Benefit-Risk Appraisal of Medicines
A systematic approach to decision-making

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Balancing benefits and risks forms an integral part of everyday life – personal, financial and professional; yet there is little agreement as to how this can be measured and expressed.

Take two clinical scenarios. First, a medicine has the potential to cure cancer or successfully treat a severe infection without causing major adverse effects; second a medicine is used for the treatment of transient muscle aches but causes frequent skin rashes. In each of these instances the benefit–risk balance is obvious. But most therapeutic options are not so easy and more often concern marginal benefits and risks which are difficult to assess. In addition, the same experimental information on risks and benefits of a new medicine may be interpreted differently by the drug developer, the regulator, the healthcare professional and the patient.

None of this is new. The lexicon of risk has been inconclusively debated for years and used differently by various stakeholders. What is lacking is a systematic approach to decision making and communication. In therapeutics the need for such an approach has never been greater. As powerful new medicines for hitherto untreatable diseases are produced, all concerned parties must decide whether their potential for benefit outweighs that for causing harm, and should be able to engage in a dialogue to express this.

Such an assessment is not only made at the time of application for marketing authorization of a new product. At each stage of the development process, both preclinical and clinical, risk and benefit are continually balanced. As more evidence accrues as on the effectiveness and safety of a medicine when it is in widespread clinical use, this balance may change markedly and require regulatory action, resulting in either allowing its more extensive use for new indications or in limiting its usage to specified groups of patients. The latter represents a special problem for the regulator. By restricting the use of a new medicine to a group of patients who, for example, may have already failed treatment with other therapeutic agents which may have resulted in impairment of an already compromised immune system, the regulator may cause the balance to swing against its further successful use. Formal assessment of the benefit
risk balance and its clear communication by all parties involved in this situation would facilitate more informed debate.

But another party is assuming greater importance in the discussion surrounding benefit and risk. Approval by health technology assessors and reimbursers decides whether already financially pressed healthcare systems will allow a new drug to be widely used. Although such decisions are predominantly made on considerations of clinical and cost effectiveness, implicit in these is an appreciation of risk and benefit. The measurements used in health technology assessment differ from those of the developer and the regulator, but can be accommodated into various models, and these considerations are discussed in the text that follows.

This book provides a review of how present concepts of benefit and risk in the assessment of medicines have developed and how these are interpreted in various countries by various stakeholders. It describes a framework in which various models can be accommodated, illustrating these with important worked clinical examples. The authors have contributed to this field for many years and their ideas have been refined by workshops, discussions and debates reports of which are helpfully included as appendices to the book. This will not be the last word in a rapidly moving field but as an expression of the current state of the art, it has much to commend it.

Professor Sir Alasdair Breckenridge CBE
Chair of the Medicine Healthcare products Regulatory Agency (MHRA)
This project began in the year 2000 as the result of increasing questions and challenges about the benefit-risk appraisal decisions by major regulatory agencies. This was originally intended for publication in the drug safety/pharmacoepidemiology literature. However, later it became evident that, given the continued debate and a greater need for a systematic, explicit and transparent approach to decision-making, to target the manuscript just at a limited audience would probably bypass the very groups who would benefit most from its message. Furthermore, the book is wider in its scope and includes the entire work of the project including its conceptualisation and rationale.

The book progressed in three phases: firstly an understanding of current practices of benefit-risk appraisal including the CIOMS recommendations and existing models; secondly, a review of benefit-risk appraisals in other industries and their approach to decision-making; and thirdly, the development of a new model for benefit-risk appraisal of medicines based on the multi-criteria decision analysis technique and the proposal of a future framework for benefit-risk appraisal of medicines.

In an attempt to openly debate these issues of concern to the pharmaceutical industry, regulatory authorities, practitioners and patients, the authors communicated their work and its practical application through a series of workshops and reports which are reflected as appendices in this book. The chapters are carefully selected to develop a systematic approach to the debate and at the same time to foster the way of thinking in order to make the book of interest to a wider audience. Moreover, the subject has a wide appeal and that coupled with the pioneering work presented by the authors should indisputably place this book next to an essential reading or reference list for the pharmaceutical industry and regulatory authorities worldwide as well as students pursuing postgraduate degrees in pharmacoepidemiology/pharmacovigilance, clinical research, pharmaceutical medicine, pharmacy and medicine.
We welcomed the opportunity of working together for the preparation of this book and thank the publishing team at John Wiley for their patience and understanding during the rather long preparation period for this book. Our thanks go to our families and friends for their support while this book was in preparation.

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CHAPTER 1
Concept and Scope of Benefit–Risk Evaluation of Medicines

1.1 HISTORICAL BACKGROUND

The regulation of modern medicines started after the thalidomide tragedy, which was undoubtedly the most significant adverse event in pharmaceutical history. It was a tragedy because the toxic effects of the medicine were expressed through the damage to the unborn foetus between the fortieth and fiftieth days of gestation after the mother had taken therapeutic doses of the medicine as a sedative or hypnotic during the pregnancy. The baby was born with characteristic reduction deformities of the limbs with shortening or complete absence of long bones, the hands and feet being attached as ‘flippers’ or absent altogether (Burley, 1988). The plight of these children, about 1000 who were born in the United Kingdom and several thousands in West Germany, caused widespread horror and emotional reactions and calls for all medicines to be the subject of governmental control and regulation in order to avoid a repetition of such an event.

A previous disaster in 1938, when 107 deaths were caused in the United States by the consumption of an ‘elixir’ of sulfanilamide containing a toxic solvent, had led to the setting up of new legislation in the United States whereby manufacturers of medicines had to be registered, had to carry out safety tests and were liable to receive factory inspections and seizure of products in violation (Burley, 1988). The thalidomide tragedy led to the strengthening of the regulatory process, particularly in respect of prescription medicines and the introduction of the requirement for pre-marketing submission to the regulatory authorities in the United States as well as in Europe.
Already in 1962, after the thalidomide tragedy had become known, MacGregor and Perry (1962) made the following very wise comments with regard to the impact of thalidomide on regulations worldwide:

Such hazards can become apparent only on prolonged clinical use of drugs in human patients. Tragedies will no doubt continue to occur with new remedies, and this is part of the price to be paid for therapeutic progress, because we cannot, as a community, ask for new drugs without being prepared to accept such risks. We cannot legislate ourselves out of this dilemma...

Since 1962, a significant number of breakthrough medicines have been put on the market in a vast number of therapeutic areas such as hypertension, heart failure, hypercholesterolaemia, schizophrenia, cancer, human immunodeficiency virus (HIV), etc. The regulatory authorities have assessed all these products with regard to their quality, safety and efficacy, but the emphasis was usually put on the safety. Whenever Food and Drug Administration (FDA) Commissioners were called to testify before Congress, the charge was usually ‘Why did you put this drug on the market which later turned out to be toxic?’ It was not until the acquired immune deficiency syndrome (AIDS) epidemic surfaced that Congress began to ask the FDA why certain medicines were not on the market (Lasagna, 1998). The statement by the FDA (1999b) provides a very good and balanced perspective with regard to the benefits (efficacy) and risks (safety) of medicines: ‘Although medical products are required to be safe, safety does not mean zero risk. A safe product is one that has reasonable risks, given the magnitude of the benefit expected and the alternatives available. All participants in the medical product development and delivery system have a role to play in maintaining this benefit–risk balance by making sure that products are developed, tested, manufactured, labelled, prescribed, dispensed, and used in a way that maximizes benefit and minimizes risk.’

The role of regulatory authorities is well defined in this respect, and regulatory authorities approve a new medicine or confirm approval of a marketed medicine when they judge that the benefits of using a medicine outweigh the risks for the intended population and use, and they ensure that the medicine is truthfully and adequately labelled for the population and use (Food and Drug Administration, 1999b). The key question is however how the regulatory authorities judge whether the benefits outweigh the risks, or in other words, how is the benefit–risk balance of a medicine established? This basic question triggered this book, also because it is recognized that balancing the benefits and risks is probably one of the most difficult tasks for anyone involved either in the development of new medicines or in the post-approval re-assessment of marketed medicines, and that basic research is still needed in this area (Edwards and Hugman, 1997). The next question is then whether methods, models or other tools have been developed or can be used to aid the regulatory authorities and others in determining the overall benefit–risk balance of...
medicines. Since the regulatory authorities are not the only stakeholder with regard to medicines, these questions should be considered in the context of how the other stakeholders (pharmaceutical companies, prescribers, and patients) judge whether the benefits of a medicine outweigh the risks.

An overview on benefit–risk assessment is provided in the next sections of this chapter. Following a review of the regulatory systems for assessing medicines, definitions, views and perceptions of benefits and risks will be outlined. Next, concepts as well as current practices in benefit–risk assessment will be discussed, and finally an overview on the use of methods and models for benefit–risk assessment will be provided.

1.2 THE REGULATORY SYSTEMS FOR ASSESSING MEDICINES

As outlined below, the concept of benefit versus risk is well captured in the EU and US legislation, which provide the legal framework for benefit–risk assessments by the regulatory authorities.

Europe

In the European Union, medicines must meet the three exclusive criteria laid down in the Community law which are quality, safety and efficacy, for a marketing authorization to be granted (Brunet, 1999). In Directive 2001/83/EC on the Community code relating to medicinal products for human use it is stipulated that a marketing authorization shall be refused if: (a) the risk–benefit balance is not considered to be favourable, or (b) its therapeutic efficacy is insufficiently substantiated by the applicant, or (c) its qualitative and quantitative composition is not as declared (Official Journal of the European Communities, 2004). Furthermore, in the preambles to this Directive, the following is stated:

The concepts of harmfulness and therapeutic efficacy can only be examined in relation to each other and have only a relative significance depending on the progress of scientific knowledge and the use for which the medicinal product is intended. The particulars and documents which must accompany an application for marketing authorization for a medicinal product demonstrate that potential risks are outweighed by the therapeutic efficacy of the product.

As an example of the application of the EU regulations, in the United Kingdom the Committee on Safety of Medicines (CSM) looks for evidence of the medicine’s safety, efficacy and quality when considering an application for a product licence. The CSM also uses benefit–risk analyses for medicines already licensed, and they