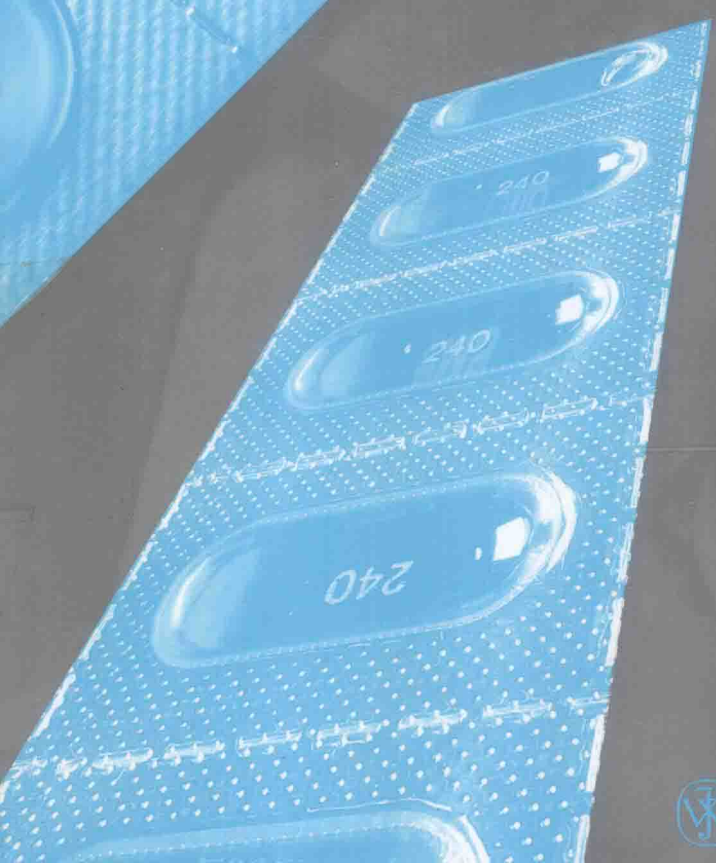
Pharmacovigilance



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Preface

The editors of this volume have looked upon pharmacovigilance as being the study of the safety of marketed drugs under the practical conditions of clinical usage in large communities. However, some aspects of this definition need qualification: safety cannot be considered apart from efficacy in most situations. For example, an ineffective drug used in a serious and life-threatening disease would be unsafe. Those individuals conducting pharmacovigilance are concerned not only with marketed drugs but also with their pre-marketing data—but our working definition serves a practical purpose.

Spontaneous reporting of suspected adverse drug effects is central to pharmacovigilance—which is the systematic search for signals of drug toxicity. When such a signal is detected it has to be verified, explored, and understood—realising that the drug may be acceptably safe if used by individuals who are not at especially high risk by virtue of genetic constitution, metabolism, or other characteristics that could alter individual risk.

Pharmacovigilance is conducted by a very large number of people concerned with protecting populations from serious unintended adverse consequences of medication exposure. It is important to recognise that most medications carry some risk due to their pharmacologic properties or to other factors. The evaluation of risk must be conducted in the context of the patient benefit derived from treatment, the severity of the condition being treated, and other objective and subjective factors (such as the patient's values). Each of the stakeholders—the patient, physician, pharmaceutical company, academic investigator, government—may have a different perspective on the same set of evidence. For example, a patient may be willing to accept a high risk of side-effects for benefits of the treatment for a condition that might be considered trivial by others. A regulatory agency may consider the burden of the same side-effects to be too high, given their view of the risk–benefit equation. A governmental or third-party payer might see the issue from an even different perspective, since a payer may not wish to bear the cost of the treatment or the cost of treating an adverse event. It is perhaps not surprising that each group may take a different view of the same evidence. In addition, each group may also be swayed by intense external pressures to take action to protect specific interests, for example to protect the public against potential harm or to protect against legal liability. These pressures may lead to early decisions based on incomplete scientific data.

There have been mistakes and errors in the field of pharmacovigilance: some drugs have been withdrawn when the benefit to large numbers of patients has not been properly balanced against the harm done to very few highly susceptible subjects. Identifying the patients most susceptible to risk and finding ways to channel medications to the appropriate patients would have been more rational. It is always highly desirable to subject the signal to the formal processes of pharmacoepidemiology (such as case–control, cohort, large simple randomised trial, etc.) before taking gross action on a weak or questionable signal. We have to weigh benefit against risk and the benefit may be to a large population affected by a serious

disease and the risk may be to a small population of susceptibles.

This book intends to help bring more rigorous considerations of scientific evidence to the various sectors that face critical decisions about how to act in the face of incomplete information. Our hope is that future decisions will be improved, and that public policy decisions can be made more transparent in the process.

The tension between regulator (government oversight agencies) and regulated (pharmaceutical industry) that was apparent in earlier years must be viewed in a more complex environment in which additional sectors also have considered opinions of the evidence, and possess strong interests as well. All sectors must grapple with the evidence and the pros and cons of decisions and the consequences of these decisions. The subject is not easy and its participants are frequently highly exposed. If this book is of any help to those exposed to political pressure, media pressure, their own indecision and anxieties, etc., then it will have been worth the effort taken to produce it.

The book falls into four parts: the basis of pharmacovigilance, signal generation, pharmacovigilance and the system–organ classes, and, finally, lessons and directions. We have eliminated some duplication but not all of it: people come at the same thing from different directions and sometimes those different viewpoints need to be preserved. Some subjects, for a variety of reasons, have been inadequately covered (signal generation in important countries and developing areas of the world; dictionaries and MedDRA; pharmacovigilance as conducted by some of the big companies, other than those already reviewed; non-US medical devices legislation; renal, cardiovascular and respiratory adverse drug reactions, etc.). Some of these subjects have been left for expansion in our second edition; some have been omitted this time round because, for example, we do not intend to cover all the system–organ classes in each edition but will choose different themes as time goes by.

A large number of people are concerned with pharmacovigilance but they are a very small number compared with the populations that they set out to protect. We hope that this volume will be of help to them and we thank our many authors for their contributions.

The editors wish to express their considerable appreciation to John and Celia Hall who took over the management of the production of this book in difficult circumstances and whose contribution is much appreciated. Professor Mann also wishes to acknowledge the considerable support of his personal assistant, Mrs Susan Jerome.

Ronald D. Mann
Elizabeth B. Andrews

Foreword

My introduction to the world of drug toxicity took place in 1965 when a patient attending our Hypertension Clinic at Hammersmith Hospital in London donated blood for transfusion and problems in cross matching the blood sample were encountered. This was found to be due to a positive direct Coombs' test (DCT). The hypertensive patient in question was being treated with α-methyldopa, which at that time was one of the most widely used antihypertensive drugs in the world and had been so for several years. When a possible connection between α-methyldopa and a positive DCT was postulated, initial hilarity and scepticism were rapidly replaced by curiosity and interest when blood samples from a further 202 patients treated with the same drug revealed 40 (20%) patients with the same haematological abnormality, while none of a control group of 76 hypertensive patients on other forms of therapy demonstrated a positive DCT. This led to a series of investigations to document the clinical epidemiology of the adverse effect and to investigate the underlying immunological abnormality. We learned several lessons from this episode. The first was that careful observation and high clinical suspicion are of crucial importance in order to identify a drug toxicity problem. The second lesson was that even though a drug has been on the market for several years and is widely used, unusual adverse reactions may still be identified, stressing the importance of continuing watchfulness. The term "post-marketing drug surveillance" had not been introduced in 1965.

The history of drug safety, pre- and post-thalidomide, has been documented many times. In many respects, this history parallels the development of what we now call rational, or evidence-based, therapeutics. One of the editors of this book, Ronald Mann, elsewhere describes how the United Kingdom in 1914 was on the point of adopting a drug regulatory system very akin to that which we have today. This occurred because around the turn of the last century there was widespread public concern and professional scepticism about the therapeutic value and the safety of patent medicines which were widely promoted and used. In 1909 the British Medical Association published a booklet entitled *Secret Remedies* detailing the excesses and shortcomings of these medicines; this proved to be a best seller which was reprinted several times in quick succession. Such was the level of public anxiety caused by this publication that a Parliamentary Select Committee was established to examine the whole topic of patent medicines. The Committee, which took evidence over three years, pulled no punches in interviewing the purveyors of these products, and its final report recommended in considerable detail how the public should be protected from the frequently unjustifiable and often fraudulent claims of the manufacturers of proprietary medicines. These recommendations included the creation of a Commission whose role was to oversee drug quality, safety and efficacy, drug advertising should be controlled and the Ministry of Health should regulate the field. The publication of the report of the Select Committee on 4 August 1914

was totally overshadowed by *force majeure*, namely the outbreak of the First World War, and the report sat gathering dust on the Ministry's shelves with no action being taken. As Ronald Mann succinctly states, "It is not altogether fanciful to look on the children of the thalidomide disaster as late and unwilling victims of World War One."

Post thalidomide there was a worldwide realisation that the introduction of new therapies and the continuing use of existing therapies had to be regulated based on sound scientific principles. As part of this, systems for doctors to report adverse reactions to drugs were set up; in the United Kingdom a yellow card was used to file the reports. But by the 1980s there was an increasing realisation that all was not well with the methods available to assess adverse drug reactions, and while spontaneous reporting using yellow cards or their like continued to make a valuable contribution to drug safety, other methods had to be devised to help attribute adverse effects to specific drugs. It was suggested that the methodology being pioneered by epidemiologists might make a contribution to study the response of the population to both the adverse and beneficial effects of drugs, thus obtaining a better assessment of risk and benefit. In particular, prospective and retrospective cohort studies, case–control studies, and linked data bases might help unravel the problems of drug safety surveillance. Thus, pharmacoepidemiology arose as a new discipline. The limitations of applying the techniques of the epidemiologist to drug surveillance are, of course, widely appreciated. The clinical data used can rarely be as robust as those from the laboratory and the introduction of bias is a constant risk. Furthermore, the pharmacology of the drugs used and the pathophysiology of the diseases involved have to be understood.

In general, scientists involved in drug safety have espoused the adoption of the principles of pharmacoepidemiology into pharmacovigilance with enthusiasm. However, from time to time, post-marketing safety surveillance studies fall below the required standards, usually due to poor trial design or the total lack of a comparator group. If sound principles are not followed, then such studies are worthless in scientific terms and make no meaningful contribution to pharmacovigilance.

The concept of balancing risk and benefit is now firmly embedded in modern drug treatment. Doctors, patients and the public are familiar with the concept of iatrogenic disease. Large-scale randomised control trials (a particular example of a prospective cohort study) are particularly valuable in defining the balance of risk and benefit and few modern medicines are introduced without being subjected to this form of analysis. One weakness of this approach is that risks and benefits usually have different end points. For example, a trial of an angiotensin converting enzyme inhibitor to investigate the beneficial reduction of stroke, heart failure or myocardial infarction in patients with hypertension has to be balanced against increasing the incidence of cough and rash. Formal decision analysis is one way of dealing with issues like this, but medicine is often uncomfortable with this approach. Another problem is that in any clinical trial there may be a cohort of patients who may show great benefit, but the overall risk–benefit balance of the trial may be negative. Unless one can clearly define the population who will show a beneficial response, perhaps using pharmacogenetic methodology, a drug may be discarded by a developer or rejected by a regulatory authority.

No branch of science stands still. It either makes significant advances or sinks back and becomes irrelevant, and pharmacovigilance is no exception. Looking to the future, perhaps we should be less focused on finding evidence of harm and more interested in extending our knowledge of safety. A specification of what is known about a medicine at the time of licensing should form the basis of what is required to extend understanding of its safety as it is introduced into the community. Risk–benefit decisions in clinical practice and drug regulation are often complex, but other disciplines have also struggled with these problems and medicine should be more prepared to adopt techniques such as formal decision analysis to improve its decision making. Outcome measures should be classified on a hierarchical basis; hard end points such as mortality and morbidity are not always available

and imaginative work on surrogate end points of drug safety should be encouraged and validated. As in all branches of medicine, the systematic audit of the processes involved and the outcomes measured should be mandatory and should form the basis of the milestones to be set for the development of the medicine once it becomes widely used. Finally, on perhaps a more mundane level, increasing emphasis should be placed on the provision of comprehensive, and at the same time comprehensible, information on the medicine for the prescriber and the patient. One currently sees an unfortunate tendency for such documentation to become more legalistic and less user friendly. Unless the house physician prescribing for a patient at 3 a.m. has easy access to the essential information he requires, or a patient can understand why he is taking a medicine and what the outcomes are likely to be, all the work that has gone into the development of the drug is valueless. A new approach to providing relevant information on medicines is urgently needed, but sadly this sometimes seems to become more distant as the practice of medicine becomes more complex.

I know of no book with a remit as extensive as this. As the editors say in their preface, repetitions are bound to occur and omissions (some of which they have already defined) are inevitable. The book is a *tour de force* and is a great tribute to the driving energy, enthusiasm and professionalism of Ronald Mann and Elizabeth Andrews, and I am extremely proud to be associated with it.

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