MANN’S PHARMACOVIGILANCE
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Third edition

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<tr>
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<th>Position</th>
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The publication of a third edition of this book in twelve years bear’s ample testimony to the continuing importance of pharmacovigilance, the study of the safety of marketed medicines.

It is also a memorial to the founding editor, Professor Ronald Mann, who sadly died in December 2013, shortly before the new edition appeared. It had already been decided by the new editors to rename the book Mann’s Pharmacovigilance, made more prescient by recent events. Ron Mann, as he was universally known, had spent a professional lifetime in the field of drug safety as a regulator, as an educator and as a physician. I had the privilege of working with him at the (then) UK Medicines Control Agency some twenty years ago when the word pharmacovigilance had not even been invented. Ron’s quest to instil scientific rigour into the then disorganised field of drug safety represented a great step forward in the regulation of medicines, and the three editions of this book clearly demonstrate this achievement. The title Mann’s Pharmacovigilance is richly deserved.

Over the lifetime of the book, several trends in drug safety have become more evident. We have seen advances in the science of pharmacovigilance and with this, progress in the technology to allow them. Examples such as the electronic submission of case reports and the invention of automated data mining techniques have been matched by greater attention to benefit-risk assessment rather than mere considerations of drug safety, and by emphasis on proactive risk management planning. The frameworks of medicines regulation – the scientific, the legal and the public health – are increasingly accepted not only by major regulatory authorities but by those in the developing world. The role of the patient has become more insistent and that of the health care professional more important.

Drug safety is no longer the preserve of the regulator and the pharmaceutical industry. These trends are clearly reflected in the changes in the structure of this third edition of Mann’s Pharmacovigilance. Three major changes can be seen. First there is evidence of greater global reach, with descriptions of spontaneous reporting systems in many more countries than covered in previous editions. Second, there is more focus on active surveillance using multiple population based databases. There are new chapters on collaborative efforts to enhance signal detection and evaluation. Thirdly, the scope of the book has broadened beyond drugs and medical devices with new chapters on vaccine surveillance and the evaluation of the safety of biologics. In many respects, vaccine safety practice is more effective than that of medicines; we should also question whether the techniques of medicines surveillance as currently applied are appropriate for biopharmaceutical products, or whether a new approach is needed.

Ron Mann would have approved of these changes.

Alasdair Breckenridge
January 2014
Introduction: Updated from Second Edition

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BACKGROUND

Pharmacovigilance – the study of the safety of marketed drugs under the practical conditions of clinical use in large communities – involves the paradox that what is probably the most highly regulated industry in the world is, from time to time, forced to remove approved and licensed products from the market because of clinical toxicity. Why is such close regulation not effective in preventing the withdrawal of licensed products? The question has been with us from the very early days of the 1960s and remains with us today, and its consideration tells us a great deal about pharmacovigilance.

The greatest of all drug disasters was the thalidomide tragedy of 1961–1962. Thalidomide had been introduced, and welcomed, as a safe and effective hypnotic and anti-emetic. It rapidly became popular for the treatment of nausea and vomiting in early pregnancy. Tragically, the drug proved to be a potent human teratogen that caused major birth defects in an estimated 10,000 children in the countries in which it was widely used in pregnant women. The story of this disaster has been reviewed elsewhere (Mann, 1984).

The thalidomide disaster led, in Europe and elsewhere, to the establishment of the drug regulatory mechanisms of today. These mechanisms require that new drugs shall be licensed by well-established regulatory authorities before being introduced into clinical use. This, it might be thought, would have made medicines safe – or, at least, acceptably safe. But Table 1.1 summarizes a list of 46 licensed medicines withdrawn, after marketing, for drug safety reasons since the mid 1970s in the UK.

Why should the highly regulated pharmaceutical industry need, or be compelled, to withdraw licensed medicines for drug safety reasons? Why do these problems of licensed products being found toxic continue despite the accumulated experience of more than 50 years since the thalidomide tragedy?
Table 1.1 Drugs withdrawn in the UK by the marketing authorization holder or suspended or revoked by the Licensing Authority, 1975–2010.

<table>
<thead>
<tr>
<th>Brand name (drug substance)</th>
<th>Year action taken</th>
<th>Major safety concern</th>
</tr>
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<tbody>
<tr>
<td>Secholex (polidexide)</td>
<td>1975</td>
<td>Safety concerns because of impurities</td>
</tr>
<tr>
<td>Eraldin (practolol)</td>
<td>1975</td>
<td>Ocutilomucocutaneous syndrome</td>
</tr>
<tr>
<td>Opren (benoxaprofen)</td>
<td>1982</td>
<td>Hepatotoxicity, serious skin reactions</td>
</tr>
<tr>
<td>Devryl (clomacran phosphate)</td>
<td>1982</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Flonint (indoprofen)</td>
<td>1982</td>
<td>Gastrointestinal toxicity</td>
</tr>
<tr>
<td>Zomax (zomepirac)</td>
<td>1983</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Osmosin (indomethacin-modified release)</td>
<td>1983</td>
<td>Small-intestine perforations</td>
</tr>
<tr>
<td>Zelmid (zimeldine)</td>
<td>1983</td>
<td>Neurotoxicity</td>
</tr>
<tr>
<td>Flenac (fenclofenac)</td>
<td>1984</td>
<td>Lyell’s syndrome</td>
</tr>
<tr>
<td>Methrazone (teprazone)</td>
<td>1984</td>
<td>Serious skin reactions, multisystem toxicity</td>
</tr>
<tr>
<td>Althesin (alphaxolone plus alphadolone)</td>
<td>1984</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Pexid (perhexilene)</td>
<td>1985</td>
<td>Hepatotoxicity, neurotoxicity</td>
</tr>
<tr>
<td>Suprol (suprofen)</td>
<td>1986</td>
<td>Nephrotoxicity</td>
</tr>
<tr>
<td>Merital (nomifensine)</td>
<td>1986</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>Unicard (dilevalol)</td>
<td>1990</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Glauline eye drops 0.6% (metipranolol)</td>
<td>1990</td>
<td>Uveitis</td>
</tr>
<tr>
<td>Halcion (triazolam)</td>
<td>1990</td>
<td>Psychiatric reactions</td>
</tr>
<tr>
<td>Micturin (terodiline)</td>
<td>1991</td>
<td>Arrhythmias</td>
</tr>
<tr>
<td>Teflox (temafloxacin)</td>
<td>1992</td>
<td>Multisystem toxicity</td>
</tr>
<tr>
<td>Centoxin (nebucumab)</td>
<td>1993</td>
<td>Mortality</td>
</tr>
<tr>
<td>Roxim (remoxipride)</td>
<td>1994</td>
<td>Aplastic anemia</td>
</tr>
<tr>
<td>Volital (pemolin)</td>
<td>1997</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Romazin (troglitazone)</td>
<td>1997</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Serdolect (sertindole)</td>
<td>1998</td>
<td>Arrhythmias</td>
</tr>
<tr>
<td>Tasmar (tolcapone)</td>
<td>1998</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Ponderax (fenfluramine)</td>
<td>1998</td>
<td>Cardiac valvular disease</td>
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<tr>
<td>Adifax (dexfenfluramine)</td>
<td>1998</td>
<td>Cardiac valvular disease</td>
</tr>
<tr>
<td>Posicor (mibefradil)</td>
<td>1998</td>
<td>Drug interactions</td>
</tr>
<tr>
<td>Trovan (trovafloxacin)</td>
<td>1999</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Grepafloxacin (Raxar)</td>
<td>1999</td>
<td>QT interval prolongation</td>
</tr>
<tr>
<td>Prepulsid (cisapide)</td>
<td>2000</td>
<td>QT interval prolongation</td>
</tr>
<tr>
<td>Alec (pumactant)</td>
<td>2000</td>
<td>Adverse comparative trial results</td>
</tr>
<tr>
<td>Droleptan (droperidol)</td>
<td>2001</td>
<td>Increased cardiac risks</td>
</tr>
<tr>
<td>Lipobay (cerivastatin)</td>
<td>2001</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Kava-Kava</td>
<td>2001</td>
<td>Liver toxicity</td>
</tr>
<tr>
<td>Anorectic agents (amfepramone, phentermine)</td>
<td>2000</td>
<td>Heart valve disorders</td>
</tr>
<tr>
<td>Vioxx (rofecoxib)</td>
<td>2004</td>
<td>Increased cardiovascular event risks</td>
</tr>
<tr>
<td>Non-proprietary (co-proxamol)</td>
<td>2005</td>
<td>Use in suicide</td>
</tr>
<tr>
<td>Bextra (valdecoxib)</td>
<td>2005</td>
<td>Stevens–Johnson syndrome</td>
</tr>
<tr>
<td>Prexige (lumiracoxib)</td>
<td>2007</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Carisoma (carisoprodol)</td>
<td>2007</td>
<td>Abuse potential</td>
</tr>
<tr>
<td>Trasylol (aprotinpin)</td>
<td>2007</td>
<td>Death following cardiac surgery</td>
</tr>
<tr>
<td>Accomplia (rimonabant)</td>
<td>2008</td>
<td>Depression, Suicide</td>
</tr>
<tr>
<td>Raptiva (efalizumab)</td>
<td>2009</td>
<td>Progressive Multifocus Leukoencephalopathy</td>
</tr>
<tr>
<td>Reductil (sibutramine)</td>
<td>2010</td>
<td>Cardiovascular mortality</td>
</tr>
<tr>
<td>Avandia (rosiglitazone)</td>
<td>2010</td>
<td>Increased cardiovascular event risk</td>
</tr>
</tbody>
</table>
Partly, the problem is one of numbers. For example, the median number of patients contributing data to the clinical safety section of new drug licensing applications in the UK is only just over 1500 (Rawlins and Jefferys, 1991). Increasing regulatory demands for additional information before approval have presumably increased the average numbers of patients in applications, especially for new chemical entities; nevertheless, the numbers remain far too small to detect uncommon or rare adverse drug reactions (ADRs), even if these are serious.

The size of the licensing applications for important new drugs cannot be materially increased without delaying the marketing of new drugs to an extent damaging to diseased patients. Thus, because of this problem with numbers, drug safety depends very largely on the surveillance of medicines once they have been marketed.

A second reason for difficulty is that the kinds of patients who receive licensed medicines are very different from the kinds of volunteers and patients in whom premarketing clinical trials are undertaken. The patients in formal clinical trials almost always have only one disease being treated with one drug. The drug, once licensed, is likely to be used in an older group of patients, many of whom will have more than one disease and be treated by polypharmacy. The drug may also be used in pediatric patients, who are generally excluded from initial clinical trials. The formal clinical trials may be a better test of efficacy than they are of safety under the practical conditions of everyday clinical usage.

A third problem is that doctors may be slow or ineffective in detecting and reporting adverse drug effects. Many of the drugs summarized in Table 1.1 were in widespread, long-term use before adverse reactions were detected, and even now hospital admissions due to ADRs have shown an incidence of between 2.4% and 3.6% of all admissions in Australia, with similar or greater figures in France and the USA (Pouyanne et al., 2000). Even physicians astute in detecting adverse drug effects are unlikely to identify effects of delayed onset.

A fourth reason for difficulty is that drugs are often withdrawn from the market for what may be very rare adverse effects – too infrequent by far to have shown up in the pre-licensing studies – and we do not yet have effective means in place for monitoring total postmarketing safety experience. This situation may well change as large comprehensive databases such as the Clinical Practice Research Datalink (CPRD, formerly the GPRD) in the UK and the Mini-Sentinel Network of databases in the USA become more widely used for signal detection and evaluation. These databases record, in quite large and representative populations, all usage of many specific medicines and clinical outcomes and can be used to systematically screen for and evaluate serious adverse events. Because they contain comprehensive information on some important data, such as age, sex, dose, and clinical events on all patients in the represented population, they are systematic compared with spontaneous reporting systems. They may offer a better chance of detecting long-latency adverse reactions, effects on growth and development, and other such forms of adverse experience.

Some of the difficulties due to numbers, patient populations, and so on were recognized quite early. The Committee on Safety of Drugs in the United Kingdom (established after the thalidomide disaster, originally under the chairmanship of Sir Derrick Dunlop, to consider drug safety whilst the Medicines Act of 1968 was being written) said – quite remarkably – in its last report (for 1969 and 1970) that “no drug which is pharmacologically effective is without hazard. Furthermore, not all hazards can be known before a drug is marketed.” This then has been known for over 40 years. Even so, many prescribers still seem to think that licensed drugs are “safe,” and they are surprised when a very small proportion of licensed drugs have to be withdrawn because of unexpected drug toxicity. Patients themselves may have expectations that licensed drugs are “completely safe” rather than having a safety profile that is acceptably safe in the context of the expected benefit and nature of the underlying health condition.

The methodological problems have been long recognized. The Committee on Safety of Medicines, the successor in the UK to the Dunlop Committee, investigating this and related problems, established a Working Party on Adverse Reactions. This group, under the chairmanship of Professor David Grahame-Smith, published its second report
in July 1985. The report supported the continuation of methods of spontaneous reporting by professionals but recommended that postmarketing surveillance studies should be undertaken on “newly-marketed drugs intended for widespread long-term use”; the report also mentioned record-linkage methods and prescription-based methods of drug safety surveillance as representing areas of possible progress (Mann, 1987).

Similar reviews and conclusions have emerged from the USA since the mid 1970s. A series of events in the USA recently created a resurgence of interest in drug safety evaluation and management. The Prescription Drug User Fee Act (PDUFA) of 1992 provided additional resources at the Food and Drug Administration (FDA) for drug reviews through user fees and established target time-lines for FDA reviews. The shorter approval times led to some medications being approved sooner in the USA than in Europe, in contrast to the pre-PDUFA experience. A few highly visible drug withdrawals led to a perception that perhaps drugs were being approved too quickly. Lazarou et al. (1998) published the results of a meta-analysis that estimated that 106,000 fatal adverse reactions occurred in the USA in 1994. This and other articles (Wood et al., 1998) stimulated considerable public, congressional, and regulatory attention on reducing the societal burden of drug reactions and medication errors (FDA, 1999; Institute of Medicine, 1999; United States General Accounting Office, 2000). As a result, greater attention and resources are currently being devoted to signal generation and evaluation by the FDA, industry, and academic centers. Moreover, efforts are underway to develop better tools to manage recognized risks through a variety of interventions, such as communications with healthcare providers and patients, restricted product distribution systems, and other mechanisms. Additional effort is being focused on measuring the success of these risk-management interventions. This new initiative represents a fundamental shift in the safety paradigm in the USA and offers new challenges to pharmacovigilance professionals. In fact, the shift is not restricted to the USA, as both the FDA and the European Medicines Agency (EMEA) in 2005 issued guidance documents for industry on signal detection, evaluation, good pharmacovigilance practice and recommendations for managing risks after the approval (FDA, 2005a–c).


We have long recognized then that the safety of patients depends not only on drug licensing by regulatory bodies, but also on postmarketing drug safety surveillance, pharmacovigilance. It is also important to note that the same postmarketing information needed to confirm new safety signals is also needed to refute signals and protect the ability of patients to benefit from needed medicines that may be under suspicion due to spurious signals.

DIAGNOSING ADVERSE DRUG REACTIONS

There are two types of ADRs. Type A reactions are common, predictable, usually dose-dependent, and appear as excessive manifestations of the normal pharmacology/toxicology of the drug; they are seldom fatal. Type B reactions are uncommon, unpredictable, often independent of dose, and usually represent abnormal manifestations of the drug’s pharmacology/toxicology; they involve relatively high rates of serious morbidity and mortality.

ADRs frequently mimic ordinary diseases and, if they are uncommon, may easily be overlooked. They
tend to affect the skin, hematopoietic system, and lining of the gut (situations in which there is rapid cell multiplication) or the liver or kidneys (where drugs are detoxified and excreted). These special sites are frequently involved in iatrogenic (doctor-induced), type B illnesses, such as toxic epidermal necrolysis, aplastic anemia, pseudomembranous colitis, drug-induced hepatitis, or nephritis.

A high index of suspicion is needed if ADRs are to be successfully diagnosed. The clinician always has to think: “Could this be drug-induced – is this an ADR?” The question is important, for withdrawal of the cause of an ADR is usually essential.

Iatrogenic ADRs are usually uncommon or rare, and this adds to the difficulty of diagnosis. Some are avoidable, such as skin rashes in patients with glandular fever given ampicillin. Some are accidental, such as the noniatrogenic disaster of an asthmatic given a beta-adrenergic blocking agent by another member of the family. It is a truism that the detection of common or uncommon ADRs requires vigilance. Many of the known serious ADRs have been recognized by astute clinicians with a high level of awareness, and such awareness is likely to be just as important as new methods of pharmacovigilance are developed as it has been in the past.

Linked with this problem of diagnosing ADRs is the problem of understanding them. Why does one patient in 10 000 get some bizarre type B reaction and the rest of this population not get it? Clearly, our increasing knowledge of clinical pharmacology, drug metabolism, and genetics will contribute to our understanding of these things, and these subjects are explored in many of the chapters in this book.

CURRENT METHODS OF PHARMACOVIGILANCE

Pharmacoepidemiology is the study of the use of, and effects of, drugs in large numbers of people. As the term implies, this form of enquiry uses the methods of epidemiology; it is concerned with all aspects of the benefit/risk ratio of drugs in populations. Pharmacovigilance is a branch of pharmacoepidemiology but is restricted to the study, on an epidemiological scale, of drug events or adverse reactions.

“Events,” in this context, are happenings recorded in the patient’s notes during a period of drug monitoring; they may be because of the disease for which the drug is being given, some other intercurrent disease or infection, an adverse reaction to the drug being monitored, or the activity of a drug being given concomitantly. They can also be because of drug–drug interactions.

Public health surveillance methods are used to identify new signals of possible ADRs. Studies in pharmacoepidemiology are intended to be either “hypothesis generating” or “hypothesis testing,” or to share these objectives. Hypothesis-generating studies, with a recently marketed drug, aim to detect unexpected ADRs; hypothesis-testing studies aim to prove whether any suspicions that may have been raised are justified.

HYPOTHESIS-GENERATING METHODS

SPONTANEOUS ADVERSE DRUG REACTION REPORTING

Doctors (in some countries, other healthcare professionals, and patients as well) are provided with forms upon which they can notify a central authority of any suspected ADRs that they detect. In the UK, the “yellow card” has been used for this purpose since 1964. Similar forms are provided in the FP10 prescriptions pads, the British National Formulary, and other sources. In the USA, the MedWatch form is used and is made broadly available to health professionals to encourage reporting.

The great strength of spontaneous reporting is that it operates for all drugs throughout the whole of their lifetime; it is the only affordable method of detecting really rare ADRs. The data may represent merely the suspicions of the reporter, but they provide the opinion of a doctor or health professional attending a real-life patient. The main weaknesses are that there is gross underreporting, and the data provide a “numerator” (the number of reports of each suspected reaction) only. Moreover,
some case reports are described in the medical literature but may not be reported by the clinician; such published case reports are subsequently reported by industry sponsors through the spontaneous reporting system. Nevertheless, the scheme is invaluable, and it is essential that health professionals should be provided with the means of reporting their suspicions.

Spontaneous reporting has led to the identification and verification of many unexpected and serious ADRs. These findings have resulted in many marketed drugs being withdrawn or additional information being provided to guide safer use of the product.

A variety of formal epidemiological studies can be undertaken to generate or test hypotheses.

**PRESCRIPTION–EVENT MONITORING**

Prescription–event monitoring (PEM), as conducted in the UK and New Zealand, represents a “hybrid” method, combining aspects of public health surveillance and spontaneous reporting with aspects of formal epidemiological studies. In the UK, this important technique takes advantage of many features of the British National Health Service (NHS). Within the NHS, prescriptions written by general practitioners are sent, once they have been dispensed, to a central Prescription Pricing Authority (PPA). The PPA provides confidential copies of certain prescriptions for newly introduced drugs that are being monitored to the Drug Safety Research Unit (DSRU) at Southampton. At 6 or 12 months after the first prescription for an individual drug in an individual patient, the DSRU sends a “green form” questionnaire to the general practitioner who wrote the original prescription. Changing requirements regarding confidentiality and the effect that these have had on PEM are discussed in the appropriate chapter of this volume.

Thus, the prescriptions provide the “exposure data” showing which patients have been exposed to the drug being monitored, and the green forms provide the “outcome data” showing any events noted during the period of monitoring. Pregnancies, deaths, or events of special interest can be followed up by contact between the DSRU and the prescribing doctor who holds, within the NHS, the lifetime medical record of all of their registered patients.

The great strengths of this method are that it provides a numerator (the number of reports) and a denominator (the number of patients exposed), both being collected over a precisely known period of observation. Furthermore, nothing happens to interfere with the doctor’s decision regarding which drug to prescribe for each individual patient, and this avoids selection biases, which can make data interpretation difficult. The main weakness of PEM is that only 50–70% of the green forms are returned, and the experience of the patients whose forms are not returned may differ from those returned. In addition, because PEM limits follow-up to 6 or 12 months, it cannot identify events of long latency. Thus, it is of great importance that doctors should continue to support the scheme by returning those green forms that they receive.

So far, some 100 drugs have been studied by PEM, and the average number of patients included in each study (the cohort size) has been over 10 000. This is a substantial achievement and a tribute to the general practitioners who have participated. PEM in the UK and a similar program in New Zealand are unique in providing a monitored-release program that can detect or help refute new signals in the early life of a medicine.

Considerable interest centers around those patients who produce major ADRs that are too rare to be detected in cohorts of around 10 000 patients. How many of these patients have inborn errors of metabolism or other rarities that reflect features of the patient rather than the drug? We do not have adequate facilities to investigate the genetic and metabolic features of those patients who produce these very rare type B adverse reactions.

**OTHER HYPOTHESIS-GENERATING METHODS**

Other systematic methods are used in signal generation. In some cases, data being collected for general public health surveillance, such as cause-of-death files, cancer registries, and birth defect registries are used to identify patterns of events that might be associated with medication use. Other programs, such as case–control surveillance of birth defects,