The IMPORTANCE *of* PHARMACOVIGILANCE

Safety Monitoring of medicinal products

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the UPPSALA MONITORING CENTRE

WHO Collaborating Centre for
International Drug Monitoring

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PREFACE

The Quality Assurance and Safety: Medicines team in WHO aims to assure the safety of medicines by ensuring reliable and timely exchange of information on drug safety issues, promoting pharmacovigilance activities throughout the Organization and encouraging participation in the WHO Programme for International Drug Monitoring. This team is developing a series of publications on Safety Monitoring of Medicinal Products. This text was developed in consultation with the WHO Collaborating Centre for International Drug Monitoring and the national pharmacovigilance centres participating in the WHO Programme for International Drug Monitoring. The draft was widely circulated and discussed at two informal consultations with international experts in pharmacovigilance. The WHO Department of Essential Drugs and Medicines in Geneva held these consultations. Contributions were made by:

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CHAPTER 1

INTRODUCTION

The purpose of this document is:

- to present the case for the importance of pharmacovigilance,
- to record its growth and potential as a significant discipline within medical science, and
- to describe its impact on patient welfare and public health.

It highlights the need for critical examination of the strengths and weaknesses of present pharmacovigilance systems in order to increase their impact. It anticipates developments necessary to meet the challenges of the next ten years. It argues that the distinctive approaches adopted by different countries in response to their individual needs should be supported and fostered. The document also highlights the importance of collaboration and communication at local, regional and international levels, to ensure pharmacovigilance delivers its full benefits.

Pharmacovigilance and all drug safety issues are relevant for everyone whose life is touched in any way by medical interventions. The document is intended for the following, wide-ranging readership:

- Policy makers at all levels of healthcare, particularly those concerned with drug policy
- Staff and consultants in national drug regulatory authorities
- Healthcare practitioners including doctors, nurses and pharmacists
- Pharmaceutical industry executives and scientists
- Professional staff in national pharmacovigilance centres
- Editors of medical and scientific journals
- Health epidemiologists
- Health economists
- Professional staff of poison and drug information centres
- Health administrators
- Consumer groups and patient support groups
- Legal advisors in health care
- Schools of health sciences, and
- The concerned layperson.

COMMON ABBREVIATIONS USED IN THIS DOCUMENT:

ADR	Adverse Drug Reaction
ICH	International Conference on Harmonization
UMC	*the* Uppsala Monitoring Centre (The WHO Collaborating Centre for International Drug Monitoring)
WHO	The World Health Organization

Other abbreviations and specialized terms appear in the Glossary.

CHAPTER 2

A SHORT HISTORY OF INVOLVEMENT IN DRUG SAFETY MONITORING BY WHO

This chapter introduces the events and ideas that have underpinned the foundation and early development of pharmacovigilance over the last thirty years under the aegis of the World Health Organization. In 2002, more than 65 countries have their own pharmacovigilance centres. Membership of the WHO Programme for International Drug Monitoring is co-ordinated by the WHO Collaborating Centre for International Drug Monitoring, known as *the* Uppsala Monitoring Centre (UMC).

The evolution of pharmacovigilance in recent years and its growing importance as a science critical to effective clinical practice and public health science are described. The national pharmacovigilance centres have become a significant influence on the drug regulatory authorities, at a time when drug safety concerns have become increasingly important in public health and clinical practice. Pharmacovigilance is now firmly based on sound scientific principles and is integral to effective clinical practice. The discipline needs to develop further to meet public expectations and the demands of modern public health.

Background

According to Article 2 of its constitution, the World Health Organization has a mandate from its Member States

> *to develop, establish, and promote international standards with respect to food, biological, pharmaceutical and similar products*

There is also provision made in Article 21 of the constitution of the World Health Assembly to adopt regulations concerning

> *standards with respect to the safety, purity and potency of biological, pharmaceutical and similar products moving in international commerce.*

It was not until the disaster caused by thalidomide in 1961 that the first systematic international efforts were initiated to address drug safety issues. At that time many thousands of congenitally deformed infants were born as the result of exposure in utero to an unsafe medicine promoted for use by pregnant mothers. The Sixteenth World Health Assembly (1963) adopted a resolution (WHA 16.36) [(1)] that reaffirmed the need for early action in regard to rapid dissemination of information on adverse drug reactions and led, later, to creation of the WHO Pilot Research Project for International Drug Monitoring in 1968. The purpose of this was to develop a system, applicable internationally, for detecting previously unknown or poorly understood adverse effects of medicines. A WHO technical report followed based on a consultation meeting held in 1971.[(2)]

From these beginnings emerged the practice and science of pharmacovigilance. Systems were developed in Member States for the collection of individual case histories of ADRs and evaluation of them. The collection of international ADR reports in a central database, would serve the important function of contributing to the work of national drug regulatory authorities, improve the safety profile of medicines, and help avoid further disasters.[(3)]

From pilot to permanence

The principal achievement of the 1971 WHO consultation meeting was:

- to advocate establishment of national centres for drug monitoring,
- to provide guidelines
- to identify the contribution that national centres might make to the international system.

In so doing, it was envisaged that the time necessary to recognize that a drug produces an adverse reaction might be reduced, and the importance of the reaction more readily assessed. It was noted that

- data collection from health practitioners,
- systematic monitoring of populations,
- review of health statistics and of drug utilization data, and
- effective analysis of input data

would be necessary for the objectives of pharmacovigilance to be achieved. Special attention would need to be paid to new drugs. Specialized reference centres would be required to provide additional data to National Centres and for investigation of particular drug safety problems.

Since the start of the International Programme in 1968 much has been accomplished:

- The pilot project has developed into the WHO Programme for International Drug Monitoring now co-ordinated by *the* Uppsala Monitoring Centre (UMC) in Uppsala, Sweden, with oversight by an international board
- The Programme has expanded to include more than sixty member countries
- In many countries, regional reporting centres, interest groups, dedicated internal medicine and pharmacology department units, drug and poison information centres and other non-governmental organizations have developed
- The idea that pharmacovigilance centres are a luxury, affordable only in the developed world, has been replaced by a realization that a reliable system of pharmacovigilance is necessary for public health and for the rational, safe and cost-effective use of medicines in all countries. Where no established regulatory infrastructure exists, a drug monitoring system is an effective and cost-efficient means of detecting and minimizing injury to patients and averting potential disaster.

Professional interest

The creation of the International Society of Pharmacoepidemiology (ISPE) in 1984 and of the European Society of Pharmacovigilance (ESOP – later ISoP – the International Society) in 1992 marked the introduction of pharmacovigilance formally into the research and academic world, and its increasing integration into clinical practice. Specialist medical journals have appeared, and a number of countries have implemented active surveillance systems to complement conventional methods of drug monitoring. Examples of such systems are:

- the prescription event monitoring systems (PEM) in New Zealand and the United Kingdom
- record linkage systems in the United States of America and Canada
- case control studies in the United States of America.

Pharmacovigilance activities have also evolved as a regulatory activity. In the early 1980s, in close collaboration with the WHO, the Council for International Organizations of

Medical Sciences (CIOMS) launched its programme on drug development and use. CIOMS provided a forum for policy makers, pharmaceutical manufacturers, government officials and academics to make recommendations on the communication of safety information between regulators and the pharmaceutical industry. The adoption of many of the recommendations of CIOMS by the International Conference on Harmonization (ICH) in the 1990s has had a notable impact on international drug regulation.

Widening horizons

Within the last decade, there has been a growing awareness that the scope of pharmacovigilance should be extended beyond the strict confines of detecting new signals of safety concerns. Globalization, consumerism, the explosion in free trade and communication across borders, and increasing use of the Internet have resulted in a change in access to all medicinal products and information on them. These changes have given rise to new kinds of safety concerns such as:

- illegal sale of medicines and drugs of abuse over the Internet
- increasing self-medication practices
- irrational and potentially unsafe drug donation practices
- widespread manufacture and sale of counterfeit and substandard medicines
- increasing use of traditional medicines outside the confines of the traditional culture of use
- increasing use of traditional medicines and herbal medicines with other medicine with potential for adverse interactions.

There is a need for a reconsideration of pharmacovigilance practice in the light of the lack of clear definition of boundaries between:

- food,
- medicines (including traditional medicines, herbal medicines and 'natural products'),
- medical devices, and
- cosmetics.

Increasing public expectation of safety in relation to all of these adds another dimension of pressure for change. National pharmacovigilance centres are in no position to address all these safety concerns on their own, but they are especially able to detect and anticipate the impact of such problems on the safety of patients. Through strong links with the national drug regulatory authority as well as to other countries, National Centres are in a position to influence decision-making on drug and other health-related policies.

The purpose of pharmacovigilance

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. Recently, its concerns have been widened to include: [4]

- herbals
- traditional and complementary medicines
- blood products
- biologicals
- medical devices
- vaccines.

Many other issues are also of relevance to the science:

- substandard medicines
- medication errors
- lack of efficacy reports
- use of medicines for indications that are not approved and for which there is inadequate scientific basis
- case reports of acute and chronic poisoning
- assessment of drug-related mortality
- abuse and misuse of medicines
- adverse interactions of medicines with chemicals, other medicines, and food.

The specific aims of pharmacovigilance are to:

- improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions,
- improve public health and safety in relation to the use of medicines,
- contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use, and
- promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.[5]

Pharmacovigilance has developed and will continue to develop in response to the special needs and according to the particular strengths of members of the WHO Programme and beyond. Such active influence needs to be encouraged and fostered; it is a source of vigour and originality that has contributed much to international practice and standards.

CHAPTER 3

PARTNERS IN PHARMACOVIGILANCE

A complex and vital relationship exists between a wide range of partners in the practice of drug safety monitoring. Sustained collaboration and commitment are vital if the future challenges in pharmacovigilance are to be met and the discipline is to continue to develop and flourish. These partners must jointly anticipate, understand and respond to the continually increasing demands and expectations of the public, health administrators, policy officials, politicians and health professionals. There is little prospect of this happening in the absence of sound and comprehensive systems that makes such collaboration possible. The partners concerned, and the present constraints under which they function, are described in this chapter. The constraints include training, resources, political support, and most especially scientific infrastructure. Understanding and tackling these would set the scene for future development of the science and practice of pharmacovigilance.

The WHO Quality Assurance and Safety: Medicines Team

The Quality Assurance and Safety: Medicines team is responsible for providing guidance and support to countries on drug safety matters. The team is part of the Department of Essential Drugs and Medicines Policy, within the WHO Health Technology and Pharmaceuticals cluster. The purpose of the department is:

> *to help save lives and improve health by closing the huge gap between the potential that essential drugs have to offer and the reality that for millions of people – particularly the poor and disadvantaged – medicines are unavailable, unaffordable, unsafe or improperly used.* [6]

WHO works towards fulfilling this mission by providing global guidance on essential drugs and medicines, and working with countries to implement national drug policies. These are designed to ensure:

- equity of access to essential drugs
- drug quality and safety
- rational use of drugs.

The explicit objectives of the Quality Assurance and Safety: Medicines team are:

- to ensure the quality, safety and efficacy of all medicines by strengthening and putting into practice regulatory and quality assurance standards.

For this policy to meets its objectives, the scope of pharmacovigilance needs to be extended to include the safety of all related health technologies, including medicines, vaccines, blood products, biotechnology, herbal medicines and traditional medicines.

the Uppsala Monitoring Centre

The principal function of *the* Uppsala Monitoring Centre is to manage the international database of ADR reports received from National Centres.[7] In 2002 this database held nearly three million case reports. The majority of national contributing centres have easy electronic access to these. *the* UMC has established standardized reporting by all National Centres and has facilitated communication between countries to promote rapid identification of signals.

A sophisticated Bayesian confidence propagation neural network (BCPNN) programme was created in 1998, which partly automates the signal detection system, and provides earlier alert signals than previous methods.[8]
The effectiveness of this system depends on:

- the size of the database
- the quality of the reports received from the contributing centres
- the timeliness of such reporting
- an active and reliable reporting culture within participating countries.

An international advisory panel of clinical experts determines the validity and clinical importance of the signals generated.

In recent years *the* UMC has expanded its role as a communications and training centre and clearing-house for information on drug safety. Through

- mail discussion groups,
- website development,
- newsletters
- annual National Centre meetings,

the UMC team, in collaboration with the WHO, facilitates and encourages the international collaboration, which was identified in 1972 as being vital for the success of pharmacovigilance.

The terminologies developed within the WHO programme for coding adverse reactions and medicines have been widely adopted by National Centres, manufacturers and drug regulators. In recent years, the introduction of a new terminology known as MedDRA (Medical Dictionary for Drug Regulatory Activities) has replaced the World Health Organization Adverse Reaction Terminology (WHO-ART) in developed countries. WHO-ART remains the mainstay of communicating adverse reactions in most developing countries within the International Programme.

Another project at *the* UMC is the creation of an ADR monitoring system for herbal and traditional medicines. (The growing importance of such a system is further referred to in Chapter 4 on Drug Regulation (page 21-22)).

While *the* UMC has achieved much in improving the activities, support and recognition of individual National Centres, much more could still be done in providing training and encouraging expertise at a national level. There needs to be better consultation and communication between developed and developing countries when discussions on international harmonization of pharmacovigilance issues are taking place.

More effective communication of information is being promoted and encouraged through the WHO International Drug Monitoring Programme and *the* UMC. They are working towards playing a more pro-active role in working together with countries in addressing specific safety concerns and establishing a system that would make possible an evaluation of safety concerns of international importance by a supranational body of experts. An example of such a system, as it applies to vaccine safety, is described in Chapter 6 (page 30, footnote).

The National Pharmacovigilance Centres

At present, post-marketing surveillance of medicines is mainly co-ordinated by national pharmacovigilance centres. In collaboration with *the* UMC the National Centres have achieved a great deal in:

- collecting and analysing case reports of ADRs
- distinguishing signals from background 'noise'
- making regulatory decisions based on strengthened signals
- alerting prescribers, manufacturers and the public to new risks of adverse reactions.

The number of National Centres participating in the WHO International Drug Monitoring Programme has increased from 10 in 1968 when the Programme started to 67 in 2002. The centres vary considerably in size, resources, support structure, and scope of activities. Collecting spontaneous reports of suspected ADRs remains their core activity.

National Centres have played a significant role in increasing public awareness of drug safety. As a result, pharmacovigilance is increasingly seen as more than a regulatory activity, having also a major part to play in clinical practice and the development of public health policy. This development is partly attributable to the fact that many national and regional centres are housed within hospitals, medical schools or poison and drug information centres, rather than within the confines of a drug regulatory authority.

The scope of activities of National Centres has expanded to include communication of information about benefit, harm, effectiveness and risk to practitioners, patients and the public. Major centres in developed countries have established active surveillance programmes using record linkage and prescription event monitoring systems (PEM) to collect epidemiological information on adverse reactions to specific drugs. Such systems have already been implemented in New Zealand, the United Kingdom, Sweden and the United States of America.[9]

In the nature of their work, National Centres have also become familiar with real or contrived drug scare crises, which they have managed with variable success. Some centres are also involved in training undergraduate and qualified healthcare professionals in pharmacovigilance and the importance of reporting ADRs. The extent of such activities varies between countries.

The source and extent of funding of different National Centres also varies significantly. Most ministries of health fund their National Centre, at least in part. The entire cost of a pharmacovigilance system, compared with the national expenditure on medicines or the cost of ADRs to the nation is very small indeed.[10]

With the rapid spread of drug information across the globe, there is a recognized need for routine and rapid communication between National Centres and between national regulatory authorities. Many regulatory authorities in different regions of the world have developed close ties with each other to discuss safety data obtained on particular medicines and on the regulatory decisions being made in response to them.

Policies and regulatory guidelines are often discussed between National Centres. The International Conference for Drug Regulatory Authorities (ICDRA), the Annual Meetings of National Pharmacovigilance Centres Participating in the WHO Programme for International Drug Monitoring and other similar conferences facilitate such discussions.

The development of pharmacoepidemiology as a discipline would not have happened without the collaborative efforts of the pharmaceutical industry and academia. The infrastructure of databases, registries and published studies to support post-approval surveillance activities can largely be attributed to the needs of the pharmaceutical industry and drug authorities. Borrowed from the financial sector, the concepts of risk assessment and risk management were modified to reflect the needs of healthcare.

The pharmaceutical industry has prime responsibility for the safety of medicines. Manufacturers are uniquely placed for monitoring the safety of medicines, from the start of drug development and thereafter throughout the lifetime of the drug. Many companies have developed innovative and efficient monitoring systems that have contributed to the detection of new safety signals. The pharmaceutical industry has made many technological advances in drug developments that have improved the safety of new drugs.[11]

The number of staff in the pharmaceutical industry involved in pharmacovigilance is growing. This has been in response to the high regulatory standards that have been set at national and international levels and the increasing requirement for post-approval monitoring set by national drug regulatory authorities. Communication and exchange of information between the industry and regulatory authorities has improved as a result of the regional and international harmonization arrangements that have emerged in recent years. Continuing professional education, patient education, and sponsorship by industry of drug information activities have also contributed to safer use of medicines.

Hospitals and Academia

The efforts of clinical pharmacology and pharmacy departments around the world have resulted in the development of pharmacovigilance as a clinical discipline, A number of medical institutions have developed adverse reaction and medication error surveillance systems in their clinics, wards and emergency rooms. Case-control studies and other pharmacoepidemiological methods have increasingly been used to estimate the harm associated with medicines once they have been marketed.

The expansion of scientific knowledge in drug safety is attributable to greater awareness and academic interest in this field. Academic centres of pharmacology and pharmacy have played an important role through teaching, training, research, policy development, clinical research, ethics committees (institutional review boards) and the clinical services they provide.[12] In many medical institutions, particularly in the developed world, ADR monitoring is recognized as an essential quality assurance activity.

Greater integration of pharmacovigilance into clinical practice is still needed. Drug safety should feature in the medical and pharmacy curricula. Access to updated, unbiased and clinically relevant drug information is currently inadequate. Research and postgraduate training in the field remains neglected by many schools of health sciences. The growing alliance between the industry and academia and drug regulatory authorities has implications for pharmacovigilance. These are referred to in Chapters 4 and 5.

Health Professionals

The success or failure of any spontaneous reporting system depends on the active participation of reporters. Although limited schemes for reporting by patients have been initiated recently, health professionals have been the major providers of case reports of suspected ADRs throughout the history of pharmacovigilance.

Originally physicians were the only professionals invited to report as judging whether disease or medicine causes a certain symptom by exercising the skill of differential diagnosis. It was argued that accepting ADR reports from physicians only, would ensure high quality information and minimize the reporting of unrelated, random associations. Studies have shown, however, that different categories of health professionals will observe different kinds of drug related problems.[13, 14]
Only by inviting reports from all professionals involved in the care of patients will it be possible to detect the full spectrum of complications related to pharmaceutical treatment. If, for example, only general practitioners contribute to the pool of information, medicines used primarily by specialists will not be covered. To get a representative picture of the reality, all sectors of the healthcare system would need to be involved, such as public and private hospitals, general practitioners, nursing homes, retail dispensaries, and clinics for traditional medicine. Wherever medicines are being used there should be a readiness to observe and report unwanted and unexpected medical events.

Patients

Only a patient knows the actual benefit and harm of a medicine taken. Observations and reports made by a health professional will be an interpretation of a description originally provided by the patient, together with objective measurements. Some believe strongly that direct patient participation in the reporting of drug related problems will increase the efficiency of the pharmacovigilance system and compensate for some of the shortcomings of systems based on reports from health professionals only.[15]

Patients who suspect they have been affected by an ADR are normally recommended to report to their doctor to enable the doctor to report it to the pharmacovigilance centre. However, since only 5% of doctors are estimated to participate in any pharmacovigilance system, this process is not efficient in ensuring that the patient's concerns are being recorded. There are studies indicating that systems for recording patient concerns might identify new drug safety signals earlier than the professional reporting systems alone. [16]

Other Partners

The contribution of other partners in drug safety including the media, advocacy groups, and lawyers needs to be acknowledged. These partners in pharmacovigilance have directly or indirectly facilitated the development of new and robust drug policies and decisions, while highlighting deficiencies and weaknesses in existing drug safety policies. In many instances these groups or individuals have the capacity to voice, and often change, public opinion. Moreover, they often facilitate active public debate and discussion of issues, which have direct relevance to their health. In many countries, policy-makers engage pro-actively with these partners when important matters of public interest are being considered. Co-operation and open lines of communication with non-governmental agencies including the media and consumer advocacy groups is likely to facilitate the creation of policies and legislation on pharmacovigilance which will enjoy widespread public support and confidence.

Much needs to be done to improve the relationship between these and other partners in pharmacovigilance. Misrepresentation of data and sensationalism of drug safety concerns in the media and in courtrooms has given rise to unfounded rumours and misplaced concerns about the safety of potentially valuable medicines.

Situations where there has been divergence in perspective on specific issues of safety between these and other partners, have resulted in a devastating impact on public confidence in regulatory bodies and other organizations. It is important that all partners recognize the considerable responsibility inherent in conducting activities relating to pharmacovigilance and of communicating them effectively.

CHAPTER 4

PHARMACOVIGILANCE IN DRUG REGULATION

Sound drug regulatory arrangements provide the foundation for a national ethos of drug safety, and for public confidence in medicines. The issues with which drug regulatory authorities have to contend besides the approval of new medicines, include:

- clinical trials
- safety of complementary and traditional medicines, vaccines and biological medicines
- developing lines of communication between all parties with an interest in drug safety and ensuring that they are open and able to function efficiently, particularly at times of crisis.

Pharmacovigilance programmes need strong links with regulators to ensure that authorities are well briefed on safety issues in everyday practice that may be relevant to future regulatory action. Regulators understand that pharmacovigilance plays a specialized and pivotal role in ensuring ongoing safety of medicinal products. Pharmacovigilance programmes need to be adequately supported to achieve their objectives.

Introduction

A new medicine must pass three hurdles before its approval by the national drug regulatory authority. Sufficient evidence is required to show the new drug to be

- of good quality,
- effective, and
- safe for the purpose or purposes for which it is proposed.

Whereas the first two criteria must be met before any consideration can be given to approval, the issue of safety is less certain. Safety is not absolute, and it can be judged only in relation to efficacy, requiring judgement on the part of the regulators in deciding on acceptable limits of safety.

There is a possibility that rare yet serious adverse events (such as those occurring with a frequency of, say, one in five thousand) will not be detected in the pre-registration development of the drug. For example, fatal blood dyscrasia occurring in 1 in 5,000 patients treated with a new drug is only likely to be recognized after 15,000 patients have been treated and observed, provided that the background incidence of such a reaction is zero or a causal association with the drug is clear.[a]

Clinical trial regulation

In recent years there has been a substantial increase in the number of clinical trials in developed and developing countries. Clinical trials in the United States of America alone nearly doubled between 1990 and 1998.[17] With sequencing of the human genome, clinical research in potential new drug therapies is likely to increase even further.

[a] This arbitrary 'rule of three' is based on the experience that for any given adverse effect approximately three-fold the number of patients need to be treated and observed for the side effect to become manifest and reliably linked with the drug assuming a background incidence of zero of the effect being observed.

There is also a growing alliance between academia and the pharmaceutical and biotechnology industries. This has given rise to serious and widespread concern over ethical and scientific issues such as:[18-21]

- the potential for conflict of interest
- unethical patient recruitment practices
- inadequacy of informed consent
- lack of capacity to ensure on-going monitoring of clinical trials and adherence to principles of sound and ethical clinical practice
- poor reporting and management of adverse events.

For drug regulators, the changing trends over recent years in the conduct of clinical trials present special and urgent challenges, particularly in ensuring that the rights and health of patients and their communities are protected. In their approval of clinical trials, regulatory bodies look at safety and efficacy of new products under investigation. They must also pay attention to the general standards of care and safety of study subjects, in conjunction with the appropriate institutional review boards (IRBs).

Medicines that are required for diseases such as tuberculosis, malaria, HIV/AIDS and meningococcus A meningitis, and those which may have a questionable or uncertain effectiveness - safety profile, require careful surveillance when first introduced on a large scale into communities.[22]

The increasing complexity of clinical trials presents further challenges to regulators. [23] Study designs often require large cohorts of participants. In many instances trials are carried out at various sites in several countries. Local ethics committees and drug regulators are not always aware of patients' and investigators' experiences at other international sites. Clinical trials are increasingly contracted to clinical research organizations and patient recruitment agencies, which act as intermediaries between the sponsors of the study, the investigators and the patients.

Responsibility for ensuring proper conduct of the clinical trial may, in such circumstances, be divided between the parties. Information requested by ethics committees and regulators may be difficult to obtain in a short time. Regulators and ethics committees do not always have the capacity to carry out these functions effectively. This may have serious implications for the safety of patients.

Safety monitoring during clinical trials is now recognized as one of the major concerns for new drug development. This is currently being addressed by a CIOMS working group. Three main topics are being addressed:

1) the collection of adverse experience information
2) assessment/monitoring of clinical data
3) reporting/communication of clinical data.

A standardized reporting system for safety concerns arising during clinical trials might serve as a helpful tool for regulatory agencies, and for ethics committees (institutional review boards), provided there were full exchange of information between them and the investigators and sponsors. Expedited electronic submission of safety reports in ICH countries has facilitated the reporting process to some extent; however, routine review of safety information requires considerable resources, expertise, support and commitment from those involved.

Once research into new drugs is in the post-marketing stage (Phase IV studies) safety may be monitored to comply with the conditions of registration, particularly when there are unresolved concerns. This may lead to improved and more rapid changes in labelling or even withdrawal of a new drug from the market.[24] Routine application of principles of good clinical practice that ensure patient safety and strict compliance with prescribed regulatory requirements would substantially improve standards of clinical trials. [25]

Post-marketing safety monitoring

It is now generally accepted that part of the process of evaluating drug safety needs to happen in the post-marketing (approval) phase, if important innovations are not to be lost in an unduly restrictive regulatory net. Judgement as to whether and how this might happen lies with the regulators.

The stronger the national system of pharmacovigilance and ADR reporting, the more likely it is that reasonable regulatory decisions will be made for the early release of new drugs with the promise of therapeutic advances. Legislation governing the regulatory process in most countries allows for conditions to be placed on approvals, such as a requirement that there should be detailed pharmacovigilance in the early years after a drug's release.

Careful safety monitoring is not confined, however, to new drugs or to significant therapeutic advances. It has an important role to play in the introduction of generic medicines, and in review of the safety profile of older medicines already available, where new safety issues may have arisen. In a developing country, these latter considerations are likely to be more important than the benefits a novel therapeutic entity might bring to an already pressed health service.

While spontaneous reporting remains a cornerstone of pharmacovigilance in the regulatory environment, and is indispensable for signal detection, the need for more active surveillance has also become increasingly clear. Without information on utilization and on the extent of consumption, spontaneous reports do not make it possible to determine the frequency of an ADR attributable to a product, or its safety in relation to a comparator.[26] More systematic and robust epidemiological methods that take into account the limitations of spontaneous reporting are required to address these important safety questions. They need to be incorporated into post-marketing surveillance programmes.

There are other aspects of drug safety that have been rather neglected until now, which should be included in monitoring latent and long-term effects of medicines.
These include:

- detection of drug interactions
- measuring the environmental burden of medicines used in large populations
- assessing the contribution of 'inactive' ingredients (excipients) to the safety profile
- systems for comparing safety profiles of similar medicines
- surveillance of the adverse effects on human health of drug residues in animals, e.g. antibiotics and hormones.

A more difficult question is whether pharmacovigilance has resulted in inappropriate removal from the market of potentially useful medicines as a result of misplaced fears or false signals.

The CIOMS report [27] on benefit-risk assessment of medicines after marketing has contributed to a more systematic approach to determining the merit of available medicines. Systematic medical and prescription record linkage, with drug utilization studies, would contribute to greater accuracy. This is a responsibility that falls outside the strict traditional terms of reference of national pharmacovigilance centres.

Promotional activities

The safety of medicines in the development stage is increasingly affected by the constraints placed by sponsors on the study plan, laboratory programme and the open sharing of information as the research agenda is negotiated with clinical collaborators.[28] There is growing public concerns that close collaboration between academia and the pharmaceutical industry may adversely affect medical practice and clinical research.[17, 29 & 30]

A worrying development for drug safety is 'direct to consumer' advertizing by pharmaceutical manufacturers, other sellers of medicines and parties with a vested interest. Spending on this activity has doubled in the USA over the past four years.[19] While it may improve patients' understanding and is in keeping with the need to improve access to drug information, lack of reliability and accuracy may compromise patient care and safety.

Even where direct advertizing of prescription medicines to consumers is illegal, the Internet provides a medium that makes communication possible across borders. This may make national regulations about advertizing ineffective. Websites now make it possible to buy and sell prescription drugs such as benzodiazepines without controls. These developments in communication all have an impact on the safety of medicine.[31]

All these issues suggest the need for more thorough monitoring of drug safety and scrutiny of advertizing. Resources and expertise are necessary to ensure that promotional materials contain accurate and balanced information, and that practices are ethical. Self-regulation by industry is unlikely to be sufficient in many countries. Regional or international collaboration in the implementation of a regulatory code of practice for advertizing medicinal products, overseen by an impartial advisory body, would help in this regard.[32] Misrepresentation and lack of full disclosure may have equally important and potentially serious safety implications. Certain international medical journals have developed a uniform policy that reserves the right to refuse to publish drug company-sponsored studies unless the researchers are guaranteed scientific independence. A joint editorial, which outlines the rationale for this policy, states that this action is a response to the industry's increasingly tight control over research, results and, in many cases, whether and how results are made public.[33] More collaboration with journalists and the media needs to be fostered to ensure the objectivity and reliability of published medical information.

International harmonization of drug regulatory requirements

Harmonization of various elements of drug regulatory activities has been undertaken in the last decade by various intergovernmental organizations at regional and inter-regional levels. The driving force of these efforts was the increase of global trade in pharmaceutical products and the growth in complexity of technical regulations related to drug safety and quality.

Harmonization activities related to drug regulation are being pursued in all WHO regions. The ICH initiative, which started in 1990, is an inter-regional venture covering seventeen

high-income countries. The guidelines produced by these groups of specialists drawn from the regulatory authorities and pharmaceutical companies of ICH members represent the latest thinking and are having an impact on all countries. [34, 35]

WHO has observer status in all ICH activities. Discussions are in progress to consider the implications of the ICH process and globalization of its guidelines. This includes describing the benefits of the process and explaining concerns about extending its influence to non-ICH countries. If ICH moves into the field of pharmacovigilance, the group should be encouraged to capitalize on the work already carried out by WHO in this area. All ICH countries should be encouraged to participate more actively in the WHO Programme for International Drug Monitoring.

Promoting communication in the field of drug safety

Society has a great concern about coping with the dangers of modern life. Medicinal products are among the technological advances that have provided society with great benefits and added risks. Knowledge of the public perception of these risks is essential if they are to be managed effectively. How safe is safe enough? Which risks are acceptable? These are two critical questions that providers of medicines need to consider when communicating with patients and the public. Recognizing that there is variance between expert views of risk and public perception, there is a need to analyse and understand the differences much more thoroughly. It is not sufficient for the experts to be satisfied with the evidence for safety. The pharmaceutical industry, governments and healthcare providers must build public trust through effective risk communications. This can be achieved only once the public mindset is examined and understood.[36, 37]

Some regulatory authorities are increasing the transparency with which they conduct their affairs. However, many authorities continue to be constrained by real or notional secrecy provisions, intended to protect the intellectual property rights of pharmaceutical manufacturers. The problem with secrecy is that it creates an environment of distrust and misunderstanding.

It is now expected of regulators that they should deal with drug regulation, including drug safety issues, with a new commitment to openness, including patients and their representatives in the process. In this regard, considerable progress has been made in many countries, notably in the regulation of drugs for HIV/AIDS and cancer.

There has been a tendency for drug safety issues to be dealt with in a way that protects the interests of pharmaceutical manufacturers in the first instance.[5] National pharmacovigilance centres, provided they have the necessary expertise and resources, are especially well placed to collect, evaluate and make recommendations on drug safety, free of other constraining influences. It should be possible to protect patient confidentiality by applying careful standard operating procedures.

The greatest challenge for National Centres, as it is for drug regulatory authorities, is to promote and maintain effective and open communication of information regarding the benefit, harm, effectiveness and risk of medicines, including the uncertainty of knowledge in this area, with the public and the health professions. The 1998 Erice Declaration on Communicating Drug Safety Information called for a united effort on the part of all interested parties in

establishing a new culture of transparency, equity and accountability in the communication of drug safety information. Much has already been accomplished internationally in achieving this. Since Erice, many regulatory authorities have extended their communication activities, developed websites and newsletters, and have actively engaged with the media to provide the public with updated safety information.

The principles of good communication, and the extent to which they may have been achieved and are achievable, are considered in Chapter 5.

Risk and crisis management

The importance of an efficient system for dealing with drug safety risks and crises has become increasingly evident in recent years. Drug safety issues tend rapidly to take on international significance. The speed with which information spreads in the modern world means that drug safety concerns are no longer confined to individual countries. Often the media and general public are informed at the same time as, or even before, the national regulatory authority. When crises arise, whether they are real or perceived, local safety issues or concerns arising abroad, regulatory authorities are expected to meet them openly, efficiently, thoroughly and rapidly.

Many national authorities have identified the need for developing an organizational plan for managing risks and for communication and action during crises.[38] Regulators themselves often react under duress in a drug safety crisis within a legislative or administrative framework that is inadequate or excessively restrictive. There should be clear yet flexible operating procedures so that their response is not delayed, unnecessarily complicated, or unduly cautious (undue caution may result in removal of a product from the market even when there may be no justification and a more thoughtful and less drastic response would be appropriate). In such circumstances, the greater the disparity in safety information between the pre-registration evaluation and the real situation in practice, the greater is the likelihood that the regulatory response will be inappropriate. When crises arise, the regulatory authority has powers to suspend registration, impose special conditions, or severely restrict use to certain patients or prescribers. The authority may require manufacturers to change the product information in a specified manner. These decisions are normally communicated by drug alerts, general letters to doctors and pharmacists, press statements, through websites, newsletters and journal publications, depending on the type and urgency of the message and those who are being addressed.

Pharmacovigilance and the national drug regulatory authority

The limitations of pre-marketing drug safety data are well-recognized.[39] They are aggravated by increasing pressure on drug regulators from the pharmaceutical industry to shorten the review time for new medicines. Registration approval of a new drug is likely to be followed by robust marketing and rapid exposures of thousands even millions of patients to it.[40] The implications for drug safety of this evolving situation need to be addressed.

Pharmacovigilance has become an essential component of drug regulation.[41] For the foreseeable future in developing countries, this is likely to take the conventional form of spontaneous monitoring, even though it is a far from perfect system. Many developing countries do not have rudimentary systems in place for the purpose, and even where pharmacovigilance systems do exist, active support and participation among health

professionals, regulators and administrators is likely to be lacking. Underreporting of ADRs by healthcare professionals remains a major problem in all countries.
Within the national drug regulatory authority post-marketing surveillance is normally understood to serve a distinct function, separate from the process of evaluation and approval of new medicines. Post-marketing surveillance draws on its own special sources of information, infrastructure and expertise, although there is good reason for these systems and resources to be shared with other disciplines.

For example, it is necessary that in the proper conduct of pharmacovigilance there should be access to the information on which the original determination of risk and harm was made. Pre-registration files, including the advice and opinions of the original evaluators of the data, are required if a balanced and clinically relevant decision is to be made. Beyond response to events and media reporting, active enquiry and detailed clinical investigation are the essential tools of this work.

In many countries pharmacovigilance and drug regulatory approvals are linked by an ADR advisory committee appointed by, and directly reporting to, the national regulatory authority.[42, 43] The committee consists, amongst others, of independent experts in clinical medicine, epidemiology, paediatrics, toxicology and clinical pharmacology. Such an arrangement inspires confidence amongst health personnel and it can be expected to make a substantial contribution to public health.

Herbal and Traditional Medicines

The use of herbal and traditional medicines raises concerns in relation to their safety.[44, 45] There is wide misconception that 'natural' means 'safe'. There is the common belief that long use of a medicine, based on tradition, assures both its efficacy and safety. There are examples of traditional and herbal medicines being adulterated or contaminated with allopathic medicines, chemicals such as corticosteroids, non-steroidal anti-inflammatory agents and heavy metals. Many traditional medicines are manufactured for global use and they have moved beyond the traditional and cultural framework for which they were originally intended. Self-medication further aggravates the risk to patients. When traditional and herbal medicines are used in conjunction with other medicines there is the potential of serious adverse drug interactions.

As with other products intended for human use (medicines, dietary supplements and foods), herbal medicines should be incorporated within a regulatory framework. These products should be governed by standards of safety, quality and efficacy that are equivalent to those required for other pharmaceutical products. Difficulties in achieving this arise from the growth of an ambiguous zone between foods and medicines, into which an increasing number of herbal products fall. The regulatory status of herbal products differs significantly from country to country. Currently less than 70 countries regulate herbal medicines and few countries have systems in place for the regulation of traditional health practitioners.

These disparities in regulation between countries have serious implications for international access to and distribution of such products. For instance, in one country a herbal product may be obtainable only on prescription and from an authorized pharmacy, whereas in another country, it may be obtainable from a health food shop, or even, as has become common practice, by mail order or Internet.

For all these reasons, inclusion of herbal and traditional medicines in national pharmacovigilance programmes has become important and inevitable. Healthcare providers, including traditional health practitioners, regulators, manufacturers and the public share a responsibility for their informed and safe use. The World Health Organization has produced guidelines for assessment of the safety, efficacy and quality of herbal medicines.[46]

New systematic approaches for monitoring the safety of plant-derived medicinal products are being developed.[47] A number of national pharmacovigilance centres are now monitoring the safety of traditional medicines. For that to succeed, the collaboration and support of consumers, traditional health practitioners, providers of traditional and herbal medicines and other experts is necessary. More attention needs to be given to research and to training of healthcare providers and consumers in this area.

Vaccines and biological medicines

For several reasons, vaccines and biologicals require modified systems of safety monitoring. They are often administered to healthy children. This applies particularly to vaccines used within a national immunization programme. In many countries, those exposed to a particular vaccine represent the entire birth cohort and therefore a sizeable part of the entire population. People's expectations of safety are high, and they are reluctant to countenance even a small risk of adverse events. Concerns regarding vaccine safety, real or imagined, may result in loss of confidence in entire vaccine programmes. This can result in poor compliance and a consequent resurgence in morbidity and mortality of vaccine-preventable disease.

It is essential that there should be adequate safety surveillance supporting immunization programmes. The skills and infrastructure to deal with genuine adverse events are essential in preventing or managing misplaced fear caused by false or unproven signals from patients and health workers that might adversely affect immunization cover. For example, concerns about the safety of whole-cell Pertussis resulted in dramatic reductions in vaccines coverage and a resurgence of Pertussis in many countries.[48]

The difficulties in monitoring and dealing with vaccine safety are complicated by the problems inherent in determining the causal link between an adverse event following immunization and a vaccine.[49, 50] For example, information on dechallenge and rechallenge is often missing, and vaccines are given to most of the country's birth cohort at an age when coincidental disease is likely. Several vaccines are likely to be administered concurrently. The possibility of programmatic errors[b] should never be overlooked.

However, the responsibility of the regulatory authority is by no means limited to the safety of vaccines used in immunization programmes. Several biological products are used in specific patient populations as preventive or curative measures. The efficient regulation of these products is crucial in order to avoid potential harm to the public as a result of substandard manufacture or improper transportation and storage of imported vaccines and biologicals.

[b] A programmatic error is a medical incident that was caused by some error in the transportation, storage, handling or administration of vaccines.

In recent years, the safety of biological products and blood products has come under public scrutiny.[51] Concerns about the safety of medicinal products of animal origin have been raised in connection with variant Creutzfeldt-Jacob disease (vCJD), and with contamination of blood and blood products by infectious organisms such as HIV and hepatitis B.[52] The quality of screening and sterilization procedures and appropriate selection of donors are linked to the risks of contamination. Such safety issues related to the use of plasma-derived medicinal products should fall under the aegis of pharmacovigilance programmes. For that to happen, pharmacovigilance centres would have to consider the special issues related to safety of these products. Expertise in biological products, virology and medical microbiology would be required.

New vaccines for pandemic diseases such as HIV/AIDS and malaria are in the later phases of development. Clinical trials in large patient populations are being considered for testing the efficacy and safety of these vaccines. Special ethical, legal and regulatory challenges are raised in the conduct of such clinical trials, especially the implications vaccines may have for the epidemiology of disease and the possible direct and indirect risks of harm associated with the introduction of vaccines into large communities.

Other products likely to be regulated by the drug regulatory authority include veterinary medicines, biotechnology products, and genetically derived or genetically modified medicinal products. These products are all likely to pose unusual challenges in safety monitoring. They will require special and possibly various types of expertise to assess safety concerns arising from their use. Such expertise may not be available within the regulatory authority. Collaboration and consultation with appropriate experts within the country or in other countries may be necessary.

CHAPTER 5

PHARMACOVIGILANCE IN CLINICAL PRACTICE

> Safety monitoring of medicines in common use should be an integral part of clinical practice. The degree to which clinicians are informed about the principles of pharmacovigilance, and practise according to them, has a large impact on health care quality. Education and training of health professionals in drug safety, exchange of information between national centres, the co-ordination of such exchange, and linking clinical experience of drug safety with research and health policy, all serve to enhance effective patient care. National programmes for pharmacovigilance are perfectly placed for identifying research necessary for better understanding and treatment of drug-induced diseases.

Introduction

Drug safety monitoring is an essential element for the effective use of medicines and for high quality medical care. It has the potential to inspire confidence and trust among patients and health professionals in medicines and contributes to raising standards of medical practice. Pharmacovigilance is a clinical discipline in its own right – one that contributes to an ethos of safety and serves as an indicator of the standards of clinical care practised within a country. Healthcare practitioners are in a position to make good use of their patients' positive and negative experiences of treatment to contribute to medical science and to an improved understanding of disease and of the medicines.

There are three approaches that might serve to increase awareness and interest in drug safety among clinicians, and to address research issues. These are described in the following sections.

Education, training and access to reliable information

Adverse reactions tend to be viewed, incorrectly, as 'side effects' and thus as distractions from patients' and doctors' priorities. Learning about the scope and severity of ADRs should start early in professional training. Good safety monitoring encourages healthcare practitioners to take fuller responsibility for the medicines they use. It improves clinical effectiveness and increases the confidence with which they and their patients use medicines.

To achieve something nearer ideal practice more attention needs to be given to training health professionals in diagnosis, management and prevention of ADRs. Not all signals are as specific and dramatic, and readily diagnosed, as were the phocomelia and micromelia caused by thalidomide. Recognition of less obvious adverse effects requires clinical alertness, accurate diagnosis and an understanding of the principles of causality assessment.[53]

Health professionals are more likely to identify and report important ADRs if they have confidence in their ability to diagnose, manage and prevent such reactions. National pharmacovigilance centres and training institutions play a central role in this by encouraging inclusion of the principles and methods of pharmacovigilance and the study of iatrogenic disease at undergraduate and postgraduate levels in schools of medicine, pharmacy and nursing.

Pharmacology curricula should give a higher priority to the study of the safety of medicines. This would lead to an enhanced awareness of the balance between the benefits and harms of medicines. An integrated approach to therapeutic decision-making might be encouraged. Excessive and irrational drug use contributes to adverse reactions.[54, 55] The misuse of medicines is largely caused by the poor quality and inaccessibility of drug information available to practitioners. These problems are worsened by:

- aggressive and inaccurate marketing and advertizing
- uninformed patient use and their demands for the latest medicines
- lack of accurate drug information.

Indicators of inappropriate drug use can be obtained from spontaneous reports of ADRs. Case examples may serve as useful teaching tools for improving the safe use of medicines. In some countries an overwhelming volume of information (as opposed to effective communication of critical information) can serve as a deterrent to rational use.

Medication errors and ADRs are well documented in hospitalized and non-hospitalized patients, and they contribute substantially to morbidity and mortality.[56, 59] They also contribute to the number of hospital admissions and are known to occur in the community setting. Many are predictable and preventable.[60]

This suggests considerable opportunity for minimizing the risks of ADRs through rational use, monitoring and follow-up. Early detection is important, particularly in hospitals where systems for detecting ADRs and medication errors will save lives and money. Such systems might be linked to institutional, regional or national pharmacy and therapeutics committees so that information can be used to educate professional staff in safe drug use.[61, 62]

Prospective hospital-based surveillance reduces the risk and severity of ADRs.[63] There is, furthermore, a need to provide health professionals with the skills required to evaluate drug information critically and to decide how the safety profile of a drug (e.g. developed from population data) might be applied to a particular patient. Often, the manufacturer's product information and promotional materials are the only information available to the practitioner. Evidence-based and comprehensive sources may not be available. Availability of balanced and reliable drug information is likely to improve standards of use and to reduce the frequency of adverse reactions. Information that includes patients' subjective experiences of adverse reactions would be most useful to patients and to prescribers of medicines. Product safety information, the way it is currently presented, often consists of lists of adverse reactions, perhaps rated in order of frequency, without real description of how these might affect quality of life. Moreover, prescribers should be free to practise without being subjected to the vested interest of manufacturers and any conflict in interest.

There are also other opportunities for integrating pharmacovigilance into clinical practice through training and education. Participation of National Centre staff in continuing education programmes, conferences, scientific publications and e-mail discussion groups all contribute. The National Centre might serve as a teaching base, and as a training centre for medical and pharmacy interns, post-graduate students, pharmacology registrars (residents) and drug information staff. Research in ADRs and pharmacoepidemiology in departments of internal medicine and pharmacology should be encouraged and promoted.

In the training of health professionals [64] it is important to develop competence in evaluating and communicating information about benefit, harm, effectiveness and risk to the patient. Difficulties in communication between patients and healthcare providers represent an important and preventable potential source of harm. The following elements are likely to reduce significantly the risks of adverse effects and their severity:

- an adequate drug history of the patient
- rational prescribing and dispensing
- proper counselling
- the provision of clear and understandable drug information.

Communication with health professionals

A further strategy for integrating pharmacovigilance into clinical practice is the creation of open lines of communication and broader collaboration between health professionals and National Centres. For this to happen, National or regional centres need to be situated so that two-way communication between health practitioners and professional staff of the centre is easy. Drug information and poison centres are ideal locations for this purpose, since many poisoning reports and drug information queries are in fact ADRs.[65] The staff of these centres are in an ideal position to support the work of pharmacovigilance.

Pharmacovigilance centres should provide ready access to clinical expertise and sharing of resources, including databases. Communication materials developed by drug information and poison centers, including newsletters and other publications, can be utilized for disseminating drug alerts and other drug safety information to the professions.

Academic departments and university hospitals have proved effective places for national and regional pharmacovigilance centres for a number of reasons. These include the following:

(i) Pharmacovigilance can readily be linked with experimental and clinical pharmacology, and epidemiology in that environment

(ii) The location makes peer review of adverse reaction reports easier and more efficient, and it provides ready access to hospital specialists in university departments. From such a base, an advisory panel for the National Centre with scientific and medical experts can be created

(iii) The information obtained from spontaneous reports can be incorporated into undergraduate and postgraduate teaching in the health sciences

(iv) Health professionals are likely to feel confident in reporting problems and therapeutic dilemmas to an academic unit with which they are familiar and that they know will consider their reports thoroughly and expertly

(v) Effective medical education strategies such as academic detailing[66], feedback on individual cases, reminders and soliciting the support of acknowledged experts are most readily achievable under these circumstances.[67]

Clinicians making reports expect ready access to the centre and to specialized advice and feedback. They should be encouraged to publish unusual or interesting case reports without delaying submission of such reports to the National Centre. Newsletters, publications and responses by letter or telephone encourage dialogue with clinicians. Collaboration with professional accreditation bodies and associations, academic institutions, continuing education organizations, third party funders (e.g. managed care institutions, medical insurance companies) and other non-governmental organizations adds to the scope and quality of the work of the National Centre.

Linking clinical findings with research and policy

Careful study of adverse drug events may identify diagnostic features, syndromes or pathogenic mechanisms. Moreover, clinical, pathological and epidemiological information relating to adverse reactions is necessary for a full understanding of the nature of an adverse reaction and for identifying patients at risk.

Although spontaneous reporting is the mainstay of passive surveillance, the information obtained is inherently limited and likely to be insufficient for regulatory and clinical decisions. Active or intensive surveillance programmes [68] for addressing serious safety concerns have had success in identifying and quantifying drug safety issues, using:

- case control networks
- hospital-based intensive monitoring systems
- record linkage systems
- epidemiological studies.

Information received from pharmacovigilance centres should feed directly into drug policy and drug utilization practice. Safety information from National Centres has a bearing on essential drugs programmes, standard treatment guidelines, and national and institutional formularies.

Measuring the impact of such information on drug utilization and on the quality of patient care has considerable research potential. It is necessary that drug regulatory decisions should be based on safety information that reflects national as well as international experience, and that this has been thoroughly and expertly reviewed. Drug utilization patterns also need to be taken into account.[53]

ADRs have the potential to provide insights into structure-activity relationships, pharmacokinetic, pharmacodynamic and genetic factors affecting the action of medicines. They may provide leads for other novel, indications. This is why it is important for the negative connotation of an ADR to be removed and for systems to be developed that enable medical, pharmaceutical and chemical information to be applied constructively to a better understanding of how drugs work.[69]

CHAPTER 6

PHARMACOVIGILANCE AND INTERNATIONAL HEALTH

Pharmacovigilance is an activity that has international significance. The current global network of pharmacovigilance centres, co-ordinated by the Uppsala Monitoring Centre, would be strengthened by an independent system of review. This would consider contentious and important drug safety issues that have the potential to affect public health adversely beyond national boundaries.

The Erice Declaration provides a framework of values and practice for collection, analysis and subsequent communication of drug safety issues. In providing for this, it asserts scientific and clinical issues on the one hand and the right of the public to be openly and fully informed on the other. It is a process that requires the active commitment of all involved – regulators, policy makers, health personnel, journalists, and (not least) pharmaceutical manufacturers. Scrupulous attention is required in the practice of pharmacovigilance to the issues of patient confidentiality.

Introduction

Until recently, pharmacovigilance has been confined mainly to detection of adverse drug events that were previously either unknown or poorly understood. Its particular purpose was to contribute to a scientific understanding of the safety profile of a rather small number of drugs and to advise national regulatory authorities. In this document it is proposed that pharmacovigilance has the potential to move beyond its previously rather confined limits, and to serve a higher priority within public health. How that might happen is the subject of this chapter.

The burden of ADRs on public health

Despite the progress in pharmacovigilance that has been made, the burden on public health of ADRs remains significant.[60] Pharmacoeconomic studies on the costs of adverse reactions suggest that governments pay considerable amounts from health budgets towards covering costs associated with them.[70] In most countries the extent of this expenditure has not been measured.

The relationship between drug utilization patterns and the frequency of ADRs is poorly understood. However, it has become increasingly clear that the safety profile of medicines is directly linked with socio-political, economic and cultural factors that in turn affect access to medicines, their utilization patterns and public perceptions of them.[71, 72]

Drug utilization

Drug utilization patterns are a major determinant in drug safety. For instance, the use of injectable medicines is more common in developing countries.[73] The parenteral route is likely to be associated with a high risk of adverse effects when injections are administered by inadequately sterilized equipment or poorly trained personnel. It is estimated that unsafe injection practice may lead to 780,000 to 1.56 million cases of hepatitis B, 250,000 to 500,000 cases of hepatitis C and 50,000 to 100,000 cases of HIV, annually in Africa.[74]

Self-medication and the lack of regulatory control measures over the sale of drugs further increase the risk of adverse reactions. The number of drugs in each prescription is highest in developing countries.[73] Factors such as illiteracy, concomitant use of traditional medicines, and the continued availability of impure and irrational pharmaceutical preparations contribute further to the risk.

Sound drug legislation, policy and an essential drugs programme that includes education of health professionals and patients in rational use of medicines are measures that should ensure better health care in all countries. Pharmacovigilance programmes could learn from the social mobilization practices that have been introduced in programmes for injection safety during immunization.[74] Social mobilization includes the three-pronged approach of:

- increasing public awareness,
- ensuring advocacy for decision-makers, and
- sensitization of health workers.

This encourages a consumer-based demand for safe medicines from a public that is informed about the safety profile of the medicines they use. The incorporation of pharmacovigilance into these activities should ensure that such measures are relevant locally, and that they promote public confidence in the process.

A partnership with patients

The ready availability of safer and more effective medicines of good quality inspires confidence and trust among patients. Pharmacovigilance is an essential part of the public programmes that underpin the reliable availability of sound medicines and it needs to be understood, supported and promoted at the highest levels.

For this to be achieved it is necessary for information about drug safety programmes to be easily available to the public so that the central role of the patient in the rational and safe use of medicines is understood. The public has in recent years increasingly influenced health professionals' prescribing and patterns of drug use. This influence and greater awareness on the part of the public is attributable in part to the role of the media and Internet. High expectations of all service providers and medical institutions have developed.

Available information is not always reliable or scientifically valid. Direct advertizing to the consumer of prescription medicines has become commonplace in many countries. With this information patients feel more able to make their own therapeutic decisions, without assistance from doctor or pharmacist. The result has been increasing self-medication, licit and illicit sale of medicines over the Internet, and over-prescribing by doctors on patients' demand. This has had considerable effect on increased prescribing.[75, 76]

If variations in the way medicines are used alter their safety profile, then there is a need for research to be conducted into how the process works. It also needs to be determined how access to drug information might influence patient safety, including patients' perception of safety and the level of harm they are prepared to accept for different medicines. The social and cultural aspects of pharmaceutical use and the expectations and concerns of patients need to be further studied. The outcome of such research should make possible a better formulation of policies with a view to reducing patient risk.[77]

Public health programmes and responsible media coverage aimed at increasing access to drug information have made it possible for patients in many countries to take greater responsibility for their own health and for the decisions they make, and in the wider involvement of patients in decisions. This is reflected, in the creation of patient charters and patients' bills of rights,[75] and in the work of patient advocacy groups. For example, patients with HIV/AIDS have been instrumental in creating international awareness of the impact of the disease and in improving access to therapies and communication of the associated risks. It is a welcome development in some places that patients' concerns are now recognized as having a legitimate part to play at the heart of the decision-making process.

Such public health programmes, however, need not focus only on patients but could be used for the benefit of the general public as well. Such awareness-building and educational initiatives should also include children and elderly populations and could be greatly facilitated through partnerships with the media, educational institutions, other governmental and non-governmental organizations.

The Erice Declaration

The Erice Declaration (1997) represented significant progress in the light of these changes.[5] The Declaration challenges all the players:

- public health administration
- health professionals
- the pharmaceutical industry
- government
- drug regulators
- the media
- consumers

to strive towards the highest ethical, professional and scientific standards in protecting and promoting safe use of medicines. The Declaration urges governments and others involved in determining policies relating to the benefit, harm, effectiveness and risk of medicines to account for what they communicate to the public and patients. It calls for honesty when communicating drug safety information, even when such information may be incomplete and investigations still underway. It further asks that patients be openly informed of the facts, assumptions and uncertainties of the safety profiles of the medicines they use.

Some efforts have been made subsequently to achieve the goals formulated at Erice. Many regulatory agencies have websites to keep the public informed of their regulatory decisions and of drug safety concerns. In the Philippines and Australia videos and television programmes on ADRs are used to encourage reporting. Newsletters, bulletins and electronic distribution lists are increasingly used to communicate safety information globally. The WHO has made considerable efforts to train drug regulators and national immunization staff in communicating information to the media on adverse effects following immunization.[c]

[c] Details on the training in vaccines safety can be viewed at the following website:
http://www.who.int/vaccines-access/Vaccines/Vaccine_Quality/GTN/aefi.htm

There are, however, several challenges facing pharmacovigilance programmes in achieving the aspirations of the Erice Declaration. These include the following:

(i) The difficulties and risks in communicating conflicting or contentious messages to the public. For instance, during the course of immunization programmes, communication of new safety concerns associated with the vaccine(s), or with programmatic errors, may result in a dramatic fall in coverage. Nonetheless, an approach of secrecy in such circumstances is likely to erode public trust and confidence, and it fails to respect the rights of the public to participate in decision-making. Not only do facts and figures need to be shared with the public, but also the process by which the data is assessed and how decisions are made should be shared openly.

(ii) Communication between national drug regulatory authorities and national pharmacovigilance centres needs to be improved so that regulatory decisions with possible international implications are rapidly communicated to regulators, to avoid widespread public concern or panic.

The pharmaceutical industry shares responsibility for sound communication with the public and health professionals for drug safety issues. This would be helped if manufacturers were routinely to communicate new safety information to regulators and pharmacovigilance centres in all countries where the drug concerned is marketed.

Regulators and manufacturers should have mutually agreed procedures for managing a crisis and for dealing with any new safety information. Manufacturer and regulator need to have an established common view and be in agreement as to what they regard as a new safety concern and what constitutes a crisis, so that problems of miscommunication and lack of trust are minimized when crises do arise.

A critical link in the chain of drug safety crisis management is the knowledge, competence and approach of journalists. They depend, for balanced reporting, on an understanding of how drugs work, of benefit, harm, effectiveness and risk, and on being able to distinguish between relative and absolute risk. That requires astute and thoughtful briefing from the responsible reporting official in the ministry of health or drug regulatory authority, and ability and understanding on the part of health reporters. A platform that encourages debate and discussion between regulators, manufacturers, consumers and the media would do much towards achieving these objectives. This applies as much to investigations in progress as it does to the conclusions that are reached.

The real cost, time, skills and human resources necessary to communicate drug safety issues pro-actively to the media, the public and health professionals need to be carefully considered. Such planning and resources need to be given a higher priority than in the past. Local issues such as culture, literacy and the socio-economic status of the population at risk may have bearing on the way the message is presented. Communication of information must ensure that participants' rights to confidentiality are protected.

The costs to society of drug-related problems

When considering the cost of disease to society, ADRs and what is spent on detecting, preventing and managing them need to be included in the analysis. As pharmaceuticals become an increasingly prominent item in health budgets, and reliance is increasingly

placed on physicians for controlling costs and curtailing their prescribing practices, pharmacovigilance has growing importance in addressing health costs. The management of HIV/AIDS in developing countries is illustrative of these issues. Within the debate over drug prices and intellectual property rights there are in addition important concerns regarding widespread use of potentially toxic medicines in developing countries with poor resources. Antiretroviral treatment regimens commonly involve two or three potentially toxic agents. Monitoring safety and efficacy in this situation involves regular laboratory testing of liver function, haematology, viral resistance by CD4 cell count and viral load. Furthermore, treatment of the serious and not uncommon adverse effects of such treatment, which include dermatological, hepatic, haematological, metabolic and neurological disturbances, adds even further to the health budget.

Pharmacovigilance activities are expanding around the world. This is reflected in the increasing number of national pharmacovigilance centres that have been established in recent years. There are still many countries where no formal systems for pharmacovigilance are in place. To ensure that the existing centres are effective, their impact on public health and health costs should be measurable and the benefits demonstrable. Only then will widespread support and long-term sustainability of pharmacovigilance centres be assured.

Encouraging product stewardship

Product stewardship may be defined as:

- the demonstrable process by which a business can identify and manage its safety, health and environmental performance as applied to the development, manufacture, marketing, use and disposal of its products (including packaging).[d]

The principle requires pharmaceutical manufacturers to assume responsibility for the impact of their activities 'from cradle to grave', including consideration of the key influences in regulatory, customer and community contexts. The main underlying concern of the manufacturers is product liability, driven by legislation that requires products to have a safety profile which meets statutory requirements and public expectations. It is aimed at encouraging manufacturers to aspire to a new level of responsibility for the integrity of their products.

Responsibility for their products extends to all manufacturers (including those who produce generic medicines) and suppliers of raw materials. More broadly, the idea of stewardship is applicable to all industries. The principles of stewardship in the pharmaceutical industry include:

- compliance with policies and legislation that would assure patients' and public confidence in their medicines
- research that is scientifically sound, ethical and safe for trial participants
- determining the impact of the manufacturing process on the safety of a medicine, for the patient and the environment (this includes adhering to principles of conservation and protection of the environment, and to recycling of resources)
- training and education of personnel and of patients in the optimum use of pharmaceutical products

[d] Modified from: Gibson B, Product Stewardship in the Chemical Industry. ATSE Focus 1997 (98): http://www.atse.org.au/publications/focus/ focus-gibson.htm.

- storage and transport of medicinal products in a way that ensures quality at the time they are used by patients
- safe disposal of waste, raw materials, and of the end-products and their packaging (for example, injections, chemotherapeutic agents)
- rational and appropriate use of medicines by patients and by health professionals, requiring sound drug information, good product information (package insert/data sheet), including information on benefit, harm, effectiveness and risk, and how the total package of information can be communicated most effectively
- ensuring that sales and marketing observe the highest ethical standards that will instil public trust and confidence.

Adoption of the idea of stewardship would have important implications for the activities of pharmaceutical manufacturers. Many have already partly adopted the principles, but much remains to be done before the industry can be said to subscribe to these standards and comply fully with them. The standards cannot be achieved by industry alone. Sound legislation, a competent national drug regulatory authority, and informed prescribers and consumers are necessary for stewardship to succeed.

Protecting patient confidentiality

When patients are prescribed medicines for prevention or cure of disease they have a right, of which they should be informed, to decide whether or not to accept what is offered. They are also entitled to confidentiality. Physicians have a duty to protect that right and to use information from treatment only in relation to that patient's care, unless they are expressly allowed otherwise by prior informed consent.

These rights and duties are not absolute. In some instances, the needs of public health may override those of the individual patient for protection of confidentiality. Public health requirements such as mandatory notification of certain diseases may justify disclosure of patient information. But even when such disclosure is required in terms of public health need, it remains the responsibility of the health worker to protect patient confidentiality as far as possible.

In most countries, the law does not require that ADRs should be reported, and National Centres in those circumstances do not have the legal protection afforded where there are mandatory reporting systems. It is essential that healthcare personnel should obtain the consent of the patient when identity is disclosed on an ADR form or in a drug surveillance study.

It is ultimately in the patient's interest that healthcare personnel should have access to good information from other patients who have been exposed to the drug. Only by encouraging reporting can regulatory agencies and manufacturers take responsibility for the safety, efficacy and quality of the drugs they have approved or marketed for public consumption.

National Centres have to maintain high standards of data protection when information has been received on patients who have not given their informed consent. Patients should also be helped to understand that the information they provide is likely to contribute to an international understanding of drug safety.[78]

International response to drug safety issues

Certain safety issues are likely to have a global impact with possibly serious consequences for public health. When this happens, a cohesive international assessment and response is needed.[79] Such a system would need to be supported by member countries. Its terms of reference should be quite clear and generally agreed. There would need to be access to all data relating to a product under consideration, including product information protected by secrecy laws and patient case records when necessary.

The aggressive marketing of new medicines by pharmaceutical manufacturers and the resultant rapid exposure over a short period of time of large numbers of patients to them warrant the creation of a system for global assessment of drug safety concerns. The WHO has supported the creation of an independent advisory panel composed of a broad spectrum of medical disciplines including clinical pharmacologists, regulators, academics and epidemiologists. The functions of this panel will be to provide advice to WHO on safety issues relating to medicinal products, including its Collaborating Centre for International Drug Monitoring (*the* UMC) and through it to the Member States of WHO.

CHAPTER 7

CONCLUSION AND CONSIDERATIONS FOR THE FUTURE

For all medicines there is a trade-off between the benefits and the potential for harm. To minimize the harm, it is necessary that medicines of good quality, safety and efficacy are used rationally, and that the expectations and concerns of the patient are taken into account when therapeutic decisions are made. To achieve this is to serve public health, and to foster a sense of trust in patients in the medicines they use that would extend to confidence in the health service in general.

The discipline of pharmacovigilance has developed considerably since the 1972 WHO technical report, and it remains a dynamic clinical and scientific discipline. It has been essential to meet the challenges of the increasing range and potency of medicines (including vaccines), which carry with them an inevitable and sometimes unpredictable potential for harm.

The risk of harm, however, is less when medicines are used by an informed health profession and by patients who themselves understand and share responsibility for their drugs. When adverse effects and toxicity appear – particularly when previously unknown in association with the medicine – it is essential that they should be analysed and communicated effectively to an audience that has the knowledge to interpret the information. This is the role of pharmacovigilance. Much has already been achieved.

But more is required for the integration of the discipline into clinical practice and public policy.

The following is a summary of some of the serious challenges facing pharmacovigilance programmes in the next ten years, describing in brief the potential implications of such trends on the evolution of the science.

Major challenges are:

1) **Globalization**. The globalization of drug distribution and the increased exposure of massive populations to large volumes of medicines. These include novel chemical entities used for symptomatic relief and lifestyle modification as well as medicines used in developing countries to curb the prevalence of pandemic diseases such as HIV/AIDS, malaria and tuberculosis. The use of medicines on such a large scale and within such a short period of time calls for a better and more efficient level of international pharmacovigilance.

2) **Web-based sales and information**. The Internet, in addition to its many benefits, has also facilitated the uncontrolled sale of medicines (including herbal and traditional medicines) across national borders. Drug information in all forms and with varying levels of accuracy is distributed internationally through this medium. Such information covers: prescription drugs, unregistered medicines, highly controlled substances and traditional and herbal medicines with questionable safety, efficacy and quality. Regulatory decisions on drug safety made in distant countries

are available to the international public at the same time as national drug regulatory authorities. Aggressive marketing by manufacturers and distributors through the Internet often results in excessive and, probably irrational, use of medicines. All these changes in drug use are likely to have important consequences on public health and safety.

3) **Broader safety concerns**. The scope of pharmacovigilance continues to broaden as the array of medicinal products grows. There is a realization that drug safety is more than the monitoring, detection and assessment of ADRs occurring under clearly defined conditions and within a specific dose range. Rather, it is closely linked to the patterns of drug use within society.

   Problems resulting from:
   - irrational drug use
   - overdoses
   - polypharmacy and interactions
   - increasing use of traditional and herbal medicines with other medicines
   - illegal sale of medicines and drugs of abuse over the Internet
   - increasing self medication practices
   - substandard medicines
   - medication errors
   - lack of efficacy

   are all within the domain of pharmacovigilance. Current systems need to evolve in order to address this broad scope adequately.

   Another aspect of broadened scope is the lack of clear boundaries between:
   - blood products
   - biologicals
   - medical devices
   - cosmetics
   - food additives
   - vaccines.

4) **Public health versus pharmaceutical industry economic growth**. There may be shortcomings and at times conflicting interests within the pharmaceutical industry when dealing with public health concerns arising from drug safety issues. The industry needs to overcome weaknesses in safety monitoring during clinical trials [80] and post-marketing surveillance.[81] Manufacturers should take a more proactive approach to drug safety rather than maintaining defensive tactics. This calls for a heightened level of product stewardship and recognition of responsibility to public and environmental health.

5) **Monitoring of established products**. The generic sector of the pharmaceutical industry has not fully recognized its responsibility to continuously monitor the safety of its products throughout the world. There is the erroneous belief that generic drugs are inherently safe even when they interact with other medicines. The generic sector is the largest supplier of essential drugs.

6) **Developing and emerging countries**. Outside the OECD countries, the pharmaceutical industry has not been committed to pharmacovigilance activities, particularly the drug safety issues involving medicines used in communities with overburdened health care systems, different patterns of drug use and different co-morbid conditions. Other problems to be tackled include:
   - irrational and potentially unsafe drug donation practices, and
   - widespread manufacture and sale of counterfeit and substandard medicines.

7) **Attitudes and perceptions to benefit and harm**. These trends have dramatically changed the way in which medicines are used by society. Healthcare providers, patients and the public have responded in different ways to these changing trends as has been described in previous chapters. Their perception of benefit and harm and the level of acceptable risk for medicines in the face of these rapid developments have not been considered in a meaningful way. The harm caused by medicines has been shown to be significant. Morbidity and mortality from drug-induced diseases are only recently being recognized as an important item on the public health agenda in developed and developing countries.

8) **Outcomes and Impact**. Along with increased public awareness over safety of medicines, there is an increasing public gaze on the performance of the health professions, industry and regulators. Increased accountability must lead to more research into the effectiveness of pharmacovigilance and its place in improving public perception. A major focus must be to empower health practitioners and patients themselves with useful information that improves individual therapy, aids the diagnosis and management of medicine-induced disease, and generally leads to a reduction of iatrogenic diseases.

Current pharmacovigilance systems need to be reviewed and developed further in the face of these important future challenges. The following summarize some of the priority areas that need to be addressed either at a national or international level:

Detection of ADRs

1) Improve detection and accurate diagnosis of ADRs by healthcare providers and patients.
2) Encourage active surveillance of specific drug safety concerns through epidemiological methods such as case control studies, record linkage and epidemiological studies.
3) Consider special activities and expertise required for the detection of safety concerns related to vaccines, biologicals, veterinary medicines, herbal medicines, biotechnology products and investigational drugs.
4) Improve signal detection systems by facilitating the rapid availability of ADR data that may have international relevance.
5) Revisit the definitions of terms used within the field of pharmacovigilance including the definitions of specific ADRs to ensure reliability and universal understanding of data obtained through ADR reporting systems.
6) Develop and implement ADR detection systems that could benefit populations with restricted access to health care.

Assessment of ADRs

7) Further development of automated signal detection systems used in spontaneous monitoring programmes.
8) Improvements in assessment of drug safety concerns that are of international relevance.
9) Foster collaborative links both at local and international level that could allow countries to assess and respond appropriately to drug safety crises.
10) Consider methods by which information on local patterns of drug use can be integrated with pharmacovigilance information during assessment of benefit and harm at a national level.

Prevention

11) Improve access to reliable and unbiased drug information at all levels of health care.
12) Improve access to safer and more effective medicines for neglected diseases prevalent in developing communities.
13) Encourage awareness of drug safety and rational drug use among health professionals and the public.
14) Integrate pharmacovigilance activities into national drug policies and the activities arising from these (e.g. standard treatment guidelines, essential drugs lists etc.).
15) Further incorporation of pharmacovigilance principles into clinical practice and academic medicine.
16) Encourage the principles of product stewardship among the various partners in health care.
17) Improve regulation and pharmacovigilance of traditional and herbal medicines.
18) Develop systems which assess the impact of preventive actions taken in response to drug safety problems.

Communication

19) Improve communication and collaboration between key partners in pharmacovigilance both locally and internationally.
20) The principles of good communications practice in pharmacovigilance and drug regulation should be encouraged, and the resources and expertise to deliver co-opted. Different solutions are likely to be developed in different countries and regions, and the experience should be shared.
21) Develop a better understanding of patients, their expectations of medicines and their perception of risk associated with the use of medicines in order to facilitate programmes that will better inform the public on the benefit and harm associated with medicine.
22) Develop sustained and active relationships with the media in order to facilitate effective and accurate communication of drug information to the public.
23) Encourage harmonization of drug regulatory and pharmacovigilance activities by incorporating the wider international community in the development of harmonization policies.

Outcomes and Impact

24) Conduct on-going research to assess the cost-effectiveness of contemporary pharmacovigilance systems in contributing to patient welfare and public health.
25) Consider the sensitivity and specificity of current signal detection and assessment methods and the extent to which contemporary pharmacovigilance systems have been successful in detecting and preventing potential disasters while avoiding the premature withdrawal of safe and useful medicines from the market.

Taking medicines, and prescribing them, are among the commonest of activities of people who are unwell and of those who care for them. It makes sense that those medicines should be monitored to equally demanding standards as those evident in the development and evaluation of drugs, and that prescribing habits and the extent of rational and cost-effective use should be reviewed.

Responsibility for the holistic approach to drug safety that is encompassed in the science and practice of pharmacovigilance, as reflected in this report, has to be shared if ideal practice is to be achieved. The scientists, clinicians, pharmaceutical manufacturers, drug developers, regulators, public policy makers, patients and the general public all have their own complementary roles in achieving what is envisaged. Among the important issues are information, information sharing and broader communication. What we need is a continuing and dynamic development of modern professional practice. We must recognize that solutions to the challenges will come from those inspired and committed individuals and institutions round the world with a vision of improved public health and patient safety. Most important in this venture, is the need for a new spirit of sharing of information and intelligence in line with the vision and aspirations of the Erice Declaration.

GLOSSARY

Adverse Event/Adverse Experience - Any untoward medical occurrence that may appear during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment.

Adverse Reaction - A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

Active surveillance system - The collection of case safety information as a continuous pre-organized process.

Bayesian confidence propagation neural network (BCPNN) - A computer architecture that mimics the network of cerebral neurones (neural network) and that uses a logic that determines the disproportionality of relationships between any of the items in the database including complexes of items compared with the background of the remaining or selected items. Changes in the disproportionality can be monitored, as new data are added or different patterns of items selected.

Benefit - An estimated gain for an individual or a population. See also: Effectiveness/risk; benefit/harm.

Biologicals - A medical product prepared from biologic material of human, animal or microbiologic origin (such as blood products, vaccines, insulin).

Benefit /harm - Benefit and harm are the positive and negative subjective qualitative experiences of individual patients. These are not usually assessed except in modern quality of life studies or in case reports. Benefit and harm at a societal level may also be considered, but then must include relative effectiveness and risk, the impact of all the outcomes on society and include cost analysis.

Case control study - Study that identifies a group of persons with the unintended drug effect of interest and a suitable comparison group of people without the unintended effect. The relationship of a drug to the drug event is examined by comparing the groups exhibiting and not exhibiting the drug event with regard to how frequently the drug is present.

Clinical trial - A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the objective of ascertaining their efficacy and safety. Clinical trials are generally classified into Phases I to IV. Phase IV trials are studies performed after marketing of the pharmaceutical product. They are carried out on the basis of the product characteristics for which the marketing authorization was granted and are normally in the form of post-marketing surveillance.

Cohort study - A study that identifies defined populations and follows them forward in time, examining their rates of disease. A cohort study generally identifies and compares exposed patients to unexposed patients or to patients who receive a different exposure.

Complementary/Alternative Medicine - These terms are used interchangeably with traditional medicine in some countries. They refer to a broad set of healthcare practices that are not part of that country's own tradition and are not integrated into the dominant health care system. They have not usually been tested in specified clinical indications by an objective scientific discipline.

Counterfeit Medicine - A medicine that is deliberately and fraudulently mislabelled with respect to identity and/or content and/or source.

Drug/medicine - Any substance in a pharmaceutical product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient. The term drug/medicinal product is used in a wider sense to include the whole formulated and registered product, including the presentation and packaging, and the accompanying information.

Drug Alerts - The action of notifying a wider audience than the initial information holder(s) of a suspected association between a drug and an adverse reaction. Note that the term is used in different contexts that can be confusing, for example, an alert may be from a manufacturer to a regulator or from a regulator to the public.

Effectiveness/risk - The balance between the rate of effectiveness of a medicine versus the risk of harm is a quantitative assessment of the merit of a medicine used in routine clinical practice. Comparative information between therapies is most useful. This is more useful than the efficacy and hazard predictions from pre-marketing information that is limited and based on selected subjects.

Ethics committee - An independent body (a review board or an institutional, regional or national committee), constituted of medical professionals and non-medical members whose responsibility is to verify that the safety, integrity and human rights of the subjects participating in a particular clinical trial are protected and to consider the general ethics of the trial, thereby providing public reassurance. Ethics committees should be constituted and operated so that their tasks can be executed free from bias and from any influence of those who are conducting the trial.

Generic (multisource pharmaceutical product) - The term 'generic product' has somewhat different meanings in different jurisdictions. Generic products may be marketed either under the non-proprietary approved name or under a new brand (proprietary) name. They are usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after the expiry of patent or other exclusivity rights.

Herbal medicine - Includes herbs, herbal materials, herbal preparations and finished herbal products.

International Conference on Harmonization (ICH) - The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

Lack of efficacy - Unexpected failure of a drug to produce the intended effect as determined by previous scientific investigation.

National pharmacovigilance centre - A single, governmentally recognized centre (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyse and give advice on all information related to drug safety.

Pharmacoepidemiology - The study of the use and effects of drugs in large numbers of people.

Pharmacovigilance - The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

Prescription event monitoring - System created to monitor adverse drug events in a population. Prescribers are requested to report all events, regardless of whether they are suspected adverse events, for identified patients receiving a specified drug.

Product stewardship - The demonstrable process by which a business can identify and manage its safety, health and environmental performance as applied to the development, manufacture, marketing, use and disposal of its products (including packaging).

Record linkage - Method of assembling information contained in two or more records, e.g., in different sets of medical charts, and in vital records such as birth and death certificates. This makes it possible to relate significant health events that are remote from one another in time and place.

Risk evaluation - Risk evaluation is the complex process of determining the significance or value of the identified hazards and estimated risks to those concerned with or affected by the process.

Risk management - The making of decisions concerning risks, or action to reduce the consequences or probability of occurrence.

Side effect - Any unintended effect of a pharmaceutical product occurring at a dose normally used in man, which is related to the pharmacological properties of the drug.

Signal - Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

Spontaneous reporting - System whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority.

Traditional Medicine - Traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness. The terms 'complementary medicine' / 'alternative medicine' / 'non-conventional medicine' are used inter-changeably with traditional medicine in some countries.

Unexpected Adverse Reaction - An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug.

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This volume presents a critical examination of the strengths and weaknesses of present systems of safety monitoring in order to increase their impact and provides an overview of the challenges facing pharmacovigilance in the future. It also highlights the importance of collaboration and communication at local, regional and international levels, to ensure pharmacovigilance delivers its full benefits.

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