1

Introduction

Ye maun understand I found my remarks on figures, whilk . . . is the only true demonstrable root of human knowledge.

Sir Walter Scott, *Rob Roy*

Statisticians know that words are important to statistics, yet surely their importance is not fully recognized.

William Kruskal

Opinions are made to be changed – or how is truth to be got at? We don't arrive at it by standing on one leg.

Lord Byron, *letter to Murray*

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1.1 DRUG DEVELOPMENT

Drug development is the process not only of finding and producing therapeutically useful pharmaceuticals and of turning them into high-quality formulations of usable, effective and safe medicines, but also of delivering valuable, reliable and trustworthy information about appropriate doses and dosing intervals and about likely effects and side-effects of these treatments. Drug development is a process carried out by *sponsors* (mainly pharmaceutical companies) and its acceptability is ultimately judged by *regulators*. It is an extremely complex business and the risks are high, but the potential rewards are also considerable.

It takes many years for a project to reach development. First, basic research must be undertaken to validate concepts and mechanisms. Assessments of commercial potential for diseases and therapies are also needed and these will continue throughout the life of a project. Next, a lead compound must be identified for a particular indication. This will then be subjected to a battery of screening tests to assess its potential in terms of therapeutic activity. Back-up compounds will also be investigated. If a compound looks promising, it will also be evaluated from both safety and practical points of view. Will it be easy to formulate? How many steps are involved in the synthesis? How difficult will it be to manufacture in large-scale quantities? Before a treatment can go into development, not only must satisfactory answers have been obtained to all these questions but a viable pharmaceutical formulation permitting further study must be

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available. This can be an extremely delicate matter, involving work to develop suitable solutions, pills, patches or aerosols as the case may be.

If and when a molecule is accepted into development, animal studies will be undertaken in order to check safety and to establish a dose at which studies in humans may be undertaken. Once basic toxicological work has been undertaken, 'phase I' may begin and the first such studies may start. These will be single-dose studies in which lower doses are tried first and cautiously increased until a maximum tolerated dose may be established. In many indications such studies are carried out on healthy volunteers, but where the treatment is highly aggressive (and hence intended for serious diseases) patients will be used instead. In the meantime, longer-scale toxicological studies with animals will have been completed. Pharmacokinetic studies in humans will be undertaken in which the concentration–time profile of the drug in blood will be measured at frequent intervals in order to establish the rate at which the drug is absorbed and eliminated. These studies together, if successful, will permit multiple-dose studies to be undertaken.

Once maximum tolerated doses have been established, phase II begins and dose finding studies in patients are started. This is usually an extremely difficult phase of development but, if the drug proves acceptable, the object is that preliminary indications of efficacy should be available and that a firm recommendation for doses and dose schedules should emerge. Once these studies have been completed, the pivotal phase III studies can begin. These have the object of proving efficacy to a sceptical regulator and also of obtaining information on the safety and tolerability of the treatment.

A successfully completed development programme results in a dossier – an enormous collection of clinical trial and other reports, as well as expert summaries covering not only the clinical studies as regards efficacy and safety but also preclinical studies and other technical reports as well as details of the manufacturing process. If successful, the package leads to registration, but even during the review process, phase IV studies may have been initiated in order to discover more about the effect of the treatment in specialist subpopulations, or perhaps with the object of providing data to cover price negotiations with *reimbursers*.

Regulatory dossier: A mountain of documents which takes a forest of trees to obscure the wood.

Once a drug has been launched on the market, the process of monitoring and 'pharmacovigilance' begins in earnest, since the drug will now be used by far more persons than was ever the case in the clinical trials in phases I to III, and rare side-effects, which could not be detected earlier, may now appear. Some further phase IV postmarketing studies may be initiated and further work extending indications or preparing new formulations may be undertaken.

1.2 THE ROLE OF STATISTICS IN DRUG DEVELOPMENT

There is no aspect of drug development in which statistics cannot intrude: from screening chemicals for activity to forecasting sales. Because the efficacy and safety of treatments

has to be judged against a background of considerable biological variability, all of the judgements of efficacy boil down in the end to a numerical summary of evidence whose message can only be understood with the help of the science of statistics. It is the norm that clinical trials are planned jointly by a statistician and a physician. Statisticians are also becoming more active in the shaping of projects as a whole. Furthermore, whereas in the past in Europe, the expert reports for a dossier would largely be a subjective qualitative assessment of evidence from individual trials, regulators increasingly expect to see quantitative summaries, so called meta-analyses. Hence statistics is increasing its empire throughout the drug development process.

For many years now, the Food and Drugs Administration (FDA) in the United States has employed statisticians to assist in its review process, and this is now gradually being imitated in Europe by various national regulatory agencies, although the European Medicines Agency (EMEA) has yet (as far as I am aware) to follow suit. Statistical issues have long been covered by FDA general guidelines and there are now separate specific statistical guidelines produced by the Committee for Proprietary Medicinal Products (CPMP) in Europe, and by the Japanese Ministry of Health and Welfare. The International Conference on Harmonisation (ICH) is also addressing the subject. There are also many national and international societies specifically for statisticians in the pharmaceutical industry. The exact duties of the statistician working in drug development are covered in some detail in Chapter 5.

1.3 THE OBJECT OF THIS BOOK

As implied by our chapter quotations, this book is about figures, words and opinions; more precisely, it is an attempt to give a largely verbal account of the various opinions that are held by those who figure. The purpose is not to present an authoritative prescription as to how to deal with each particular application of statistics in drug development. I myself am far too cynical to believe that such statements are possible. Instead, the object is to make the reader think about genuine statistical controversies in drug development. In many cases the issues are deep, and thinking about them will increase understanding about scientific problems of evidence and inference as they relate to pharmaceuticals and their role in medicine and health, whether or not the reader's thinking about them concludes in resolution of the issues in question to his or her satisfaction. I hope the process is not only beneficial but enjoyable.

In complete contrast to my first book, *Cross-over Trials in Clinical Research* (Senn, 1993, 2002), this book includes very few concrete examples. There are a number of reasons, of which two are particularly important. First, it is not my object to teach the reader how to *calculate* anything. There is no need, therefore, of data to calculate upon. Second, the book is deliberately minimalist and I have eliminated anything that interferes with proceeding to discussing the issues.

The scope of the book is statistics in drug development in humans. I have taken this to include issues concerning the value of drugs that we may develop (Chapter 24) and also in monitoring drugs that we have developed (Chapter 23). With the exception of these two chapters, however, the book as a whole is concerned with matters affecting clinical trials in phases I to IV. There are many other areas in which statistics in the pharmaceutical industry are important thus I have not covered, including, for example, chemometrics and classification of molecules in research, screening for

efficacy, toxicology, pharmaceutical development, stability testing, process optimization and quality control. If I have left these out it was partly because one has to drawn the line somewhere but mainly because what I know about them could be written on the back of an envelope. This does not mean I have left them out without regrets: I would have enjoyed learning about them, but it would have been unrealistic to have included them and, in any case, I wanted a book that reflected my actual experience of drug development. I hope that the book nonetheless serves to give an impression of how wide the subject is, but the reader should bear in mind that it is wider yet than covered in these pages.

1.4 THE AUTHOR'S KNOWLEDGE OF STATISTICS IN DRUG DEVELOPMENT

The fact that I have eliminated from this book the subjects about which I know nothing does not mean that I am equally knowledgeable about all those that remain. I think it is appropriate for me to warn the reader of strengths and weaknesses. If we exclude the chapters in Part 1, then chapters 6 through to 18 are strengths, as is chapter 22; chapters 19, 21 and 23 are weaknesses and chapters 20 and 24 fall somewhere between the two. Chapter 25 on pharmacogenetics, which is new, is a bit of an odd one out. My knowledge of genetics is poor. However, equally relevant to this chapter is an understanding of sources of variability and also of trial design, which are both areas in which I have researched extensively over the years. Extensive references, in many cases with recommendations for further reading, are given in each chapter.

1.5 THE READER AND HIS OR HER KNOWLEDGE OF STATISTICS

Ideally, nobody should study statistics who hasn't studied it already. The least stimulating aspect of the subject (I will not say the easiest since it has difficulties of its own), is the mechanics of calculation. Although many of the horrors of this topic have been eliminated by modern computing, it is inevitable that a first course in statistics will not avoid dealing with these algorithmic matters in some detail. (And those readers who find computing to be a horror in its own right have my sympathy.) Only in a second course, where many of the rudiments of 'how' have been answered, can the more interesting 'why', 'when' and 'whether to' questions be addressed.

> **Statistics**: A subject which most statisticians find difficult but in which nearly all physicians are expert.

Throughout this book it is assumed that the reader already has some basic familiarity with statistics, such as may be obtained, for example, by the excellent elementary text on medical statistics by Campbell, Machin and Walters (Campbell *et al.*, 2007). For a more detailed coverage I recommend Altman (1991) or van Belle *et al.* (2004), and

for a more advanced level Armitage and Berry (2001). Some basic familiarity with statistics in clinical trials as covered, for example, in the classic text by Pocock (1983) is also assumed. Other treatments of statistics in clinical trials that I can recommend are the broad but elementary book by Wang and Bakhai (2006), the mathematically more advanced text by Matthews (2006), or the more comprehensive treatment by Piantadosi (2005). As regards the drug development process itself, I have found Hutchinson (1993) extremely useful to give to my own students wanting a quick introduction, and useful guides to the major classes of drug are Youngson (1994) and Henry (1994). Nevertheless, there is no heavy reliance on this assumed knowledge and the reader's memory will be jogged from time to time regarding relevant matters.

1.6 HOW TO USE THE BOOK

Part 1 consists of four chapters that give a crash course on statistics in drug development by presenting four different perspectives of the matter: historical, methodological, technical and professional. The least authoritative of these is the first, Chapter 2, which gives the historical view and where I have had to rely on secondary sources via the expert commentaries of others (with the exception of the history of the *t*-test, (Senn and Richardson, 1994) and Fisher's involvement in trials in humans (Senn, 2006), where I have undertaken some original researches myself). Nevertheless, if one does not consider the history of a subject, however crudely, one is all too vulnerable to the myth of 'present perfect' and I felt that it was important to cover history. Consideration of past imperfect helps to introduce a sense of proportion.

> **Analysis plan**: A detailed description of the intended analysis written before un-blinding data in the pharmaceutical industry and somewhat later, if at all, elsewhere.

The crucial chapters are Chapters 3 and 4, which give the 'iron rations' of the subject, covering basic statistical notions of causality and experimentation and introducing the two major schools of statistics: the frequentist and the Bayesian. (However, the general issue of Bayesian versus frequentist methods is too big for me to tackle seriously, preoccupying as it does many of the finest minds in the statistical profession. It cannot be entirely ignored, however, and it does break surface at various points throughout the rest of the book. Historical and philosophical accounts are given in my book *Dicing with Death* (Senn, 2003).) Chapter 5 explains something of the duties and concerns of the medical statistician working in drug development and may help to set the scene for the issues that follow. Chapters 2–5 together make a suitable one-day introductory course to clinical trials. Indeed, as mentioned in the preface to the first edition, they grew out of a course I gave while still working at CIBA-Geigy, which I left in 1995, and I have frequently given such courses both before and since the appearance of the first edition in 1997.

The issues themselves are covered in Part 2 and are grouped in chapters by broad theme which may be read in almost any order (or not at all) as the reader wishes. The chapters from Chapter 19 onwards are rather more technical and specialized than

Chapters 6–18, which are closely related to a postgraduate course I gave for many years at the University of Neuchatel, and it may help to have read some of these earlier chapters first. The grouping reflects drug development more than it reflects statistics. For example, if a purely statistical arrangement had been envisaged, there would have been a chapter on random-effect models, with entries on meta-analysis, multicentre trials and n-of-1 trials, rather than separate chapters on these topics with sections dealing with random-effect models. Certain such statistical topics are therefore more profitably hunted down via the index rather than the table of contents. The topics chosen are also those that are *particularly* relevant to drug development. Thus, topics that are relevant only because they affect the whole of statistics, such as, 'what should the role of robust statistics be?', are scarcely touched on. A few of the chapters in Part 2 have technical appendices, where I felt that the matters covered were not, or were not easily, available in the literature. These may be safely ignored by all but the more statistically minded.

In some of the chapters the reader will come across terms highlighted in bold type. This is an indication that these are important concepts and is usually a sign that there is an entry in the glossary. An exception is Chapter 2, where I have also highlighted the names of important historical figures.

The chapters can be used in a number of ways: by junior statisticians in order to get a quick overview of issues affecting a particular type of trial they are working on for the first time, by physicians and other life-scientists working in the pharmaceutical industry to help them discuss statistical issues with their statistical colleagues, and by university departments as the basis for student seminars and journal clubs.

Finally, for those who find controversy unsettling, I can do no better than quote the heroine of William Boyd's *Brazzaville Beach*: 'I have taken new comfort and refuge in the doctrine that advises one not to seek tranquility in certainty, but in permanently suspended judgement.' From *Brazzaville Beach* by William Boyd, published by Sinclair-Stevenson. Reprinted by permission of The Random House Group Ltd.

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