Progress on the Development of a Benefit/Risk Framework for Evaluating Medicines

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Determining the benefit/risk (BR) balance of a new medicine is one of the most important steps in its development, review and postapproval reassessment. Recently, regulatory agencies and sponsors have begun to develop appropriate benefit/risk frameworks (BRFs) that enable collaborative scientific discussion of a product's therapeutic profile. Despite these early steps, there is room for improving communications among regulatory agencies and industry stakeholders. Specifically, there remains a need for clear, concise and unambiguous communication of findings about benefits and risks. The CMR International Institute for Regulatory Science (the Institute) recently convened a workshop to address the issues of improving communications regarding BR assessments within and across regional agencies and industry organizations.

Progress Toward a Harmonized BRF

Recommendations for the development of a BRF emerged from previous Institute workshops and other major meetings. These recommendations include development of a common lexicon, case study comparisons of the different frameworks, compilation of a list of benefit and risk parameters that would be reviewed systematically, and an analysis of the values assigned to these parameters by all stakeholders, including regulatory authorities, health technology assessment agencies and patients.

A five-step process for BR assessment has been proposed by the Institute (**Figure 1**). Using this process, tables summarizing product safety and efficacy data from a company's drug approval application are constructed. Next, a value tree is developed (**Figure 2**) and BR parameters are prioritized. Following the assignment of values to the BR parameters, the BR assessment is completed when weights can be assigned using expert judgment.[1,2]

CASS Initiative

A task force of representatives from Health **C**anada, **A**ustralia's Therapeutic Goods Administration, **S**wissmedic and the **S**ingapore Health Science Authority (the CASS Group) has been formed by the Institute to determine the feasibility and the practical application of a systematic and standardized approach to BR assessment. To date, the group has agreed on the structured framework, developed a list of efficacy and safety parameters and decided on the use of a modified version of the BR template developed by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP). This approach draws on the work pioneered by Dr Fillip Mussen of Johnson & Johnson Pharmaceutical Research and Development in Belgium, under the direction of Professors Stuart Walker and Sam Salek at the Centre for Socioeconomic Research, Welsh School of Pharmacy at the University of Wales. In 2010, working closely with the assessors from these agencies, the group will initiate a pilot study to evaluate the BR assessment for several products on which a final regulatory decision is about to be made. To aid in this review, a pro forma has been developed based on the CHMP Assessment Template.

Concurrently, the European Medicines Agency has initiated its benefit/risk methodology project, which aims to adapt or develop tools and processes to conceptualize and make explicit BR weighting and comparisons, thereby providing an aid for making regulatory decisions, training assessors and communicating BR decisions to stakeholders. The agency has also initiated the Electronic Summary of Product Characteristics (e-SPC) Project, which will structure the BR information of the SPC so that it can be linked to electronic health records and prescribing systems to support prescribing decisions and improve the quality of pharmacotherapy.

The Benefit Risk Action Team (BRAT) of the Pharmaceutical Research and Manufacturers of America (PhRMA) is also establishing a structured BRF that will increase the transparency, predictability and consistency with which BR assessments are conducted. The BRAT BRF employs a six-step approach in which outcomes are prospectively identified; data sources are identified; a customized value tree is created; key BR metrics are quantified; and the importance of the BR outcomes are evaluated. The sixth step, which is the ultimate regulatory review decision, is not considered within the scope of this framework but is left to the expert judgement of the regulators.

Challenges to BR Communication

Fundamental barriers to BR communication include the lack of common terminology and disagreement on standards of evidence among stakeholders. For example, the existing framework for regulatory evaluation of medicines is based on measurement of safety and efficacy rather than benefit and risk. Although a seemingly small distinction, this discrepancy may be a significant impediment to the exchange of information.

The existence of multiple constituencies within regulatory agencies and industry has emerged as another important barrier to BR communication. Within agencies, there may be difficulty connecting with all relevant parties, and their varying levels of interest and experience may require individualized communication. Within industry, it may be difficult to achieve consensus on BR messages and the strategy for their communication.

BR Value Assignment

Development of a BRF continues to focus on overcoming communication issues surrounding the critical steps of assigning values to options

Figure 1. Five Steps of Evaluating the Benefits and Risks of New Medicines

A Framework for Benefit Risk Assessment

Starting Point	Data on efficacy and safety from company submission	
	Therapeutic indication	
	Options to be addressed	
Step 1	Construction of summary tables	
Step 2	Value tree	
	All possible benefits	All possible risks
Step 3	Assessment of importance and prioritisation	
	Selected benefits	Selected risks
Step 4	Assignment of values for each benefit and risk criteria for each option (qualitative or semi-quantitative?)	
Step 5	Benefit/risk assessment	
	Expert judgment	

and weights to BR criteria. Although both agencies and industry currently apply these metrics to BR parameters, the rationale for how this is done is not always explicit or transparent. This complex topic will require specific, structured discussion, possibly following the application of a BRF to a number of case studies.

Benefit Communication

It should be possible to assess the effectiveness of a medicine with the same methodologies and databases currently used to monitor safety signals. A future focus for public postmarketing communications should, therefore, be on distilling the wealth of information contained in the integrated summaries of safety and efficacy down to a practical level so that they are helpful to healthcare professionals and patients alike.

The Anti Rheumatic Therapy in Sweden (ARTIS) database is an example of a successful program of postmarketing efficacy and safety data collection. A collaboration of the Medical Products Agency and the Swedish Society for Rheumatology started in 1999, ARTIS combines patient information from regional and national clinics, registries and centers for pharmacovigilance, resulting in data useful for clinical epidemiology, health economics and medical management.[3]

Transparent BR Communications and Predictable Pharmaceutical Development

Understanding and communicating benefits and risks start with an understanding of the data, and require the benefits and key risks to be conceptualized in a clear, understandable manner without confusing terms, allowing direct comparisons between the two. Novel graphic representations of benefits and risks have been suggested to advance understanding and communication among all stakeholders. To construct these graphics, key identified benefits are derived from the primary outcome measure in clinical trials for a medicine. Next, key risks are hypothesized, and these events are extrapolated to a hypothetical population of treated patients. In one technique, a number is calculated to represent the difference between incidences of the positive primary outcome measure and incidences of adverse events arising from the use of the new medicine, resulting in a BR score for the therapy that can be clearly visualized.

BR Assessment Throughout the Product Development Continuum

BR criteria should be applied in all stage-gate decisions in the pharmaceutical development lifecycle. At the time of the Phase 1 go/no go decision for a new medicine, it is possible to build on the disease area BR assessment by determining whether the product is likely to meet minimally acceptable thresholds for benefits and risks based on preclinical data and mechanism of action. At this point, it is critical to identify important areas for information collection to close gaps in knowledge about the product's BR profile and to ensure that this information will be prospectively collected during the clinical development program. Incorporating BR criteria is particularly important to inform Phase 3 go/no go decisions when the stakes are higher. Ideally, BR criteria are used at the time of regulatory application submission to present data on the new product's benefits and risks in comparable scales, for example, lives potentially saved by a medicine compared with lives potentially lost from the medicine's adverse effects. The time of dossier submission is also the appropriate time to begin to address the expected approaches to mitigate identified risks and enhance benefits of treatment in risk management or pharmacovigilance plans.

REMS

Risk Evaluation and Mitigation Strategies (REMS), while not warranted for most medicines, should be regarded as an opportunity for BR optimization for some compounds in both the premarket and postapproval stages of pharmaceutical development. The REMS instituted by Biogen Idec for natalizumab (Tysabri) is presented as an example of BR optimization.

Natalizumab, approved for the treatment of relapsing multiple sclerosis, was voluntarily withdrawn from the market after numerous instances of treatment-associated progressive multifocal leukoencephalopathy (PML). The medicine was reintroduced with a restricted distribution and risk management plan, including the creation and maintenance of a robust network of trained neurologists. Close links and rapid, effective communication to the patient population substantially reduced time to diagnosis and treatment, made early detection and treatment feasible, and resulted in a lower-than-expected mortality rate among those who developed PML.[4] The REMS for natalizumab was instrumental in ensuring that those who can benefit most from this treatment for MS continue to have the opportunity to receive treatment while mitigating the consequences of PML in the few who develop it; the REMS also improved the precision of the estimated impact of the treatment on the disease by making a well-controlled therapy available to all potential patients. REMS programs should facilitate targeted and efficient BR communication with regulators in a time-constrained environment.

The Way Forward

Relevant and timely recommendations for change are important outputs of all Institute workshops. The following suggestions were made by workshop participants to improve communication of benefits and risks between industry and regulatory agencies.

1. Support the Institute's continued development of the framework for BR assessment.
   - Input from a wider group of stakeholders, including patients, healthcare professionals and payers, should be sought.
   - A dataset from a group of pharmaceutical companies could be used to test the practical application of the framework.
   - A scorecard utilizing sponsor/agency feedback would be useful to evaluate the BRF, and a case study could also be used to evaluate other frameworks for BR assessment currently being evaluated by various agencies.

2. Ensure BRFs have certain key features.
   - BRFs should consider new mechanisms of action and precedents set in the drug class and therapy class, for interacting with an agency without disclosing other proprietary information.
   - BRFs should evolve from being predominantly qualitative with minimal data in early stages to being increasingly quantitative and detailed.
   - BRFs should concentrate on safety and efficacy with a focus on pivotal parameters.
   - BRFs should incorporate clear data collection methodology.

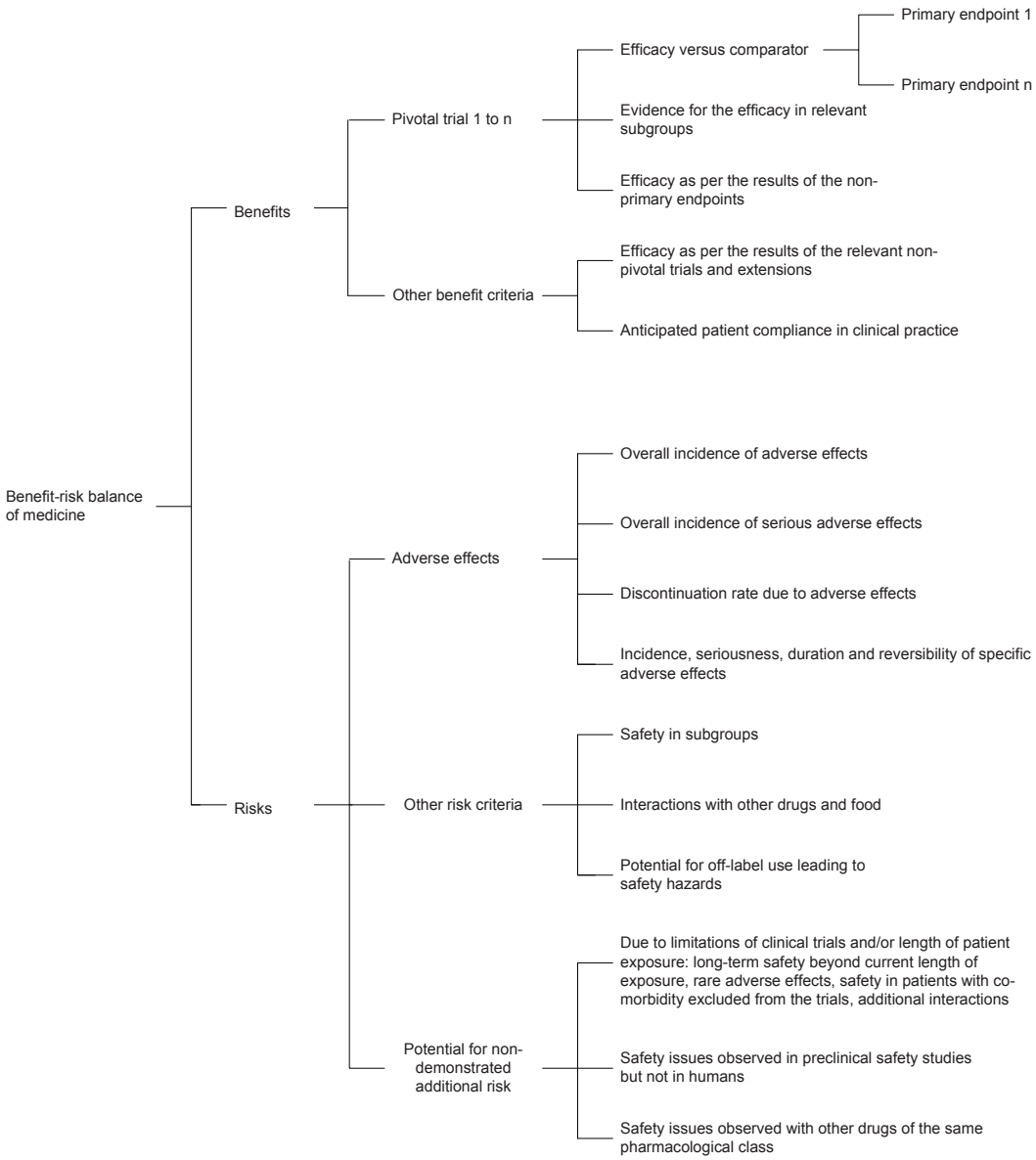
3. Transparency is key in BR assessment.
   - Simplifying complex factors in BR assessment is essential but not to the extent that essential information is lost.
   - Simple BR presentation tools, potentially using visualization, should be developed and used.
   - FDA and the European Medicines Agency should be encouraged to prepare and make publicly available case studies and lessons from BR assessments.

4. Section 2.5.4 of the Common Technical Document (clinical overview of the application) and European Public Assessment Reports could be improved with better guidance for the BR assessment.
   - Sponsors should be encouraged to use the proposed BRF to construct the BR summary in their marketing authorization applications.

5. Optimize timing and characteristics of BR communication.
   - Early interaction between sponsors and agencies is key.
   - Using disease knowledge to define BR parameters, sponsors should focus on these parameters early in a product's development cycle and seek agreement on the framework with agencies.
   - Although the best time for an informed BR discussion with an agency is at the end of Phase 2, most still occur at the time of the market authorization application submission; there is also potential value in BR discussion at the end of Phase 3 to help guide the expectations of regulatory reviewers.
   - A clear, deductive audit trail is needed to improve BR communications.

6. Ensure risk management plans have certain key features.
   - Risk management plans should incorporate discussion, as appropriate, on how to compare health outcomes, including a value placed on each parameter assessed.

Figure 2. Benefit and Risk Criteria Used to Construct a Value Tree[3]



- Systematic, retrospective analyses of safety issues either identified early or appearing late in development should be part of the risk management plan.

Conclusion

Important progress has been made in the development of a standardized BR assessment framework, and it is this common framework that has been recognized as the first step in open and clear communication between stakeholders in the development of new medicines. Clear graphic representations, dynamic REMS programs and workshops such as those conducted by the CMR International Institute for Regulatory Science are important tools in bridging communication gaps between regulatory agencies and sponsors of new therapies and facilitating a discussion of the details and outcomes of BR assessments. Continuing efforts in this important work will result in consistent, expedited and transparent evaluation of the risks and benefits of new medicines globally.

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