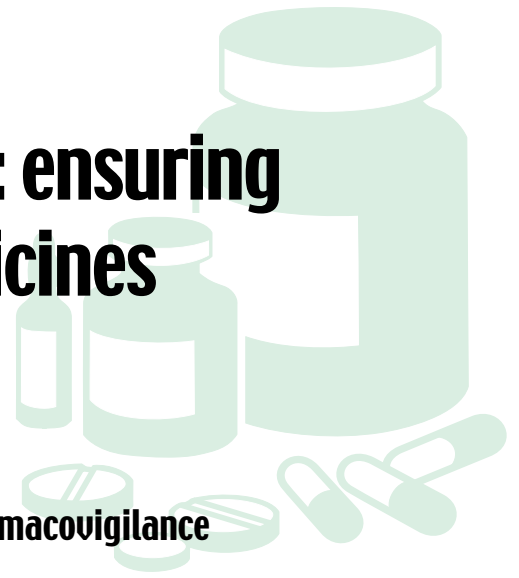




Pharmacovigilance: ensuring the safe use of medicines



Modern medicines have changed the way in which diseases are managed and controlled. However, despite all their benefits, evidence continues to mount that adverse reactions to medicines are a common, yet often preventable, cause of illness, disability and even death. In some countries, adverse drug reactions (ADRs) rank among the top 10 leading causes of mortality. Aside from the intrinsic dangers associated with the products themselves, individual patients may exhibit particular and unpredictable sensitivities to certain medicines. In addition, if more than one medicine is prescribed, there is always a risk of negative interactions. The selection and use of the best and safest medicine(s) for a given individual out of the many choices available thus requires considerable skill on behalf of the prescribing practitioner.

In order to prevent or reduce harm to patients and thus improve public health, mechanisms for evaluating and monitoring the safety of medicines in clinical use are vital. In practice this means having in place a well-organized pharmacovigilance system. Pharmacovigilance – an umbrella term used to describe the processes for monitoring and evaluating ADRs – is a key component of effective drug regulation systems, clinical practice and public health programmes.

Why pharmacovigilance is needed

The processes involved in the clinical development of medicines are illustrated in Figure 1. Once put onto the market, a medicine leaves the secure and protected scientific environment of clinical trials and is legally set free for consumption by the general population. At this point, most medicines will only have been tested for short-term safety and efficacy on a limited number of carefully selected individuals. In some cases as few as 500 subjects, and rarely more than 5000, will have received the product prior to its release.

For good reason, therefore, it is essential that new and medically still evolving treatments are monitored for their effectiveness and safety under real-life conditions post release. More information is generally needed about use in specific population groups, notably children, pregnant women and the elderly, and about the efficacy and safety of chronic use, especially in combination with other medicines. Experience has shown that many adverse effects, interactions (i.e. with foods or other medicines) and risk factors come to light only during the years after the release of a medicine (see Table 1).

Box 1 What is pharmacovigilance?

WHO defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

Figure 1 Clinical development of medicines

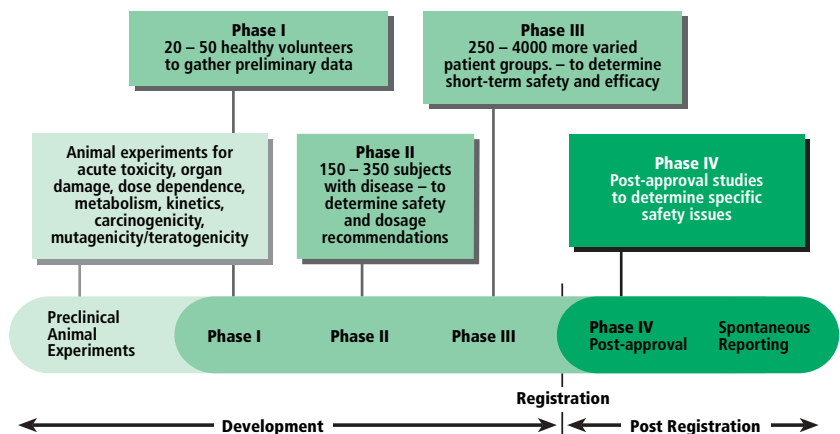




Table 1 Classical examples of serious and unexpected adverse reactions

Medicine	Adverse reaction
Aminophenazone (amidopyrine)	Agranulocytosis
Chloramphenicol	Aplastic anaemia
Clioquinol	Myelo optic neuropathy (SMON)
Erythromycin estolate	Cholestatic hepatitis
Fluothane	Hepatocellular hepatitis
Methyldopa	Haemolytic anaemia
Oral contraceptives	Thromboembolism
Practolol	Sclerosing peritonitis
Reserpine	Depression
Statins	Rhabdomyolysis
Thalidomide	Congenital malformations

Box 2 Adverse drug reactions: the example of thalidomide

Thalidomide was introduced in 1957 and widely prescribed as an allegedly harmless treatment for morning sickness and nausea. It was soon linked to a congenital abnormality which caused severe birth defects in children of women who had been prescribed this medicine during pregnancy. By 1965, thalidomide had been removed from the market in most countries. Nevertheless, it continued to be used for the treatment of leprosy, and in more recent years, its indications have been extended to a much wider range of medical conditions. These uses are allowed only under strict supervision and specialist advice. Despite these precautions, between 1969 and 1995, 34 cases of thalidomide embryopathy were registered in leprosy endemic areas in South America by the Latin American Collaborative Study of Congenital Malformations.

The aims of pharmacovigilance

Events such as the thalidomide tragedy highlight the extreme importance of effective drug monitoring systems for all medicines. The principal aims of pharmacovigilance programmes are:

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

Over the last decade, it has been increasingly recognized that the scope of pharmacovigilance needs to be extended beyond the strict confines of detecting new signals of safety concerns. Globalization, consumerism, the resulting explosion in free trade and communication across borders, and increasing use of the Internet have all contributed to a change in the way people access medicinal products and information about them. These changing patterns in drug use require a shift in the approach to pharmacovigilance, more specifically, towards one that is more closely linked, and thus better able to respond, to the prevailing patterns of drug use within society.

Partners in pharmacovigilance

The management of the risks associated with the use of medicines demands close and effective collaboration between the key players in the field of pharmacovigilance. Sustained commitment to such collaboration is vital if the future challenges in pharmacovigilance are to be met, and if the discipline is to continue to develop and flourish. Those responsible must jointly anticipate, describe and respond to the continually increasing demands and expectations of the public, health administrators, policy officials, politicians and health professionals. However, there is little prospect of this happening in the absence of sound and comprehensive systems which make such collaboration possible. The constraints typically include lack of training, resources, political support, and most especially scientific infrastructure. Understanding and tackling these are an essential prerequisite for future development of the science and practice of pharmacovigilance.

Box 3 Monitoring the safety of medicines: key partners

- Government
- Industry
- Hospitals and academia
- Medical and pharmaceutical associations
- Poisons and medicines information centres
- Health professionals
- Patients
- Consumers
- The media
- World Health Organization

Pharmacovigilance in national drug policy

The provision of good quality, safe and effective medicines and their appropriate use is the responsibility of national governments. The establishment of a national medicine regulatory agency and a designated

centre for the study of adverse reactions are central to the achievement of these functions. Multi-disciplinary collaboration is of great importance; in particular, links need to be forged between various departments of the ministry of health and also with other stakeholders, such as the pharmaceutical industry, universities, nongovernmental organizations (NGOs) and those professional associations having responsibility for education on rational use of medicines and pharmacotherapy monitoring.

Box 4 Key elements of pharmacovigilance in national drug policy

- Establishment of national pharmacovigilance systems for the reporting of adverse events, including national and, if appropriate, regional pharmacovigilance centres.
- Development of legislation/regulation for medicine monitoring.
- National policy development (to include costing, budgeting and financing).
- Continuing education of health-care providers on safe and effective pharmacotherapy.
- Provision of up-to-date information on adverse reactions to professionals and consumers.
- Monitoring the impact of pharmacovigilance through process indicators and outcome.

Pharmacovigilance in the regulation of medicines

Robust regulatory arrangements provide the foundation for a national ethos of medicine safety, and for public confidence in medicines. To be effective, the remit of drug regulatory authorities needs to go further than the approval of new medicines, to encompass a wider range of issues relating to the safety of medicines, namely:

- clinical trials;
- the safety of complementary and traditional medicines, vaccines and biological medicines;
- the development of lines of communication between all parties which have an interest in medicine safety, ensuring that they are able to function efficiently and ethically, particularly at times of crisis.

In order to achieve their respective objectives, pharmacovigilance programmes and drug regulatory authorities must be mutually supporting. On the one hand, pharmacovigilance programmes need to maintain strong links with the drug regulatory authorities to ensure that the latter are well briefed on safety issues in everyday clinical practice, whether these issues are relevant to future regulatory action or to concerns that emerge in the public domain. On the

other, regulators need to understand the specialized and pivotal role that pharmacovigilance plays in ensuring the ongoing safety of medicinal products.

Box 5 Pharmacovigilance in practice: the example of cerivastatin

Cerivastatin was first approved as a lipid-regulating agent in 1997. By 2000 a total of 549 cases of rhabdomyolysis associated with cerivastatin use had been reported to the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden. Consequently a signal was issued regarding an association between cerivastatin, myopathy and rhabdomyolysis.

In November 1999 in the United States, and in March 2000 in Canada, prescribing information was changed to include a contraindication for the combined use of cerivastatin and gemfibrozil, another lipid-regulating medicine. A similar action was taken in Australia in February 2001, and a warning issued to alert prescribers to the possibility of rhabdomyolysis occurring with all statins. In June 2001 Europe-wide regulatory action was taken to contraindicate the combined use of cerivastatin and gemfibrozil. On 8 August 2001, the manufacturer voluntarily withdrew cerivastatin from the market on the grounds of an increased risk of rhabdomyolysis, particularly when used in combination with gemfibrozil.

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 the quality of health care. Education and training of health professionals in medicine safety, exchange of information between national pharmacovigilance centres, the coordination of such exchange, and the linking of clinical experience of medicine safety with research and health policy, all serve to enhance effective patient care. A regular flow and exchange of information in this way means that national pharmacovigilance programmes are ideally placed to identify gaps in our understanding of medicine-induced diseases.

Pharmacovigilance in disease control public health programmes

The monitoring of medicine safety in countries where there is no regulatory or safety monitoring system in place, or in remote areas with little or no health care surveillance or infrastructure, has been identified as a matter for concern. The problems are especially apparent in situations that involve the use of medicines in specific communities, for example, for the treatment of tropical diseases such as malaria,



leishmaniasis and schistosomiasis, and for the treatment of HIV/AIDS and tuberculosis. In some settings several disease control initiatives involving the administration of medicines to large communities are being implemented within the same population with little knowledge of, or regard to, how these various medicines could interact with each other. Pharmacovigilance should be a priority for every country with a public health disease control programme.

Box 6 Malaria: an example of pharmacovigilance in public health

In view of the increasing resistance to existing antimalarial medicines, several countries have switched to using combinations of various artemisinin derivatives as their first- and second-line treatments for malaria. The change to artemisinin combination therapies (ACTs) has provided a timely opportunity to introduce a pharmacovigilance system in those countries that hitherto had no established systems for safety monitoring of medicines. In 2003, participants from five African countries were trained in the basic methods of medicine safety monitoring with a view to facilitating the introduction of a common system of pharmacovigilance for new antimalarial treatments. Since then two of these countries have formally established a pharmacovigilance centre; the others are also making progress in monitoring antimalarials.

Communicating the outcome of pharmacovigilance

It is not sufficient for the experts to be satisfied with the safety evidence for a given medicine. The public perception of the hazards associated with medicines is an equally important factor. How safe is safe enough? Which risks are acceptable? These are critical questions that providers of medicines need to

Table 2 Communicating messages about medicine safety

Vehicle	Issued by
'Dear Doctor' letters	Pharmaceutical manufacturers
Medicine alerts	National health authorities
Media statements	National health authorities/ pharmacovigilance centres
Patient information leaflets	Pharmaceutical manufacturers/ national health authorities/ pharmacovigilance centres
Newsletters	National pharmacovigilance centres and WHO
Personal feedback to reporters	National pharmacovigilance centres

consider when communicating with patients and the general public. The pharmaceutical industry, governments and health-care providers have a duty to build public trust through effective communication of risk. This can only be achieved once the public mindset has been examined and fully understood.

Available methods for communicating messages about the safety of medicines are listed in Table 2. Medical journals and web sites maintained by national agencies are other methods of communication. The choice of method employed tends to depend on the urgency and seriousness of the issue in question.

WHO Programme for International Drug Monitoring

As a means of pooling existing data on ADRs, WHO's Programme for International Drug Monitoring was started in 1968. Initially a pilot project in 10 countries with established national reporting systems for ADRs, the network has since expanded significantly as more countries worldwide developed national pharmacovigilance centres for the recording of ADRs. Currently, 86 countries participate in the programme, which is coordinated by WHO together with its collaborating centre in Uppsala, Sweden (Figure 2). The collaborating centre is responsible for maintaining the global ADR database, Vigibase. At present the database contains more than three million ADR reports (Figure 3).

The WHO Collaborating Centre analyses the reports in the database to:

- identify early warning signals of serious adverse reactions to medicines;
- evaluate the hazard;
- undertake research into the mechanisms of action to aid the development of safer and more effective medicines.

Through an advisory committee, WHO plays an important role in the provision of expert advice on all matters relating to the safety of medicines. The Committee also exists to facilitate consistent policies and action among member countries and to advise those who may be concerned about action taken in another country.

The success of WHO's International Drug Monitoring Programme is entirely dependent on the contributions of national pharmacovigilance centres. Such centres provide an essential pool of experience and competence which has been instrumental in the continuous development of the WHO programme and of pharmacovigilance as a whole. Ideally every country should have a pharmacovigilance centre.

Figure 2 The WHO International Drug Monitoring network, membership as of 2004

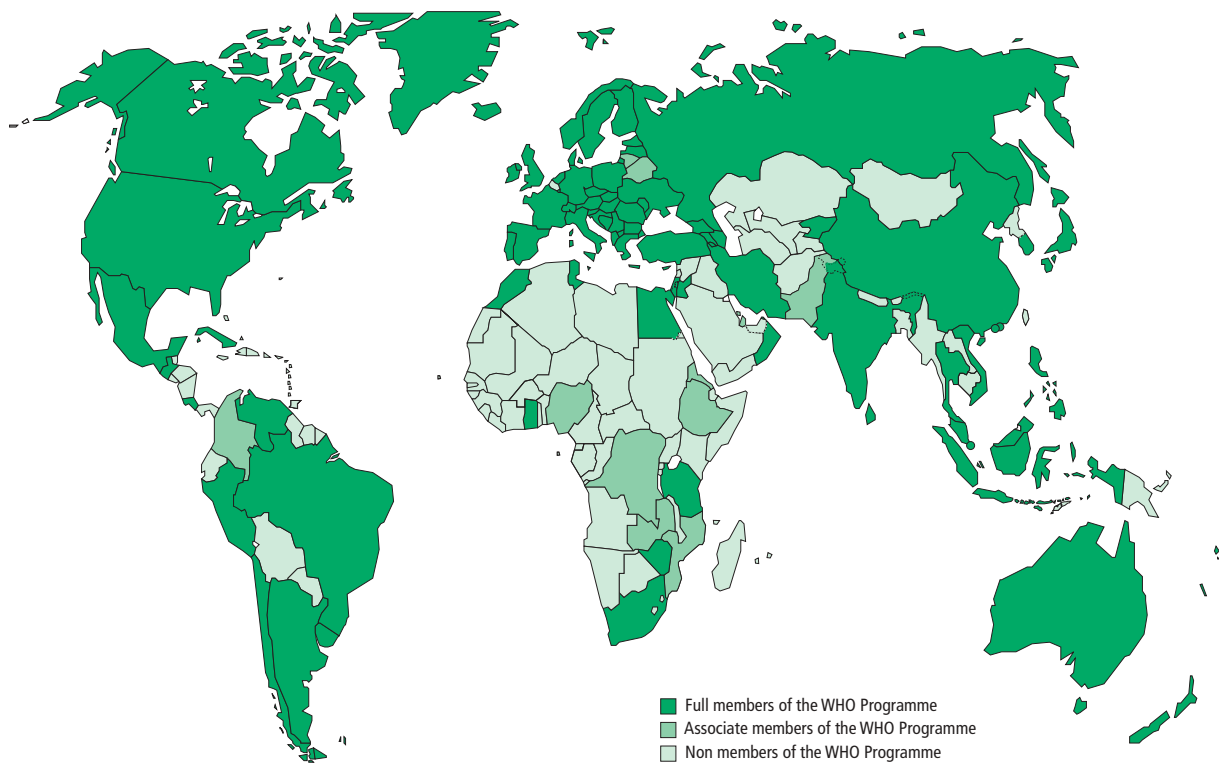
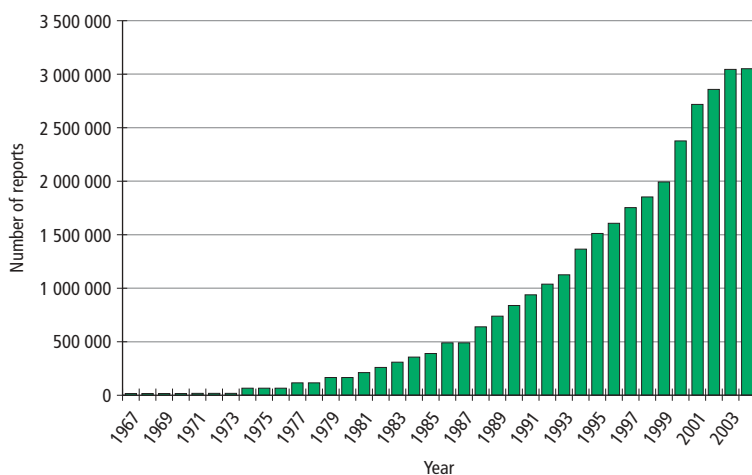


Figure 3 Cumulative number of reports received by the WHO, as of April 2004



Conclusion

Despite its 40-year history, pharmacovigilance remains a dynamic clinical and scientific discipline. It continues to play a crucial role in meeting the challenges posed by the ever increasing range and potency of medicines, all of which carry an inevitable and some-

times unpredictable potential for harm. When adverse effects and toxicity do appear – especially when previously unknown – it is essential that these are reported, analysed and their significance communicated effectively to an audience that has the knowledge to interpret the information.

For all medicines there is a trade-off between the benefits and the potential for harm. The harm can be minimized by ensuring 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 among patients in the medicines they use that would extend to confidence in the health service in general;
- ensure that risks in drug use are anticipated and managed;
- provide regulators with the necessary information to amend the recommendations on the use of the medicines;
- improve communication between the health professionals and the public;
- educate health professionals to understand the effectiveness/risk of medicines that they prescribe.

This is the important role of pharmacovigilance.



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