Summary Template. Similar to the observations for the BR Template, the BR Summary Template offered an explicit display of identified benefits and risks, weighting and valuing which are absent in the US FDA format. This format presents a general write-up under six headings, while the BR Summary Template provides guided information through the various structured questions in its five sections. Therefore, it appears that the BR Summary Template may have the potential to increase transparency for this type of communication with the additional features of listing identified benefits and risks, weighting, valuing and visualisation.

EMA's EPAR Executive Summary

The Executive Summary of the EPAR was compared with the BR Summary Template in assessing the utility of the former in fulfilling the requirements of the BR Summary Template. Unlike the US FDA's Risk Benefit Assessment, there is no official format to the Executive Summary. As such, the BR Summary Template, which presents structured, concise information leading to the benefit-risk decision, exceeds the utility of the Executive Summary in the EPAR. The BR Summary Template may communicate the outcomes in a more transparent manner than the Executive summary in the EPAR.

Table 7.8 Comparison of reference agencies' report templates with the BR Summary Template

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

Table 7.8 Comparison of reference agencies' report templates with the BR Summary Template (continued)

BR Summary Template	US FDA	EMA	Health Canada	TGA
Content	Benefit-risk framework	EPAR – Executive Summary	SBD	AusPAR
7.1 Conclusion				
7.1.1 For negative benefit-risk balance, discussion on the harms	Benefit-risk summary assessment	Not available	Section 2	Section 6
7.1.2 Discussion on evolution of the benefit-risk balance	Benefit-risk summary assessment	Not available	Section 2	Section 6
7.1.3 Discussion on outstanding issues and other significant information (hearings, advisories, patients, consumers, stakeholder inputs)	Benefit-risk summary assessment	Not available	Section 2	Section 6
7.1.4 Discussion on pharmacovigilance plans and risk mitigation plans	Risk Management	Not available	Section 2 & 4	Section 6
7.1.5 Discussion on need for further studies	Risk Management	Not available	Section 2 & 4	Section 6
7.1.6 Any other information relevant to the benefit-risk decision	Benefit-risk summary assessment	Not available	Section 2	Section 6
7.1.7 Conclusion on the benefit-risk balance for proposed indication	Benefit-risk summary assessment	Not available	Section 2	Section 6
7.1.8 Recommendation indication	Benefit-risk summary assessment	Not available	Section 1	Section 6

Health Canada's Summary Basis of Decision

In keeping with the understanding that the SBD was designed as a summary, it is therefore important to compare the utility of the SBD in fulfilling the requirements of the BR Summary Template. The BR Summary Template allows the conclusions of each contributing section (quality, non-clinical, clinical and benefit-risk assessment) to be presented. It should be stated that the BR Summary Template, for sections 8.3 (identified benefits and risks), 8.4 (weighting and valuing) and 8.5 (benefit-risk management), was designed to highlight the key concerns in the assessment that led to the final recommendations in a more structured and guided manner. The two former functions were absent in the SBD.

TGA's AusPAR

The AusPAR appears to represent the functional sections (sections 1 to 5) of the BR Summary Template, taking into account that the BR Summary Template was not designed to accommodate the level of details in the AusPAR. Section 6 (overall conclusion, risk/benefit assessment) of the AusPAR was then compared to the BR Summary Template and was found to be at least similar to the contents required, with the added potential of the BR Summary Template being able to present outcomes on weighting, valuing and visualisations, as well as listing the identified benefits and risks.

Part IV – Case study of US FDA's and EMA's summary reports on Zaltrap®

Zaltrap® (aflibercept) was approved by both US FDA and EMA and the publicly available Medical Review and EPAR were retrieved from the internet. Only the Risk Benefit Assessment (Section 1) from US FDA's Medical Review and Executive Summary of the EPAR were used to complete the fields in the BR Summary Template. Both the Risk Benefit Assessment and Executive Summary appear to have provided similar information (Table 7.9), but presented in a different manner. The Executive Summary was written in a continuous descriptive prose but the Risk Benefit Assessment of the US FDA's was presented under six headings. Overall, the BR Summary Template is more structured in presenting the information for the benefit-risk decision.

Table 7.9 Case study using Zaltrap® – Comparison of US FDA and EMA summaries with BR Summary Template

BR Summary Template	US FDA	EMA
Content	Risk Benefit Assessment	EPAR – Executive Summary
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
3.1.2 Listing of all risks, and justification for inclusion and exclusion	Not available	Not available
4.1 Clinical study summary	√	√
5.1 Risks: Overall summary	√	√
6.1 Weighting and valuing of benefits and risks	Not available	Not available
7.1 Conclusion		
7.1.1 For negative benefit-risk balance, discussion on the harm	Not available	Not available
7.1.2 Discussion on evolution of the benefit-risk balance	Not available	√
7.1.3 Discussion on outstanding issues and other significant information (hearings, advisories, patients, consumers, stakeholder inputs)	Not available	Not available
7.1.4 Discussion on pharmacovigilance plans and risk mitigation plans	√	Not available
7.1.5 Discussion on need for further studies	√	√
7.1.6 Any other information relevant to the benefit-risk decision	√	Not available
7.1.7 Conclusion on the benefit-risk balance for proposed indication	√	√
7.1.8 Recommendation indication	√	√

US FDA's Risk Benefit Assessment

The BR Summary Template was completed with the information (Figure 7.1) from the Risk Benefit Assessment for Zaltrap®. The decision context of the BR Summary Template could be sufficiently completed with information from the Risk Benefit Assessment section. Similar to the EMA's Executive Summary, quality, non-clinical and human pharmacology conclusions were excluded from the Risk Benefit Assessment. However, as both clinical safety and efficacy conclusions were available

in the Risk Benefit Assessment, the clinical conclusion in the BR Summary Template was completed easily.

The benefits were included for the benefit-risk assessment but no reasons were provided for their inclusion. There was no information provided on those benefits which were reviewed but subsequently excluded. Safety parameters included were inferred by the reasons provided in the Risk Benefit Assessment but the risks reviewed and subsequently excluded were not documented. Weighting (relative importance) and valuing were not documented, as was the case for the EMA's Executive Summary. However, there were no specific comments on the uncertainties relating to the listed benefits and risks. The structured section of the BR Summary Template could be completed from this Risk Benefit Assessment. Overall, the utility of the BR Summary Template over the US FDA's Risk Benefit Assessment appears to be in providing a more structured and guided discussion of the decisions leading to the eventual benefit-risk balance.

EPAR's Executive Summary

The BR Summary Template was completed with the information (Figure 7.1) from the EPAR's Executive Summary. The Executive Summary has no structure and is presented in a single section. The quality, non-clinical, human pharmacology conclusions of the BR Summary Template could not be completed as they were absent from the Executive Summary. As there was no specific safety summary, the clinical conclusion of the BR Summary Template was incomplete. The benefits presented in the Executive Summary were included for the benefit-risk assessment, but no reasons provided for their inclusion. Similarly, as there were no indications for inclusion or exclusion, it is assumed that all safety parameters considered were included in the Executive Summary.

Figure 7.1 The BR Summary Template completed with US FDA Risk Benefit Assessment and EPAR Executive

US FDA Medical Review – Risk Benefit Assessment

Summary Template for the Benefit-Risk Assessment of Medicines

Participant(s):

HSA - Singapore

Compound Identifier(s):	Aflibercept / AVE005
Product name/ Brand name / Generic name:	Zaltrap
Active Ingredient(s)/ Strength(s)/ Dosage form:	Aflibercept, 100mg/4mL vial, 200mg/8ml vial
Proposed Indication:	Aflibercept is indicated in combination a FOLFIRI chemotherapy regimen for patients with metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin containing regimen.

EMA EPAR – Executive Summary

Summary Template for the Benefit-Risk Assessment of Medicines

Participant(s):

HSA - Singapore

Compound Identifier(s):	Aflibercept
Product name/ Brand name / Generic name:	Zaltrap
Active Ingredient(s)/ Strength(s)/ Dosage form:	Aflibercept, 100mg/4mL vial, 200mg/8mL vial
Proposed Indication:	Zaltrap in combination with irinotecan/5-fluoouracil/ folinic acid (FOLFIRI) chemotherapy is indicated in adults with metastatic colorectal cancer (MCRC) that is resistant to or has progressed ater an oxaliplatin-containing regimen.

US FDA Medical Review – Risk Benefit Assessment

This section provides a summary of the key outcomes of Benefit Risk analysis undertaken.

Summary 1.1 Background (Decision Context):

Summary 1.1.1 Specify the proposed therapeutic indication

Metastatic colorectal carcinoma is a progressive disease with a fatal outcome. Median survival after diagnosis of the disease is approximately 22 months.

(Proposed indication not available from Risk Benefit Assessment but extracted from cover page of the Clinical Review)

Summary 1.1.2 Treatment modalities evaluated in this submission

In the adjuvant setting against placebo in patients with MCRC, background treatment with FOLFIRI.

Summary 1.1.3 Is this product for an unmet medical need? Please select: Yes

Reason: Please provide justification for your decision on the product fulfilling or not fulfilling an unmet medical need

Currently approved therapeutic options are reasonably well tolerated but provide limited effiacy (ie bevacizumab in the second line setting used in combination with oxalipatin median survival is 13 months compared to 10.8 mpnths in the chemotherapy/placebo arm., HR 0.75, 95% CI 0.63, 0.89). No monoclonal antibody targeting the VEGF pathway has been approved specifically in combination with FOLFIRI, a chemotherapy regimen commonly used in the US after progression following an oxaliplatin-containing regimen.

EMA EPAR – Executive Summary

This section provides a summary of the key outcomes of Benefit Risk analysis undertaken.

Summary 1.1 Background (Decision Context):

Summary 1.1.1 Specify the proposed therapeutic indication

Colorectal cancer (CRC) is one of the most common cancers in both men and women, and the second most common cause of cancer mortality in Europe. Significant advances in the treatment of metastatic CRC have been made during the last 25 years with the introduction of chemotherapy agents. Current therapies used in clinical practice for first and second line treatment of metastatic CRC include irinotecan or oxaliplatin, each in combination with bolus and infusional 5FU/ LV. Standard second-line treatments for metastatic CRC have also evolved to include the addition of targeted biologic therapies such as bevacizumab, cetuximab and panitumumab. Despite these advances, the prognosis of patients with metastatic CRC undergoing second-line treatment is poor and the expected median overall survival is only approximately one year.

In November 2012, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended the authorisation of aflibercept (Zaltrap) in combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) chemotherapy in the treatment of adults with metastatic colorectal cancer (MCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen. The recommended dose of aflibercept, administered as an intravenous infusion over 1 hour, is 4 mg/kg of body weight, followed by the FOLFIRI regimen. This is considered as one treatment cycle. The treatment cycle is repeated every 2 weeks.

Summary 1.1.2 Treatment modalities evaluated in this submission

The demonstration of clinical benefit for aflibercept was based on a single randomised, double-blind controlled trial of aflibercept versus placebo in MCRC patients being treated with FOLFIRI after failure of an oxaliplatin based regimen (EFC10262- VELOUR).

Summary 1.1.3 Is this product for an unmet medical need? Please select: Yes

Reason: Please provide justification for your decision on the product fulfilling or not fulfilling an unmet medical need

Despite these advances, the prognosis of patients with metastatic CRC undergoing second-line treatment is poor and the expected median overall survival is only approximately one year.

US FDA Medical Review – Risk Benefit Assessment

Summary 2.1 Overall Summaries:

Summary 2.1.1 Quality Conclusion:

If box ticked - No relevant findings for the clinical benefit-risk assessment ☐

If there are relevant findings please comment:

Not available from Risk Benefit Assessment.

(However, required details are available from relevant sections of the Medical Review and Chemistry Review)

Summary 2.1.2 Non-Clinical Conclusion:

If box ticked - No relevant findings for the clinical benefit-risk assessment ☐

If there are relevant findings please comment:

Not available from Risk Benefit Assessment.

(However, required details are available from relevant sections of the Medical Review and Pharmacology Review)

Summary 2.1.3 Human Phamacology Conclusion:

Only the important results and issues that have an impact on the benefit-risk balance should be described. In addition, unresolved issues or uncertainties should be identified and their impact on the balance assessment should be clearly stated. This includes Bioequivalence, Pharmacokinetic and Dynamic profile, as well as PK, & PD interactions, special populations, dose findings etc.

Not available from Risk Benefit Assessment.

(However, required details are available from relevant sections of the Medical Review and Clinical Pharmacology and Biopharmaceutics Review)

Summary 2.1.4 Clinical Conclusion:

Only the important results and issues that have an impact on the benefit-risk balance should be described. In addition, unresolved issues or uncertainties should be identified and their impact on the balance assessment should be clearly stated. This includes study design, dosage, population and comparators.

There are no drugs approved for the treatment of mCRC specifically in combination with FOLFIRI and no drugs have been approved for patients with prior bevacizumab treatment in the first-line setting. VELOUR was a well conducted study that showed that the addition of aflibercept to the FOLFIRI regimen resulted in a survival benefit, with a statistically significant log rank test with a p-value of 0.0032 (which met the pre specified efficacy boundary of 0.0466) and an estimated hazard ratio of 0.817 (95.34% CI: 0.713 to 0.937). The use of aflibercept resulted in a risk of death reduction of 18.3% when compared to placebo/FOLFIRI. Median overall survival (95.34% CI) in the placebo arm was 12.06 months (11.072 to 13.109), compared to 13.50 months (12.517 to 14.949) in the aflibercept arm. This benefit was supported by subgroup and sensitivity analyses, as well as the increased median PFS and response rates observed in the aflibercept arm. Furthermore, patients with prior exposure to bevacizumab appeared to benefit from treatment with aflibercept, although this benefit was of a smaller magnitude than in patients who have not been exposed bevacizumab (median OS for patients with prior exposure to bevicizumab in the placebo arm 11.7 months vs 12.5 months in the aflibercept arm; HR 0.86, 95% CI 0.67, 1.1).

The analysis of the database shows that aflibercept toxicity is within range (both in the type of events and the incidence rates) of bevacizumab, the only other VEGFR2 biologic inhibitor approved. Although the incidence rates of hypertension and proteinuria were higher than with bevacizumab, these differences may be a reflection of differences in monitoring as these toxicities are better understood. There are no new or unexpected safety signals when compared with bevacizumab.

EMA EPAR – Executive Summary

Summary 2.1 Overall Summaries:

Summary 2.1.1 Quality Conclusion:

If box ticked - No relevant findings for the clinical benefit-risk assessment ☐

If there are relevant findings please comment:

Not available from Executive Summary

(However, required details are available from Quality aspects discussion in the EPAR)

Summary 2.1.2 Non-Clinical Conclusion:

If box ticked - No relevant findings for the clinical benefit-risk assessment ☐

If there are relevant findings please comment:

Not available in Executive Summary

(However, required details are available from Non-clinical aspects discussion in the EPAR)

Summary 2.1.3 Human Phamacology Conclusion:

Only the important results and issues that have an impact on the benefit-risk balance should be described. In addition, unresolved issues or uncertainties should be identified and their impact on the balance assessment should be clearly stated. This includes Bioequivalence, Pharmacokinetic and Dynamic profile, as well as PK, & PD interactions, special populations, dose findings etc.

Not available in Executive Summary

(However, required details are available from Clinical aspects discussion in the EPAR)

Summary 2.1.4 Clinical Conclusion:

Only the important results and issues that have an impact on the benefit-risk balance should be described. In addition, unresolved issues or uncertainties should be identified and their impact on the balance assessment should be clearly stated. This includes study design, dosage, population and comparators.

The demonstration of clinical benefit for aflibercept was based on a single randomised, double-blind controlled trial of aflibercept versus placebo in MCRC patients being treated with FOLFIRI after failure of an oxaliplatin based regimen (EFC10262- VELOUR). In this trial, the risk of death associated with aflibercept was reduced by 18% compared to that observed in the control group. Aflibercept was associated with an improvement of 2.23 months in duration of median progression-free survival and of 9% in objective response rate.

The trial also included a subgroup of patients whose disease had progressed after treatment with bevacizumab. In this subgroup analysis, a trend towards a favourable effect on overall survival was observed for aflibercept, but no definitive conclusions could be drawn.

(No safety specific summary available from Executive Summary)

US FDA Medical Review – Risk Benefit Assessment

BENEFIT RISK SUMMARY CONT:

Summary 3.1 Identified Benefits and Risks

Summary 3.1.1 Benefits documented

List all **benefits** of treatment for this indication as inferred in the submission	Please tick here if Benefit Identified by Reviewer but not by company	Please indicate which **benefits** you believe are justified to be included in the benefit risk assessment by ticking the box	Please explain your main reason **for inclusion or exclusion** of the benefit parameter
Overall survival	☐	☑	Not available from Risk Benefit Assessment. ◆
Death reduction (HR)	☐	☑	Not available from Risk Benefit Assessment. ◆
Progression-free survival	☐	☑	Not available from Risk Benefit Assessment. ◆
Response rates	☐	☑	Not available from Risk Benefit Assessment. ◆
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	

EMA EPAR – Executive Summary

BENEFIT RISK SUMMARY CONT:

Summary 3.1 Identified Benefits and Risks

Summary 3.1.1 Benefits documented

List all **benefits** of treatment for this indication as inferred in the submission	Please tick here if Benefit Identified by Reviewer but not by company	Please indicate which **benefits** you believe are justified to be included in the benefit risk assessment by ticking the box	Please explain your main reason **for inclusion or exclusion** of the benefit parameter
Overall survival	☐	☑	Not available in Executive Summary ◆
Risk of death (HR)	☐	☑	Not available in Executive Summary ◆
Progression-free survival	☐	☑	Not available in Executive Summary ◆
Objective response rate	☐	☑	Not available in Executive Summary ◆
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	

US FDA Medical Review – Risk Benefit Assessment

BENEFIT RISK SUMMARY CONT:

Summary 3.1.2 Risks documented

List all **risks** of treatment for this indication as inferred in the submission	Please tick here if Risk Identified by Reviewer but not by company	Please indicate which **risks** you believe are justified to be included in the benefit risk assessment by ticking the box	Please explain your main reason **for inclusion or exclusion** of the risk parameter
Hypertension	☐	☑	Adverse events of special interest
Proteinuria	☐	☑	Adverse events of special interest
Arterial thrombotic events	☐	☑	Adverse events of special interest
Haemorrhage	☐	☑	Adverse events of special interest
Fistula	☐	☑	Adverse events of special interest
GI perforation	☐	☑	Adverse events of special interest
Leukopenia, neutropenia, thrombocytopenia	☐	☑	Adverse events of special interest
Reversible posterior leukoencephalopathy	☐	☑	Known treatment effect with anticancers and targeted VEGFR inhibitors
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	
	☐	☐	

EMA EPAR – Executive Summary

BENEFIT RISK SUMMARY CONT:

Summary 3.1.2 Risks documented

List all **risks** of treatment for this indication as inferred in the submission	Please tick here if Risk Identified by Reviewer but not by company	Please indicate which **risks** you believe are justified to be included in the benefit risk assessment by ticking the box	Please explain your main reason **for inclusion or exclusion** of the risk parameter
Hypertension	☐	☑	Not available in Executive Summary
Haemorrhage	☐	☑	Not available in Executive Summary
Fistulae	☐	☑	Not available in Executive Summary
Diarrhea	☐	☑	Not available in Executive Summary
Neutropenia	☐	☑	Not available in Executive Summary
Stomatitis	☐	☑	Not available in Executive Summary
Asthenic conditions	☐	☑	Not available in Executive Summary
Ulceration	☐	☑	Not available in Executive Summary
Dehydration	☐	☑	Not available in Executive Summary
Infections and infestations	☐	☑	Not available in Executive Summary
Weight decrease	☐	☑	Not available in Executive Summary
GI disorders	☐	☑	Not available in Executive Summary
	☐	☐	
	☐	☐	
	☐	☐	

US FDA Medical Review – Risk Benefit Assessment

Summary 4.1 Clinical Study Summary

Study Ref. Type	Study Design (N)(duration) R, C, DB, OL (N=)(weeks/months) ·Non-inferiority/Superiority/ Observational study ·State primary objective ·State primary efficacy parameter	Treatment ·Treatment arm Active (name, dose, freq, duration) ·Comparator arm Placebo / Active (name, dose, freq, duration)	Conclusion ·Results of primary efficacy parameter ·Results of other relevant efficacy endpoints ·Conclusion of study (outcomes, strength of study, weight of evidence, and clinical significance)	
VELOUR Pivotal	Superiority design Primary objective of comparing efficacy. Primary efficacy parameter based on death / survival.	Treatment: Aflibercept, IV, 4mg/kg over 1 hour, in combination with FOLFIRI, every 2 weeks. Comparator: Placebo, IV, over 1 hour, combination with FOLFIRI, every 2 weeks.	Median OS: 13.50 months vs 12.06 months in placebo. Median OS reduced by 1.44 months. Risk of death reduced by 18.3% (HR 0.817, CI 0.713 - 0.937). PFS: 6.9 months vs 4.7 months placebo, HR 0.756 ORR: 20% vs 11% in placebo	-
				-
				-
				-
				-

Legend
R: Randomised **C:** Controlled **DB:** Double blinded **OL:** Open label **N:** Number of subjects

Click to add a study +

EMA EPAR – Executive Summary

Summary 4.1 Clinical Study Summary

Study Ref. Type	Study Design (N)(duration) R, C, DB, OL (N=)(weeks/months) ·Non-inferiority/Superiority/ Observational study ·State primary objective ·State primary efficacy parameter	Treatment ·Treatment arm Active (name, dose, freq, duration) ·Comparator arm Placebo / Active (name, dose, freq, duration)	Conclusion ·Results of primary efficacy parameter ·Results of other relevant efficacy endpoints ·Conclusion of study (outcomes, strength of study, weight of evidence, and clinical significance)	
VELOUR Pivotal	Superiority design. Primary objective is efficacy in MCRC patients after oxaplatin-regimen failure. Primary efficacy endpoint is median overall survival.	Treatment: Aflibercept, IV, 4mg/kg over 1 hour, followed by FOLFIRI. Repeat cycle every 2 weeks. Comparator: Placebo, IV, over 1 hour, followed by FOLFIRI. Repeat cycle every 2 weeks.	Median OS: 13.5 months vs 12.1 months in placebo. Median OS reduced by 1.44 months. Risk of death reduced by 18% (HR 0.817, CI 0.713 - 0.937, p=0.0032). PFS: increased by 2.23 months ORR: increased by 9%	-
				-
				-
				-
				-

Legend
R: Randomised **C:** Controlled **DB:** Double blinded **OL:** Open label **N:** Number of subjects

Click to add a study +

US FDA Medical Review – Risk Benefit Assessment

Summary 5.1 RISKS: Overall Summary
Table of pooled overall incidence of events can be added below

Adobe **Acrobat** users can click here to attach a file: Attach a file *(Note: this will not activate in Adobe **Reader**)*

Click in the space below to upload an image: (jpeg, gif, png): *(Available to both Adobe Reader and Acrobat users)*

No tables or figures available

EMA EPAR – Executive Summary

Summary 5.1 RISKS: Overall Summary
Table of pooled overall incidence of events can be added below

Adobe **Acrobat** users can click here to attach a file: Attach a file *(Note: this will not activate in Adobe **Reader**)*

Click in the space below to upload an image: (jpeg, gif, png): *(Available to both Adobe Reader and Acrobat users)*

No tables or figures available

US FDA Medical Review – Risk Benefit Assessment

BENEFIT RISK SUMMARY CONT:

Summary 6.1 Weights and values

Benefits	Relative Importance (weighting)	Valuing the options: Investigated product	Comparator	Placebo	Comment on strength and uncertainty of benefit
Overall survival	Not available from risk benefit assessment.	13.50 months		12.06 months	Not available from Risk Benefit Assessment.
Death reduction (HR)	Not available from risk benefit assessment.	0.817			Not available from Risk Benefit Assessment.
Progression-free survival	Not available from risk benefit assessment.	6.9 months		4.7 months	Not available from Risk Benefit Assessment.
Response rates	Not available from risk benefit assessment.	20%		11%	Not available from Risk Benefit Assessment.

Please describe methodology used for assessing relative importance: eg Ranking or point allocation and also what is has been used in relation to valuing the options e.g. % change, Number of patients, etc

Not available from Risk Benefit Assessment.

EMA EPAR – Executive Summary

BENEFIT RISK SUMMARY CONT:

Summary 6.1 Weights and values

Benefits	Relative Importance (weighting)	Valuing the options: Investigated product	Comparator	Placebo	Comment on strength and uncertainty of benefit
Overall survival	Not available in Executive Summary	13.5 months		12.1 months	Not available in Executive Summary
Risk of death (HR)	Not available in Executive Summary	0.817			Not available in Executive Summary
Progression-free survival	Not available in Executive Summary	Not available from executive summary; improvement by 2.23 months over placebo		Not available from executive summary	Not available in Executive Summary
Objective response rate	Not available in Executive Summary	19.8%		11.1%	Not available in Executive Summary

Please describe methodology used for assessing relative importance: eg Ranking or point allocation and also what is has been used in relation to valuing the options e.g. % change, Number of patients, etc

Not available in Executive Summary

US FDA Medical Review – Risk Benefit Assessment

BENEFIT RISK SUMMARY CONT:

Risks	Relative Importance (weighting)	Valuing the options Investigated product	Comparator	Placebo	Comment on strength and uncertainty of each risk	Was the value or weight of this risk altered or mitigated by the ability to control the use of the medicine once on the market?
Hypertension	Not available from Risk Benefit Assessment.	41%		11%	Not available from Risk Benefit Assessment.	Through product labeling and use by oncologists.
Proteinuria	Not available from Risk Benefit Assessment.	62%		41%	Not available from Risk Benefit Assessment.	Through product labeling and use by oncologists.
Arterial thrombotic events	Not available from Risk Benefit Assessment.	2.6%		1.65%	Not available from Risk Benefit Assessment.	Through product labeling and use by oncologists.
Haemorrhage	Not available from Risk Benefit Assessment.	38%		19%	Not available from Risk Benefit Assessment.	Through product labeling and use by oncologists.
Fistula	Not available from Risk Benefit Assessment.	9 patients		3 patients	Not available from Risk Benefit Assessment.	Through product labeling and use by oncologists.
GI perforation	Not available from Risk Benefit Assessment.	3 patients		3 patients	Not available from Risk Benefit Assessment.	Through product labeling and use by oncologists.
Leukopenia, neutropenia, thrombocytopenia	Not available from Risk Benefit Assessment.	16%, 36%, 3%		12%, 30%, 2%	Not available from Risk Benefit Assessment.	Through product labeling and use by oncologists.
Reversible posterior leukoencephalopathy	Not available from Risk Benefit Assessment.	0		0	Not available from Risk Benefit Assessment.	Through product labeling and use by oncologists.

Please describe methodology used for assessing relative importance: eg Ranking or point allocation and also what is has been used in relation to valuing the options e.g. % change, Number of patients, etc

Not available from Risk Benefit Assessment.

EMA EPAR – Executive Summary

BENEFIT RISK SUMMARY CONT:

Risks	Relative Importance (weighting)	Valuing the options Investigated product	Comparator	Placebo	Comment on strength and uncertainty of each risk	Was the value or weight of this risk altered or mitigated by the ability to control the use of the medicine once on the market?
Hypertension	Not available in Executive Summary				Not available in Executive Summary	Not available in Executive Summary
Haemorrhage	Not available in Executive Summary				Not available in Executive Summary	Not available in Executive Summary
Fistulae	Not available in Executive Summary				Not available in Executive Summary	Not available in Executive Summary
Diarrhea	Not available in Executive Summary				Not available in Executive Summary	Not available in Executive Summary
Neutropenia	Not available in Executive Summary				Not available in Executive Summary	Not available in Executive Summary
Stomatitis	Not available in Executive Summary				Not available in Executive Summary	Not available in Executive Summary
Asthenic conditions	Not available in Executive Summary				Not available in Executive Summary	Not available in Executive Summary
Ulceration	Not available in Executive Summary				Not available in Executive Summary	Not available in Executive Summary
Dehydration	Not available in Executive Summary				Not available in Executive Summary	Not available in Executive Summary
Infections and infestations	Not available in Executive Summary	11.3		6.3	Not available in Executive Summary	Not available in Executive Summary
Weight decrease	Not available in Executive Summary				Not available in Executive Summary	Not available in Executive Summary
GI disorders	Not available in Executive Summary	20		11	Not available in Executive Summary	Not available in Executive Summary

Please describe methodology used for assessing relative importance: eg Ranking or point allocation and also what is has been used in relation to valuing the options e.g. % change, Number of patients, etc

Not available in Executive Summary

US FDA Medical Review – Risk Benefit Assessment

BENEFIT RISK SUMMARY CONT:

Summary 7.1 Conclusion

Summary 7.1.1 If the benefit-risk balance is assessed to be negative, describe the harm (e.g. in terms of lack of efficacy, toxicity) that the drug may cause if used in the proposed indication

Not applicable.

Summary 7.1.2 Describe how the benefit-risk balance is expected to evolve over time (e.g. when late side effects emerge or long-term efficacy decreases)

Not available from Risk Benefit Assessment. ◆

(However, required details are available from sections on Review of Efficacy and Review of Safety)

Summary 7.1.3 Describe outstanding issues, and other significant information eg, submission of additional reports by the company to address those issues, hearings and advisory group recommendations, information from other jurisdictions (eg advisory committees, scientific experts, patients, consumers, consumer advocates and other stakeholders)

Not available from Risk Benefit Assessment. ◆

(However, required details are available from sections on Review of Efficacy and Review of Safety)

Summary 7.1.4 Make reference to the evaluation of the pharmacovigilance plan and risk minimization plan if any. Describe any communication or particularly significant information to the medical profession, patients or the public that is required. Describe restrictions to product availability or usage

A post marketing commitment (PMC) is proposed to obtain the data of study NCT0062241, a Phase 1 study of aflibercept in children with refractory solid tumors. This study was conducted under the NCI aflibercept IND 100137 by the Children's Oncology Group (protocol COGADVL0714) and it is complete. The purpose of this PMC is to analyze this data to include it in the pediatric section of the Zaltrap label.

Summary 7.1.5 Describe the need for further studies (e.g. the need for studies to improve the benefit-risk balance with further optimization studies, the need for intensive additional follow up measures or specific obligations, and the need for further development including any paediatric development plans.

A post marketing commitment (PMC) is proposed to obtain the data of study NCT0062241, a Phase 1 study of aflibercept in children with refractory solid tumors. This study was conducted under the NCI aflibercept IND 100137 by the Children's Oncology Group (protocol COGADVL0714) and it is complete. The purpose of this PMC is to analyze this data to include it in the pediatric section of the Zaltrap label.

EMA EPAR – Executive Summary

BENEFIT RISK SUMMARY CONT:

Summary 7.1 Conclusion

Summary 7.1.1 If the benefit-risk balance is assessed to be negative, describe the harm (e.g. in terms of lack of efficacy, toxicity) that the drug may cause if used in the proposed indication

Not applicable.

Summary 7.1.2 Describe how the benefit-risk balance is expected to evolve over time (e.g. when late side effects emerge or long-term efficacy decreases)

In terms of balance of benefits and risks, the overall toxicity of aflibercept in the studied combination regimen was considered significant, not always manageable, and in some patients ultimately leading to termination also of the chemotherapy.
However, despite this toxicity, there was still a small but clinically relevant survival advantage of 1.44 months (median).
Thus, the benefits associated with aflibercept were considered to outweigh the risks.

Summary 7.1.3 Describe outstanding issues, and other significant information eg, submission of additional reports by the company to address those issues, hearings and advisory group recommendations, information from other jurisdictions (eg advisory committees, scientific experts, patients, consumers, consumer advocates and other stakeholders)

Not available in Executive Summary ◆

(However, required details are available from the Benefit-risk Balance section in the EPAR)

Summary 7.1.4 Make reference to the evaluation of the pharmacovigilance plan and risk minimization plan if any. Describe any communication or particularly significant information to the medical profession, patients or the public that is required. Describe restrictions to product availability or usage

Not available in Executive Summary ◆

(However, required details are available from Pharmacovigilance discussion in the EPAR)

Summary 7.1.5 Describe the need for further studies (e.g. the need for studies to improve the benefit-risk balance with further optimization studies, the need for intensive additional follow up measures or specific obligations, and the need for further development including any paediatric development plans.

In order to optimise benefit–risk balance, it is essential to identify the proper target population for therapy. This might be possible to accomplish through the judicious use of biomarkers in all phases of clinical drug development. However, no validated predictive serum or plasma biomarkers have been identified during the development of aflibercept that correlate with treatment outcomes. Thus, the CHMP has requested to the applicant company to analyse plasma and tissue samples from the available trials, with the primary aim to identify biomarkers to allow better selection of the population likely to experience a beneficial effect following treatment with aflibercept.

US FDA Medical Review – Risk Benefit Assessment

Summary 7.1.6 Please provide any other information considered by the agency relevant to the benefit risk decision that is not covered elsewhere in the proforma.

The risks of aflibercept use in the treatment of MCRC whose disease had progressed after a first-line treatment with an xoaplatin-containing regimen will be managed through product labeling. The risks are also managed in that this drug will be administered by oncologists who have specific training in the administration of anti-neoplastic drugs and in the management of toxicities related to these drugs.

Summary 7.1.7 Please provide a clear conclusion on the benefit-risk being positive or not for the proposed indication.

In summary, the approval is recommended based on a prolongation of overall survival with an acceptable toxicity profile (toxicity in this setting refers to the additional toxicity of aflibercept when added to the FOLFIRI regiment), for which the oncology community has experience in its management. The study effects were supported by secondary endpoints including PFS and ORR.

Summary 7.1.8 Please provide the indication recommended following the outcome of the benefit-risk balance.

Approval is recommended for the use of aflibercept in combination with the FOLFIRI regimen for the treatment of patients with metastatic colorectal carcinoma that is resistant to or has progressed after an oxaliplatin-containing regimen.

Reviewers Name: Sandra J Casak

Signature:

Date: 28 March 2012

Manager sign-off or Peer review

Reviewers Name: Steven J Lemery

Signature:

Date: 28 March 2012

EMA EPAR – Executive Summary

Summary 7.1.6 Please provide any other information considered by the agency relevant to the benefit risk decision that is not covered elsewhere in the proforma.

Not available in Executive Summary ◆

(However, required details are available from the User conclusion discussion and Benefit-risk Balance section in the EPAR)

Summary 7.1.7 Please provide a clear conclusion on the benefit-risk being positive or not for the proposed indication.

In terms of balance of benefits and risks, the overall toxicity of aflibercept in the studied combination regimen was considered significant, not always manageable, and in some patients ultimately leading to termination also of the chemotherapy. However, despite this toxicity, there was still a small but clinically relevant survival advantage of 1.44 months (median). Thus, the benefits associated with aflibercept were considered to outweigh the risks.

Summary 7.1.8 Please provide the indication recommended following the outcome of the benefit-risk balance.

In November 2012, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended the authorisation of aflibercept (Zaltrap) in combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) chemotherapy in the treatment of adults with metastatic colorectal cancer (MCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen. The recommended dose of aflibercept, administered as an intravenous infusion over 1 hour, is 4 mg/kg of body weight, followed by the FOLFIRI regimen. This is considered as one treatment cycle. The treatment cycle is repeated every 2 weeks.

Reviewers Name: Kristina Dunder and Daniela Melchiorri (information extracted from EPAR)

Signature:

Date: 30 October 2012

Manager sign-off or Peer review

Reviewers Name: Not available

Signature:

Date: Not available

Sufficient information was provided in the Executive Summary to complete the BR Summary Template's clinical study information and table, but no weights, values or comments on uncertainties were available. As for safety information, there was much less available information which did not allow any weighting and valuing to be documented. The above observations are expected as weighting is carried out implicitly but not explicitly in many agencies. However, the safety exposure information was written entirely as a paragraph and could not be uploaded as an image into the BR Summary Template, thus eliminating the opportunity to present these data. The structured discussion of the BR Summary Template was not adequately completed using the Executive Summary. In conclusion, more information beyond the EMA's Executive Summary would be required to complete the fields for the BR Summary Template. This is due to the extensive structure and guiding questions in the BR Summary Template and the need for conducting the exercise on identifying benefits, risks and allocating weights and values.

DISCUSSION

The comparisons conducted in this study showed that the publicly available assessment reports from the four reference agencies are similar and generally allow the information generated through the course of the evaluation to be described. The differences between these reports are largely due to format arrangement and headings provided for each section. While there is no universal template for an assessment report, this finding suggests that with small differences among the format of these reports, there does not appear to be major discrepancies on how such information should be presented. This may also suggest that given the commonalities among the formats, only minor changes may be required to their current formats in order to achieve a potential universal standard structure.

The publicly available assessment reports are the means for documenting the relevant information made available to stakeholders and to communicate the basis and justification for these decisions. The US FDA has made recent efforts, as detailed in PDUFA V, to provide a Risk benefit assessment, based on their benefit-risk framework, which detailed their considerations contributing to the regulatory decision and features an additional succinct benefit-risk assessment summary. EMA had commissioned an external expert to improve its communication of benefits and

risks (EMA, 2011e). The EPAR has been using the Executive summary to provide concise information. Health Canada had completed its two phases of the initiative to improve documentation and communication to the public, with an emphasis on the discussion of the benefit-risk balance and the basis of the decision (Health Canada, 2012a and 2012b). Likewise, TGA has commenced a project targeted at improving communication of information to patients and physicians (TGA, 2013). It can thus be concluded that these agencies recognise the need to effectively communicate the basis of their decisions through a concise documentation tool and have been active in refining these as seen specifically in the initiatives undertaken.

In an effort to improve documentation and communication of benefit-risk decisions, it should be determined if these activities are of relevance to the different stakeholders, as highlighted in the above EMA study in 2011. The objectives of the regulator preparing the document may frequently not meet the expectations of the stakeholders who will be receiving the information. Therefore, it is vital to agree on who these stakeholders are and assess their expectations. In the traditional healthcare model, the key stakeholders are the physicians and their patients. However, in the contemporary context of today's regulatory science, it appears that such information on the basis of benefit-risk decisions are also sought by health technology assessment agencies, pharmaceutical companies and patient advocacy groups.

For most patients, their primary concern would be to know if the product is effective and safe, while the physicians would want to know the details to make a better informed decision when choosing an optimal treatment for their patients. It is therefore important that the basic information on proof of efficacy and safety concerns be well documented and explained clearly. For pharmaceutical companies, a documented transparent decision-making process will enable them to understand the basis of the regulatory decision, the rationale for the inclusion and exclusion of benefits and risks as well as the views on the final benefit-risk balance, as described as one of the initiatives under US FDA's PDUFA V on improving the collaboration with the industry (FDA, 2012a). This would therefore provide a suitable platform to discuss any discrepancies in interpretation or difference in opinions. HTA agencies, in their course of evaluating the product for pricing and reimbursement, would also

want to understand the rationale for the approval of a product (MHRA, 2013b). The failure to do so would render a product not being accessible to patients and affecting the healthcare system in terms of cost and clinical management. The accurate documentation of the benefits and risks of a product would also assist in a comparison with other existing treatment options, aiding the HTA agencies in reviewing the product for inclusion. Importantly, patients and patient advocacy groups increasingly seek to understand the decisions taken for the approval and availability of a product and provide inputs to decision makers on the issues that matter to them. Assessment reports of major regulatory agencies are often accessed by smaller agencies in the emerging markets to support their local decisions and thus these regulatory agencies should also be considered as key stakeholders for the publicly available assessment reports. In lieu of the vast difference in expectations, regulatory agencies should seek to understand the spectrum of needs of the various stakeholders and assess if the current approaches are valid and effective. As the purpose of such documentation is to communicate to stakeholders, further research is required to ascertain expectations and obtain more opinions on the way forward.

Certain jurisdictions may require publication of the assessment reports as a move to increase the transparency of the decision-making processes while different jurisdictions may require varying amounts of information to be made public. As discussed above, it is also not known if the current practices of providing the publicly available assessment reports actually achieve the transparency required or desired by the stakeholders as there are no studies describing this type of feedback from pharmaceutical companies, physicians, patients, or regulatory agencies. In the process of writing an assessment report, reviewers should provide information to support and justify the decisions made. However, achieving transparency through the provision of information does not always correlate to effective communication. The vast amount of unstructured information provided may possibly hamper understanding and thus communication. The use of summaries like the Executive Summary of the EPAR and the Risk Benefit Assessment of US FDA aims to further improve communication through concise information. However, as seen in this case study using Zaltrap®, a more structured and guided discussion may further help improve both transparency and communication and prevent the omission of information assessed by the reviewer but deemed important to stakeholders. The

comparison of the summaries showed that there are elements missing which could facilitate effective communication. As such, the elements from the BR Summary Template found missing in the summaries of the reference agencies may serve as a starting platform to enhance the effectiveness in communicating benefit-risk decisions.

In the pursuit of improved communication, there should be a balance between the amount of information provided to satisfy the transparency of the process versus the impact of interpretation and understanding by the recipient. Key messages may be difficult to find from the vast amount of information in the assessment reports and hence mitigate the purpose of these reports. Further studies should be considered to investigate the effectiveness of communication using the various templates among different stakeholders. It has been observed that although the EMA provided guidance on the assessment of benefits and risks, the pertinent considerations by the reviewers have not been explicitly featured in the EPAR. Through this study it was found that only the BR Template and BR Summary Template provides an appropriate, structured and guided approach based on the EMA's Reflection paper (EMA, 2008). This ensures that the relevant considerations have been taken into account and made available to the recipient for their understanding. The provision of a list of identified benefits and risks and visualisations aims to facilitate communication by reducing the amount of text needed to convey these messages.

As a result of this study, future attempts to improve the quality of communication should consider the following and include:

- A listing of benefits and risks, with justification for their roles in assessing the benefit-risk balance
- Valuing the identified benefits and risks
- Weighting (relative importance) of the identified benefits and risks
- Providing visualisations of the outcomes
- Utilising guided discussions and structured questions (e.g. deliberations on uncertainties, consistency of outcomes across studies, additional risks compared to standard of care) to illustrate key discussion points leading to benefit-risk decisions

Given that there are minimal differences among the existing templates of the reference agencies, it is timely to consider the feasibility of a universal template. The BR Template and BR Summary Template were based on the EMA's Reflection paper for the assessment of benefits and risks and also allow the documentation of these considerations in support of the decision. Unlike the existing templates, the guided discussion, structure, listings of identified benefits and risks, application of values and weights and visualisation, of the BR Template serve to improve effective communication. Familiarity with a standard template and its presentation format will enhance the stakeholders' experience in seeking and understanding the key messages. A universal framework for the assessment of benefits and risks will be required to bring focus among the agencies, which would then facilitate the implementation of a standard, universal documentation tool. An 8-step universal benefit-risk framework has been developed which incorporated the existing ones by major regulatory agencies and those used by pharmaceutical companies. Given that the BR Template and BR Summary Template was developed using the principles from this universal framework, there is now the opportunity to explore the universal use of these two templates. However, as the basis for publicly available assessment reports, it would be prudent to seek more confirmative opinions from stakeholders on the feasibility and utility of such an initiative through the conduct of further studies.

In the course of this study, some areas for improvement were identified for the BR Template and BR Summary Template. These included expanding the discussion on pharmacovigilance and RMP/REM, which would then align to the recent requirements for PBRER's and the emphasis on post-market activities. As stakeholders are increasingly seeking their opinions to be acknowledged, there should also be dedicated and defined areas for inputs from the various stakeholders, particularly patients. These improvements may enable the BR Template to accommodate the requirements in the post-marketing setting as well as a tool for product life cycle management. If used as a universal template, it could trace and document the evolution of the benefit-risk balance of a product and provide meaningful comparisons using valid baselines. Ultimately, this may translate to an increase in consistency, transparency and the quality of decision-making.

SUMMARY

- The format of existing reports of major regulatory agencies are generally similar
- The areas found lacking in existing formats are the listing of benefits and risks, assigning of weights and values, visualisation and a more detailed, systematic standardised structure
- Given the difference in expectations from various stakeholders, it is important to further investigate their needs and how future templates can satisfy these requirements
- The BR Template and BR Summary Template appear to have an advantage over existing formats as they are based on the principles of benefit-risk assessment common to major regulatory agencies
- Finally, there is potential for the BR Template and the BR Summary Template to be further researched to meet the various needs of the stakeholders

CHAPTER 8

General discussion

The evaluation of medicines has traditionally been conducted as separate assessments of efficacy and safety, in which a regulatory decision is based on proven efficacy supported by clinical studies matched with an acceptable safety profile. The trend in the assessment of benefits and risks is currently towards a holistic discussion of the benefits, risks and the overall benefit-risk balance. This allows for a clear view of the relationship between the benefits identified and the risks potentially expected from the treatment and how the eventual balance is achieved to justify a regulatory decision for the medicine. Over the years major regulatory agencies and pharmaceutical companies have indeed made progress in improving the frameworks for the assessment of benefit-risk balances, but these are largely based on individual efforts due to the lack of a common universal framework. This suggests the beginning of a challenge to implement a universal framework, as these stakeholders are striving to develop a framework specific to their own jurisdictions and suited to their purposes. Without a universal framework, the current lack of consistency in making regulatory decisions and transparency of communication may be further perpetuated, leading to misunderstandings among the stakeholders and the potential unavailability of important medicines in some jurisdictions.

In reviewing the current environment on the use of benefit-risk assessment frameworks, it was found that both agencies and companies were using either qualitative or semi-quantitative systems. Among the companies, different approaches may be employed for product development and during regulatory submission. The majority of organisations who are currently using semi-quantitative systems were not satisfied and many expressed concerns about adopting a methodology that did not match the requirements of the other stakeholders, given that there is no one framework that is recognised by all. It was hoped that a universal framework would be structured, standardised and be applied throughout product development to submission for registration. Indeed, when the reason was sought as to why semi-quantitative or quantitative systems were not used, the majority indicated the lack of a scientifically, validated universal framework.

A disparity was observed in the opinions of the current methodologies used for the assessment of benefits and risks. While the agencies and companies considered Bayesian statistics and MCDA as useful and relevant, these were not the main tools

they were utilising, namely the qualitative approach, NNT/NNH and evidence based benefit-risk model. In the assessment of benefits and risks, most agencies and companies frequently assigned values to these parameters but not the assignment of weights or relative importance. It could be that weighting was carried out implicitly and considered during the evaluation of the overall benefit-risk balance. In communicating benefit-risk decisions, none of the agencies had used visualisation tools, while the companies had such tools for internal communication and infrequently for health professionals and patients**.** Therefore this lack of a universal framework could have led to the inconsistent approaches in the assessment and communication of benefits and risks across the agencies, companies and within these organisations themselves.

The agencies and companies believed that a benefit-risk framework should be used for the life cycle of a medicine. This is a consistent finding as confirmed by an earlier workshop conducted by CIRS (CMR, 2008) for various stakeholders including the agencies and companies. Such a framework should enhance the quality of communication and enable the assessment of benefit-risk management plans. In developing a framework for the future, it would be useful to have a coordinating group to guide its direction and application and to involve relevant stakeholders. A framework should confer the advantages of an appropriate documentation and the enhancement of communication.

Seven factors were identified which both agencies and companies agree would be relevant to reviewing a framework. These included logical soundness, comprehensiveness, acceptability of results, practicality, specificity and sensitivity, presentation (visualisation) and scope. The first four factors are similar to those used in the first and second work packages by the EMA in their benefit-risk methodology project (EMA, 2010 and 2011b) with the last factor generativeness not being used in this research. However, in order to reflect the scientific robustness that is critical for the assessment of benefits and risks, statistical concepts of specificity and sensitivity was added to the list. As it was then known that the graphical presentation of results would help communication (CMR, 2010; CIRS, 2011), visualisation was added as a factor to review if the framework would support this up-coming communication

strategy. Lastly, to ensure that the benefit-risk assessment framework would be applicable to all scenarios and for the entire product life cycle, scope was added as the final factor in reviewing such frameworks. In the review of benefit-risk assessment methodologies, the IMI PROTECT (2011b) had referenced the EMA's criteria in the fore-mentioned work packages and had put the required emphasis on visual presentation. Therefore, it is believed that this new set of seven factors for reviewing a benefit-risk assessment framework not only encompassed those used for two other major projects, but is also a reflection of the contemporary ideals among the agencies and companies for such frameworks.

The lack of an accepted and validated framework was a significant barrier for agencies and companies. Additional barriers included the absence of a consensus on the needs of the stakeholders and direction of the purpose and utility of a framework, as well as the lack of acceptance by the major regulatory agencies. In addition, the universal framework should be comprehensible, easy to understand and use, be flexible and accommodate the different scientific methods of assessing benefits and risks. The outcomes of EMA's work packages (2011d and 2012) and IMI PROTECT (2011b), both of which utilised the PrOACT-URL framework, confirmed that a qualitative and flexible framework would be required to achieve the above.

The requirements for a universal framework ought to be sought from the stakeholders whose inputs will directly affect the benefit-risk decision and the final regulatory outcome. These have been identified as the regulatory agencies, pharmaceutical companies, physicians, HTA agencies and the patients. While this study obtained only the views of the agencies and the companies, there are on-going studies to assess the contribution of the other stakeholders to the decision-making process. These include patients' involvement (EMA, 2011e; FDA 2013) and health technology assessment (HTA) agencies (EMA, 2013c). While the study was conducted with major and medium-sized agencies and companies it may not represent the entire regulatory environment.

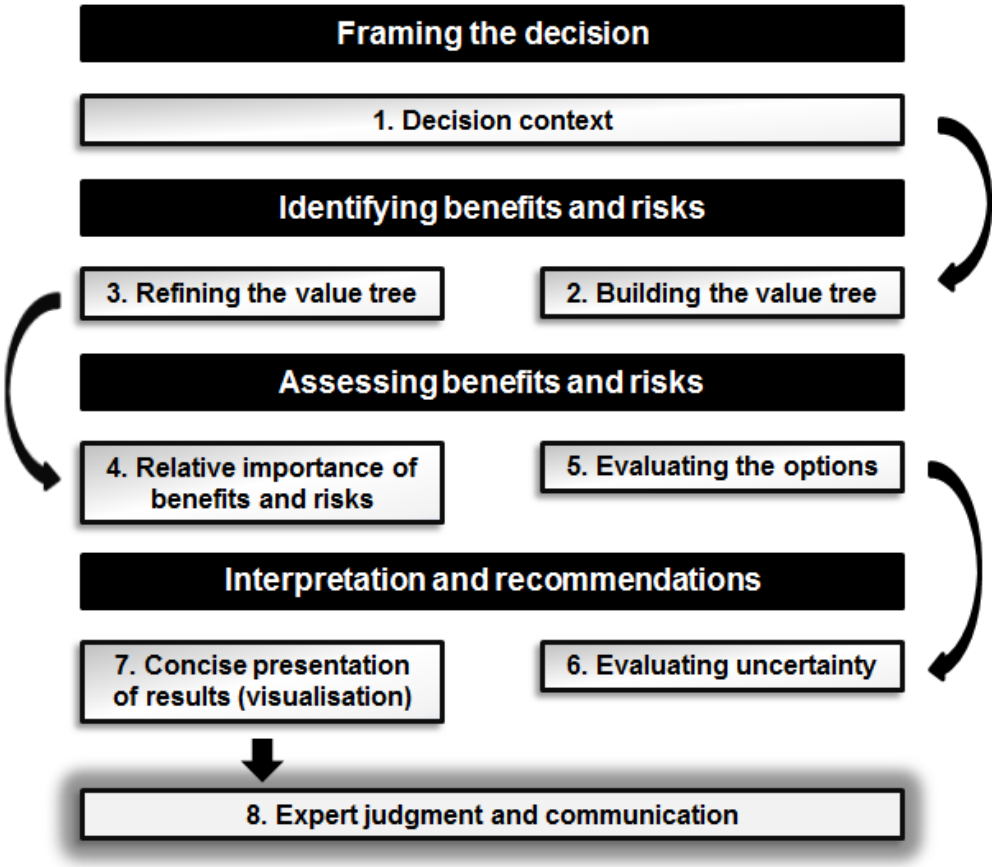
While there is no common framework for major regulatory agencies and companies, some do have their own frameworks for the assessment of benefits and risks. The EMA's 8-step PrOACT-URL (EMA, 2010) (also used by the IMI PROTECT), the US

FDA's 5-step benefit-risk framework (FDA, 2013a), the BRAT 6-step framework (Coplan et al, 2011), the CIRS' 7-step framework (CMR, 2010) and Novo Nordisk's Benefit-Risk Assessment in New and old Drugs (BRAIN; CMR, 2010) were compared. With the exception of the US FDA's framework, the rest were based on the principles of MCDA, which was earlier confirmed in the course of this research as a useful and relevant methodology. The eventual 8-step framework which has been developed in this research includes the defining of the decision context, building the value tree, refining the value tree, evaluating the options, assigning relative importance of the benefits and risks, evaluating the uncertainties, presenting the outcomes in a graphical manner and finally applying expert judgment and communicating the decision. Across the frameworks compared and the final 8-step framework, there are four common requirements considered fundamental to assessment, namely framing the decision, identifying the benefits and risks, assessing the benefits and risks and lastly interpreting and recommending a decision. However, the differences among the frameworks lie in the activities conducted to fulfil these requirements. Apart from the framework used by the US FDA, the rest advocated the use of weighting and valuing and the use of either an effects table (as in the case of PrOACT-URL) or other appropriate visualisation tools. This observation may be related to the fact that these frameworks follow the principles of MCDA while the US FDA was a unique qualitative framework. However, it should be noted that while the US FDA framework did not explicitly advocate the use of the weighting, valuing and visualisation it appears that it would be able to accommodate such activities.

Between the final 8-step universal framework (Figure 8.1) and the EMA's PrOACT-URL, the latter had more emphasis on the discussion of risk tolerance and the consistency of decisions i.e. linked decisions. While this may be discussed as part of the uncertainties or implied with the use of weightings under the new framework, there may be value in soliciting directly the views on the risks the evaluator is willing to accept and how well the basis of the recommended decision aligns to previous ones made for similar scenarios. Among the BRAT framework, BRAIN and the new 8-step framework, it appears the former two encourages the use of quantitative tools to provide a metric representation of the effects and scores, while the new framework may accommodate a qualitative discussion instead. Overall, the 8-step framework

has struck a balance between more prescriptive frameworks requiring some quantitative outcomes and those which otherwise are too general in guiding the assessment of benefits and risks. As such, the universal utility of the final 8-step benefit-risk assessment framework is supported by the above comparison and it was developed with elements common to the other existing frameworks and used by the two major regulatory agencies and pharmaceutical companies. Hence, if all the processes of the final 8-step framework are carried out, the outcomes are expected to complete and fulfil the requirements of the other existing frameworks. This universal benefit-risk assessment framework is expected to enhance the objectivity and transparency of the decision-making process by providing a structured approach that could be adopted by regulatory agencies and pharmaceutical companies.

Figure 8.1 The 8-step universal benefit-risk assessment framework



In order to utilize the steps of the framework, a system for documentation of the assessment outcomes and effective communication must be in place. In the absence of the principles and methodologies for benefit-risk assessment from other major

regulatory authorities, the published reflection paper by EMA (2008) was used as a reference for the development of the tool to document and communicate the outcomes of assessment and the basis of the decision in a consistent and transparent manner. The developmental version of the Benefit-risk (BR) Template was tested for functionality by the Consortium, consisting of TGA, Health Canada, SwissMedic and HSA. This was carried as a retrospective feasibility study. The final version consists of two sections, namely the “BR Template” and “Benefit-risk Summary”. The template was then reviewed against the core elements of the universal framework, namely framing the decision, identifying the benefits and risks, assessing benefits and risks, interpretation and recommendations. In relating to the 8-step universal framework, the BR Template fully supports these requirements. To facilitate the use of the framework and template, a user manual was developed. This consisted of two sections, namely a glossary and instructions for completing the template. Consequently, the Benefit-risk Assessment Support System (BRASS) was developed and consisted of the 8-step Benefit-risk assessment framework, the Benefit-risk Template and the User Manual.

It could be argued that the evaluation of BRASS by the four agencies of the Consortium would not represent the opinions of all stakeholders and thus undermines its utility as a universal framework. However, it should be noted that the universal framework was reflective of the current principles used by the major reference regulatory authorities and companies. As justified above and also at a workshop (CIRS, 2012b) attended by senior decision-makers of agencies and companies there was an agreement that the final 8-step universal framework covered the essential elements in other existing frameworks.

Subsequently, a prospective study was therefore conducted with three agencies, namely TGA, Health Canada and HSA, to review the potential value of the BR Template and user manual. In order to achieve consistency in evaluating the responses of the agencies, a study evaluation tool was developed which included four sections namely user-friendliness, documentation, applicability and general comments. Navigation functions were found sufficient to guide the user in the locating different sections of the template. The user manual too was found to be

adequate though more specific details and examples of use could be provided. Overall, the BR Template and User Manual were found to be user-friendly.

The BR Template was studied for its appropriateness in documenting relevant information supporting the benefit-risk decision, the benefits and risks, weights and values, study outcomes, safety information and overall conclusion. For information to support the decision, the template was found satisfactory in documenting the various relevant conclusions, with proposed modifications to allow greater details to be presented. The template was found more acceptable in documenting benefits than risks and consequently there were recommendations to provide greater clarity in the risk definitions and how these are to be selected for the benefit-risk assessment. Divergent views were obtained for the template's use in documenting weights and values. However, this observation is very probably related to the current state of knowledge in applying weights and values for the assessment of benefits and risks. It is expected that in the future when more assessors are better acquainted with the concepts and application of weights and values, the opinions of the use of the template for this aspect would be better reflected.

In reviewing its applicability, the BR Template was assessed on its ability to contribute to decision-making, consistency in standard of assessment, transparency, communication to stakeholders and consistency of decisions between agencies. With the exception of one agency, the above functions were deemed to be fulfilled by the template. The main concern of Health Canada, who disagreed, was that the template was neither able to capture critical thinking, nor other significant contributing factors such as the additional analyses that the reviewers requested from sponsors. If clarification is provided on the existing availability of appropriate sections in the BR Template to discuss these other contributing factors, it is believed that all three agencies would agree on the template's applicability. All the agencies agreed that the BR template can ensure consistency in decision-making through improving regulatory memory, acting as an audit tool and contributing to post-marketing activities. The outcomes demonstrated the value of the template and user manual and its potential use in documenting and communicating benefit-risk decisions. Overall, all three agencies found the template and user manual fit for purpose with amendments. Importantly, all three agencies found the BR Template useful in

documenting the uncertainties relevant to the identified benefits and risks. The potential and practicality of the BR Template in documenting, reporting and decision-conferencing of benefit-risk decisions was therefore demonstrated. It would be of interest to evaluate the use of the template with an established mature agency, in particular the EMA, since their guidance was the basis of the template (EMA, 2008). This would help to convince stakeholders that the BR Template is applicable across regulatory agencies of all levels of establishment and maturity.

To assess the template's ability to act as a suitable tool for communication, the three agencies were asked if they are willing the share the completed BR Template and the summary section with stakeholders. Though it appeared there are reservations in sharing the entire completed BR Template, this view was due to concerns over confidentiality and memorandums of understanding with the stakeholders and not the functionality of the template. One agency, HSA, however felt that information for the public and media should be amended as the BR Template may contain information that is too technical for their understanding. Regarding the more succinct BR Summary section, the agencies would consider sharing this with stakeholders provided more details can be provided in this section and if the information is amended to tailor to the level of understanding for patients and media. It is noted that both TGA and Health Canada already provide public available reports and would thus be comfortable with the inclusion of more in-depth contents. HSA on the other hand is establishing itself as a maturing agency and may be more conservative in making available the information relating to their decisions. Nonetheless, the BR Template and the BR Summary Template allows amendments and can be tailored to suit each agency's needs.

Given the different regulatory capacities and maturation of the regulatory agencies across the world, some are leading this field while others, like those from the emerging markets, would likely leverage on the decisions of the major regulatory agencies. Therefore it is important that the basis of the decisions of the major agencies is effectively communicated to the rest of the stakeholders, which would include the agencies from the emerging markets. Although there may be publicly available assessment reports, these may contain a significant amount of information to review that would require both time and scientific capabilities that are not available.

The potential use of the BR Summary section as a stand-alone tool for documenting and communicating benefit-risk decisions was thus identified, in the hope that it may aid the emerging markets. Consequently, this section was extracted and transformed into a stand-alone tool, now known as the BR Summary Template.

A retrospective study was conducted using the BR Summary Template across different reviewers and products. The study evaluation tool and user manual for the review of the BR Template were modified to suit the BR Summary Template. In general the BR Summary Template was found to be fit for purpose by a group of reviewers across a range of products in documenting the benefit-risk outcomes from abridged applications. The potential of the BR Summary Template is thus found to be suitable in fulfilling its role in documenting, reporting and decision-conferencing of benefit-risk decisions. However, there were reservations in sharing with patients, patient advocacy groups, media and in public domains as the use of technical terms and medical jargon may be lead to confusion and misinterpretation.

Indeed, for the emerging markets that are more resource constrained with respect to their scientific capabilities, the BR Summary Template may also serve as a template for the assessment of medicines and as an internal standard in their pursuit to develop the capabilities of their agencies. There should be further studies to assess the use of the BR Summary Template in aiding emerging markets in their pursuit of improving their regulatory standards. This is in line with the earlier findings from a CIRS workshop (CMR, 2008) to include the emerging markets earlier in the development of benefit-risk frameworks, so as to increase the worldwide acceptance of a universal framework. The framework, through unifying the current practices by major regulatory agencies and pharmaceutical companies, may be seen as the definitive standard for a systematic assessment of benefits and risks. Likewise, the BR Template and BR Summary Template are useful tools to be considered for assessing, documenting and communicating benefit-risks decisions. It is important to understand that in the pursuit of an international impact of the developed framework and templates, the entire spectrum of stakeholders should be considered. Views from the Middle Eastern, Asian and Central American countries and their potential contribution have not, as yet, been sought. The implementation of the framework and

templates may serve as a starting point to initiate further collaboration with these countries.

As expectations of stakeholders evolve, it is pertinent that all information leading to a regulatory decision for a medicine is made available. This communication is vital to making an informed decision, especially for physicians in choosing a treatment best suited for their patients and HTA agencies in deciding reimbursement. Hence all considerations taken for making the decision should be made clear so that the stakeholder may relate them to their situation and apply these to their own decisions. While it is noted that both EMA (2008, 2010) and US FDA (2013) have undertaken initiatives to enhance the benefit-risk evaluation of a product, there is currently no standard template for the documentation and communication of the evaluation outcomes of benefit-risk decisions. Individual agencies would have their own internal evaluation report templates and also those for publicly available assessment reports, resulting in similar information being presented in different formats for the stakeholders. Earlier findings in the course of this research showed that both regulatory agencies and pharmaceutical companies believe that a benefit–risk framework would enhance the quality (transparency and consistency) of communication and should provide documentation for a structured discussion, acting as a tool for communication among peers within the organisation and between the organisation and stakeholders. Various agencies including the US FDA, EMA, TGA and Health Canada have embarked on improving the communication of information relating to benefit-risk decisions, but there is limited information on how well these publicly available reports are meeting the needs of the various stakeholders. The BR Template and BR Summary Template were designed to enhance effective documentation and communication of decisions and have been showed to be fit for purpose. The publicly available assessment reports from four major agencies, namely the US FDA (Medical Review), EMA (EPAR), Health Canada (SBD) and TGA (AusPAR), were therefore compared to see if they would adequately fulfil the functions found in the BR Template and BR Summary Template.

The format of the reference agencies' reports are generally similar but when compared with the BR Template were found to lack the key features that list the

identified benefits and risks, application of values and weights (relative importance) and visualisation of the assessment outcomes. In addition, the BR Template presents a structure of guided questions to document relevant discussions and considerations contributing to the final benefit-risk decision. Similar findings were observed when the US FDA's Risk Benefit Assessment, EPAR's Executive Summary, Health Canada's SBD and TGA's AusPAR were compared to the BR Summary Template. To further illustrate the use of the BR Summary Template, a case study was conducted using a recent US FDA Medical Review (FDA, 2012b) and EPAR (EMA, 2013c) for the same product, Zaltrap® (aflibercept). This product is indicated for use, in combination with 5-fluorouracil, leucovorin, irinotecan (known as the FOLFIRI regimen), in patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen. Only the Risk Benefit Assessment from US FDA's Medical Review and Executive Summary of the EPAR were used to complete the fields in the BR Summary Template. Overall, the BR Summary Template is found to be more structured in presenting the information for the benefit-risk decision.

There is a strong implication that the observed failure to list benefits, risks, apply weights and values may not allow the effective communication of the decision. It is therefore important that these parameters should be documented or stakeholders may not fully understand the thought processes that contribute to the benefit-risk decision, thus resulting in a major drawback in the impact of communication. It was observed that the above features were omitted in the major reference agencies' publicly available assessment reports. Hence, these widely accessible reports may not be effective in relaying the basis of decisions, leading to stakeholders misinterpreting the information. Such scenarios may lead to the lack of access to the patients should the HTA agencies not agree with the decision by the regulator, or a lack of trust to the healthcare administration for the perceived lack of transparency. In cases of disputes, the lack of appropriate documentation could eliminate a platform for discussing the potential areas of disagreement. There should be clear direction in providing documentation that communicates accurately the basis of the decision. The mere provision of materials may not always achieve this goal. The current reports by the reference agencies could afford more explicit opinions through listing the selected benefits and risks and their relative importance, as well as a structured discussion on the considerations leading to the final decision. While it is understood that relative

importance of the parameters are assessed implicitly, for effective communication of benefits and risks (CMR, 2004, 2005 and 2010), it is imperative they are made explicit in any publicly available documents.

Visualisation in communication of benefits, risks and the resulting balance was unanimously agreed to be of value by both agencies and companies. There is a lack of experience with this approach and of any agreement on a global level as to the best visualisation tool. It would seem that agencies and companies may prefer the incorporation of more details for discussion, while physicians and patients may prefer an overview to understand the decision taken. The fifth work package of IMI PROTECT (2013c and 2013d) provided various principles for the assessment of visualisation techniques, as well as specific techniques for the different benefit-risk methodologies. However, it is expected that for the successful implementation of visualisation techniques, further work will be required to understand the needs of the stakeholders and identify the appropriate corresponding visualisation tools, as well as obtain consensus at a global level. It appears that the work by IMI PROTECT would be a suitable starting platform for future international collaborations in pursuing universal acceptable visualisation tools. Training programs for the application of such tools should also be developed, as it is expected that this strategy for communicating benefit-risk decisions through graphical representation would be new to many stakeholders.

To achieve an appropriate universal benefit-risk documentation template, the BR Template should be considered as a platform or reference for further development among the reference agencies. It is however acknowledged that due to different jurisdictions, it may not be possible to implement a common template for universal use as there may be legal obligations or restrictions in the information to be provided. It is however noted that the features of the BR Template, including the unique structure and use of guiding questions, are recognised as essential criteria for any template to effectively document and communicate benefit-risk decisions.

Potential use in product life cycle management and adaptive licencing

The use of the BR Template in post-marketing activities and pharmacovigilance has as yet not been fully investigated. As part of the life cycle approach, a single

document should be used for the effective monitoring of changes in benefit-risk balances, as the initial documented benefit-risk for market approval would form the baseline for future assessment. As the BR Template documents the context of each decision, with the availability of new clinical information for efficacy and safety, each assessment can be relevant and consistent. Therefore, the BR Template should be considered for use in product life cycle management.

The utility of the BR Template to document and communicate benefit-risk decisions should be viewed in the light of the two international reports currently required for regulatory submission, namely the Common Technical Document (CTD) (ICH, 2004) and the ICH PBRER (EMA, 2013a) meant for documenting pre-approval and post-marketing information respectively. For initial marketing authorisation, the details of the product development are found in Module 3 (Quality), Module 4 (Non-clinical study reports) and Module 5 (Clinical study reports). Administration information is submitted in Module 1, which is customised to the specific regulatory requirements for each jurisdiction. Module 2 contains the summaries and can be considered akin to the BR Template and functions to succinctly communicate the rationale of development, supporting clinical outcomes and relevance to healthcare. Specifically, the CTD Module 2.5 Clinical Overview contains the clinical findings to support the submission and consideration for the registration of the product. Hence it appears plausible to introduce the 8-step universal benefit-risk assessment framework and the BR Template to guide the documentation and communication of the benefits and risks of the submitted product. By leveraging the use of an existing international submission package, the implementation of the framework and template can be consistently carried out. In a similar manner, by incorporating the framework and template within the PBRER, the consistent utility of the above can be ensured for the entire life cycle. As clinical assessment of new information for benefits and risks are required, the universal framework can ensure that consistent standards are being applied. It appears that all sections of the BR Template can be incorporated into the PBRER, especially for section 18, which is dedicated for the discussion of the integrated benefit-risk analysis for the approved indications.

In maintaining the stand for a core documentation tool, it would be an ideal situation that a single BR Template be used by all stakeholders. This would commence with

the companies in their submission to the agencies, documenting the benefit-risk balance that supports the application. The agencies will conduct the assessment as per their current processes, but would input their decisions into the same BR Template utilised by the company. This BR Template would then remain as a core document for which future benefit-risk information, for example post-marketing activities and product variations, would be appended. Indeed, this can be part of the proposed solution to have guidance on the universal framework at an international level. Future work should include collaborations with ICH and review how the universal framework and BR Template could be incorporated and its use continued from the CTD to PBRER.

Innovations in regulatory science are now exploring new strategies to allow faster access to important medicines, including adaptive licencing (AL). It may involve looking at the benefit-risk balance in a specific and limited patient population and granting an initial authorisation (Eichler et al., 2012b). Real life data on safety would be generated through the actual use of the product post-authorisation, while more clinical studies are being completed to show efficacy in another disease aspect or in a wider population. The marketing authorisation would be amended to encompass the wider use of the product as more safety and efficacy data becomes available over time. It is hoped that with such strategies it would reduce the time to obtain the full dataset that is currently required for registration and thus allow sick patients faster access to a medicine with the potential for treatment. The MHRA (2013b) recently confirmed its commitment to allow early access to useful medicines through adaptive licensing, effected via the flexibility offered in the current European law for conditional approvals. The principle behind this adaptive licencing should be supported by a robust framework for assessing benefits and risks, as well as a tool to document the various considerations as the benefit-risk balances evolve over time with new data becoming available. As indicated by Philippe de Jong et al (2013a and 2013b), there must be greater clarity, transparency and consistency in the decision-making process, especially for products undergoing the AL procedure. In addition, there should be improved public communication to the stakeholders, including patients, on the perception of efficacy and safety (Eichler et al., 2012b), as the risk tolerance and trade-offs are expectedly different for the drug treatments assessed to be suitable for AL. Similarly, scientific communication between regulators and companies should be

optimised and initiated at the early stages of product development (Philippe de Jong et al, 2013b). It therefore appears timely to share the findings of the universal framework and template developed here with the key leaders of the adaptive licencing movement, especially at this time when the major regulatory agencies are reviewing the current processes to accommodate the ideals of adaptive licencing. However, it was found that across a few regulatory agencies the jurisdiction and legal foundations for product registration differ. Hence, as for the framework, the universal implementation of AL should consider the legislative differences as a potential barrier and how such differences can be accommodated (Oye et al., 2013)

The universal benefit-risk framework and benefit-risk template - Key to a cultural change

Increasingly, patients, through advocacy groups or representatives, express their opinions on factors in healthcare so that these can be reviewed during the assessment of benefits and risks (Walker et al., 2006). Various regulatory agencies like the EMA (2011), MHRA (2013a) and the US FDA (through the Patient-Focused Drug Development program of PDUFA V; FDA, 2013a) have initiated projects to involve patients more in their regulatory processes. Indeed, the incorporation of patients' opinions and contributions to regulatory decision-making have been the recent highlight for workshops on benefit-risk assessments (CIRS, 2012a and 2013a). Existing frameworks do not explicitly indicate the involvement of patients for the assessment of benefits and risks, but these may be discussed during the documentation of the outcomes and considerations of the decision. The challenge would be to identify the tools to collect such information in an objective manner and how these might be incorporated into the proposed practices for weighting and valuing. To obtain quantified measures of patients' input, these could be done through patient reported outcomes (PRO). However, the relevance of the PROs needs to be validated with the patients themselves. Therefore, it is expected that platforms to communicate with patients and their caregivers be established so that such pertinent information can be sourced in a systematic manner. There appears to be no ideal approach for the above, and the activities may range from direct patient meetings as conducted by the US FDA, or having them represented at advisory meetings in the EU. To ensure that the universal framework and BR Template remain

relevant and useful, future refinement should look as to how the patients' contribution can be incorporated as part of the framework and effectively documented.

In some jurisdictions the accessibility of a medicine would require the approval of a third party insurance payer or a health technology assessment (HTA) agency. Therefore it is essential that the relevant information to support the use and availability of the medicine be communicated from the regulatory agency to the HTA agencies. There are also recent efforts to conduct joint reviews between EMA and the HTA agencies (EMA, 2013d), in recognition of the significant contribution of each party towards product availability and ultimately healthcare management. The initial focus of the collaboration was to review the EPAR's information on the benefits and risks of a medicine and how these can address the needs of HTA agencies. The objectives included potential changes to the EPAR template**.**

Study limitations

- The prospective study for the BR Template conducted by the three agencies was limited to using one product per reviewer. Therefore there is potential bias in the opinions received regarding the applicability of the BR Template, as these opinions are collected from only a few assessors and may be confounded by individual work experience, clinical expertise and previous exposure to other frameworks. Moreover, the limited products reviewed could not represent the different benefit-risk profiles and risk tolerance that would be encountered for regulatory submissions.
- The studies of the BR Template and BR Summary Template were conducted with only four regulatory agencies whose experience and opinions may not represent those of the major reference regulatory agencies like the EMA and the US FDA.
- The study for the BR Summary Template used only one agency from the emerging markets (HSA, Singapore) and included only abridged applications where approval had been obtained in another country.
- The case study (Zaltrap®) used for the comparison of publicly available report was one product meant for a highly unmet medical need and not across a few products for different benefit-risk balances and risk tolerance.

- The industry was not engaged as part of the study to review the utility of the BR Template and BR Summary Template.

RECOMMENDATIONS

- Agencies should include the listing of benefits and risks, assign weighting or relative importance and visualisation in their assessment and documentation of benefit-risk decisions
- Consideration should be given to using the BR Summary Template to communicate to companies, physicians and other agencies
- The BR Summary Template should be considered by the emerging markets for the exchange of information in support of their own regulatory approval processes
- The value of the framework should be determined for companies for drug development and regulatory submission
- The utility of both the universal framework and BR Template should be explored by HTA agencies
- Training programs/initiatives for change management should be explored within an organisation

FUTURE WORK

- The development of the universal framework and BR Template and the impact of this research should be assessed after 3 years. This may be conducted via the same manner to collect information on the stakeholders' current use of benefit-risk assessment frameworks as carried out in Chapter 3.
- The practicality and validity of the revised BR template should be reviewed again in the three agencies and also the EMA, whose guidance formed the basis of the template. The study involving the EMA should also elucidate how effectively the items in the reflection paper are being represented in the BR template.
- The applicability of the BR template in the post-marketing setting for assessing, documenting and communicating changes in benefit-risk balances (via the PBRERs) should be investigated. This would assess the utility of the template for product life cycle management.

- The use of the stand-alone BR Summary Template should be further investigated by leading emerging agencies, through using different products and evaluations, in sharing assessment reports with other emerging markets, including Asian, Central American and the Middle Eastern countries.
- The incorporation of weights and values for the assessment of benefits and risks and the presentation of such information into the publicly available assessment reports should be studied for its impact on the communication of benefit-risk decisions to stakeholders.
- The framework and the template should be reviewed to optimise the contribution of patients, in terms of time involvement and objective information, to the benefit-risk decision-making process. This may be aligned to the current activities undertaken by the US FDA's PDUFA V.
- The various needs of the stakeholders for a benefit-risk document should be verified as these needs are expected to vary between academia, regulatory affairs, healthcare and the lay patients. This would allow the validation of the template to communicate effectively according to various stakeholder needs.

In an attempt to ensure the framework and template are used in a contemporary setting, the function of the framework should align to the current interests of regulatory science, namely life cycle management and adaptive licencing. However this can only be achieved if the use in post-marketing activities can be demonstrated. To establish the framework as universal, all stakeholders, including those from the emerging markets, should be incorporated into future studies to ascertain its value in these respective countries.

CONCLUSION

While there was previously no common framework, the criteria for the development of a universal benefit-risk framework have now been identified and it is confirmed that the purposes of such a framework are to enhance the documentation and communication of decisions to the various stakeholders in a manner that is structured, transparent and consistent. The 8-step universal benefit-risk assessment framework, a documentation tool and the user manual, have now been developed to effectively meet the need for a common universal framework.

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PUBLICATIONS

Oral presentations

Leong J, McAuslane N, Walker S, Salek S (2012). Development and application of a universal benefit-risk assessment framework for medicines. Poster presentation. DIA 48th Annual Meeting.

Publications

Leong J, McAuslane N, Walker S, Salek S (2013). Is there a need for a universal benefit-risk assessment framework for medicines? Regulatory and industry perspectives. Pharmacoepidemiol Drug Saf; 22(9):1004-12. doi: 10.1002/pds.3464. Epub 2013 Jun 5.

Summary and Proforma Template for the Benefit-Risk Assessment of Medicines

Compound Identifier(s):	
Product name/ Brand name / Generic name:	
Active Ingredient(s)/ Strength(s)/ Dosage form:	
Claimed Indication:	

Please complete a new form for each indication

Please complete the proforma which will auto-populate the Summary.
The sections in the proforma that populate the summary are highlighted in green.
It has been decided for this pilot exercise that the summary can only be completed via the proforma.

All data will be treated in strict confidence.
No data or information will be revealed to any third party

Quick Links

Print Full Form | Email Full Form | View Full Form
Print Summary | Email Summary | View Summary

1

Product Name:

Indication:

PROFORMA SECTION

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Product Name:

Indication:

PROFORMA SECTION

SECTION 2. Background

The aim of this proforma is to provide the means whereby the key benefits and risks, together with the uncertainties (strengths of evidence and limitations of data) that drive the benefit-risk assessment can be documented systematically in the light of the available evidence and therapeutic indication in accordance with the CHMP Assessment Template. This section contains a mixture of factual key data and interpretation through value judgments.

2.1 Specify the claimed therapeutic indication *This prefills summary 1.2.1*

2.2 Treatment modalities evaluated in this submission *This prefills summary 1.2.2*

2.3 Other currently available treatment options NOT considered or evaluated

2.4 What are the known risks with compounds of the same therapeutic class?

2.5 Is this product for an unmet medical need? *This prefills summary 1.2.3* Please select

Reasons: Please provide justification for your decision on the product fulfilling or not fulfilling an unmet medical need.

2.6 Aims of treatment and expected effect size? i.e. define if there are established minimally significant

Product Name:

Indication:

PROFORMA SECTION

SECTION 3. Overall Summary

3.1 Quality Overall Summary *This prefills summary 1.1.2 and section 7.1*

Please tick the box if there are no relevant findings in the quality assessment that will contribute significantly to the clinical assessment of benefits and risks. ☐

Please provide comments in the box below if there are relevant findings in the quality of the product that may affect significantly the clinical assessmentof benefits and risks.

Comments:

Product Name:

Indication:

PROFORMA SECTION

3.2 Non-Clinical Overall Summary

This prefills summary1.1.3 and section 7.2

Please tick the box if there are no relevant findings in the non-clinical assessment that will contribute significantly to the clinical assessment of benefits and risks. ☐

If there are relevant findings, please complete the comments section.

3.2.1 Comments:

Relevant non-clinical findings	Potential implications in human use / Requires further investigation

3.2.2 What are the conclusions from these findings implicating benefit-risk assessment for humans?

This prefills summary1.1.3 and section 7.2

This should only be filled in after the significance of the findings above is correlated to human data/further investigations from the clinical studies. Any mitigation strategies should be highlighted here.

Product Name:

Indication:

PROFORMA SECTION

3.3.1 Human Pharmacology: Overall Summary

Only the important results and issues that have an impact on the benefit-risk balance should be described. In addition, unresolved issues or uncertainties should be identified and their impact on the balance assessment should be clearly stated. This includes Bioequivalence, Pharmacokinetic and Dynamic profile, as well as PK, & PD interactions, special populations, dose findings etc

3.3.2 Human Pharmacology Conclusions: *This prefills summary 1.1.4 and section 7.3*

Product Name:

Indication:

PROFORMA SECTION

3.4.1 Clinical Overall Summary

Only the important results and issues that have an impact on the benefit-risk balance should be described. In addition, unresolved issues or uncertainties should be identified and their impact on the balance assessment should be clearly stated.

This includes study design, dosage, population and comparators.

3.4.2 Clinical Conclusions: *This prefills summary 1.1.5 and section 7.4*

Product Name:

Indication:

PROFORMA SECTION

SECTION 4. Identified Benefits and Risks

4.1 List all the BENEFITS as documented *This prefills summary 1.3.1*

List all **benefits** of treatment for this indication as inferred in the submission	Please tick here if Benefit Identified by Reviewer but not by company	Please indicate which **benefits** you believe are justified to be included in the benefit risk assessment by ticking the box	Please explain your main reason **for inclusion or exclusion** of the benefit parameter
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Product Name:

Indication:

PROFORMA SECTION

4.2 List all the RISKS as documented *This prefills summary 1.3.2*

List all **risks** of treatment for this indication as inferred in the submission	Please tick here if Risk Identified by Reviewer but not by company	Please indicate which **risks** you believe are justified to be included in the benefit risk assessment by ticking the box	Please explain your main reason **for inclusion or exclusion** of the risk parameter
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Product Name:

Indication:

PROFORMA SECTION

Section 5 Benefit and Risks - Study Information

5.1 Please complete this section for **each benefit observed** in pivotal and non-pivotal studies, which you have justified to be included in the benefit risk assessment in section 4.1

5.1.1 Benefit (*pre-filled from Table 4.1*):

5.1.2 Study Identifier	5.1.3 Type of Study	5.1.4 Describe benefit in terms of presence or absence in: Investigated Product	Comparator (Name)	Placebo (if appropriate)	5.1.5 Primary Endpoint?	5.1.6 Statistical parameters to describe results - eg Hazard ratios	Lower CI	Upper CI	P Value	Statistically Significant	5.1.7 Clinical Relevance?	5.1.8 Effect Size? Enter % or actual values	5.1.9 Studied population representative	5.1.10 Patient compliance satisfactory?	
															-

Please click here to add a new study: +

Contents | Background | Overall Summaries | Identified B&R | B&R Study Info | Weights & Values | Conclusions | B&R Summary

Product Name:

Indication:

PROFORMA SECTION

5.1.11 Was this benefit seen (consistent) across all the studies? Please select

Any Comments to be noted relevant to this Benefit across the studies:

5.1.12 Is there any evidence of this benefit in relevant subgroups? Please select

Please describe - age, sex, ethnicity, organ function, disease severity:

Comment:

5.1.13 Was there confirmation of this treatment effect (benefit) from the results of the non-primary endpoint? Please select

Comment:

5.1.14 Were patient reported outcomes also supportive of this finding? Please select

Comment:

5.1.15 Overall conclusion for this benefit for these studies:

Comment:

Product Name:

Indication:

PROFORMA SECTION

5.2 RISKS: Overall Summary
Table of pooled overall incidence of events can be added below

Adobe **Acrobat** users can click here to attach a file: Attach a file *(Note: this will not activate in Adobe **Reader**)*

Click in the space below to upload an image: (jpeg, gif, png): *(Available to both Adobe Reader and Acrobat users)*

Add another table

12

Product Name:

Indication:

PROFORMA SECTION

5.2.1 What was the overall incidence of adverse effects? If the studies do not allow you to combine to give an overall incidence please complete a separate page(s) if required. In this case please provide a descriptor of what information is being included in this table.

Please provide the descriptor information of what is included in this table:	

Investigated Product	Comparator (name)	Placebo (if appropriate)

5.2.2 What was the overall incidence of serious adverse effects?

Investigated Product	Comparator (name)	Placebo (if appropriate)

5.2.3 What was the discontinuation rate (from the medication) due to adverse effects?

Investigated Product	Comparator (name)	Placebo (if appropriate)

5.2.4 What was the dose/reduction rate (% of patient population in the study) due to adverse effects?

Investigated Product	Comparator (name)	Placebo (if appropriate)

Click here to add an additional page: Add page

Product Name:

Indication:

PROFORMA SECTION

5.3: Adverse Effects

This table should be repeated for each risk identified in section 4.2 that significantly contribute to the overall benefit-risk assessment of the medicine in this indication. **Each risk will have its own generated page.**
For each attribute please provide either figures or a description if required.

5.3.1 Name specific adverse effect and describe: Incidence, severity, seriousness, duration, reversibility

	Investigated Product	Comparator	Placebo (if appropriate)
Please specify presence or absence			
Incidence			
Severity			
Seriousness			
Duration			
Reversibility			
Contributed to withdrawal of use			
Contributed to change in dose (down titration)			
Comments:			

Product Name:

Indication:

PROFORMA SECTION

5.4 Uncertainties (Benefits & Risks) for pivotal and non-pivotal studies

5.4.1 Discuss the choice of dose, comparator and endpoints (including surrogates as appropriate)

Comment:

Was the comparator used relevant for the jurisdiction/Standard of Care? Please select

5.4.2 Comment on the design, conduct and statistical adequacy of the trial including the impact of any methodological deficiencies on the estimated benefits. Please pay attention to missing data and the methods used to account for them.

Comment:

5.4.3 Have the measurements and scales been validated? Please select

What are the unsettled issues?

Is there a need for further studies? Please select

If yes, why?

5.4.4 Describe any negative studies. Describe the quality of the supportive scientific literature and any other issues that may have an impact on the estimated benefits

Product Name:

Indication:

PROFORMA SECTION

5.4.5 Are the results consistent across different factors? E.g. pivotal trials and supportive studies, or submitted studies and literature, different populations, centres, doses, etc.

Please select

Comment on the consistency or clustering of the results in the supportive and pivotal trials:

Please note 5.4.6-5.4.9 relate specifically to risks

5.4.6 Are there known or potential interactions between this product and food/ drugs?

Please select

Comment:

5.4.7 What are the limitations of this dataset (e.g. missing data, potential risk factors, subgroups of patients not investigated but potentially susceptible to adverse effects) Discuss the implications of such limitations with respect to predicting the safety of the product.

Please indicate by ticking if subpopulation not investigated for this indication:

Paediatrics ☐ Elderly ☐ Other ☐ Please specify:

5.4.8 What is the potential for off-label use and the possible risks associated with this use? This should include the potential for overdose, abuse and misuse.

Product Name:

Indication:

PROFORMA SECTION

5.4.9 Please comment on the risk with respect to the indicated product versus standard of care:

5.4.10 Please comment on any other uncertainty that has not been covered already

Contents | Background | Overall Summaries | Identified B&R | B&R Study Info | Weights & Values | Conclusions | B&R Summary

Product Name:

Indication:

PROFORMA SECTION

SECTION 6. Benefit-Risk Summary Table & Expert Judgement

The aim of this section is to compare benefits and risks described above, putting in perspective alternative therapies or interventions (where possible and relevant) and to conclude on whether the benefit-risk balance is positive in the specified target population(s).

Weighting (relative importance based on expert judgement)	**Valuing** (objective or subjective outcomes relative to individual options)
➢ For the identified benefits and risks, the reviewer should apply their expert judgment to provide relative importance of each parameter in contributing to the benefit-risk balance, in the light of the evidence provided ➢ This is either carried out through ranking, numerical value, or qualitative descriptors such as high, medium or low. If the system of ranking is used, then this should be hierarchical and logical. Reviewers should limit themselves to using only one of these systems for both benefits and risks. ➢ Please provide a short explanation of the selected system:	➢ Provide either qualitative (e.g. high, medium, low or absent) or quantitative (utilizing the values from the study outcomes, e.g. overall survival 32% for product versus 27% for placebo) values of benefits and risks.

Product Name:

Indication:

PROFORMA SECTION

SECTION 6. Weighting and valuing *This prefills summary 1.4*

Please provide the information for only those Benefits and Risks that contribute to the final Benefit Risk balance

6.1 Benefits Populated from 4.1	Weighting (relative importance) Using selected relative importance system	Valuing the options			Comment on strength and uncertainty of benefit
		Investigated product	Comparator	Placebo	

Contents | Background | Overall Summaries | Identified B&R | B&R Study Info | Weights & Values | Conclusions | B&R Summary

Product Name:

Indication:

PROFORMA SECTION

6.2 Risks Populated from 4.2	Weighting (using the selected system)	Valuing the options			Comment on strength and uncertainty of each risk	Was the value or weight of this risk altered or mitigated by the ability to control the use of the medicine once on the market?
		Investigated product	Comparator	Placebo		

Product Name:

Indication:

PROFORMA SECTION

SECTION 7. Conclusions

In conclusion, the following potential points should be considered as appropriate as detailed in the Guidance document of CHMP, March 2008.

7.1 Quality Conclusions *This has been prefilled from 3.1 and prefills summary 1.1.2*

If box ticked - No relevant findings for the clinical benefit-risk assessment ☐

If there are relevant findings please comment

7.2 Non-Clinical Conclusions *This has been prefilled from 3.2 and prefills summary 1.1.3*

If box ticked - No relevant findings for the clinical benefit-risk assessment ☐

If there are relevant findings please comment

7.3 Human Pharmacology Conclusions: *This has been prefilled from 3.3.2 and prefills summary 1.1.4*

7.4 Clinical Conclusions: *This has been prefilled from 3.4.2 and prefills summary 1.1.5*

7.4.1 If the benefit-risk balance is assessed to be negative, describe the harm (e.g. in terms of lack of efficacy, toxicity) that the drug may cause if used in the claimed indication *This prefills summary 1.5.1*

7.4.2 Describe how the benefit-risk balance is expected to evolve over time (e.g. when late side effects emerge or long-term efficacy decreases) *This prefills summary 1.5.2*

Product Name:

Indication:

PROFORMA SECTION

7.4.3 Describe outstanding issues, and other significant information eg, submission of additional reports by the company to address those issues, hearings and advisory group recommendations, information from other jurisdictions (eg advisory committees, scientific experts, patients, consumers, consumer advocates and other stakeholders) *This prefills summary 1.5.3*

7.4.4 Make reference to the evaluation of the pharmacovigilance plan and risk minimization plan if any. Describe any communication or particularly significant information to the medical profession, patients or the public that is required. Describe restrictions to product availability or usage *This prefills summary 1.5.4*

7.4.5 Describe the need for further studies (e.g. the need for studies to improve the benefit-risk balance with further optimization studies, the need for intensive additional follow up measures or specific obligations, and the need for further development including any paediatric development plans) *This prefills summary 1.5.5*

7.4.6 Please provide any other information considered by the agency relevant to the benefit risk decision that is not covered elsewhere in the proforma: *This prefills summary 1.5.6*

7.4.7 Please provide a clear conclusion on the benefit-risk being positive or not for the claimed indication. *This prefills summary1.1.1*

Product Name:

Indication:

PROFORMA SECTION

7.4.8 Please provide the indication recommended following the outcome of the benefit-risk balance.
This pre-fills summary xxx

Please use this space to input any references cited:

Reviewers Name:

Signature:

Date:

Manager sign-off or Peer review

Reviewers Name:

Signature:

Date:

Product Name:

Indication:

SUMMARY SECTION

BENEFIT RISK SUMMARY:

This section provides a summary of the key outcomes of Benefit Risk analysis undertaken. Please note the information in this Summary section (1-5) are drawn from the proforma and the section of the proforma in which the information is held is given in brackets.

Summary 1.1 Benefit-Risk Conclusion:

Summary 1.1.1 Please provide a clear conclusion on the benefit-risk being positive or not for the claimed indication. (proforma section 7.4.7)

Summary 1.1.2 Quality Conclusion: (proforma section 7.1)

If box ticked - No relevant findings for the clinical benefit-risk assessment ☐

If there are relevant findings please comment

Summary 1.1.3 Non-Clinical Conclusion: (proforma section 7.2)

If box ticked - No relevant findings for the clinical benefit-risk assessment ☐

If there are relevant findings please comment

Summary 1.1.4 Human Phamacology Conclusion: (porforma section 7.3)

Summary 1.1.5 Clinical Conclusion: (proforma section 7.4)

Product Name:

Indication:

SUMMARY SECTION

Summary 1.2 Decision Context:

Summary 1.2.1 Specify the claimed therapeutic indication (proforma section 2.1)

Summary 1.2.2 Treatment modalities evaluated in this submission (proforma section 2.2)

Summary 1.2.3 Is this product for an unmet medical need? (proforma section 2.5) Please select

Comment

Product Name:

Indication:

SUMMARY SECTION

BENEFIT RISK SUMMARY CONT:

Summary 1.3 Identified Benefits and Risks

Summary 1.3.1 Benefits documented (proforma section 4.1)

List all **benefits** of treatment for this indication as inferred in the submission	Please tick here if Benefit Identified by Reviewer but not by company	Please indicate which **benefits** you believe are justified to be included in the benefit risk assessment by ticking the box	Please explain your main reason **for inclusion or exclusion** of the benefit parameter
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Product Name:

Indication:

SUMMARY SECTION

BENEFIT RISK SUMMARY CONT:

Summary 1.3.2 Risks documented (proforma section 4.2)

List all **risks** of treatment for this indication as inferred in the submission	Please tick here if Risk Identified by Reviewer but not by company	Please indicate which **risks** you believe are justified to be included in the benefit risk assessment by ticking the box	Please explain your main reason **for inclusion or exclusion** of the risk parameter
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Product Name:

Indication:

SUMMARY SECTION

BENEFIT RISK SUMMARY CONT:

Summary 1.4 Weighting and valuing (benefits from proforma section 6.1, risks from proforma section 6.2)

6.1 Benefits Populated from 5.1.1	Weighting (Relative importance) Using selected relative importance system	Valuing the options			Comment on strength and uncertainty of benefit
		Investigated product	Comparator	Placebo	

Contents | Background | Overall Summaries | Identified B&R | B&R Study Info | Weights & Values | Conclusions | B&R Summary

Product Name:

Indication:

SUMMARY SECTION

BENEFIT RISK SUMMARY CONT:

6.2 Risks Populated from 5.3.1	Weighting (Using the selected system)	Valuing the options			Comment on strength and uncertainty of each risk	Was the value or weight of this risk altered or mitigated by the ability to control the use of the medicine once on the market?
		Investigated product	Comparator	Placebo		

Product Name:

Indication:

SUMMARY SECTION

BENEFIT RISK SUMMARY CONT:

Summary 1.5 Benefits-Risk Management

Summary 1.5.1 If the benefit-risk balance is assessed to be negative, describe the harm (e.g. in terms of lack of efficacy, toxicity) that the drug may cause if used in the claimed indication (proforma section 7.4.1)

Summary 1.5.2 Describe how the benefit-risk balance is expected to evolve over time (e.g. when late side effects emerge or long-term efficacy decreases) (proforma section 7.4.2)

Summary 1.5.3 Make reference to the evaluation of the pharmacovigilance plan and risk minimization plan if any. Describe any communication or particularly significant information to the medical profession, patients or the public that is required. Describe restrictions to product availability or usage (proforma section 7.4.3)

Summary 1.5.4 Make reference to the evaluation of the pharmacovigilance plan and risk minimization plan if any. Describe any communication or particularly significant information to the medical profession, patients or the public that is required. Describe restrictions to product availability or usage (proforma section 7.4.4)

Summary 1.5.5 Describe the need for further studies (e.g. the need for studies to improve the benefit-risk balance with further optimization studies, the need for intensive additional follow up measures or specific obligations, and the need for further development including any paediatric development plans. (proforma section 7.4.5)

Summary 1.5.6 Please provide any other information considered by the agency relevant to the benefit risk decision that is not covered elsewhere in the proforma. (proforma section 7.4.6)

Appendix II

Summary and Proforma Template for the Benefit-Risk Assessment of Medicines

Professor Sam Salek,
Mr James Leong,
Cardiff University

User Manual

Table of Contents

Introduction

This manual has been developed as an aid for the user in completing the Proforma and Summary template. First, it provides guidance to the user on how to complete the template, through understanding the terms used in this the glossary and clarifications offered at various sections. Then, it assists the user in the technical functions of making amendments and manoeuvring through the document.

Throughout this manual, a red arrow " ⟵ " will be used to indicate sections where additional clarifications are provided to guide the user in completing the template.

Glossary

Term	Definition
Adverse event*	Also known as Adverse experience, it is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
Adverse reaction/effect*	In the pre-approval setting when the therapeutic dose(s) may not be established, it is all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. For marketed medicinal products, it refers to a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.
Benefit	A potential favourable effect seen to be promoting or enhancing the current state of health, resulting from the treatment using the Product**
Benefit-risk assessment	Also referred to as Assessment and known as Benefit-risk evaluation, it is the review of scientific data in support of the proposed indication of the Product, conducted by a Reviewer/Assessor
Benefit-risk balance	Also known to as Benefit-risk profile or outcome, it is the expert opinion cumulative of the consideration of the benefits and risks - weighing the relative contribution and the uncertainties of the evidence provided, incorporating the current medical knowledge and experience - and recommending a positive or negative outcome
Company/Sponsor	Refers to the owner of the Product, and whom initiates the Submission
Comparator	An investigational or marketed product (i.e. active control) used as a reference in a clinical trial.
Effect size	The quantum of difference arising from the comparison between treatment outcomes of the Product with the comparator; it contributes to the overall interpretation of effectiveness and clinical relevance
Investigated product	Also referred to as the Product, it is the entity on which the Submission of an application for market authorization is based, and for which the clinical studies are conducted
Medicines	For the purpose of this Template, this refers to pharmacological products for use in human with the intention of medical

	intervention
Patient reported outcomes	Observations as part of a study related to the results obtained directly from the patients, which may include patients' satisfaction, tolerability, symptoms, patient preferences, quality of life and interruptions to daily living
Proforma	Part of the Template; consist of various sections providing the details of the basis on benefit-risk balance decisions
Reviewer	Also known as evaluator or assessor, personnel trained in the scientific evaluation of data, and using clinical judgment to provide a recommendation on the benefit-risk balance of the Product
Risk	Also known as harm, an unfavourable effect or adverse reactions/effects on patients' health, public health or the environment resulting from exposure to the Product**
Seriousness (of adverse event/reaction/effect)*	A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: • results in death, • is life-threatening (at risk of death at the time of the event) • requires inpatient hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability/incapacity, or • is a congenital anomaly/birth defect.
Severity (of adverse event/reaction/effect)*	The intensity of a specific adverse event which may or may not be of medical significance or seriousness, which is defined by a set of criteria.
Submission	An application sent for review to the regulatory authorities by the Company, for the market authorization of the proposed indications of the Product
Summary: Benefit-Risk	Part of the Template; consist of the conclusions of various aspects of assessment, and the final benefit-risk balance
Template	Refers to the entire document comprising the Summary and Proforma
Valuing	An exercise of providing qualitative or quantitative figure (values) reflecting of the effect observed from the studies; this assist in the interpretation of effect size and relevance of treatment
Weighting	An exercise of expert judgment indicating the relative importance of the available options, commonly done through a logical system of rank assignment (weights)

*Adapted from ICH Harmonised Tripartite Guideline. E2A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. October 1994.
**Adapted from European Medicines Agency (EMA). Benefit-risk methodology project. Work Package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment; August 2010.

Completing the Benefit/Risk Template – Cover page

The Cover page is meant to provide basic information of the Product for which this assessment will be based on.

Compound Identifier(s):	Refers to the entity used during the product development and clinical studies. There may be more than one compound identifier as a result of multiple studies, but they should refer to the same compound being studied for the proposed indication.
Product name/ Brand name / Generic name:	Product name or Brand name - Refers to the entity proposed by the company for market authorization and is considered a trademark, proprietary or commercial entity. Generic name – Refers to the entity other than the Product or Brand name which identifies the product and may be an official non-proprietary name of the medicine.
Active Ingredient(s)/ Strength(s)/ Dosage form:	Refers to the pharmacological component of the product; information on strength and dosage form should be included. For products with more than one active ingredient, each component should be listed as appropriate. For products with multiple strengths, all strengths should be listed.
Proposed Indication:	Refers to the original proposed indication included in the submission. This does NOT represent the recommended indication as a result of the completed assessment. Any amendments to the proposed indication should be presented in Section 7 Conclusions. For submissions with multiple proposed indications, a separate assessment using a new template for each indication is required.

Completing the template – Proforma Sections

The Proforma section provides details of the assessment of benefits and risks, and illustrates the basis of decision on benefit-risk balance in a logical flow. It contributes to information in the Summary.

Clarifications are provided for selected subsections to guide the user in putting in the correct information.

Note: Subsections which do not currently have any clarifications attached is due to none being raised. Following your use of this template, comments and further clarifications thought to be required are welcomed so that these can be included in the next iteration of the user manual.

SECTION 1. BACKGROUND

This section focuses on the justification for the proposed indication and use of the product, in the context of medical need. This section helps to address the varying medical needs of countries due to medical practices and social differences.

SECTION 1. Background

The aim of this proforma is to provide the means whereby the key benefits and risks, together with the uncertainties (strengths of evidence and limitations of data) that drive the benefit-risk assessment can be documented systematically in the light of the available evidence and therapeutic indication in accordance with the CHMP Assessment Template. This section contains a mixture of factual key data and interpretation through value judgments.

1.1 Specify the proposed therapeutic indication *This prefills summary 8.2.1*

The proposed indication here refers to the one listed on the cover page.

1.2 Treatment modalities evaluated in this submission *This prefills summary 8.2.2*

This refers to the overall management of the medical condition as expressed in the proposed indication, including supportive care and the current available treatment options reviewed in this submission.

1.3 Other currently available treatment options NOT considered or evaluated

This should provide a high-level overview on alternative pharmacological management. Non-pharmacological alternatives may also be listed here as these will contribute to the assessment of the medical need (section 1.5).

1.4 What are the known risks with compounds of the same therapeutic class?

For products with various pharmacological classes for the same therapeutic function, kindly indicate and discuss in relation to the appropriate pharmacological class.

For products that are first in class, kindly indicate so and provide inferences to any related classes (therapeutic or pharmacological).

1.5 Is this product for an unmet medical need? *This prefills summary 8.2.3* Please select

Reasons: Please provide justification for your decision on the product fulfilling or not fulfilling an unmet medical need.

1.6 Aims of treatment and expected effect size? i.e. define if there are established minimally significant clinical benefits in the light of both internally and publically available guidelines.

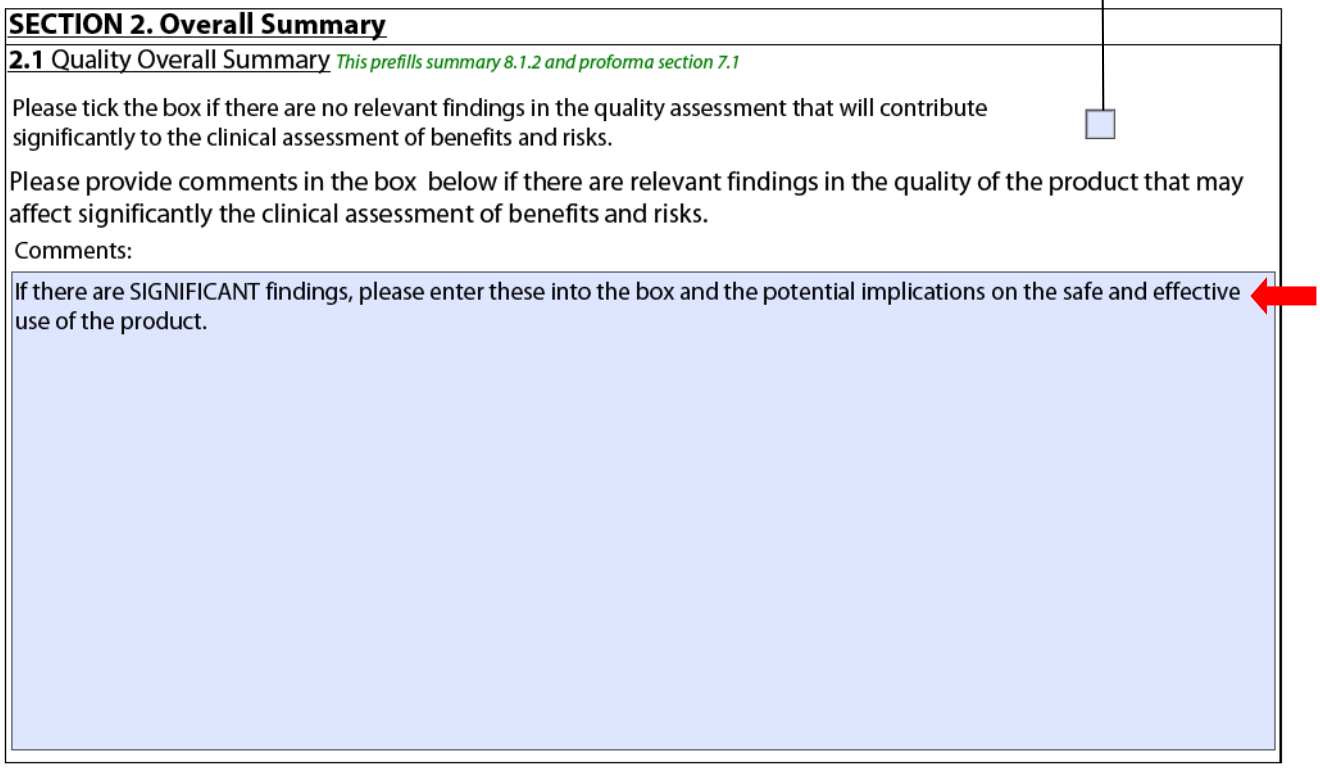
This should allude to the expected outcomes in the management of the medical condition as expressed in the proposed indication and how the effect size would be considered clinically relevant and supported by existing guidelines.

SECTION 2. OVERALL SUMMARY

2.1 QUALITY OVERALL SUMMARY

This section accounts for the issues observed during assessment of the quality of the product that may impact the efficacy and safety. Comments should be provided in the instance where there are significant concerns amounting to potential negative consequences in clinical outcomes.

Please tick this box if there are NO findings from the quality assessment that may impact the safe and effective use of the product.



2.2 NON-CLINICAL OVERALL SUMMARY

This section accounts for the issues observed during the assessment of non-clinical data that may impact the efficacy and safety in humans. Comments should be provided in the instance where there are significant findings & their potential implications for the safe & effective use of the product in humans.

Please tick this box if there are NO findings from the non-clinical assessment that may impact the safe and effective use of the product in humans.

If there are SIGNIFICANT findings, please enter these into the box as well as the potential implications for the safe and effective use of the product in humans.

2.2 Non-Clinical Overall Summary

This prefills summary 8.1.3 and proforma section 7.2

Please tick the box if there are no relevant findings in the non-clinical assessment that will contribute significantly to the clinical assessment of benefits and risks. ☐

If there are relevant findings, please complete the comments section.

2.2.1 Comments:

Relevant non-clinical findings	Potential implications in human use / Requires further investigation

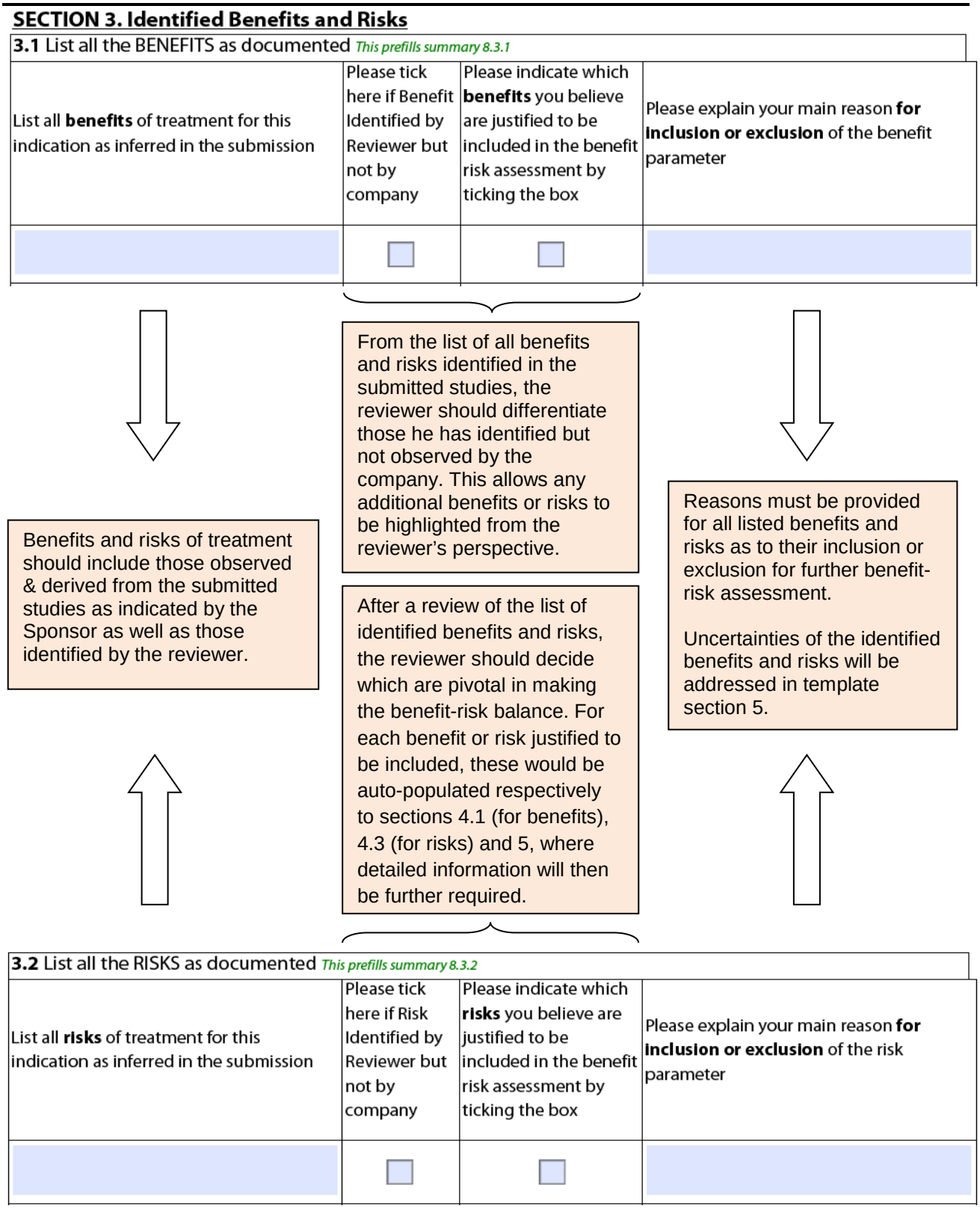
2.2.2 What are the conclusions from these findings implicating benefit-risk assessment for humans?

This prefills summary 8.1.3 and proforma section 7.2

This should only be filled in after the significance of the findings above is correlated to human data/further investigations from the clinical studies. Any mitigation strategies should be highlighted here.

SECTION 3. IDENTIFIED BENEFITS AND RISKS

This section provides a clear basis for the identification of major benefits and risks parameters that will be used in constructing the benefit-risk balance.



Section 4. Benefits and Risks – Study information

This section expounds on the benefits and risks considered for constructing the benefit-risk balance. Inputs will require information from the studies. The considerations for assessment are adapted from the EMA reflection paper (2008) and these are attached in Annexes A and B for benefits and risks respectively.

Section 4 Benefit and Risks - Study Information

4.1 Please complete this section for **each benefit observed** in pivotal and non-pivotal studies, which you have justified to be included in the benefit risk assessment in section 3.1

4.1.1 Benefit (*pre-filled from Table 3.1*):

4.1.2 Study Type & Identifier	4.1.3 Type of Study	4.1.4 Describe benefit in terms of presence or absence in: Investigated Product	Comparator (Name)	Placebo (if appropriate)	4.1.5 Primary Endpoint?	Statistical parameters to describe results - eg Hazard ratios If NNT or NNH are available please provide in this box as NNT- or NNH-	4.1.6 Effect Size? Enter % or actual values	Lower CI	Upper CI	P Value	Statistically Significant	4.1.7 Clinical Relevance?	4.1.8 Studied population representative	4.1.9 Patient compliance satisfactory?	
															-
Please click here to add a new study:															+

List the statistical parameter applied to investigate the endpoint used to confirm the benefit, or in the case of non-inferiority and equivalence studies, the pre-defined margins or deltas not to be exceeded.

A "Yes" should be chosen for non-inferiority or equivalence studies when the pre-defined limits were not exceeded and the objectives met.

A "N/A" should be chosen for studies that no statistical analyses were conducted e.g. observational studies.

4.2.1 What was the overall incidence of adverse effects? If the studies do not allow you to combine to give an overall incidence please complete a separate page(s) if required. In this case please provide a descriptor of what information is being included in this table.

Please provide the descriptor information of what is included in this table:	

Investigated Product	Comparator (name)	Placebo (if appropriate)

4.2.2 What was the overall incidence of serious adverse effects?

Investigated Product	Comparator (name)	Placebo (if appropriate)

4.2.3 What was the discontinuation rate (from the medication) due to adverse effects?

Investigated Product	Comparator (name)	Placebo (if appropriate)

4.2.4 What was the dose/reduction rate (% of patient population in the study) due to adverse effects?

Investigated Product	Comparator (name)	Placebo (if appropriate)

This refers to the proportion of patients in each of the treatment groups who required a reduction in the dose of the study treatment as a result of adverse effects.

4.4 Uncertainties (Benefits & Risks) for pivotal and non-pivotal studies

4.4.1 Discuss the choice of dose, comparator and endpoints (including surrogates as appropriate)

Comment:

Was the comparator used relevant for the jurisdiction/Standard of Care? Please select

4.4.2 Comment on the design, conduct and statistical adequacy of the trial including the impact of any methodological deficiencies on the estimated benefits. Please pay attention to missing data and the methods used to account for them.

Comment:

4.4.3 Have the measurements and scales been validated? Please select

What are the unsettled issues?

Is there a need for further studies? Please select

If yes, why?

4.4.4 Describe any negative studies. Describe the quality of the supportive scientific literature and any other issues that may have an impact on the estimated benefits

4.4.5 Are the results consistent across different factors? E.g. pivotal trials and supportive studies, or submitted studies and literature, different populations, centres, doses, etc. Please select

Comment on the consistency or clustering of the results in the supportive and pivotal trials:

The uncertainties in this section concerns the studies' design, conclusions and consistency.

Inputs for uncertainties for individual benefits and risks should be provided in section 5.1 and 5.2 respectively.

SECTION 5. BENEFIT-RISK SUMMARY TABLE & EXPERT JUDGMENT

This section allows the reviewer to apply his expert judgment on the identified benefits and risks. The use of weighting and valuing enables the review to articulate the basis of his recommendation on the benefit-risk balance. Kindly refer to the Glossary for the terms “Weighting” and “Valuing”, as well as the pointers in the template.

Weighting (relative importance based on expert judgement)	**Valuing** (objective or subjective outcomes relative to individual options)
➢ For the identified benefits and risks, the reviewer should apply their expert judgment to provide relative importance of each parameter in contributing to the benefit-risk balance, in the light of the evidence provided ➢ This is either carried out through ranking, numerical value, or qualitative descriptors such as high, medium or low. If the system of ranking is used, then this should be hierarchical and logical. Reviewers should limit themselves to using only one of these systems for both benefits and risks. ➢ Please provide a short explanation of the selected system:	➢ Provide either qualitative (e.g. high, medium, low or absent) or quantitative (utilizing the values from the study outcomes, e.g. overall survival 32% for product versus 27% for placebo) values of benefits and risks. ➢ When possible please use quantification

SECTION 6. VISUALISATION

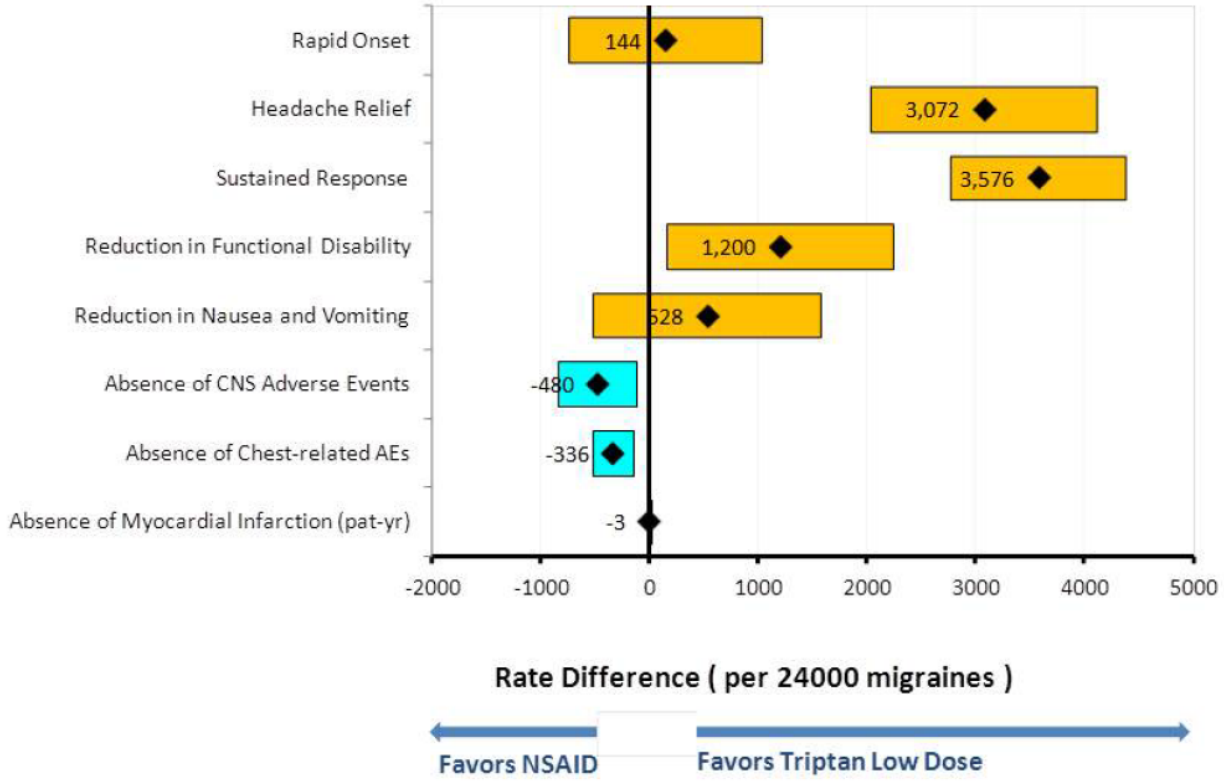
This section allows the reviewer to include any graphical presentation of the outcomes from the studies or to illustrate the benefit-risk balance of the product. Please note that for images to be uploaded into the box, it must be saved in JPEG, GIF or PNG format.

Section 6. Visualisation

If available please provide in this section a copy of any visualisation used to illustrate the benefit risk of product (e.g. forest plot, tornado diagram etc.)

Adobe **Acrobat** users can click here to attach a file: Attach a file *(Note: this will not activate in Adobe **Reader**)*

Click in the space below to upload an image: (jpeg, gif, png): *(Available to both Adobe Reader and Acrobat users)*



SECTION 7. CONCLUSIONS

This section collates the conclusions from quality, non-clinical, human pharmacology and clinical sections. The final decision on the benefit-risk balance of the Product for the proposed indication will be discussed here. Considerations for assessing the benefit-risk balance are adapted from the EMA reflection paper (2008) and these are attached in Annex C.

Sections 7.1, 7.2, 7.3 and 7.4 of the template do not require input from the user, and do not allow editing of the presented information. The information is auto-populated, and the source of each sub-section is denoted by the respective Proforma section in parentheses. Input is only required from section 7.4.1 onwards.

7.4.1 If the benefit-risk balance is assessed to be negative, describe the harm (e.g. in terms of lack of efficacy, toxicity) that the drug may cause if used in the claimed indication *This prefills summary 8.5.1*

7.4.2 Describe how the benefit-risk balance is expected to evolve over time (e.g. when late side effects emerge or long-term efficacy decreases) *This prefills summary 8.5.2*

7.4.3 Describe outstanding issues, and other significant information eg, submission of additional reports by the company to address those issues, hearings and advisory group recommendations, information from other jurisdictions (eg advisory committees, scientific experts, patients, consumers, consumer advocates and other stakeholders) *This prefills summary 8.5.3*

7.4.4 Make reference to the evaluation of the pharmacovigilance plan and risk minimization plan if any. Describe any communication or particularly significant information to the medical profession, patients or the public that is required. Describe restrictions to product availability or usage *This prefills summary 8.5.4*

7.4.5 Describe the need for further studies (e.g. the need for studies to improve the benefit-risk balance with further optimization studies, the need for intensive additional follow up measures or specific obligations, and the need for further development including any paediatric development plans) *This prefills summary 8.5.5*

This section should also consider any further studies required to mitigate findings from non-clinical studies (Section 2.2.2).

7.4.6 Please provide any other information considered by the agency relevant to the benefit risk decision that is not covered elsewhere in the proforma: *This prefills summary 8.5.6*

7.4.7 Please provide a clear conclusion on the benefit-risk being positive or not for the proposed indication. *This prefills summary 8.1.1*

The conclusion here refers to the benefit-risk balance of the Product for this proposed indication, and does not constitute a final regulatory decision.

7.4.8 Please provide the indication recommended following the outcome of the benefit-risk balance.

This pre-fills summary 8.2.2

Amendments should include all changes to proposed indication and/or dosing regimen, with annotations provided. Please provide justification for the amendments.

For negative benefit-risk balance resulting in a recommendation for non-approval, kindly indicate so.

These recommendations do not necessarily constitute final regulatory decision or market authorizations.

Please use this space to input any references cited:

Reviewers Name:

Signature:

Date:

Manager sign-off or Peer review

Reviewers Name:

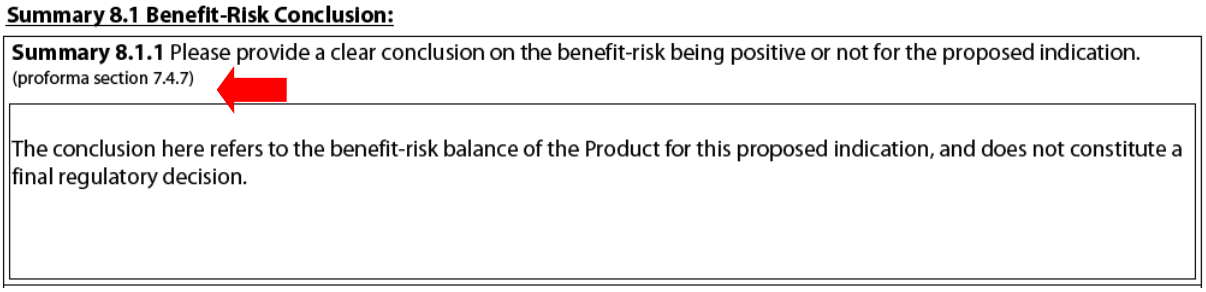
Signature:

Date:

Completing the template – Summary Section

The Benefit-Risk Summary Section provides the conclusions of various aspects of benefit-risk assessment, as well as the resulting benefit-risk balance. It is used as a succinct document to communicate the essential decisions for the submission.

This section of the template does not require input from the user, and does not allow editing of the presented information. The information is auto-populated, and the source of each sub-section is denoted by the respective proforma section in parentheses. An example is shown below:



For amendments to this section, it should be done through editing of the respective sources in the Proforma section. Please refer to the manual section “Making changes to the template” for assistance in making amendments.

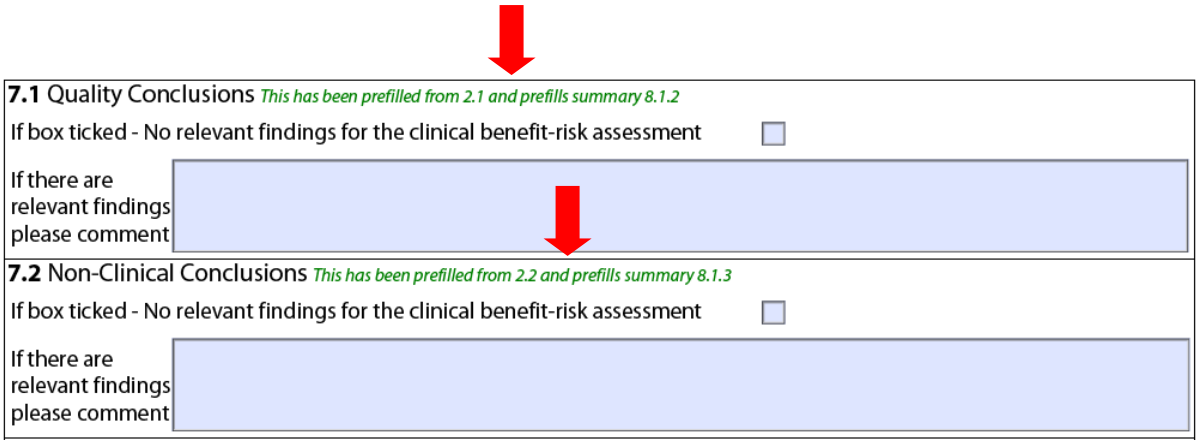
Making changes to the template

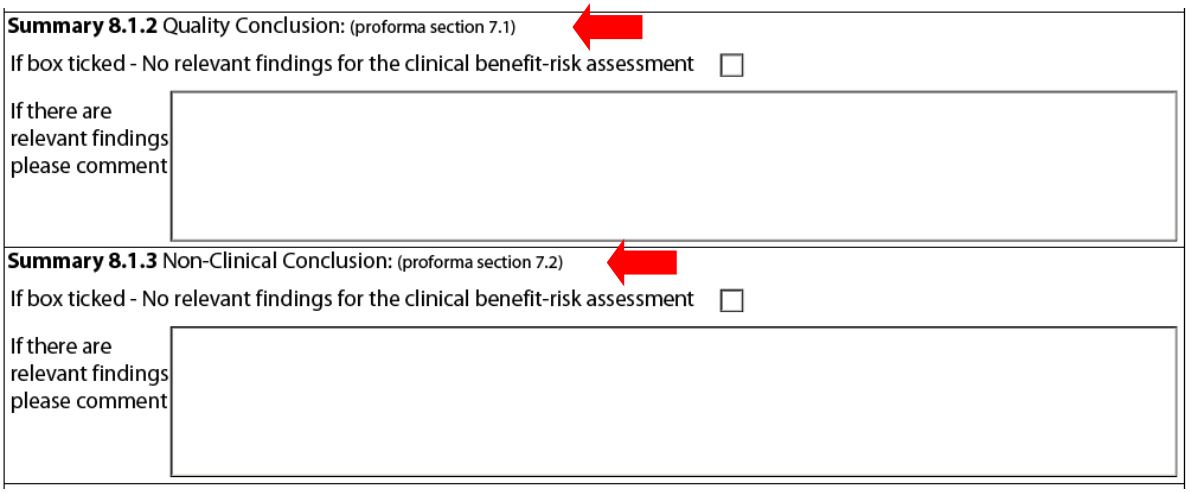
To maintain consistency and validity of the information throughout the document, editing has been limited to source sections and sections that do no fill another in the document.

The following fields do NOT allow editing of the information:

- Entire Section 8, the Summary section
- Sections 5.1 and 5.2 (the selected benefits and risks are populated from source sections 3.1 and 3.2 respectively)
- Sections 7.1 to 7.4.

To edit the above sections, refer to the source location of the information which is usually listed at the end of the statement of the subsection.





Navigating through the template

A taskbar at the top of each page allows instant access to the desired section through a click at the relevant tab.

For your convenience, the various tabs are correlated to the sections shown in the figure below.

Contents	Background	Overall Summaries	Identified B&R	B&R Study Info	Weights & Values	Visualisation	Conclusions	B&R Summary
	Proforma							**Summary**
	Section 1	Section 2	Section 3	Section 4	Section 5	Section 6	Section 7	Section 8

Annex A

Criteria for assessing efficacy or favourable effects*

1. Efficacy (primary endpoint) versus comparator and its clinical relevance
2. Magnitude of treatment effect
3. Clinical relevance of the primary endpoints
4. Statistical significance of the efficacy results
5. Representiveness of the studied population for the population targeted in the label
6. Discussion of dose
7. Evidence for the efficacy in relative subgroups
8. Design conduct and statistical adequacy of the trial
9. Confirmation of treatment effect by results of non-primary endpoints
10. Validation of scales and outcome measures
11. Patient preferred outcomes
12. Confirmation of efficacy by results of relevant non-pivotal trials and extensions
13. Anticipated patient compliance (and patient convenience)
14. Clustering (consistency) of results of the pivotal trials

*Adapted from European Medicines Agency (EMA). Reflection Paper on Benefit-risk Assessment Methods in the context of the Evaluation of Marketing Authorisation Applications of Medicinal Products for Human Use; March 2008.

Annex B

Criteria for assessing harms or unfavourable effects*

1. Overall incidence of adverse effects (from clinical trials)
2. Overall incidence of serious adverse effects (from clinical trials
3. Discontinuation rate due to adverse effects (from clinical trials)
4. Incidence, seriousness and duration of specific adverse effects (from clinical trials and post-marketing surveillance)
5. Interaction with other drugs and food
6. Safety in subgroups (e.g. race and sex)
7. Potential for off label use leading to safety hazards
8. Potential for non-demonstrated additional risk due to limitations of clinical trials and/or short market exposure.
9. Potential for non-demonstrated additional risk due to safety issues observed in pre-clinical safety studies but not in humans
10. Potential for non-demonstrated additional risk due to safety issues observed with other medicines of the same pharmacological class

*Adapted from European Medicines Agency (EMA). Reflection Paper on Benefit-risk Assessment Methods in the context of the Evaluation of Marketing Authorisation Applications of Medicinal Products for Human Use; March 2008.

Annex C

Criteria for assessing benefit-risk balance*

Amount of evidence to characterise the benefit-risk balance:
Availability of comparative data and their limitations and potential deficiencies
Interpret of key benefits and risks
from perspectives of different stakeholders, including patients and treating physicians
Level of risk acceptability
corresponding to the perceived degree of clinical benefit in the specific context
Relating the benefits to the risks when possible:
Using logical comparisons e.g. potential lives saved as a result of treatment compare to potential lives lost as a result of adverse reactions
Factors affecting the benefit-risk balance:
Situations that may alter the current balance e.g. different patient or disease characteristics
Sensitivity of the benefit-risk balance:
Discussion on the potential changes to the balance if the fundamental assumptions are to be amended
Other appropriate discussions:
Effectiveness of proposed treatment compared to available options
For negative benefit-risk balanced, describe the potential harm incurred upon exposure for the claimed indication
Evolution of benefit-risk balance over time
Outstanding issues, submission or reports to address identified issues
Evaluation of pharmacovigilance plan, risk mitigation plan or other post-marketing commitments including need for further studies
Opinions from scientific experts, patients, consumers or advocates and other stakeholders in the benefit-risk assessments
Conclusion on the benefit-risk being positive or not for every claimed indication.

*Adapted from European Medicines Agency (EMA). Reflection Paper on Benefit-risk Assessment Methods in the context of the Evaluation of Marketing Authorisation Applications of Medicinal Products for Human Use; March 2008.

Appendix III

Protocol for the Study of Benefit-Risk Summary: Health Sciences Authority, Singapore

1. Background

Over the past three years, the Centre for Innovation in Regulatory Science (CIRS) in association with Health Canada, the TGA in Australia, HSA in Singapore and SwissMedic have developed a structured systematic standardised approach to the benefit-risk assessment of medicines.

This includes an eight step framework, namely: Step 1: decision context; Step 2: building the value tree; Step 3: refining the value tree; Step 4: relative importance of benefits and risks; Step 5: evaluating the options; Step 6: evaluating uncertainty; Step 7: concise presentation of results (visualisation) and Step 8: expert judgement and communication.

A proforma template (in which a Summary is found) based on the EMA guidance document for benefit-risk assessment (March 2008) has been developed to document the benefit-risk decision-making process in the regulatory review. A user manual was also incorporated to guide the user in completing the proforma template.

The Summary portion of this proforma template is now extracted and further investigated for use on its own. The User Manual is correspondingly provided for this purpose to support the Summary.

2. Objectives

The overall objective is to evaluate the use of this Summary, supported by the User Manual, in documenting and communicating benefit-risk decisions through a retrospective study in HSA.

3. Methodology

Clinical reviewer involved in the assessment of product applications in the Therapeutic Products Branch will be invited to participate in this study. The study is a retrospective open-label and non-comparative trial.

Each reviewer will identify an application that had achieved regulatory decision within the last 3 months. The applications should be pertaining New Drug Applications via either the full or abridged route of evaluation.

Using the respective clinical assessment report, the assessor will transfer the relevant information required of the Summary. Upon the completion of this transfer, the reviewer will then respond to the survey. This exercise is to be supported by the User Manual provided.

All survey outcomes should be completed and submitted by July 2013.

4. Outcome

The purpose of the study report is to contribute to the overall feasibility of using the Summary in documenting the relevant discussions that will help in communicating clearly and accurately the benefit-risk decisions. This may be used by regulatory agencies of emerging markets as part of their regulatory process, or as a document for exchanging information on regulatory decisions.

James Leong
Senior Regulatory Specialist
Therapeutic Products Branch
Pre-market Division

June 2013

Appendix IV

Print Summary

Summary Template for the Benefit-Risk Assessment of Medicines

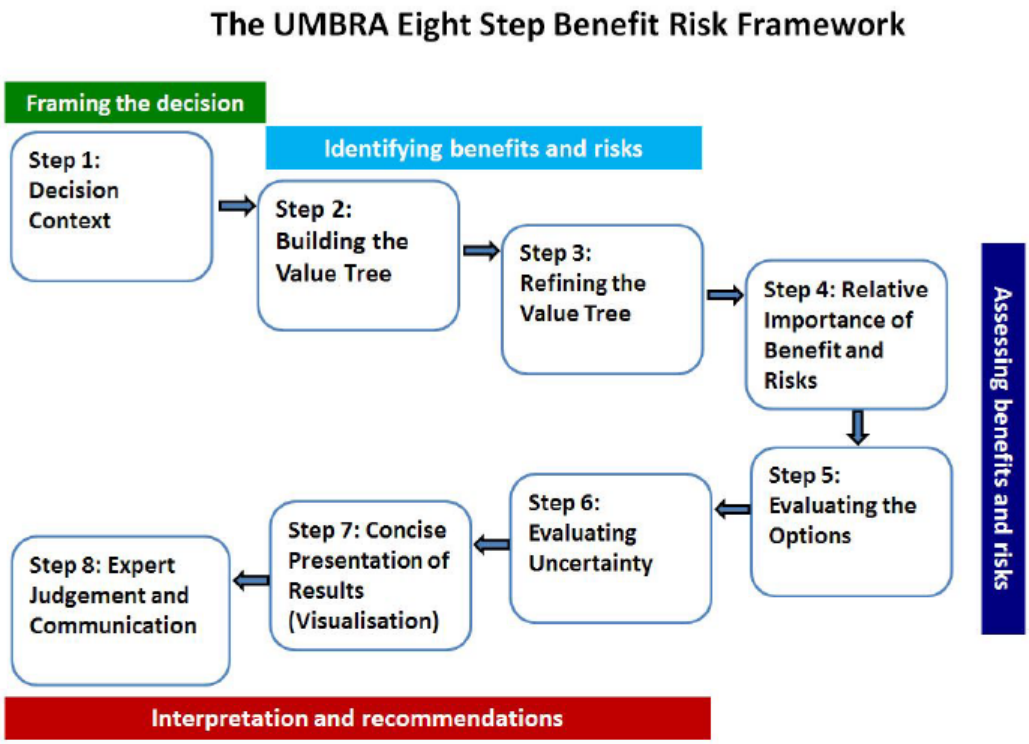
Participant(s):

HSA - Singapore

Compound Identifier(s):	
Product name/ Brand name / Generic name:	
Active Ingredient(s)/ Strength(s)/ Dosage form:	
Proposed Indication:	

Please complete a new summary form for each indication

All data will be treated in strict confidence.
No data or information will be revealed to any third party



The diagram shows the common elements of the UMBRA eight step Benefit Risk Framework that make up a systematic approach to benefit-risk assessment for medicines

At the CIRS annual workshop, 2012 (20-21 June) there was a consensus from those who are developing Benefit Risk methodologies for assessing medicines that there are four key stages namely;

- Framing the decision;
- Identifying the benefits and risks;
- Assessing the benefits and risks;
- and Interpretation and recommendation.

Underpinning these was an overarching eight step framework;

1. Discision context;
2. Building the Value Tree;
3. Value Tree refinement;
4. Assessing relative importance;
5. Evaluating options;
6. Evaluating uncertainty;
7. Concise presentation of results – visualisation;
8. Final recommendation.

All the methodologies currently being developed by regulators and companies have these steps whether explicitly or implicitly undertaken.

The UMBRA overarching framework provides the basis for a common agreement on the principles for benefit risk assessment of medicines.

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

BENEFIT RISK SUMMARY:

This section provides a summary of the key outcomes of Benefit Risk analysis undertaken.

Summary 1.1 Background (Decision Context):

Summary 1.1.1 Specify the proposed therapeutic indication

Summary 1.1.2 Treatment modalities evaluated in this submission

Summary 1.1.3 Is this product for an unmet medical need? Please select

Reason: Please provide justification for your decision on the product fulfilling or not fulfilling an unmet medical need

Summary 2.1 Overall Summaries:

Summary 2.1.1 Quality Conclusion:

If box ticked - No relevant findings for the clinical benefit-risk assessment ☐

If there are relevant findings please comment

Summary 2.1.2 Non-Clinical Conclusion:

If box ticked - No relevant findings for the clinical benefit-risk assessment ☐

If there are relevant findings please comment

Summary 2.1.3 Human Phamacology Conclusion:

Only the important results and issues that have an impact on the benefit-risk balance should be described. In addition, unresolved issues or uncertainties should be identified and their impact on the balance assessment should be clearly stated. This includes Bioequivalence, Pharmacokinetic and Dynamic profile, as well as PK, & PD interactions, special populations, dose findings etc.

Summary 2.1.4 Clinical Conclusion:

Only the important results and issues that have an impact on the benefit-risk balance should be described. In addition, unresolved issues or uncertainties should be identified and their impact on the balance assessment should be clearly stated. This includes study design, dosage, population and comparators.

BENEFIT RISK SUMMARY CONT:

Summary 3.1 Identified Benefits and Risks

Summary 3.1.1 Benefits documented

List all **benefits** of treatment for this indication as inferred in the submission	Please tick here if Benefit Identified by Reviewer but not by company	Please indicate which **benefits** you believe are justified to be included in the benefit risk assessment by ticking the box	Please explain your main reason **for inclusion or exclusion** of the benefit parameter
	☐	☐	
	☐	☐	
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	☐	☐	
	☐	☐	
	☐	☐	

BENEFIT RISK SUMMARY CONT:

Summary 3.1.2 Risks documented

List all **risks** of treatment for this indication as inferred in the submission	Please tick here if Risk Identified by Reviewer but not by company	Please indicate which **risks** you believe are justified to be included in the benefit risk assessment by ticking the box	Please explain your main reason **for inclusion or exclusion** of the risk parameter
	☐	☐	
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	☐	☐	
	☐	☐	

Summary 4.1 Clinical Study Summary

Study Ref. Type	Study Design (N)(duration) R, C, DB, OL (N=)(weeks/months) ·Non-inferiority/Superiority/ Observational study ·State primary objective ·State primary efficacy parameter	Treatment ·Treatment arm Active (name, dose, freq, duration) ·Comparator arm Placebo / Active (name, dose, freq, duration)	Conclusion ·Results of primary efficacy parameter ·Results of other relevant efficacy endpoints ·Conclusion of study (outcomes, strength of study, weight of evidence, and clinical significance)	
				-
				-
				-
				-
				-

Legend
R: Randomised **C:** Controlled **DB:** Double blinded **OL:** Open label **N:** Number of subjects

Click to add a study +

Summary 5.1 RISKS: Overall Summary

Table of pooled overall incidence of events can be added below

Adobe **Acrobat** users can click here to attach a file: Attach a file *(Note: this will not activate in Adobe **Reader**)*

Click in the space below to upload an image: (jpeg, gif, png): *(Available to both Adobe Reader and Acrobat users)*

Note: Click on an image to change it for another. To delete the image click 'Remove Table'.
You may need to add another table first as there must always be at least one table.

Remove table | Add another table

BENEFIT RISK SUMMARY CONT:

Summary 6.1 Weights and values

Benefits	Relative Importance (weighting)	Valuing the options			Comment on strength and uncertainty of benefit
		Investigated product	Comparator	Placebo	

Please describe methodology used for assessing relative importance: eg Ranking or point allocation and also what is has been used in relation to valuing the options e.g. % change, Number of patients, etc

BENEFIT RISK SUMMARY CONT:

Risks	Relative Importance (weighting)	Valuing the options			Comment on strength and uncertainty of each risk	Was the value or weight of this risk altered or mitigated by the ability to control the use of the medicine once on the market?
		Investigated product	Comparator	Placebo		

Please describe methodology used for assessing relative importance: eg Ranking or point allocation and also what is has been used in relation to valuing the options e.g. % change, Number of patients, etc

BENEFIT RISK SUMMARY CONT:

Summary 7.1 Conclusion

Summary 7.1.1 If the benefit-risk balance is assessed to be negative, describe the harm (e.g. in terms of lack of efficacy, toxicity) that the drug may cause if used in the proposed indication

Summary 7.1.2 Describe how the benefit-risk balance is expected to evolve over time (e.g. when late side effects emerge or long-term efficacy decreases)

Summary 7.1.3 Describe outstanding issues, and other significant information eg, submission of additional reports by the company to address those issues, hearings and advisory group recommendations, information from other jurisdictions (eg advisory committees, scientific experts, patients, consumers, consumer advocates and other stakeholders)

Summary 7.1.4 Make reference to the evaluation of the pharmacovigilance plan and risk minimization plan if any. Describe any communication or particularly significant information to the medical profession, patients or the public that is required. Describe restrictions to product availability or usage

Summary 7.1.5 Describe the need for further studies (e.g. the need for studies to improve the benefit-risk balance with further optimization studies, the need for intensive additional follow up measures or specific obligations, and the need for further development including any paediatric development plans.

Summary 7.1.6 Please provide any other information considered by the agency relevant to the benefit risk decision that is not covered elsewhere in the proforma.

Summary 7.1.7 Please provide a clear conclusion on the benefit-risk being positive or not for the proposed indication.

Summary 7.1.8 Please provide the indication recommended following the outcome of the benefit-risk balance.

Reviewers Name:

Signature:

Date:

Manager sign-off or Peer review

Reviewers Name:

Signature:

Date:

Appendix V

Summary Template for the
Benefit-Risk Assessment of Medicines

Professor Sam Salek,
Mr James Leong,
Cardiff University

User Manual

Table of Contents

Introduction

This manual has been developed as an aid for the user in completing the Summary template. It provides guidance to the user on how to complete the template, through understanding the terms used in the glossary and clarifications offered at various sections.

Throughout this manual, a red arrow "  " will be used to indicate sections where additional clarifications are provided to guide the user in completing the template.

Glossary

Term	Definition
Adverse event*	Also known as Adverse experience, it is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
Adverse reaction/effect*	In the pre-approval setting when the therapeutic dose(s) may not be established, it is all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. For marketed medicinal products, it refers to a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.
Benefit	A potential favourable effect seen to be promoting or enhancing the current state of health, resulting from the treatment using the Product**
Benefit-risk assessment	Also referred to as Assessment and known as Benefit-risk evaluation, it is the review of scientific data in support of the proposed indication of the Product, conducted by a Reviewer/Assessor
Benefit-risk balance	Also known to as Benefit-risk profile or outcome, it is the expert opinion cumulative of the consideration of the benefits and risks - weighing the relative contribution and the uncertainties of the evidence provided, incorporating the current medical knowledge and experience - and recommending a positive or negative outcome

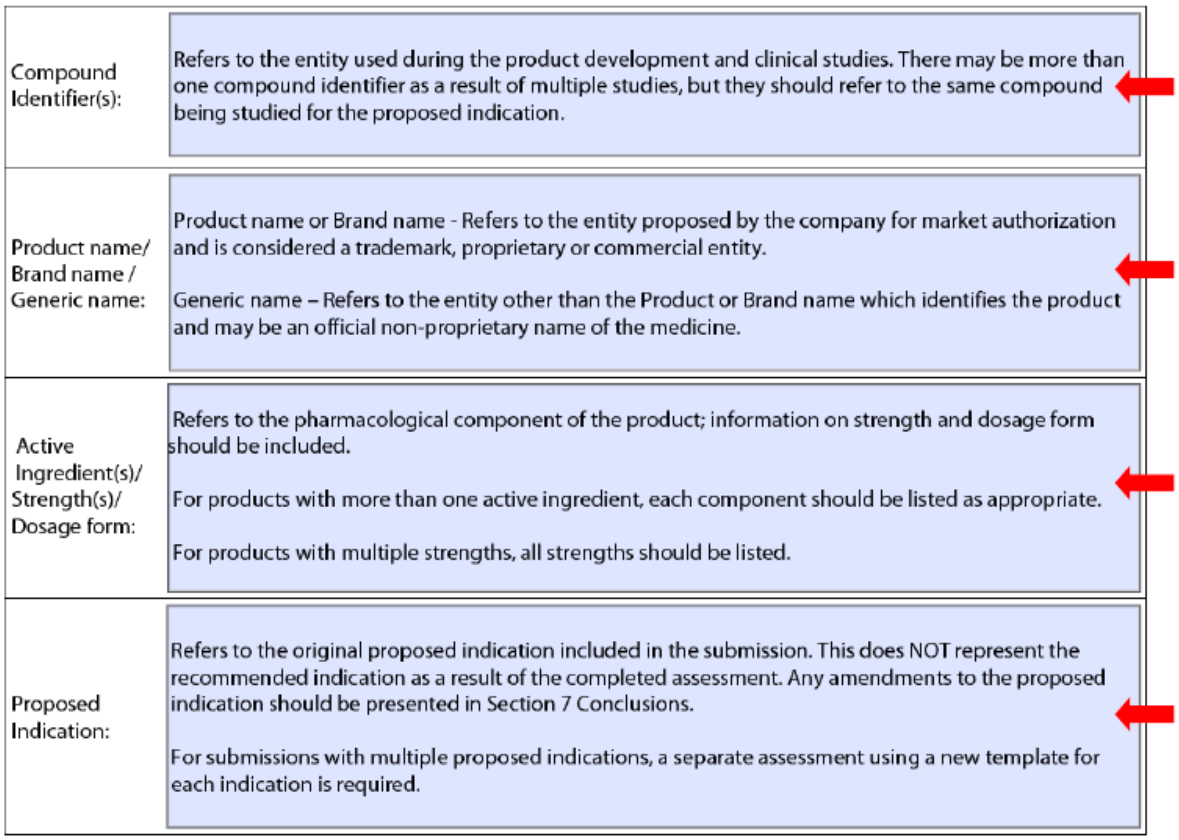
Company/Sponsor	Refers to the owner of the Product, and whom initiates the Submission
Comparator	An investigational or marketed product (i.e. active control) used as a reference in a clinical trial.
Effect size	The quantum of difference arising from the comparison between treatment outcomes of the Product with the comparator; it contributes to the overall interpretation of effectiveness and clinical relevance
Investigated product	Also referred to as the Product, it is the entity on which the Submission of an application for market authorization is based, and for which the clinical studies are conducted
Medicines	For the purpose of this Template, this refers to pharmacological products for use in human with the intention of medical intervention
Patient reported outcomes	Observations as part of a study related to the results obtained directly from the patients, which may include patients' satisfaction, tolerability, symptoms, patient preferences, quality of life and interruptions to daily living
Proforma	Part of the Template; consist of various sections providing the details of the basis on benefit-risk balance decisions
Reviewer	Also known as evaluator or assessor, personnel trained in the scientific evaluation of data, and using clinical judgment to provide a recommendation on the benefit-risk balance of the Product
Risk	Also known as harm, an unfavourable effect or adverse reactions/effects on patients' health, public health or the environment resulting from exposure to the Product**
Seriousness (of adverse event/reaction/effect)*	A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: • results in death, • is life-threatening (at risk of death at the time of the event) • requires inpatient hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability/incapacity, or • is a congenital anomaly/birth defect.

Severity (of adverse event/reaction/effect)*	The intensity of a specific adverse event which may or may not be of medical significance or seriousness, which is defined by a set of criteria.
Submission	An application sent for review to the regulatory authorities by the Company, for the market authorization of the proposed indications of the Product
Summary: Benefit-Risk	Part of the Template; consist of the conclusions of various aspects of assessment, and the final benefit-risk balance
Template	Refers to the entire document comprising the Summary and Proforma
Valuing	An exercise of providing qualitative or quantitative figure (values) reflecting of the effect observed from the studies; this assist in the interpretation of effect size and relevance of treatment
Weighting	An exercise of expert judgment indicating the relative importance of the available options, commonly done through a logical system of rank assignment (weights)

*Adapted from ICH Harmonised Tripartite Guideline. E2A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. October 1994.
**Adapted from European Medicines Agency (EMA). Benefit-risk methodology project. Work Package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment; August 2010.

Completing the Template – Cover page

The Cover page is meant to provide basic information of the Product for which this assessment will be based on.



Compound Identifier(s):	Refers to the entity used during the product development and clinical studies. There may be more than one compound identifier as a result of multiple studies, but they should refer to the same compound being studied for the proposed indication.
Product name/ Brand name / Generic name:	Product name or Brand name - Refers to the entity proposed by the company for market authorization and is considered a trademark, proprietary or commercial entity. Generic name – Refers to the entity other than the Product or Brand name which identifies the product and may be an official non-proprietary name of the medicine.
Active Ingredient(s)/ Strength(s)/ Dosage form:	Refers to the pharmacological component of the product; information on strength and dosage form should be included. For products with more than one active ingredient, each component should be listed as appropriate. For products with multiple strengths, all strengths should be listed.
Proposed Indication:	Refers to the original proposed indication included in the submission. This does NOT represent the recommended indication as a result of the completed assessment. Any amendments to the proposed indication should be presented in Section 7 Conclusions. For submissions with multiple proposed indications, a separate assessment using a new template for each indication is required.

Completing the Benefit Risk Summary template

The Summary provides the conclusions of various aspects of benefit-risk assessment, as well as the resulting benefit-risk balance. It is used as a succinct document to communicate the essential decisions for the submission.

Clarifications are provided for selected subsections to guide the user in putting in the correct information.

Note: Subsections which do not currently have any clarifications attached is due to none being raised. Following your use of this template, comments and further clarifications thought to be required are welcomed so that these can be included in the next iteration of the user manual.

Summary 1 .1 Background (Decision Context)

Summary 1.1 Background (Decision Context):

Summary 1.1.1 Specify the proposed therapeutic indication

The proposed indication here refers to the one listed on the cover page.

Summary 1.1.2 Treatment modalities evaluated in this submission

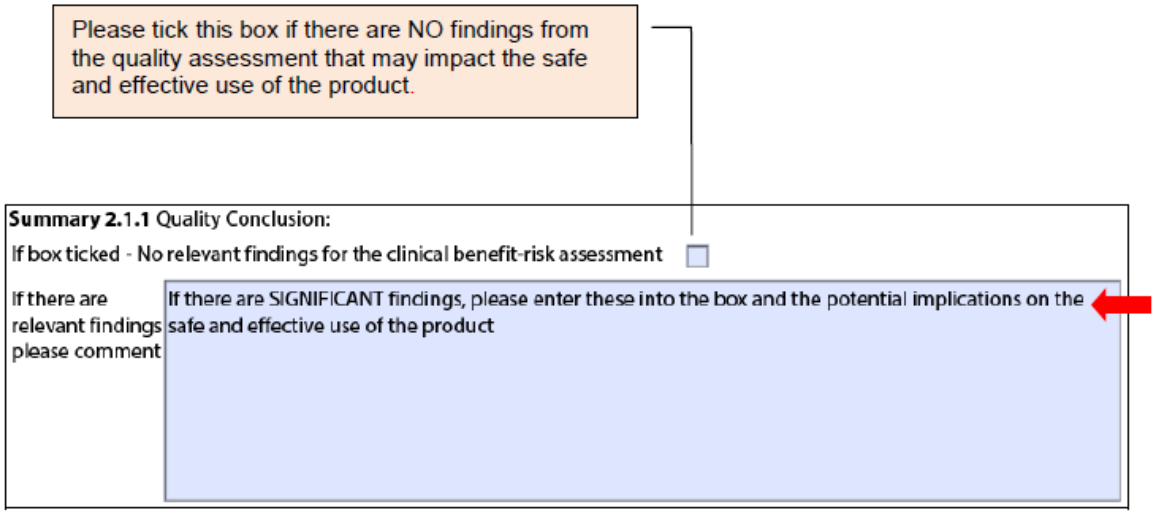
This refers to the overall management of the medical condition as expressed in the proposed indication, including supportive care and current available treatment options considered.

Summary 1.1.3 Is this product for an unmet medical need? Please select

Reason: Please provide justification for your decision on the product fulfilling or not fulfilling an unmet medical need

Summary 2.1 Overall Summaries

The Quality Conclusion accounts for the issues observed during assessment of the quality of the product that may impact the efficacy and safety. Comments should be provided in the instance where there are significant concerns amounting to potential negative consequences in clinical outcomes.



The Non-Clinical Conclusion accounts for the issues observed during the assessment of non-clinical data that may impact the efficacy and safety in humans. Comments should be provided in the instance where there are significant findings & their potential implications for the safe & effective use of the product in humans.

If there are SIGNIFICANT findings, please enter these into the box as well as the potential implications for the safe and effective use of the product in humans.

Please tick this box if there are NO findings from the non-clinical assessment that may impact the safe and effective use of the product in humans.

Summary 2.1.2 Non-Clinical Conclusion:

If box ticked - No relevant findings for the clinical benefit-risk assessment ☐

If there are relevant findings please comment

Summary 2.1.3 Human Pharmacology Conclusion:

Only the important results and issues that have an impact on the benefit-risk balance should be described. In addition, unresolved issues or uncertainties should be identified and their impact on the balance assessment should be clearly stated. This includes Bioequivalence, Pharmacokinetic and Dynamic profile, as well as PK, & PD interactions, special populations, dose findings etc.

Summary 2.1.4 Clinical Conclusion:

Only the important results and issues that have an impact on the benefit-risk balance should be described. In addition, unresolved issues or uncertainties should be identified and their impact on the balance assessment should be clearly stated. This includes study design, dosage, population and comparators.

Summary 3.1 Identified Benefits and Risks

List all **benefits** of treatment for this indication as inferred in the submission	Please tick here if Benefit Identified by Reviewer but not by company	Please indicate which **benefits** you believe are justified to be included in the benefit risk assessment by ticking the box	Please explain your main reason **for inclusion or exclusion** of the benefit parameter
	☐	☐	

From the list of all benefits and risks identified in the submitted studies, the reviewer should differentiate those he has identified but not observed by the company. This allows any additional benefits or risks to be highlighted from the reviewer's perspective.

Benefits and risks of treatment should include those observed & derived from the submitted studies as indicated by the Sponsor as well as those identified by the reviewer.

Reasons must be provided for all listed benefits and risks as to their inclusion or exclusion for further benefit-risk assessment.

Uncertainties of the identified benefits and risks will be addressed in summary 6.1.

After a review of the list of identified benefits and risks, the reviewer should decide which are pivotal in making the benefit-risk balance. For each benefit or risk justified to be included, these would be auto-populated respectively to summary 6.1, where detailed information will then be further required.

Summary 3.1.2 Risks documented

List all **risks** of treatment for this indication as inferred in the submission	Please tick here if Risk Identified by Reviewer but not by company	Please indicate which **risks** you believe are justified to be included in the benefit risk assessment by ticking the box	Please explain your main reason **for inclusion or exclusion** of the risk parameter
	☐	☐	

Summary 4.1 Clinical Study Summary

Study Ref. Type	Study Design (N)(duration) R, C, DB, OL (N=)(weeks/months) ·Non-inferiority/Superiority/ Observational study ·State primary objective ·State primary efficacy parameter	Treatment ·Treatment arm Active (name, dose, freq, duration) ·Comparator arm Placebo / Active (name, dose, freq, duration)	Conclusion ·Results of primary efficacy parameter ·Results of other relevant efficacy endpoints ·Conclusion of study (outcomes, strength of study, weight of evidence, and clinical significance)	
				-

List the statistical parameter applied to investigate the endpoint used to confirm the benefit, or in the case of non-inferiority and equivalence studies, the pre-defined margins or deltas not to be exceeded.

Summary 5.1 Risks: Overall Summary

Table of pooled overall incidence of events can be added below

Adobe **Acrobat** users can click here to attach a file: Attach a file *(Note: this will not activate in Adobe **Reader**)*

Click in the space below to upload an image: (jpeg, gif, png): *(Available to both Adobe Reader and Acrobat users)*

Summary 6.1 Weights and values

Benefits	Relative Importance (weighting)	Valuing the options			Comment on strength and uncertainty of benefit
		Investigated product	Comparator	Placebo	

Risks	Relative Importance (weighting)	Valuing the options			Comment on strength and uncertainty of each risk	Was the value or weight of this risk altered or mitigated by the ability to control the use of the medicine once on the market?
		Investigated product	Comparator	Placebo		

- *Assigning Relative Importance*

For the identified benefits and risks, the reviewer should apply their expert judgment to provide relative importance of each parameter in contributing to the benefit-risk balance, in the light of the evidence provided

This is either carried out through ranking, numerical value, or qualitative descriptors such as high, medium or low. If the system of ranking is used, then this should be hierarchical and logical. Reviewers should limit themselves to using only one of these systems for both benefits and risks.

- *Valuing*

Provide either qualitative (e.g. high, medium, low or absent) or quantitative (utilizing the values from the study outcomes, e.g. overall survival 32% for product versus 27% for placebo) values of benefits and risks. When possible, please use quantification.

A short explanation of the selected systems for assigning relative importance and valuing should be provided in the allocated box:

Please describe methodology used for assessing relative importance: eg Ranking or point allocation and also what is has been used in relation to valuing the options e.g. % change, Number of patients, etc

Summary 7.1 Conclusion

The final decision on the benefit-risk balance of the Product for the proposed indication will be discussed here. Considerations for assessing the benefit-risk balance are adapted from the EMA reflection paper (2008) and these are attached in Appendix A, B, and C.

Summary 7.1.1 If the benefit-risk balance is assessed to be negative, describe the harm (e.g. in terms of lack of efficacy, toxicity) that the drug may cause if used in the proposed indication
Summary 7.1.2 Describe how the benefit-risk balance is expected to evolve over time (e.g. when late side effects emerge or long-term efficacy decreases)
Summary 7.1.3 Describe outstanding issues, and other significant information eg, submission of additional reports by the company to address those issues, hearings and advisory group recommendations, information from other jurisdictions (eg advisory committees, scientific experts, patients, consumers, consumer advocates and other stakeholders)
Summary 7.1.4 Make reference to the evaluation of the pharmacovigilance plan and risk minimization plan if any. Describe any communication or particularly significant information to the medical profession, patients or the public that is required. Describe restrictions to product availability or usage
Summary 7.1.5 Describe the need for further studies (e.g. the need for studies to improve the benefit-risk balance with further optimization studies, the need for intensive additional follow up measures or specific obligations, and the need for further development including any paediatric development plans.
This section should also consider any further studies required to mitigate findings from non-clinical studies (Section 2.2.2).

Summary 7.1.6 Please provide any other information considered by the agency relevant to the benefit risk decision that is not covered elsewhere in the proforma.

Summary 7.1.7 Please provide a clear conclusion on the benefit-risk being positive or not for the proposed indication.

The conclusion here refers to the benefit-risk balance of the Product for this proposed indication, and does not constitute a final regulatory decision.

Summary 7.1.8 Please provide the indication recommended following the outcome of the benefit-risk balance.

Amendments should include all changes to proposed indication and/or dosing regimen, with annotations provided. Please provide justification for the amendments.

For negative benefit-risk balance resulting in a recommendation for non-approval, kindly indicate so.

These recommendations do not necessarily constitute final regulatory decision or market authorizations.

Reviewers Name:

Signature:

Date:

Manager sign-off or Peer review

Reviewers Name:

Signature:

Date:

Navigating through the template

Hyperlinks are provided at the Table of Contents to help locate the desired section.

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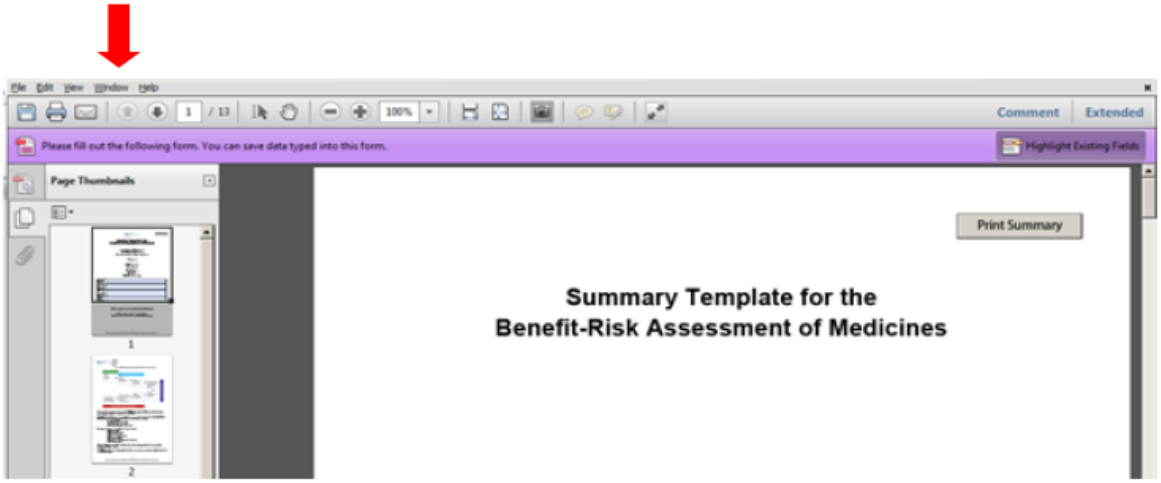
3.1	Identified Benefits and Risks	Go to Page
4.1	Clinical Study Summary	Go to Page
5.1	Table of Pooled overall Incidence of events	Go to Page
6.1	Relative Importance and Values	Go to Page
7.1	Conclusion	Go to Page

Thumbnails are available at the left side of the screen panel to help navigate to the desired page.



Appendix A

Criteria for assessing efficacy or favourable effects*

1. Efficacy (primary endpoint) versus comparator and its clinical relevance
2. Magnitude of treatment effect
3. Clinical relevance of the primary endpoints
4. Statistical significance of the efficacy results
5. Representiveness of the studied population for the population targeted in the label
6. Discussion of dose
7. Evidence for the efficacy in relative subgroups
8. Design conduct and statistical adequacy of the trial
9. Confirmation of treatment effect by results of non-primary endpoints
10. Validation of scales and outcome measures
11. Patient preferred outcomes
12. Confirmation of efficacy by results of relevant non-pivotal trials and extensions
13. Anticipated patient compliance (and patient convenience)
14. Clustering (consistency) of results of the pivotal trials

*Adapted from European Medicines Agency (EMA). Reflection Paper on Benefit-risk Assessment Methods in the context of the Evaluation of Marketing Authorisation Applications of Medicinal Products for Human Use; March 2008.

Appendix B

Criteria for assessing harms or unfavourable effects*

1. Overall incidence of adverse effects (from clinical trials)
2. Overall incidence of serious adverse effects (from clinical trials
3. Discontinuation rate due to adverse effects (from clinical trials)
4. Incidence, seriousness and duration of specific adverse effects (from clinical trials and post-marketing surveillance)
5. Interaction with other drugs and food
6. Safety in subgroups (e.g. race and sex)
7. Potential for off label use leading to safety hazards
8. Potential for non-demonstrated additional risk due to limitations of clinical trials and/or short market exposure.
9. Potential for non-demonstrated additional risk due to safety issues observed in pre-clinical safety studies but not in humans
10. Potential for non-demonstrated additional risk due to safety issues observed with other medicines of the same pharmacological class

*Adapted from European Medicines Agency (EMA). Reflection Paper on Benefit-risk Assessment Methods in the context of the Evaluation of Marketing Authorisation Applications of Medicinal Products for Human Use; March 2008.

Appendix C

Criteria for assessing benefit-risk balance*

- Amount of evidence to characterise the benefit-risk balance:
  - Availability of comparative data and their limitations and potential deficiencies
- Interpret of key benefits and risks
  - from perspectives of different stakeholders, including patients and treating physicians
- Level of risk acceptability
  - corresponding to the perceived degree of clinical benefit in the specific context
- Relating the benefits to the risks when possible:
  - Using logical comparisons e.g. potential lives saved as a result of treatment compare to potential lives lost as a result of adverse reactions
- Factors affecting the benefit-risk balance:
  - Situations that may alter the current balance e.g. different patient or disease characteristics
- Sensitivity of the benefit-risk balance:
  - Discussion on the potential changes to the balance if the fundamental assumptions are to be amended
- Other appropriate discussions:
  - Effectiveness of proposed treatment compared to available options
  - For negative benefit-risk balanced, describe the potential harm incurred upon exposure for the claimed indication
  - Evolution of benefit-risk balance over time
  - Outstanding issues, submission or reports to address identified issues
  - Evaluation of pharmacovigilance plan, risk mitigation plan or other post-marketing commitments including need for further studies
  - Opinions from scientific experts, patients, consumers or advocates and other stakeholders in the benefit-risk assessments
- Conclusion on the benefit-risk being positive or not for every claimed indication.

*Adapted from European Medicines Agency (EMA). Reflection Paper on Benefit-risk Assessment Methods in the context of the Evaluation of Marketing Authorisation Applications of Medicinal Products for Human Use; March 2008.

Appendix VI

CONFIDENTIAL

Evaluation of the use of the Benefit-risk Summary

Mr James Leong, Cardiff University

Participants:
Jalene Poh - Health Sciences Authority (HSA), Singapore

Confidentiality

- All information collected will be kept strictly confidential.
- No data that will identify a participant will be reported, or details made available to a third party.
- External reports or presentations of the data will include only anonymous figures and any appropriate analytical interpretation.
- Data will only be provided to the relevant organization concerned.

Background

Over the past three years, the Centre for Innovation in Regulatory Science (CIRS) in association with Health Canada, the TGA in Australia, HSA in Singapore and SwissMedic (collectively known as the Consortium) have developed a structured systematic standardised approach to the benefit-risk assessment of medicines.

A template based on the EMA guidance document for benefit-risk assessment (March 2008) had been developed to document the benefit-risk decision making process in the regulatory review. The original template had been evaluated in a feasibility study by the Consortium in 2010 and a retrospective pilot study in 2011. As a result of these initiatives, the Consortium had suggested modifications and additions which have now been incorporated into the current electronic version. A user manual has been developed.

An initial seven-step benefit-risk framework proposed and used in both the feasibility and pilot study has now been included in the overarching Unified Methodologies for Benefit-Risk Assessment (UMBRA) eight-step framework, which has been shown to incorporate other frameworks developed and evaluated by various groups including the FDA (five-step framework), the EMA (eight-step PROACT-URL framework) and the PhRMA's BRAT initiative (six-step framework).

CIRS has now put together a Benefit-Risk Assessment Support System (BRASS) which includes the eight-step framework, a benefit-risk template and its user manual. The Consortium is carrying out a prospective study using this package. The benefit-risk template consists of the proforma (allowing detailed discussion of the assessment) and the summary (henceforth known as the Summary; a collated document of key outcomes from the assessment). This study focuses on the Summary and its potential use apart from the proforma section.

Objectives

The objective is to:

- Determine the use for documenting benefit-risk balance within the agency
- Determine the use for communicating benefit-risk balance and conclusion to other regulatory agencies

Methodology

This is a retrospective, open-label and non-comparative study. The tool is sent to each of the clinical evaluators in HSA (Therapeutic Products Branch) involved in the assessment of benefit-risk balance and registration of medicines, at the conclusion of completing the Summary using the evaluator's most recent application fulfilling the following conditions:

- New Drug application which requires benefit-risk evaluation
- Full or abridged route of evaluation
- Regulatory decision reached within the last 3 months

Using the respective clinical assessment report, the assessor will transfer the relevant information required of the Summary. Upon the completion of this transfer, the evaluator will then respond to this tool. This exercise is to be supported by the User Manual provided.

All survey outcomes should be completed and submitted by July 2013.

Outcomes
A report of the analysed data will be made available to the agency HSA by end of August 2013.

Conclusion
The outcomes of this evaluation will contribute to the role, evolution and further development of the benefit-risk Summary.

Instructions for completion of the tool

This tool relates to your recent experience with the following system:

Benefit-risk_Summary_2013_HSA.pdf

There are 3 sections:

A. User-friendliness
B. Documentation
C. Applicability

This tool should be completed as soon as the documentation of the benefit-risk assessment using the Summary is completed.

You should relate each statement to your experience of using the Summary and tick the box that best describes your opinion.

We would appreciate if you could provide a response to all the items and submit the completed form before the end of July 2013. Please provide your responses electronically and note that the comment boxes are expandable.

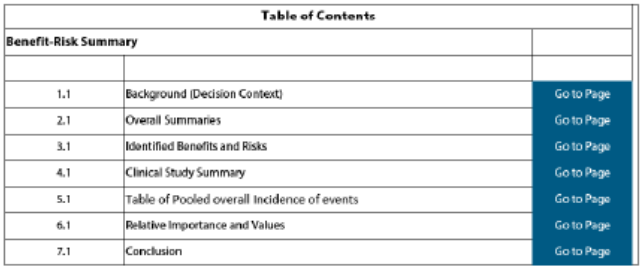
Your comments are extremely valuable, please feel free to use the boxes provided for this purpose.

A. User-friendliness

A practical summary should be easy to use and understand.

Having used the Summary to document the assessment of benefits and risks, please read through the list of items below and put a tick in the box that best describes your opinion.

Kindly provide comments if your opinion is "Fair" or "Poor".

		Excellent	Good	Fair	Poor	Did not use	Provide comments if opinion is "Fair" or "Poor"
Navigating through the Summary							
1	 Navigation to required sections using the "Go to Page" button in Table of Contents.						
2	Navigation to required sections using the page thumbnails found on the left side of screen display.						
Guidance by user manual in completing the Summary							
3	Clarity of instructions.						
4	Comprehensiveness of guidance provided.						
5	Applicability of guidance.						

Please comment on how to further improve the user-friendliness, or suggest other functions that might improve the navigation of the Summary.

B. Documentation

A functional summary should be able to document the processes leading to the final benefit-risk conclusion in a structured and systematic manner.

Having used the Summary to document the benefits, risks and the resulting balance, please read through the list of items below, and put a tick in the box that best describes your opinion.

- "**Fit for purpose**" refers to the Summary being able to achieve the item for the majority of the applications.
- "**Fit for purpose with modification**" refers to the Summary being able to achieve the item with amendments (kindly specify the changes required).
- "**Not fit for purpose**" refers to the Summary not being able to achieve the item at all.

Kindly provide comments as required for your opinion, as indicated in the section.

Summary 1.1 Background (Decision Context) (includes summaries 1.1.1 to 1.1.3)		**Fit for purpose**	**Fit for purpose with modification**	**Not fit for purpose**
1	Documents relevant information to support the decision context.		*Specify modification(s) needed:*	*Comment(s):*

Summary 2.1 Overall Summaries		**Fit for purpose**	**Fit for purpose with modification**	**Not fit for purpose**
Summary 2.1.1 Quality Conclusion				
2	Documents relevant information to support the decision context.		*Specify modification(s) needed:*	*Comment(s):*
Summary 2.1.2 Non-Clinical Conclusion				
3	Documents relevant information to support the decision context.		*Specify modification(s) needed:*	*Comment(s):*

Summary 2 Overall Summaries (continued)		Fit for purpose	Fit for purpose with modification	Not fit for purpose
Section 2.1.3 Human Pharmacology Conclusion				
4	Documents relevant information to support the decision context.		*Specify modification(s) needed:*	*Comment(s):*
Section 2.1.4 Clinical Conclusion				
5	Documents relevant information to support the decision context.		*Specify modification(s) needed:*	*Comment(s):*

Summary 3.1 Identified Benefits and Risks (includes summaries 3.1.1 and 3.1.2)		Fit for purpose	Fit for purpose with modification	Not fit for purpose
Benefits				
List all **benefits** of treatment for this indication as inferred in the submission	Please tick here **if** Benefit Identified by Reviewer but not by company	Please indicate which **benefits** you believe are justified to be included in the benefit risk assessment by ticking the box	Please explain your main reason **for inclusion or exclusion** of the benefit parameter	
	☐	☐		
6	Documents the reasons for inclusion or exclusion of all the benefits.		*Specify modification(s) needed:*	*Comment(s):*
7	Documents the relevant benefits as identified by the sponsor.		*Specify modification(s) needed:*	*Comment(s):*
8	Documents your list of benefits to be included in the benefit-risk assessment.		*Specify modification(s) needed:*	*Comment(s):*

Risks

List all **risks** of treatment for this indication as inferred in the submission	Please tick here if Risk Identified by Reviewer but not by company	Please indicate which **risks** you believe are justified to be included in the benefit risk assessment by ticking the box	Please explain your main reason **for inclusion or exclusion** of the risk parameter
	☐	☐	

9	Documents the reasons for inclusion or exclusion of all the risks.		*Specify modification(s) needed:*	*Comment(s):*
10	Documents the relevant risks as identified by the sponsor.		*Specify modification(s) needed:*	*Comment(s):*
11	Documents your list of risks to be included in the benefit-risk assessment.		*Specify modification(s) needed:*	*Comment(s):*

Summary 4.1 Clinical Study Information		Fit for purpose	Fit for purpose with modification	Not fit for purpose

Study Ref. Type	Study Design (N)(duration) R, C, DB, OL (N=)(weeks/months) ·Non-inferiority/Superiority/ Observational study ·State primary objective ·State primary efficacy parameter	Treatment ·Treatment arm Active (name, dose, freq, duration) ·Comparator arm Placebo / Active (name, dose, freq, duration)	Conclusion ·Results of primary efficacy parameter ·Results of other relevant efficacy endpoints ·Conclusion of study (outcomes, strength of study, weight of evidence, and clinical significance)	

12	Documents the outcomes and conclusions of the studies.		*Specify modification(s) needed:*	*Comment(s):*

Summary 5.1 RISKS: Overall Summary		Fit for purpose	Fit for purpose with modification	Not fit for purpose

Table of pooled overall incidence of events can be added below

Adobe **Acrobat** users can click here to attach a file: Attach a file *(Note: this will not activate in Adobe **Reader**)*

Click in the space below to upload an image: (jpeg, gif, png): *(Available to both Adobe Reader and Acrobat users)*

13	Documents the overall summary of the incidence of adverse events/effects.		*Specify modification(s) needed:*	*Comment(s):*

Summary 6.1 Weights and Values		Fit for purpose	Fit for purpose with modification	Not fit for purpose
Benefits				
	Benefits / Relative Importance (weighting) / Valuing the options: Investigated product, Comparator, Placebo / Comment on strength and uncertainty of benefit			
	For items 14 and 15, please refer to the table above.			
14	Documents the contribution of the weighting/relative importance of the benefits to the final benefit-risk decision.		*Specify modification(s) needed:*	*Comment(s):*
15	Documents the contribution of the values of the benefits from the studies to the final benefit-risk decision.		*Specify modification(s) needed:*	*Comment(s):*
Risks				
	Risks / Relative Importance (weighting) / Valuing the options: Investigated product, Comparator, Placebo / Comment on strength and uncertainty of each risk / Was the value or weight of this risk altered or mitigated by the ability to control the use of the medicine once on the market?			
	For items 16 and 17, please refer to the table above.			
16	Documents the contribution of the weighting/relative importance of the risks to the final benefit-risk decision.		*Specify modification(s) needed:*	*Comment(s):*
17	Documents the contribution of the values of the risks from the studies to the final benefit-risk decision.		*Specify modification(s) needed:*	*Comment(s):*

Summary 7.1 Conclusion (includes summaries 7.1.1 to 7.1.8)		Fit for purpose	Fit for purpose with modification	Not fit for purpose
18	Includes all the relevant information to draw a conclusion regarding the recommendation.		*Specify modification(s) needed:*	*Comment(s):*

C. Applicability

The summary used to document the benefit-risk balance should contribute significantly and apply directly to the communication of regulatory decision making.

Having used a structured systematic documentation of benefits and risks assessment, kindly indicate if this Summary should be part of standard regulatory review practices.

		Excellent	Good	Fair	Poor	Provide comments if opinion is " Fair" or "Poor"
1	The Summary's contribution to promoting effective communication to stakeholders.					
2	The Summary's contribution to achieving consistency of decisions between regulatory agencies.					
3	The Summary's advantages over the systems I am currently using in my organisation.					

		Yes	No (please provide comments)
	Irrespective of the jurisdiction in your country, are you willing to share the entire Summary with the following stakeholders? If no, please provide a reason.		
4	• Healthcare professionals		
5	• Health technologies assessment agencies (HTA)		
6	• Patients/patient advocacy groups		
7	• Other regulatory agencies		
8	• Media/public domain		
9	• Academia		

If you have any further comments, kindly use the space below:

Should you have further questions or concerns about this tool, please contact either:

Mr James Leong at email: james_leong@hsa.gov.sg

On completion, please send this to the following email:
james_leong@hsa.gov.sg

Participant's Information

Name/Signature:	**Position:**
Date:	

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