The SAFETY *of* MEDICINES IN PUBLIC HEALTH PROGRAMMES:

Pharmacovigilance an essential tool

World Health Organization

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World Health Organization

the UPPSALA MONITORING CENTRE

WHO Collaborating Centre for International Drug Monitoring

CONTENTS

PREFACE

The Quality Assurance and Safety of Medicines team of the World Health Organization (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 on pharmacovigilance in public health programmes 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 and public health experts.

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EXECUTIVE SUMMARY

Pharmacovigilance is defined as "*the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems*".

Pharmacovigilance is an arm of patient care. It aims at making the best use of medicines for the treatment or prevention of disease. No one wants to harm patients, but unfortunately any medicine will sometimes do just this. Good pharmacovigilance will identify the risks and the risk factors in the shortest possible time so that harm can be avoided or minimized. When communicated effectively, this information allows for the intelligent, evidence-based use of medicines and has the potential for preventing many adverse reactions. This will ultimately help each patient to receive optimum therapy, and on a population basis, will help to ensure the acceptance and effectiveness of public health programmes.

Significant harm to a few patients can destroy the credibility, adherence to and success of a programme. Rumours and myths about the adverse effects of medicines can spread rapidly and are difficult to refute in the absence of good data. Pharmacovigilance can provide these data. It can also provide evidence of other types of medicine-related problems including treatment failure, counterfeit medicines, poor quality medicines, interactions between medicine and food and the incorrect use of medicines. Good pharmacovigilance practice can generate the evidence that will inspire public confidence and trust.

Pharmacovigilance incorporates and provides training in the identification of adverse reactions, data collection, processing and analysis. Importantly, these activities allow for the identification of previously unsuspected adverse reactions as well as identification of their effects in pregnant women and in the very young or old, which, for new medicines, are generally unknown. The information collected also provides the tools for the effective management of problems. These include communication and minimization of risk.

In developed countries, the cost of adverse reactions in the general population is very high and under-recognized. Against the background of the high disease burden and malnutrition present in many underdeveloped countries, this cost could be proportionately higher. In any public health programme, a well-integrated pharmacovigilance system must ultimately result in cost savings through early recognition and management of these risks.

Those countries that lack the necessary facilities, expertise and resources for pharmacovigilance arguably need them the most. In working to achieve this, it is important that the traditional division between safety of medicines on the one hand and public health on the other should cease to exist. The development of pharmacovigilance within a public health programme should be seen as an important opportunity for the development within the local health service of a comprehensive national pharmacovigilance system and should be seen as an obligatory investment in the future public health of the territory.

A strength of pharmacovigilance is its international nature. Under the stimulus and coordination of the World Health Organization (WHO) and its Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre), there are currently 79 national centres networking in a strong international programme. These national centres collaborate in the WHO Programme for International Drug Monitoring, to collect reports of suspected adverse drug reactions (ADRs) and after review, send them to the Uppsala Monitoring Centre for entry into the WHO database. This is the largest database of ADR reports in the world (over 3.5 million case reports) and is a prime resource for generating signals of previously unrecognized ADRs and for the study of questions on the safety of medicines. This database would have added value if it included reports about medicines used in public health programmes and could also be a valuable resource for the programmes themselves.

The integration of pharmacovigilance may be crucial to the success of public health programmes using medicines. This document demonstrates that pharmacovigilance can and should be an integral part of every public health programme that uses medicines in order to optimize the use of scarce health resources and prevent potential tragedies. To explain how that might happen, and why, is the purpose of this report.

OBJECTIVES

The 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;
— detect problems related to the use of medicines and communicate the findings in a timely manner;
— contribute to the assessment of benefit, harm, effectiveness and risk of medicines, leading to the prevention of harm and maximization of benefit;
— encourage the safe, rational and more effective (including cost-effective) use of medicines; and
— promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

The purpose of this document is to present the case for integrating pharmacovigilance as an essential component of public health programmes (PHPs) that use medicines. It is important that active pharmacovigilance is undertaken by all PHPs that use medicines because no medicine is without adverse consequences although these vary in severity and frequency. This document highlights the importance of collaboration and communication between pharmacovigilance systems and PHPs at both the national and international levels to ensure full integration. Where there is no established pharmacovigilance system, the document argues for the importance of using a PHP as an entry point for the establishment of a fully functioning pharmacovigilance system that informs and advises the medicines regulatory authority. The document also highlights the critical strengths and weaknesses of both pharmacovigilance systems and PHPs.

This document is intended primarily for policy-makers and programme managers. More detailed information on particular programmes should be collected and made available by the specific PHP.

CHAPTER 1

INTRODUCTION

The purpose of this document is to demonstrate that pharmacovigilance can and should be an integral part of every PHP that uses medicines to optimize the use of scarce health resources and prevent potential tragedies.

The use of medicines is an important aspect of many PHPs that are designed to improve the health of a target population. Their cost to the health budget is between 6% in developed countries and 45% in some developing countries, but there are huge variations between both developed countries and developing countries. Medicines are important not only because of their capacity to treat and prevent disease and to support PHPs, but also because the confidence of the public in the health policies of their countries is inextricably linked to their confidence in the availability of medicines that are safe and effective. All medicines carry some risk of harm and it is important to monitor their effects, both intended and unwanted, so that good evidence is available upon which to base an assessment of risk versus effectiveness or risk versus benefit. Furthermore, particularly with new medicines, the early identification of unexpected adverse reactions and their risk factors is essential, so that the medicines can be used in an informed manner with the least chance of harm. This is the role of pharmacovigilance. Information gathered during pharmacovigilance may also assist in selecting the most appropriate medicine for future use.

Despite the progress that has been made in pharmacovigilance, the burden on public health of adverse reactions to medicines (traditionally referred to as ADRs) remains significant. Pharmacoeconomic studies on the costs of ADRs suggest that governments pay considerable amounts from their health budgets towards covering the costs associated with them. In a meta-analysis of 39 prospective studies from hospitals in the United States, it was shown that ADRs ranked from the fourth to sixth leading cause of death (*1*). Extrapolation of data, from a more recent prospective study in England to the whole National Health Service bed base, suggests that for patients aged > 16 years, at any one time the equivalent of up to seven 800-bed hospitals may be occupied by patients admitted with ADRs (*2*). There are also costs associated with ADRs in primary health care, but these are more difficult to assess. To the direct costs should be added the indirect costs of adverse reactions, such as loss of productivity. There are now sufficient data available to indicate that the provision of adequate strategies to detect and prevent adverse reactions is a cost-effective commitment of resources.

Health requirements and the use of medicines in different countries vary considerably for many reasons, including different burdens of disease, economic, ethnic, cultural and dietary factors, and the level of development of a system for the regulation of medicines. Decisions concerning the effectiveness and safety of a product need to be considered in each country's specific context. Vigilance regarding both safety and effectiveness of medicines must become a priority area within public health.

WHO has produced guidelines for setting up a national pharmacovigilance centre (*3*) and many WHO PHPs have developed their own guidelines. The vaccines example is included in Annex 1. This document offers a critical examination of the strengths and weaknesses of both pharmacovigilance systems and public health systems. It describes the roles and responsibilities of all parties involved and anticipates the developments that will be necessary to enable both pharmacovigilance and PHPs to meet the challenges of the coming years. The increasing public expectation of safety is one of the major elements of the need for improving the safe use of medicinal products. As effective medicines become more widely available, there is an increasing demand for their use by the public and it is imperative that these medicines are monitored for safety. National pharmacovigilance centres cannot address this issue alone. They need to work together with other parties including the local regulatory authority, managers of PHPs, health professionals, academia, governments, the pharmaceutical industry, patients and consumers, and the media.

CHAPTER 2

PUBLIC HEALTH PROGRAMMES USING MEDICINES

The important components of a PHP are education, environmental modifications, nutrition intervention, lifestyle and behavioural changes, preventive measures such as immunization, screening for hypertension and breast cancer and, in addition, pharmacotherapy.

2.1 Introduction

Public health is defined as the organized efforts of society to protect, promote and restore people's health. It is the combination of science, skills and beliefs that is directed to the maintenance and improvement of the health of all the people through collective or social actions. The programmes, services and institutions involved focus on the prevention of disease and the health needs of the population as a whole. Public health activities change in response to variations in technology and social values, but the goals remain the same: to promote health and to reduce the amount of disease, premature death and disease-related discomfort and disability in the population.

Health promotion strategies contribute to the improvement of health and the prevention of diseases in developing and developed countries alike. Public health strategy is determined in each country according to the epidemiology of prevalent diseases and the local circumstances.

Developing countries are facing a major challenge in tackling the communicable diseases that are responsible for high rates of morbidity and mortality. Infectious diseases for which effective treatment has existed for a long time, such as some diarrhoeal and respiratory diseases in children, continue to take their toll. Communicable diseases such as tuberculosis, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), sexually transmitted diseases (STDs), malaria, schistosomiasis, amoebiasis, leprosy, trachoma, lymphatic filariasis, intestinal helminthiasis, onchocerciasis, leishmaniasis and trypanosomiasis add to the disease burden. Noncommunicable diseases caused by environmental pollution and chronic diseases that result from changing lifestyles, dietary habits and patterns of behaviour add to the problem. In these countries, access to medical care is poor, largely because of the low socioeconomic level of the populations, but also for cultural and logistical reasons such as poor transportation infrastructure. Health authorities include in their basic health package PHPs aimed at reducing morbidity and mortality associated with the major common diseases. The important components of a PHP are education, environmental modifications, nutrition intervention, lifestyle and behavioural changes, preventive measures such as immunization, screening for hypertension and breast cancer and, in addition, pharmacotherapy.

Many PHPs are based on the direct administration of medicines or vaccines for the prophylaxis, treatment and control of a disease. Interventions aimed at achieving the assigned goal (i.e. reduction of morbidity and mortality rates) include mobilization of resources both nationally and internationally to support the different aspects of the programme, including the mass distribution of free medicines. These programmes may be initiated by countries themselves, or under the leadership of international organizations, particularly WHO and the United Nations Children's Fund (UNICEF). They aim to decrease morbidity and/or mortality rates or even to totally eradicate specific diseases. WHO supports Member States in initiating, organizing, guiding and implementing a number of clinical programmes. The programmes are functional thanks to the keenness, interest and support of many donors and sponsors, such as WHO, UNICEF and private sector organizations. The pharmaceutical industry is increasingly involved in either donating, or providing at reduced cost, medicines for direct administration to large populations and communities through a number of public health or disease control programmes.

Consumers and patients of affected communities are not usually involved directly in the decision-making process of the PHP. However, they influence the success of the desired outcome by accepting or rejecting the programme. The success of PHPs depends on the active participation of the population and on multisectoral involvement.

2.2 The public health environment

Without good guidance and training programmes for health-care workers in developing countries, patients could be at an increased risk of medication error and/or preventable ADRs.

2.2.1 Disease
2.2.2 Population
2.2.3 Medicine
- Counterfeit medicines
- Substandard medicines
- Donated medicines
- Medicine interactions
- Incorrect use of medicines

2.2.4 Health-care provider
2.2.5 Health-care system

In developing countries PHPs are conducted by agencies and health workers with a wide variety of skills and expertise. Patients do not usually have direct contact with a physician as would be usual with PHPs in developed countries. Consequently, without good guidance and training programmes for health-care workers, patients in developing countries could be exposed to higher risks of medication error and/or preventable ADRs. These risks could be related to disease, population characteristics, medicine, health-care providers or the health-care system. The influence of these factors is discussed below.

2.2.1 Disease

The diseases managed by the PHPs are not always well-diagnosed clinically. Treatment is often initiated in the absence of an adequate diagnosis and there may be insufficient

follow-up of patients. For example, because of inadequate diagnostic facilities, it is common clinical practice for patients to be given presumptive treatment for malaria although many of the patients treated will not have the disease (4).

2.2.2 Population

Public health programmes may treat a large population over a short period. To meet the specific needs of a particular programme, the community could be treated in one of three different ways: i.e. en masse, case-contact or individual treatment. Under these conditions, some of the patients treated may not have the disease, or treatment could be given to patients in whom there are contraindications to the use of the medicine (e.g. pregnant or breastfeeding women, young children or elderly people). In a study in Brazil, it was found that, of the medicines used during pregnancy, 40% were not from the "approved safety" category and 3% were clearly contraindicated (*5*).

In addition, factors such as literacy, nutrition and food habits in the community can have important consequences for adherence, therapeutic effectiveness and drug safety. For example, patient information on the medicines used is often absent, inadequate or too technical and is seldom in the vernacular. This could affect patients' comprehension of the correct way to use the medicines. Some medicines can compound nutritional problems in patients suffering from pre-existing malnutrition (e.g. nutritional deficiencies due to severe diarrhoea caused by antiretrovirals).

2.2.3 Medicine

Huge quantities of medicines are used each year; for example, more than US$ 316 billion was spent on medicines in 2000. However, patterns of consumption differ between high- and low-income countries. In high-income countries, "originator" (patented) pharmaceuticals account for two thirds of sales of all medicines. The total sale of medicines grew substantially between 1990 and 2000. In low-income countries such pharmaceuticals account for only about one third of total sales.

Medicines can be generic with low commercial value (for example mebendazole), new medicines with which there is limited clinical experience (e.g. new antiretrovirals) or still be undergoing clinical trials. Government agencies may be unable to exercise control over medicines of doubtful quality.

In some cases, access to a medicinal product is not through qualified health workers but through alternative systems, for example, medication may be purchased from pharmacies or street vendors.

Counterfeit medicines

Another widespread problem is that some medicines are counterfeit (Fig. 1) (*6*). Antibiotics and other essential medicines are often counterfeited and their use leads to treatment failure and sometimes death. In many cases counterfeit medicines are positively dangerous and detrimental to public health in terms of the human suffering they cause and the increased burden on the health services. Patients who take counterfeit medicines may not respond to treatment as quickly as they should and, in some instances, they may not respond at all. Treatment with ineffective counterfeit medicines such as antibiotics may have a deleterious effect on large numbers of the population. In extreme cases,

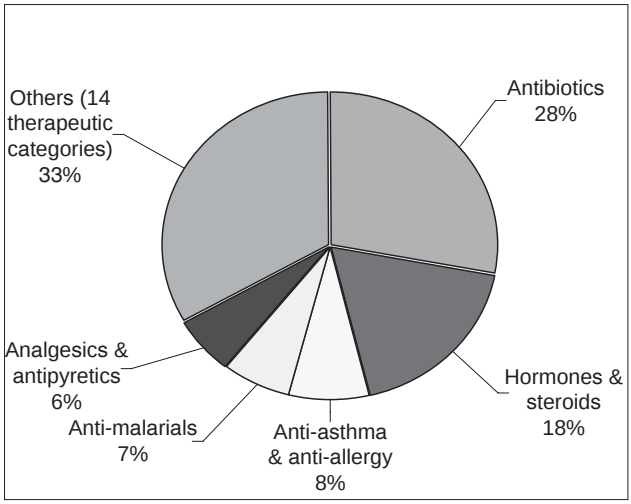

Figure 1. Reports of counterfeit medicines by therapeutic class received by WHO 1999–2002
Source: WHO database. E. Wondemagegnehu, 2002. QSM/EDM

counterfeit medicines may cause serious harm to health or exacerbate the conditions being treated because of the harmful ingredients they contain. In one case, it is alleged that placebo tablets containing no active ingredients were stolen and sold as a contraceptive medicine, leading, it was claimed, to unexpected pregnancy (*7*).

Substandard medicines

In some countries an average 10–20% of medicines fail laboratory tests for quality (unpublished data). Substandard products could result from poor manufacturing practices, unsuitable packaging, storage and distribution; or when generic drugs are produced by unregistered manufacturers. Fig. 2 shows the high failure rate in quality control tests for chloroquine tablets in some sub-Saharan African countries. This figure highlights the need to test not only for potency (amount of active ingredient), but also for dissolution rates of tablets and capsules to ensure availability of the active ingredient. Poor quality antibiotic preparations may also contribute to the development of resistance to antibiotics.

There have been several tragic examples of the results of using substandard medicines in which diethylene glycol (DEG) has been incorporated in pharmaceutical preparations, fraudulently or by mistake, leading to the death of more than 500 people, mostly children. The United States Congress passed the Federal Food, Medicine & Cosmetic Act in 1938, in reaction to a public health accident that occurred in 1937 when 105 people died from DEG poisoning. DEG is a highly toxic organic solvent that causes acute renal failure and death when ingested. It had been used as a diluent for sulfanilamide. The legislation that was passed required that new medicines be tested for toxicity before being put on the market. Yet reports of toxicity due to DEG continue to appear. In 1998 it was reported that DEG-contaminated cough syrup had caused the deaths of a number of children in India (*8*).

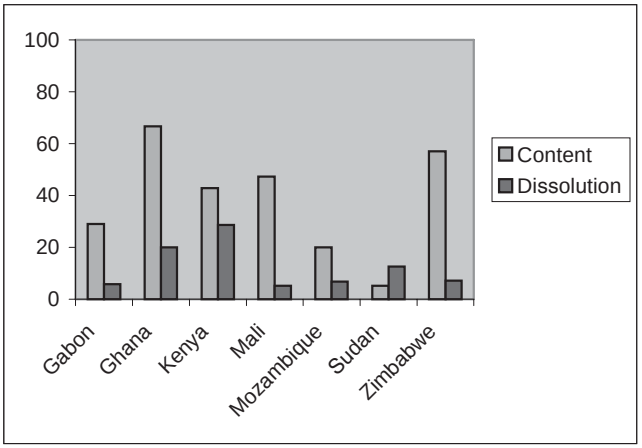

Figure 2. Percentage failures in ingredient content and dissolution in quality control tests on chloroquine tablets in seven sub-Saharan African countries
Source: The quality of antimalarials. A study in selected African countries. WHO/EDM/PAR/2003.4

Donated medicines

Donated medicines can fail to meet quality standards. In developing countries, for a variety of reasons (e.g. poverty, lack of relevant information or inadequate controls), medicines which are less safe and effective may be used. Potentially unsafe and irrational donation practices contribute to this problem. It is not uncommon for the medicines used to have already passed the date of expiry. Such medicines may have reduced efficacy and have started to decompose, which, in turn, leads to an increase in the numbers of adverse reactions. WHO has prepared guidelines for good donation practices (*9*). These guidelines outline four core principles that need to be applied before drugs are considered for donation:

— maximum benefit to the recipient;
— respect for wishes and authority of the recipient;
— no double standards in quality; and
— effective communication between recipient and donor.

Medicine interactions

The community in which a medicine is being used could also be subject to medicine–medicine, medicine–disease or medicine–food interactions. Many communities use alternative systems of medicine such as herbal medicines. Interactions between alternative and modern medicines, such as the interactions between St John's Wort and indinavir, ciclosporin and warfarin (*10*) are well documented. Food and alcohol habits in a community may also have an impact. Garlic has been shown to reduce the plasma level of saquinavir by 50%; a high alcohol intake can potentiate the effects of certain medicines.

Incorrect use of medicines

Worldwide more than 50% of all medicines are prescribed, dispensed or sold inappropriately, and 50% of patients fail to take them correctly. Common types of irrational use are:

— the use of too many medicines per patient (polypharmacy);
— inappropriate use of antimicrobials, often in inadequate dosage and frequently for non-bacterial infections;
— overuse of injections when oral formulations would be more appropriate;
— failure to prescribe in accordance with clinical guidelines; and
— inappropriate self-medication, often using prescription-only medicines.

2.2.4 Health-care provider

In response to the increasing recognition of deficiencies in the provision of health care by existing health services, the concept of delivery of primary health-care by trained non-medical, village workers and involvement of the community has emerged. This has resulted in better implementation of national PHPs. However, there is frequently an inadequate understanding of adverse reactions even among highly trained personnel and more attention needs to be given to pharmacovigilance training in the curricula for medical and nursing undergraduates. This training in turn needs to be passed on to the non-medical health-care workers.

The public health staff responsible for the dispensing of medicines and the monitoring of responses are most often paramedics with educational levels that range from primary school to university graduate. Their training involves education in public health issues such as sanitation, nutrition, hygiene, family planning and on their role in the implementation of various programmes. They lack training in the early detection and reporting of ADRs.

Non-medically trained personnel may be unable to distinguish a medicine-induced adverse effect from a disease or medical condition due to lack of knowledge of the condition and of the medicine being used. In a pilot study of the use of community volunteers to distribute azithromycin for trachoma control in Ghana, the trained community health workers were noted to have a potential role in identifying active trachoma. The concept of adverse effects was however a new one to most volunteers. When adverse events were reported at follow-up visits, the volunteers had difficulty in distinguishing patients with persistent or potentially more serious events from those in whom symptoms had abated or were abating (*11*).

2.2.5 Health-care system

Weaknesses in health-care systems and a shortage of resources lead to underdeveloped medicine control systems, unqualified health workers (with no medical background or even specific programme-related training) and poor medical services. A weak regulatory system may also fail to prevent the availability of substandard or counterfeit medicines. Facilities are usually lacking for performing laboratory tests that may help in diagnosing ADRs, for example, blood tests for anaemia, depression of white blood cell count or abnormal liver function. Due to lack of laboratory facilities, patients at risk of ADRs such as those associated with glucose-6-phosphate dehydrogenase deficiency may receive medicines which are contraindicated because the prescriber may be unaware of the patient's underlying condition. As a result, the emphasis needs to be on clinical observation for suspected adverse reactions.

2.3 Public health programmes for disease control (see Figure 3)

WHO plays an important role in the initiation, conduct and evaluation of PHPs and much effort is made to select, procure and distribute medicines, train staff and to educate the community to enlist their participation.

Decisions to start programmes for public health are taken after considerable deliberation at the international and national levels. These PHPs are considered crucial for reducing mortality and morbidity. A significant part of the programme budget is allocated to the procurement of medicines.

WHO plays an important role in the initiation, conduct and evaluation of PHPs. Numerous guidelines are produced by WHO or by Member States describing procedures for implementation and monitoring of PHPs and much effort is made to select, procure and distribute medicines, train staff and to educate the community to enlist their participation. Detailed manuals are available on the practical procedures for the handling and use of the medicines or vaccines, particularly storage, administration and

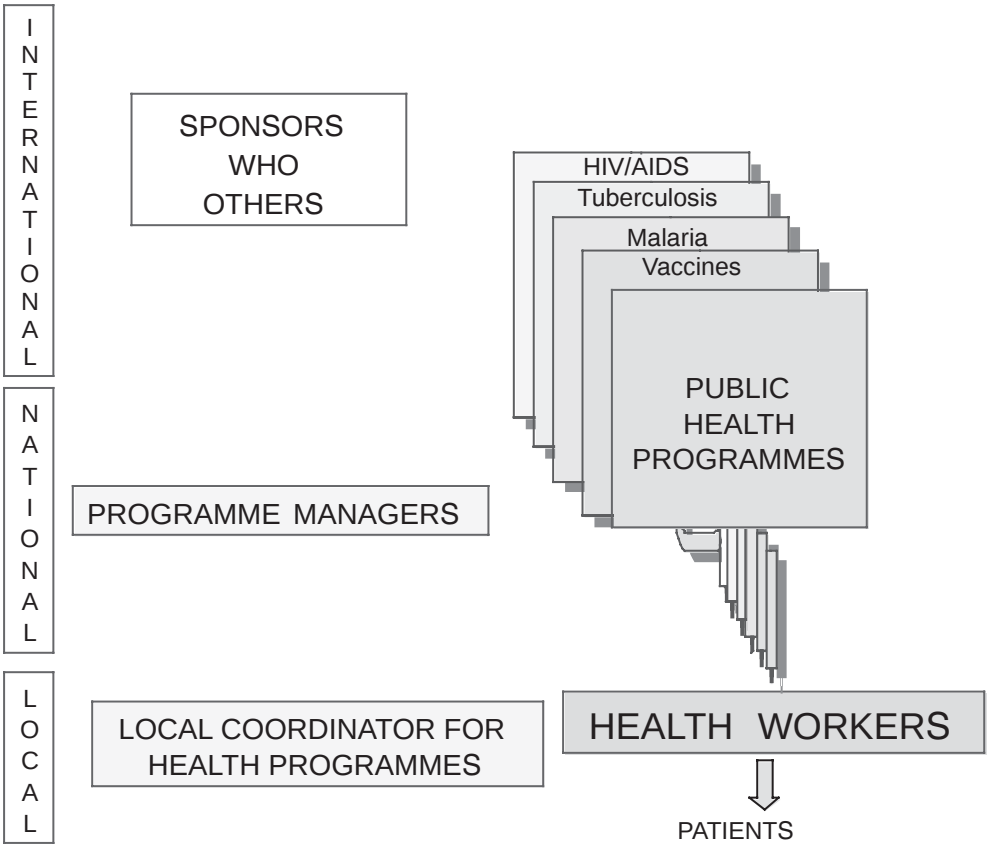

Figure 3. Organization of public health programmes

contraindications. Each programme has a standard therapeutic protocol following WHO technical guidance. Guidelines and training programmes facilitate the proper conduct of the PHPs.

The framework for evaluation of each programme is generally based on an epidemiological survey. The evaluation of success of PHPs is based mainly on the estimation of changes in the incidence and prevalence of the target disease, on the morbidity and mortality data and on the number of patients treated and the number of medicine units delivered.

It is usual for a PHP to have a vertical organization and to be operated by a programme manager. Programme managers in charge of different programmes do not necessarily collaborate. At the community level however, health professionals or community agents may be involved in several PHPs.

2.4 Future needs of public health programmes

The large population covered and the use of new medicines provide, at the same time, the potential for benefit and for harm. The possibility of harm is high, especially if adverse reactions are not monitored by a strategy aimed at good reporting and early detection, review and management.

In recognition of the various shortcomings, deficiencies and problems of implementing PHPs, newer strategies are being developed and global resources are being invoked. PHPs are evolving from disease control towards eradication. This is being accomplished by increasing the coverage of the population with mass treatment, using new medicines with greater benefits to more patients and using public-health-friendly regimens. Examples of the latter include oral administration and treatment with fewer doses. New medicines are proving effective where previously there has been resistance to treatment. There is also improved access of populations to medicines, thanks to donations by international agencies and other donors. Resource-poor countries with relatively poorly developed public health systems, ineffective medicine regulatory agencies (MRAs) and little or no pharmacovigilance are being included in the global initiatives for disease control. There is therefore a need to ensure that cheap or donated medicines are of good quality and are effective.

In the past, most medicines and vaccines used in public health for the control, treatment, prevention and eradication of disease were well known and had been in use for many years. Now new and more potent medicines with a potential for better control of diseases of public health importance are increasingly likely to be used. More diseases will come under public health management and as experience is gained, current restrictions on use may be relaxed (e.g. praziquantel in pregnancy) (*12*). The large populations covered and the use of new medicines provide, at the same time, the potential for benefit and for harm. The possibility of harm is great, especially if adverse reactions are not monitored by a strategy aimed at good reporting and early detection, review and management.

With increasing population coverage, the chances of developing adverse reactions and interactions will increase, as programmes are extended to the more “vulnerable”

populations such as the young, the elderly, pregnant women and people with malnutrition and disease. In addition, health practitioners and the public need more information about the potential benefit, rationality of use and risk of the medicines given.

Currently a significant proportion of episodes of tropical disease in countries where they are endemic are treated outside the formal health sector. To respond to this situation, a variety of new health providers are being used to dispense medicines including drug sellers and traditional healers. The pharmacovigilance systems need to recognize this trend and expand to the most peripheral level as the delivery system for drugs expands.

The public health programme manager (PHPM) has traditionally collected data on morbidity, mortality, incidence and prevalence of disease, and on control and prevention. He or she will now face the continuous challenge of having to evaluate the benefits accruing from medicine use *and* the risks involved.

The public health team and the PHPM will have to know about the risks of adverse reactions, their diagnosis, reporting and management. They will have to deal confidently with the occurrence of serious and/or unexpected adverse reactions and contribute to the effectiveness–risk assessment and any subsequent decision-making process.

CHAPTER 3

PHARMACOVIGILANCE

Pharmacovigilance is the science and activity relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicine-related problems (*13*).

3.1 Origins of pharmacovigilance

The history of pharmacovigilance goes back more than 40 years. In 1965 the eighteenth World Health Assembly, WHA 18.42, drew attention to the problem of adverse drug reaction monitoring and following further resolutions (see Annex 3) in 1966, 1967 and 1970 the International Drug Monitoring Programme came into being. In 2005, 78 member countries are participating in this Programme and the last decade has seen the participation of numerous developing countries. The programme functions on the basis of national pharmacovigilance centres coordinated by the WHO Programme for International Drug Monitoring, which consists of the WHO Collaborating Centre for International Drug Monitoring, Uppsala and the Pharmacovigilance Department of WHO, Geneva.

Recently, the concerns of pharmacovigilance have been widened to include herbal, traditional and complementary medicines, blood products, biologicals, medical devices and vaccines. Many other issues are also of relevance to the science of pharmacovigilance. These include substandard medicines, medication errors, lack of efficacy, 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 medicine-related mortality, abuse and misuse of medicines, and adverse interactions of medicines with chemicals, other medicines and foods and drinks.

3.2 Aims

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;
— detect problems related to the use of medicines and communicate the findings in a timely manner;
— contribute to the assessment of benefit, harm, effectiveness and risk of medicines, leading to the prevention of harm and maximization of benefit;
— encourage the safe, rational and more effective (including cost-effective) use of medicines; and

— promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

3.3 The cost advantage

A medicines monitoring system is an essential and cost-efficient means of detecting and minimizing injury to patients and averting potential disaster. Pharmacovigilance can help to better assess and communicate information on the effectiveness and risks of medicines and to educate and inform patients. It is also an insurance against the undetected use of ineffective, substandard or counterfeit medicines, thus minimizing the possibility of wastage of resources. The cost of a pharmacovigilance system, compared with the cost of ADRs to a nation and to the total national expenditure on medicines, is small (see Introduction). The idea that pharmacovigilance is a luxury, affordable only in the developed world, should be replaced by the realization that a reliable system of pharmacovigilance is essential for the rational, safe and cost-effective use of medicines in all countries and consequently for public health, and should produce clear advantages in relation to cost.

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 Pharmacovigilance Programme. The ultimate benefit is the safe, rational and effective use of medicines by patients.

3.4 Current practice

The success or failure of any pharmacovigilance activity depends on the reporting of suspected adverse reactions.

3.4.1 Spontaneous reporting

The definition of spontaneous reporting is as follows: "A system whereby case reports of adverse drug events are voluntarily submitted by health professionals and pharmaceutical companies to the national pharmacovigilance centre."

The success or failure of any pharmacovigilance activity depends on the reporting of suspected adverse reactions. To date, the mainstay of pharmacovigilance has been spontaneous reporting by health professionals. To detect the full spectrum of complications from pharmaceutical treatment and to gain a representative picture, all sectors of the health-care system need to be involved. This includes public and private hospitals, general practice, pharmacies, nursing homes, retail dispensaries and providers of traditional medicine. Wherever medicines are being used, there should be a readiness to observe and report unwanted and unexpected medical events.

Reports made by a health professional are an interpretation of information originally provided by a patient who has experienced the actual benefit or harm of a medicine

taken. It may also be the result of a direct observation of the effect of a medicine. Patients who suspect they have been affected by a reaction to a medicine are normally encouraged to inform their health professionals to enable them to report to the pharmacovigilance centre. In a few countries the national reporting system provides some opportunity for patient reporting. This is of particular value where there are disease-specific control programmes in operation.

3.4.2 Other methods of collecting safety data

There are various other pharmacoepidemiological methods of collecting safety information. More systematic and robust epidemiological methods that take into account the limitations of spontaneous reporting are required to address important safety questions. They need to be incorporated into postmarketing surveillance programmes.

A number of countries have implemented active surveillance systems to complement spontaneous reporting. Examples of such systems are:
— prescription event monitoring (PEM) in New Zealand and the United Kingdom;
— record linkage; and
— case-control studies.

3.4.3 National pharmacovigilance centres

National pharmacovigilance centres are responsible for:
— promoting the reporting of adverse reactions;
— collecting case reports of adverse reactions;
— clinically evaluating case reports;
— collating, analysing and evaluating patterns of adverse reactions;
— distinguishing signals of adverse reactions from "noise";[1]
— recommending or taking regulatory action in response to findings supported by good evidence;
— initiating studies to investigate significant suspect reactions;
— alerting prescribers, manufacturers and the public to new risks of adverse reactions; and
— sharing their reports with the WHO Programme for International Drug Monitoring.

National centres have played a significant role in increasing public awareness of issues relevant to the safety of medicines. As a result, in some countries, pharmacovigilance is increasingly being seen as much more than a regulatory activity as it also has 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 medicine information centres and are in collaboration with a Medicines Regulatory Authority (MRA). The scope of activities of national centres has expanded to include communication of information about the benefits, harm and effectiveness of medicines to practitioners, patients and the public.

In the nature of their work, national centres have also become familiar with real or contrived medicine scare crises, which they have managed with variable success.

[1] Noise is defined as the information which is not part of a signal or which interferes with or obscures a signal.

3.4.4 WHO Programme for International Drug Monitoring

National pharmacovigilance centres are functioning as an international network coordinated by the WHO Programme for International Drug Monitoring. The Programme has achieved much in improving the activities, support and recognition of individual national pharmacovigilance centres. It plays a key role as a communication and training centre and clearing-house for information on the safety of medicines. The WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden manages the international database of adverse reaction reports received from national centres. In 2005 this database held over 3.5 million case reports. The majority of contributing national centres have ready electronic access to these. The Centre has established standardized reporting by all national centres and has facilitated communication between countries to promote the rapid identification of signals. The terminologies developed within the WHO programme for coding adverse reactions to medicines have been widely adopted by national centres, manufacturers and medicine regulators.

More effective communication of information is being promoted and encouraged through the WHO Programme for International Drug Monitoring (*14*, *15*).

3.5 Good pharmacovigilance practice

> *To attain a coherent pharmacovigilance system it is vital that guidelines and standards are developed, which describe the practical details of the intended information flow.*

Effective pharmacovigilance relies on contributions by many people with varying educational backgrounds. The concept of pharmacovigilance is normally not well understood, either by health professionals, patients or the general population. To attain a coherent pharmacovigilance system it is most important that guidelines and standards are developed, which describe the practical details of the intended information flow. Such standard operating procedures should include information on the following:

- What constitutes a reportable adverse reaction?
- Who is expected to report an observation of a suspected medicine-related problem?
- The availability and practicalities of filling in a reporting form.
- Procedures for submission or collection of reports.
- Routines for assessment, follow-up and processing of case reports at the pharmacovigilance centre.
- Procedures for analysis of aggregated information and options for action.
- Good communication practices.
- A description of indicators by which the progress of the monitoring system may be measured (*16*).

Pharmacovigilance guidelines are the main materials available for use in the training of peripheral health workers in pharmacovigilance (*3*, *13*, *17*, *18*).

CHAPTER 4

EFFECTIVENESS AND RISK ASSESSMENT OF THERAPIES

4.1 Effectiveness and risk: benefit and harm

Estimating the risk and benefit of medicines among the populations exposed to them is essential to promote their rational and safe use and will enhance the tolerability and acceptability of mass-treatment programmes.

The effectiveness and risk profiles of many of the medicines used in PHPs in the past have been established by long experience rather than on the basis of epidemiological evidence. The modern approach to public health requires that advice be given on the best general ways of approaching the management of diseases, notwithstanding the necessity for considerable freedom to modify therapy according to individual needs. Because of the need for comparative effectiveness and risk profiles of treatment options to find the most useful medicine at the most reasonable cost, it is necessary to use the correct conceptual and practical approach to assessing the effectiveness and risk of medicines.

When new medicines are marketed, only data on animal pharmacology and toxicology, and limited information on their use in humans are available. The number of subjects who have received the medicine in randomized clinical trials before it is marketed may be as few as 100 and is never more than 5000. Although such trials are an irreplaceable tool for determining the potential benefits of the medicine, they provide only limited insight into the likely responses of patients in whom other medicines are administered concurrently; the effects on diseases other than the target disease; the effects of dose variation; nutrition, and many other factors. In clinical trials, only risks of greater than 1/1000, at best, are likely to be noted. At this stage it is not possible to say that degrees of efficacy and hazard have been established, i.e. the potential for effectiveness and risk. A practical level of knowledge of effectiveness and risk can be achieved only when tens of thousands of unselected patients have been treated, and information on the results has been gathered.

It is also important not to confuse benefit with effectiveness. Benefit, described as an overall good, is difficult to define for a society.

It is common to compare pre-marketing efficacy with the spontaneous reports of harm collected. Because the processes for collecting the information are totally different, great care must be taken in interpreting the results; indeed many assumptions need to be made before any intepretation is possible. Another common problem is the comparison of the efficacy and harm of a new medicine with what is much closer to a set of effectiveness and risk data for an older medicine, derived over years of experience.

The Council for International Organisations of Medical Sciences has produced a monograph (*19*) that gives much helpful practical advice on how to assemble information on both effectiveness and risk, and points out some of the potential pitfalls in evaluation. It proposes that the context of the evaluation should be quite clear and that any value judgements must be transparent. Nevertheless, the likely imbalance between the effectiveness data and risk data in terms of quantity, quality and the sources, remains a difficulty that is rarely addressed explicitly in comparative studies of therapies, whether pharmaceutical or other (such as surgery).

Therefore, as medicine development progresses at a rapid pace, and WHO proactively, in partnership with industry, promotes the use of new medicines for the control of diseases in developing countries, there will be a paradigm shift in approach to ADR monitoring of medicines used in national programmes.

Estimating the risk and benefit of medicines for the populations exposed to them is essential to promote their rational and safe use and will enhance the acceptability and tolerability of mass-treatment programmes. This estimation requires the monitoring of programmes to detect, evaluate and prevent adverse reactions, including effects on pregnant women, the elderly and children. Acceptance, misuse, pharmacological dependence, therapeutic errors, and therapeutic failures due to poor-quality medicine or counterfeits, all need to be evaluated to judge the efficiency of the treatment.

4.2 Decision-making in risk situations

> *A concept central to decision-making is "acceptable risk". The fundamental question is, "Acceptable to whom?"*

In critical public health situations, decisions are made either by the PHP or by the national regulator on the basis of available evidence, informed by prior experience, political context and professional judgement.

The decision could be any of the following:
— Stop the programme; investigate effectiveness/risk.
— Continue the programme, but investigate effectiveness/risk.
— Undertake additional studies.
— Issue information of public interest.
— Issue new guidelines for the PHPs.

A concept central to decision-making is "acceptable risk". The fundamental question is, "Acceptable to whom?" Individual patient health lies outside the scope of this document. These decisions are the responsibility of the health practitioner and are taken after discussion with his or her patient. The prescribing physician and the patient must still be at liberty to make their choice, although their decisions should be guided by the public health constraints specific to that locality, and based on reliable information.

In public health and community health issues, the manufacturer is responsible for making the medicine available to people, and regulators are responsible for protecting and advancing the health of the public. The latter may be considered to have consented implicitly to such decision-making, but individuals in the community are less well-

informed. The assessment of effectiveness and risk is therefore even more critical, and is likely to be challenged by individual accounts of benefit and harm, particularly if they are emphasized by the public media.

4.3 Good decision-making practices

The conventional decision-making process in public health needs to be strengthened to deal with quantitatively and qualitatively more complex issues arising out of new medicines being used in PHPs.

4.3.1 Expertise
4.3.2 Evidence base and scientific decision-making
4.3.3 Explicit predetermined criteria
4.3.4 Comparators
4.3.5 Objectivity
4.3.6 Transparency
4.3.7 Accountability

Decision-making is the process of determining the actions to be taken, who should take them, and the order and methods of taking action. It also entails judgements on the best means of monitoring, follow-up and of communicating the appropriate information to the parties concerned. Decision-making, should follow three principles, namely:
— objectivity;
— transparency; and
— accountability.

Moreover, to achieve success, there is a need to consider each decision in terms of the following headings:
— Obtaining the best data and information
— The context of the decision
— Definition of the steps to be taken to reach a decision, for example, by simplifying into sets of subsidiary decisions, and being able to sum the results of such smaller decisions into an overall strategy
— Communication and action
— Follow-up
— Impact
— Revision of the original decision as necessary.

4.3.1 Expertise

Regulators and manufacturers make decisions on the marketing or withdrawal of medicines, or changing the label or summary of product characteristics. This is often done in consultation with a team of experts either as a standing committee or an ad hoc expert committee. Consumers and patients may be directly or indirectly party to the decision or may not be involved at all.

The decision to start a programme for public health is taken after considerable deliberation at the international and national levels. The regulator (medicine controller) or manufacturer has not usually been involved until now, because the medicines used historically have been marketed for a long time. Also, in developing countries, consumers

are usually not involved directly in the decision-making process. However they influence the success of the programme by accepting or rejecting it as it begins to have an impact on them.

The conventional decision-making process in public health needs to be strengthened to deal with quantitatively and qualitatively more complex issues arising out of new medicines being used in PHPs. It is important that all the relevant players are identified and involved from the start and that procedures are outlined to enable those involved to reach the best decision.

4.3.2 Evidence base and scientific decision-making

Information should be gathered from all relevant sources and by a variety of methods. The data from all sources including initial regulatory applications, scientific publications, and information on populations exposed in different countries, among others, should be made available as completely and rapidly as possible. Computer programmes for collection and collation of data are needed to optimize data-gathering. Computer-assisted algorithms, when used appropriately, may assist in the consideration of all available data, weighting it and making the system transparent and objective.

4.3.3 Explicit predetermined criteria

International agencies such as WHO would play a key role in developing predetermined criteria for decision-making. When a new medicine is made available for public health, the efficacy and hazard data would be based on pre-marketing studies. However, once the use of a medicine has become widespread, the effectiveness–risk profile might be very different. A risk-management strategy (including assessment of effectiveness in practice) will help in making decisions, which may well vary from region to region due to regional differences in distribution of pathogens, disease presentation or perceived importance (priority) of the disease in relation to other health-related issues.

4.3.4 Comparators

Data on experience with other therapies including non-medicine interventions to assess comparative effectiveness and risk are essential to enable decisions regarding new medicines and programmes to be made. In the case of new medicines to be used for the treatment of an infectious disease, information on the effectiveness and risk of the medicines in use would be needed. Such information is usually collected in situations where its generalization to another context needs to be considered carefully. If medicines are to be used for the control of a disease, when there is no existing programme, information on the natural history of the disease together with morbidity and mortality statistics will be required.

However once the programme is implemented, especially if it is implemented in an entire region, data on comparators will not be available and it would be necessary to rely on historical data for comparison. For anti-infective agents the effectiveness and risk balance could change due to alteration (or even return) of bacterial sensitivity or resistance.

4.3.5 Objectivity

Objectivity relies on several attributes and qualities of people and processes. Of these, a willingness to be open with information and details of processes, identifying all the players who need to be included and involving them, identifying and separating fact from opinion, are key factors.

4.3.6 Transparency

It is expected that in the decision-making process, information on the options available will be considered objectively, and be made openly available for critical review.

4.3.7 Accountability

All partners in the process, including pharmaceutical manufacturers, regulators, managers of PHPs and pharmacovigilance experts are involved in ensuring the success of the PHP.

Decisions are made on the basis of data available at a given time and should be made objectively. Circumstances change; therefore the expected outcomes must either be specified or estimated. After an action has been initiated, data must continue to be collected as part of the continuous process of monitoring of effectiveness and safety.

The data should be periodically analysed to determine whether:
— the outcomes are those desired;
— new information indicates the need for further review and possible modification of the original action;
— there are sufficient data to consider undertaking a new effectiveness–risk assessment.

CHAPTER 5

PHARMACOVIGILANCE AND PUBLIC HEALTH PROGRAMMES: CURRENT SITUATION (SEE FIGURE 4)

There can be better health outcomes as a consequence of good information on safety, which allows the early identification and prevention of adverse reactions, resulting in the more rational use of medicines, and better adherence within the target population.

5.1 Strengths

Recently there have been some initiatives within countries, or under the leadership of WHO, to create and develop subsystems for pharmacovigilance to monitor the specific products used in their PHPs (e.g. vaccines, antiretroviral therapy, antimalaria programmes and anthelminthic programmes). On the other hand, some developing countries already have established pharmacovigilance centres that function independently. This situation provides all the ingredients for developing a unique and efficient pharmacovigilance system within PHPs and to integrate both systems.

Although there are fundamental limitations and weaknesses in both PHPs and pharmacovigilance systems, PHPs have some distinct advantages for undertaking pharmacovigilance, and pharmacovigilance systems can benefit from the experience of PHPs.

Public health programmes:
— often have well-established roles through undertaking important and essential health care work with large populations, often engaging in preventive and curative interventions through the use of medicines;
— frequently get better resource support than is normally given to pharmacovigilance programmes including support from international sources;
— normally have set guidelines or protocols;
— adhere to established performance monitoring and evaluation procedures;
— have established information systems to process epidemiological data;
— can often provide denominators (numbers of patients treated) which can be used for the calculation of rates or incidence of ADRs; and
— have good training programmes for health care providers.

The particular strengths of pharmacovigilance programmes are in the development of new methods for assessing the safety of medicines, including better analyses of data and signal-detection processes. As well as safety issues, pharmacovigilance programmes assess quality and efficacy and the correct indication(s) for use. All of these can provide critical support for the use of a specific medicine, often lacking in PHPs. Another strength of pharmacovigilance programmes of considerable importance to PHPs is the training and expertise in effectiveness–risk evaluation and its communication to the

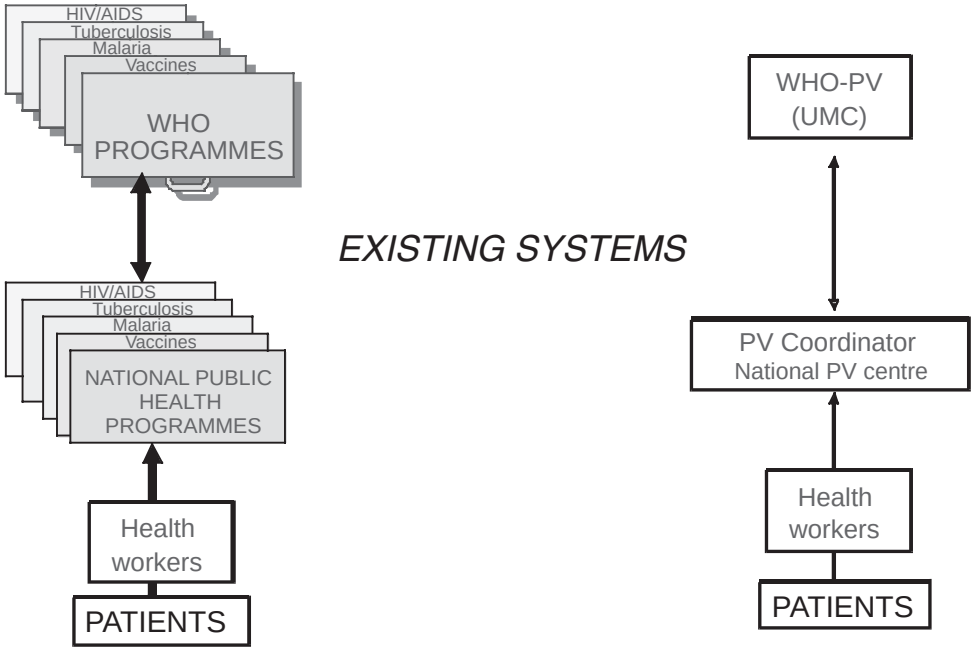

Figure 4. Pharmacovigilance and public health programmes: current systems

population, which is an essential component of good pharmacovigilance practice and is an ethical imperative (*14*).

There is clearly considerable merit in linking pharmacovigilance with PHPs. There can be better health outcomes as a consequence of good information on safety, while the early identification and prevention of adverse reactions results in the more rational use of medicines and better adherence within the target population, as a result of the reassurance that monitoring and good communication on risks and benefits provides. The identification of safety, efficacy and quality problems will also have favourable implications for decisions on medicine procurement. In addition, resources and information can be shared and duplication of effort can be avoided.

Harmonizing these programmes should strengthen the national health authority and health care delivery systems as a result of better health outcomes from the PHPs and resource savings. There are also opportunities for shared capacity building and the conduct of trials of new medicines used in PHPs. In addition, the effectiveness of pharmacovigilance will be enhanced because of the availability of denominator values and the ability to calculate the actual risk of harm and make better comparisons between medicines.

5.2 Weaknesses

Although PHPs are well-established and are considered as crucial and essential for the health of any nation, pharmacovigilance often remains incorrectly perceived as a luxury

discipline that governmental authorities cannot support and hence that only developed nations can afford. In most developing countries, there are insufficient resources within the public health system to undertake training and capacity building and to invest in systems for monitoring drug efficacy and safety. The major resources are often concentrated on developing PHPs to reduce disease morbidity and mortality and very few of these countries have a well-established pharmacovigilance system.

In most cases, PHP managers are neither aware of nor trained in the need to detect and report adverse reactions to the medicines that are used in their programmes and that have been on the market for a long time. It is assumed that the medicines used are universally safe and that there is therefore no necessity to monitor or to re-evaluate them. Staff working within PHPs in most developing countries are not trained to assist in monitoring the safety of medicines.

In reality, the implementers of PHPs are often not interested in ADR monitoring, or may underplay the significance of adverse reactions to project the safety of medicines and ensure good adherence. To discuss ADRs is perceived to have a negative impact on the PHP. Training and information about the detection and management of ADRs are seldom considered or emphasized and programmes rarely include any evaluation of benefit versus harm. For example, the manual for the revised national Tuberculosis Programme gives only a table for possible ADR symptoms (side-effects of antituberculosis medicines) and action to be taken.

PHP managers do not always collaborate with pharmacovigilance centres or other PHPs and often function independently of each other leading to duplication of effort and a lack of harmonized terminologies, data collection methods and causality assessment. The information that is collected is not added to the international database for pharmacovigilance and therefore the international community derives no benefit from it. Furthermore, medicine regulators do not always have the benefit of feedback concerning medicines used in PHPs.

In general, pharmacovigilance is not seen as a component of public health. The reasons for this include a misunderstanding of the meaning and the objectives of the discipline; the absence of facilities for receipt, management and analysis of reports; and lack of a reporting culture. It is hoped that this document will encourage clinical programme managers to develop a comprehensive understanding of the importance of pharmacovigilance.

CHAPTER 6

INTEGRATION OF PHARMACOVIGILANCE INTO PUBLIC HEALTH PROGRAMMES (SEE FIGURE 5)

6.1 Introduction

It is important to emphasize that the survival of a PHP may depend on good pharmacovigilance.

The specific needs of countries and programme managers in public health for their pharmacovigilance programmes will differ as new initiatives are undertaken, and the efforts required will depend on the existing systems and infrastructure. It is important to emphasize that survival of a PHP may depend on good pharmacovigilance.

Some countries have well-developed, functioning, national pharmacovigilance centres, which are backed by an MRA. In such countries there is also a strong public health department with separate staff dealing with each vertical disease-related programme. In other countries, the public health department may employ the same staff to handle different disease programmes and pharmacovigilance centres may be rudimentary or absent.

National pharmacovigilance centres may be centralized or decentralized. In different countries public health departments may function at different levels such as the primary, district, state and/or country levels.

The pharmacovigilance in public health model needs to be robust and flexible if it is to be implementable not only in countries with pre-existing public health and pharmacovigilance systems, but also in countries with weak or deficient public health and pharmacovigilance programmes. The pharmacovigilance in public health model should draw on the strengths of the pharmacovigilance and PHPs, avoiding duplication. The model should emphasize sharing of human resources and the expansion of knowledge on effectiveness/risk, collaboration, effective communication, integration, training and capacity building.

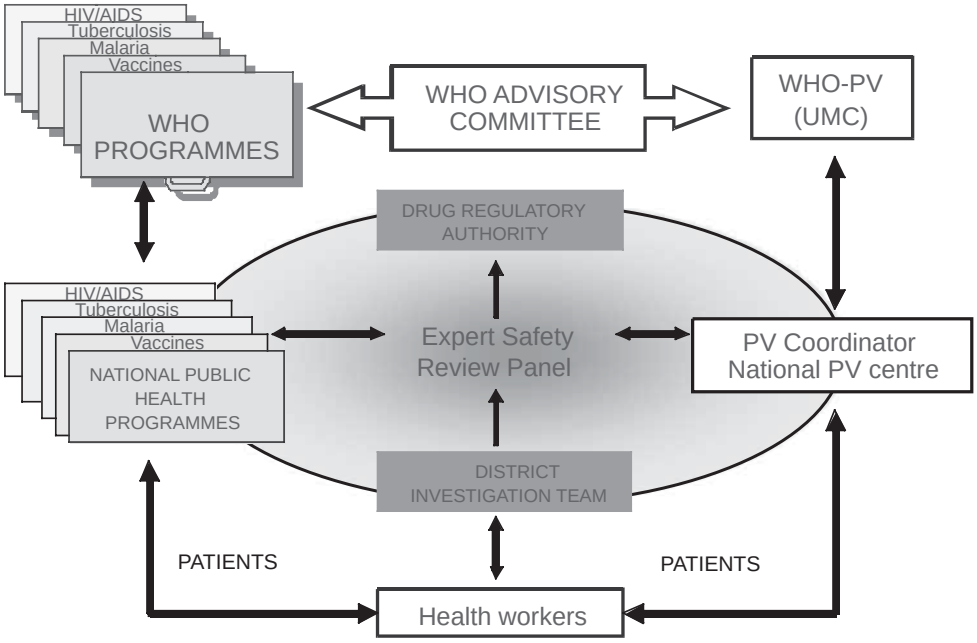

Figure 5. Integration of pharmacovigilance into public health programmes

6.2 Justification

Adverse reactions are a significant cause of morbidity and mortality and can affect adherence to treatment schedules and increase the risk of resistance and relapse of the disease.

The use of pharmaceutical preparations is one of the fastest-growing components of health care expenditure throughout the world. It accounts for 30% of the total health budget in many countries. At the same time, adverse reactions are a significant cause of morbidity and mortality. They can affect adherence to treatment schedules and increase the risk of resistance and relapse of the disease. The treatment of ADRs imposes a largely unrecognized, but considerable, financial burden on health care due to the need for hospital care or other medical interventions. Some of this cost to national health budgets and the personal cost, both financial and in terms of suffering, is avoidable. Health-care practitioners are in a position to make good use of both the positive and negative experiences of treatment to contribute to medical science and to an improved understanding of diseases and medicines.

In some countries there are now high public expectations for the safe delivery of health care, but the public rarely recognizes that pre-approval studies are not sufficient to truly characterize the effectiveness and risks of pharmaceutical products. Good pharmacovigilance practice can generate the evidence that will inspire public confidence and trust.

6.3 Requirements for pharmacovigilance in public health

The ultimate goal is the success of the public health programme.

The major aims of pharmacovigilance in public health will be the same as those of the national pharmacovigilance centre. These are:
— rational and safe use of medicines by health professionals;
— assessment and communication of the risks and effectiveness of medicines used; and
— educating and informing patients.

The ultimate goal is the success of the PHP.

The means of achieving these goals will need to take into account the peculiarities and structure of the PHPs. Pharmacovigilance systems should have the capability for the following important functional components:
— receiving and processing of reports (with verification, interpretation, coding of medicines and ADRs, and case causality assessment) and case management;
— establishing databases and procedures for data analysis and review;
— signal detection;
— decision-making, risk management, follow-up;
— good communication;
— coordination between pharmacovigilance, regulatory and public health activities;
— training of health care workers in reporting adverse reactions;
— training in all aspects of pharmacovigilance;
— promotion; and
— international linkage.

The pharmacovigilance in public health plan for a country should address these functional requirements, give details of the flow of data including feedback, and produce clear organigrams specifying roles and responsibilities. The actual designations of staff, physical locations, exact levels of responsibilities (e.g. national, state, district, primary health centre, village) will vary between countries and will depend on existing health care and regulatory structures in the country.

6.3.1 Reporting, data collection, investigation and management of adverse reactions

Public health departments usually have disease-specific programmes with dedicated staff. Programmes are generally implemented through health-care workers at the village level, who are supervised by the programme-specific staff. Pharmacovigilance programmes in public health should function optimally by utilizing this infrastructure with appropriate additions as necessary. The essential players should be:

— patients (see section 6.6.1);
— primary health-care workers/professionals (see section 6.6.2);
— district hospital (see section 6.6.4);
— district health officer (see section 6.6.4);
— district investigation team (see section 6.6.4);
— tertiary care referral hospital (see next paragraph and section 6.7);
— programme manager (see section 6.6.4);
— national pharmacovigilance coordinator/pharmacovigilance centre (see section 6.6.5 and section 6.6.8); and
— expert safety review panel (see section 6.3.3).

Their roles are described in the sections referred to and in Annex 1.

The village health worker or the physician at the primary health-care centre, together with the district health officer or programme manager, and the tertiary care referral hospital, would form the unit responsible for detecting, investigating, managing and reporting ADRs. The district health officer or programme manager should coordinate this activity. It is critical that ADRs be reported without delay.

A standardized reporting form should be available to the primary health-care worker. This person should report the ADRs to the district health officer (or equivalent). The district health officer or programme manager in association with the district investigation team will follow up reports of serious ADRs or other ADRs of interest and submit details to the national pharmacovigilance coordinator for review by the safety review panel.

The primary health-care worker should manage minor suspected ADRs. Patients with serious or severe ADRs should be referred immediately to the nearest hospital (district hospital) for investigation and management. The details of management and outcome should be included in the report submitted by the district health officer or programme manager. Staff from the PHP already performing the function of health-care delivery should be best suited to detect, investigate and manage ADRs. These staff would however need extra training in the identification and reporting of ADRs.

6.3.2 Coordination

The essential elements of pharmacovigilance in public health are the same as for pharmacovigilance in general. Essential to the success of pharmacovigilance in public health is a pharmacovigilance coordinator who will bring the relevant expertise and coordinate and integrate the pharmacovigilance activity between different vertical disease-specific PHPs.

The position of coordinator may be full-time, or initially part-time, depending on the extent and nature of development in the country, and the person appointed should be a member or secretary of the expert safety review panel (ESRP). The coordinator should be drawn from the national pharmacovigilance centre. Where no such centre exists, any dedicated medical person from an academic institution, public health or the MRA might manage this activity, but should have a scientific approach. He or she may be located physically in a university hospital or a public health department with the necessary infrastructure and secretarial assistance to enable him or her to carry out his or her duties. This person should be knowledgeable about pharmacovigilance concepts and would be a

useful resource officer to develop a national pharmacovigilance system according to international standards.

6.3.3 Database, causality (relationship) assessment and data analysis

The database
Relationship/causality assessment
Data analysis
The expert safety review panel

The database

Reports of adverse reactions should be submitted by the district or programme officers to the coordinator for inclusion in the database. The database should have all the fields necessary for adequate case assessment, accurate analyses and possible follow-up. These should include:

— location of origin of the report;
— the identity of the reporter;
— patient identification — to avoid duplication and enable follow-up if necessary (the patient must be identified in such a way as to ensure patient confidentiality);
— age and sex of patient;
— information concerning the medicine, including name and formulation, manufacturer, mode of administration, dose and dates of administration;
— indication for use;
— other morbidity and relevant history;
— concomitant medications with doses, dates and indications;
— details of the event(s) with date of onset and details of any investigations;
— adverse reaction term from a recognized dictionary, e.g. the WHO Adverse Reaction Terminology (WHO-ART) or the Medical Dictionary for Regulatory Activities (MedDRA);
— assessment of seriousness and severity; and
— management and outcome.

Relationship or causality assessment

The relationship or causality assessment should follow the WHO Guidelines (*3*). The initial step is to establish the temporal relationship of the event to the use of the medicine. This requires knowledge of the duration to onset of the event from the time of commencing treatment with the medicine, the response to withdrawal of the medicine and the result of rechallenge if this is undertaken. Causality for a particular type of event can often be established only by epidemiological means and/or a knowledge of the pharmacology of the medicine. In the context of PHPs for disease control, it is necessary to record all events that could possibly be related to the medicine. It is for the pharmacovigilance centre to assess causality.

Data analysis

The numbers of reports of particular events can be used to calculate incidence if the denominator is known. Programs should be available that will sort the data appropriately, e.g. different types of event by System Organ Class, or to enable analyses of possible risk factors such as age.

The expert safety review panel

The ESRP occupies a very special position in causality assessment. A preliminary assessment should have been undertaken and follow-up conducted if necessary, before reports are presented to the ESRP.

The panel should be constituted as follows:
— the programme manager;
— the pharmacovigilance coordinator;
— a clinical pharmacologist or a clinician who has an interest in medicines;
— a physician and disease expert;
— a pharmacist;
— a member of the MRA;
— other members with specific expertise as required e.g. a paediatrician or a gynaecologist; and
— a representative of a consumer organization may be included.

The functions of the ESRP will be to:
— review reports referred by the pharmacovigilance coordinator or programme manager;
— assess safety issues from reports of serious ADRs and/or cumulative data;
— assess safety issues that, although not serious, may affect adherence;
— assess reports that may suggest lack of efficacy and determine the likely cause;
— recommend further follow-up and investigation when indicated; and
— recommend appropriate action to the pharmacovigilance coordinator, programme manager or regulatory authority. This will include communication with health providers and/or the public.

The ESRP may be common to all PHPs or may be disease- or programme-specific.

The facilities of the national pharmacovigilance centre for the assessment of case reports, data processing and database management should be used by the coordinator, with modifications as needed. In countries where no such system exists, the pharmacovigilance coordinator should develop the facility with advice from WHO and the ESRP.

The recommendations of the ESRP should be submitted to the regional or national programme director, the national pharmacovigilance centre and/or the MRA for their decisions.

6.3.4 Special situations

New medicines become available with little or no information on their safety during use in pregnancy in humans or on risk of death among people with the diverse characteristics that will be seen in the target population.

Exposure during pregnancy

New medicines become available with little or no information on safety when used by pregnant women. To assess the safety of a medicine during pregnancy, it is essential that all women of child-bearing age are followed up to see if they were pregnant at the time of exposure to the medicine in question. Before administration of the medicine to a

woman of childbearing age, questions should be asked about the possibility that the woman is pregnant, but because many women, particularly in rural areas, may not be aware of their pregnancy in the early months, it is necessary to check later to see if they were pregnant at the time. All women who are identified as having received the medicine while pregnant should be followed up for the outcome of the pregnancy, both in terms of the health of the fetus/infant and the mother. The involvement of antenatal clinics and birthing units is essential. Country- and programme-specific procedures need to be established to collect all the relevant data. The district investigation teams should have the responsibility for investigating outcomes and should report to the national pharmacovigilance coordinator. The national pharmacovigilance coordinator should establish a pregnancy register and report current and cumulative results to the ESRP.

Deaths

It is important that all unexpected deaths following administration of the programme medicine are investigated. In many areas, and in the absence of routine follow-up, problems will arise in identifying these deaths, but a system of notification appropriate to the area should be established. In each case, the cause of death will need to be established as accurately as possible. Deaths that have occurred within a plausible time period following administration of the medicine would need to be investigated further by the district investigation team to establish the strength of the association between the death and the medicine. Guidelines for the follow-up of specific causes of death should be formulated. All deaths considered to have a possible relationship to the medicine should be reported to the district programme manager and thereafter to the ESRP.

6.3.5 Decision-making

The reporting team, district health officer or programme manager, in consultation with the supervisor, could decide to stop administration of the medicine to the affected patient, withhold a batch, or withhold treatment in the area as an interim measure, pending a final decision by the competent authority.

The MRA, with inputs from the ESRP, national pharmacovigilance centre, national PHP, WHO Collaborating Centre for International Drug Monitoring, WHO and the International Advisory Panel as appropriate, may give relevant advice.

6.3.6 International linkage

As soon as a pharmacovigilance programme is set up in a country, efforts should be made to link it formally with the WHO international network of pharmacovigilance centres. As of 2005, the WHO International Drug Monitoring Programme, comprising 78 national pharmacovigilance centres throughout the world, maintained a database containing more than 3.5 million case reports of suspected ADRs. The WHO database and the competence, support and services offered by the WHO Programme should be used for the development of the emerging national pharmacovigilance system. In the WHO database, information from developing countries is under-represented, as is information on medicines used in the treatment of tropical diseases. If PHPs sent all the information that they collected on adverse reactions to the pharmacovigilance centre in their country, this would then be forwarded to the WHO database. Experience gained from PHPs will constitute a valuable contribution to this international repository. The national pharmacovigilance coordinator should contact WHO and establish working relationships

with the WHO Collaborating Centre for International Drug Monitoring with the aim of attaining formal member status in the WHO Programme for International Drug Monitoring.

6.4 Spontaneous reporting

Spontaneous reporting is a system whereby case reports of adverse drug events are voluntarily submitted by health professionals, pharmaceutical companies or consumers to the national pharmacovigilance centre.

Spontaneous reporting is defined in section 3.4.1. It is basically the reporting of a suspected adverse reaction on the initiative of the health professional who becomes aware of the problem, or on the patient's initiative. These reports can be communicated by any means, but in countries with a well-developed pharmacovigilance system they are most often reported on the country-specific reporting card. The key feature is that reports are initiated by the health professional (or patient) and not solicited systematically. The type of reporting described in this document so far should be considered spontaneous. However, in PHPs, reporting should be more focused and intensive. Such reporting is sometimes referred to as intensified spontaneous reporting, or ideally, prospective monitoring should be undertaken as described below.

6.5 Cohort event monitoring

As well as producing data on rates, cohort event monitoring is particularly effective at identifying previously unrecognized and unsuspected adverse reactions and defining the associated risk factors.

Cohort event monitoring refers to the use of prospective, observational cohort studies of patients to whom the medicine of interest has been administered. All adverse events are recorded in the study, not only suspect adverse reactions. This makes the method particularly effective at identifying previously unrecognized and unsuspected adverse reactions. A cohort is built up of all patients receiving the medicine together with demographic data. This requires a record of patients to whom the medicine is administered. The means of recording this information will be best established when planning the PHP and may vary depending on the country (and perhaps the region), the programme and the medicine being monitored. Normally a cohort of 10 000 patients is sufficient to provide adequate statistical power, but larger numbers may be needed to enable adequate study of particular subgroups of interest. This method has been described as "prescription event monitoring" (PEM) (*20*). The term "PEM" is inappropriate for use in most PHPs and this method is better referred to as "cohort event monitoring".

Essentially the method consists of
— establishing a cohort of patients; and
— collecting information on all the adverse events that occur in these patients for a (defined) period after use of the medicine.

The cohort needs to be as complete and as representative as possible. Decisions would have to be taken on the selection of patients. Two options are available: enrolment of all patients in selected, representative regions until the cohort reaches the target figure, or a method of systematically sampling patients from the whole country, e.g. recruitment of all patients seen at clinics on a Thursday.

The recording of all adverse events is essential if new signals are not to be missed. Appropriate recording forms would need to be designed, appropriate procedures established for follow-up to obtain information on any adverse events, and staff trained in the methodology.

The method is adaptable to different situations and different needs. One approach that will help reduce potential confounding is to record adverse health events experienced by each individual for a period prior to exposure to the medicine and an equal period afterwards (e.g. 1 month).

Cohort event monitoring has the following advantages:
— the ability to produce rates;
— the ability to produce a complete adverse event and/or adverse reaction profile for the medicine(s) of interest;
— the ability to characterize reactions in terms of age, sex and duration to onset and thus produce risk factors. Other relevant information may be collected, for example on weight or comorbidity to provide the opportunity for determining other risk factors;
— the ability to make accurate comparisons between medicines using this methodology;
— the ability to establish a pregnancy register and define and calculate rates of any abnormalities. To enable the identification of women who are pregnant, an appropriate follow-up period would need to be determined (e.g. 5 months);
— because of the routine follow-up, the ability to detect, with confidence, reduced or failed therapeutic effect and thus raise suspicion of inaccurate diagnosis of disease, programme failure, poor quality or counterfeit medicines;
— the ability to record and examine details of all deaths; and
— the ability to produce rapid results in a defined population.

These advantages help overcome the many deficiencies of spontaneous reporting on which the majority of pharmacovigilance activity depends. Spontaneous reporting remains essential, and because it normally covers the whole population for an unlimited period, may have a better chance of revealing rare, serious ADRs. It should be remembered though, that common, non-serious ADRs can be more important than rare serious reactions, because they affect more people. The two systems of monitoring are thus complementary.

6.6 Roles and responsibilities

Where established, the national pharmacovigilance centre will be responsible for the development of pharmacovigilance in the public health system, will promote pharmacovigilance in the PHPs and sensitize professionals and public health staff to the reporting of adverse reactions and irrational use of medicines.

6.6.1 Patients and the public

Public awareness about adverse reactions, early reporting and management are essential for ensuring patient confidence, in and adherence to, pharmacotherapy. In some countries patient reporting is accepted and can add value, but this needs to be separate from reporting by health professionals. In some programmes (e.g. AIDS), the input and

involvement of patient interest groups can be sought while formulating the programme and should be part of the feedback–communication link.

6.6.2 Primary health-care workers

It is the responsibility of the primary health-care provider to detect, investigate, manage and report ADRs. These staff will need training on the importance of adverse reactions, diagnosis, the basic principles of causality assessment and the important elements of the adverse reactions reporting form.

Patient education is an important role of the primary health-care provider. Educating the public on ADRs is important for promoting adherence. Counselling and explanation about adverse reactions will promote patients' confidence and adherence.

The reporting of adverse reactions needs continuous stimulation. It is important to achieve a positive attitude towards pharmacovigilance. To encourage reporting, the following steps should be of help:
— easy access to reporting forms;
— training;
— acknowledgement of receipt of a report and provision of feedback to the reporter;
— participation of reporting staff in pharmacovigilance meetings, and of pharmacovigilance staff in professional meetings; and
— collaboration with the national pharmacovigilance centre.

6.6.3 Other health-care workers

Health-care workers outside the government system should also report adverse reactions. These would include, among others, nongovernmental organizations and charitable health facilities.

6.6.4 District investigation team

The district investigation team plays a central role in monitoring adverse reactions. The team should comprise a clinician in the district hospital, head nurse, pharmacist and district health officer or programme manager. The team is responsible for following up adverse reactions reported from all the health facilities within their district. (In the case of vertical programmes the specific programme manager will be responsible for medicines pertaining to that programme.) The team will play an important role in collaboration with and encouragement of reporting by primary health centre staff and hospital staff. Their detailed follow-up of suspected ADRs will be used to assess causality. The district health officer or programme manager will coordinate the investigation, report to the national pharmacovigilance coordinator, and contribute to the education of clinical staff and the public on medicine safety. The findings of investigations and conclusions of the ESRP, in terms of causality and actions to be taken, will be fed back to the reporter and patients by the district investigation team or designated individual.

When dealing with reports of ADRs, the district investigation team should:
- Review all reports.
- Decide which reports need further investigation on the basis of:

— seriousness (including all deaths);
— severity;
— exposure to medicine during pregnancy;
— apparent signals of new reactions; and
— patterns of suspected reactions which although not serious, may affect adherence and the success of the programme.

- Refer all reports to the national pharmacovigilance coordinator for processing and review by the ESRP.

6.6.5 National pharmacovigilance coordinator

The coordinator, who should be on the staff of the national pharmacovigilance centre, should function as the focal point for the national pharmacovigilance system in the PHP. Ideally this should be a full-time position. The responsibilities of the national coordinator would include coordination, communication, integration, training and supervision of the pharmacovigilance-related activities of the district investigation teams. This person would also serve as member or secretary of the national ESRP. The national coordinator should be responsible for developing the system, for the collection and storage of all reports of adverse reactions and for coordination and communication between the national pharmacovigilance centre, the district investigation teams, the national MRA, the PHP at the national level, the ministry of health, international centres, and the pharmaceutical manufacturer or supplier. The national coordinator should ensure harmonization of pharmacovigilance in public health with other national pharmacovigilance activities, promote the reporting form, and develop a national database for signal generation. The coordinator should have the necessary facilities for carrying out his or her duties. In areas where no national centre exists, the national coordinator should be based in an academic institution, tertiary care hospital or in a public health office.

The coordinator should ensure that the ADR reports are processed appropriately for assessment by the ESRP. These would generally fall into one of three categories:
— reports selected for investigation by the district investigation team, which should be considered in detail;
— reports considered to be a signal of a new adverse reaction; and
— all other reports, which may be presented in summary format, so that an overall reaction profile of the medicine can be obtained.

Depending on the volume of reports, a selection process may need to be developed so that the ESRP can give priority to the important issues.

6.6.6 National medicines regulatory authority

The regulatory authority will receive reports and recommendations from the ESRP. It will perform risk assessment and consider options for regulatory action which may involve requiring the manufacturers to make changes in the labelling of their product or may be a restriction in the use of the product, a temporary suspension or complete withdrawal. The regulatory authority may liaise with other national MRAs and it should always pass on the information on any action taken to WHO.

6.6.7 Pharmaceutical industry and marketing authorization holders

Pharmaceutical manufacturers are legally responsible for the safety and effectiveness of medicines while the product is available in the marketplace. They should provide medicines of good quality and have stewardship of their products. As essential players in the provision of medicines, they should be kept informed of the results of monitoring and relevant decisions. They also have a duty towards assessing the effectiveness and safety of a PHP and the benefits to patients. They should report adverse reactions both to the national pharmacovigilance centre (or in the absence of such to the MRA) or PHP and, in countries with no MRA they should also report to WHO through the disease control PHP.

6.6.8 The national public health and pharmacovigilance programmes

The national pharmacovigilance centre will be responsible for the development of pharmacovigilance in the public health system. The centre, jointly with the PHP, should decide, on a continuous basis, priorities in pharmacovigilance for the PHP, whether all or only a few priority medicines will be monitored, when to review adverse reactions, the duration of monitoring and the time frames for reporting and action, and should evaluate the safety of the programme. The national pharmacovigilance centre will link with WHO for technical and policy advice. It should also assist the national pharmacovigilance coordinator in training activities. The centre will promote pharmacovigilance in the PHPs and sensitize professionals and public health staff to the reporting of adverse reactions and irrational use of medicines.

The national coordinator should meet with the appropriate national PHP director to address issues relating to national and international need. The need for monitoring specific medicines may arise when new programmes are begun, or when expanding the coverage of a current programme. The beginning of a new programme could be a useful starting point for the development of a comprehensive national pharmacovigilance system with the support of all the above-mentioned players.

6.6.9 The media

The media have an important role in creating awareness in the community and among professionals. The Erice declaration (Annex 4) urges all players, including the media, to strive towards the highest ethical, professional, and scientific standards in promoting the safe use of medicines. WHO has made considerable efforts to train medicine regulators and national immunization staff in communicating information to the media on adverse events following immunization.

It is important that the media are involved from the start of a PHP and that the need for the programme is publicized together with the need for pharmacovigilance. The pharmacovigilance programme should be explained and good lines of communication should be set up between the media and the ESRP or the designated liaison person, to ensure the availability of authoritative information. The need for good information should be anticipated so that potential crises can be dealt with quickly and effectively, and public confidence maintained.

It is desirable that one person, who can speak with authority and who is widely respected, is designated to be responsible for liaison with the media. This person should be

appointed and trained in media relations before the programme begins. Professional organizations and health workers should be advised of appropriate procedures to follow when faced with public concerns or questions from the media. The procedure should generally be to refer them to the media liaison person. This approach should limit the possibility of conflicting messages coming from different sources. When communicating with the media, the following information should be available:

— A complete account of any event of concern and its appropriate context (in terms that will be understood by the lay public), e.g. a clear statement that an event is an isolated occurrence, to prevent concern that it may be widespread.
— The likelihood that there will be new cases linked to therapy with the medicine.
— An outline of actions taken or planned (depending on the stage, this will range from a plan of action to a completed investigation).
— The cause of the event (when identified with reasonable certainty).
— The corrective action that has been or will be taken.
— Guidance to the public on how to respond to concerns over the medicine including contact information for reporting further adverse events.

It is useful to assess the impact of media communications on public awareness and attitudes as this will assist the development of future communication strategies.

6.6.10 The roles of WHO and the International Advisory Committee

The role of WHO

At an international level WHO will play a key role. While supporting countries to conduct PHPs, WHO and its regional offices have a responsibility to promote the establishment and building of sustainable safety monitoring systems. WHO will take a lead role in supporting Member States in the safe use of medicinal products. WHO will serve as a repository for information from both pharmacovigilance programmes and PHPs, and will disseminate this information appropriately. WHO will identify areas requiring research and encourage and support initiatives to conduct operational research. It will assist countries to define and develop policy on monitoring the safe use of medicinal products and it will respond to controversial issues on the safety of medicines that threaten the use of medicines in a national or international PHP. It will promote and encourage uniformity of terminology and will promote and develop resource materials and provide leadership in training and capacity development.

Advisory Committee on Safety of Medicinal Products (ACSoMP)

An Advisory Committee has been established by WHO to advise on issues that:

— are important to national or international programmes and have the potential to affect them adversely if not resolved;
— cannot be met by structures and/or institutions and/or systems that are already available;
— respond to identified needs of a country that may be beyond the capability of the country or countries themselves; such responses should be made within an appropriate period of time, taking into account any existing information and the urgency of the issue; and/or
— are likely to have policy implications for countries and which should meet policy needs including policy needs throughout WHO (the latter includes the conduct of and future developments in pharmacovigilance in all programmes throughout WHO); and

— will advance and promote the future development of pharmacovigilance as a discipline.

6.7 Where there is no national pharmacovigilance system

The development of pharmacovigilance within a PHP should be seen as an important opportunity for the development of a comprehensive national pharmacovigilance system and should be seen as an obligatory investment in the future public health of the territory.

In the absence of a national pharmacovigilance system, the development of pharmacovigilance within a PHP should be seen as an important opportunity for the development of a comprehensive national pharmacovigilance system with the support of the experts involved. Indeed, this should be seen as an obligatory investment in the future public health of the territory. It can be achieved by consultation and collaboration with:

— the national MRA or ministry of health;
— WHO headquarters, Geneva; and
— WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre), Uppsala, Sweden.

The establishment of a national system for the safety of medicines, including a national pharmacovigilance centre, will facilitate pharmacovigilance within the PHP and enable pharmacovigilance to be coordinated between different PHPs, which will improve efficiency. The effect of this should be the availability of greater expertise in monitoring for safety and a more cost-effective PHP.

Guidelines on setting up and running a pharmacovigilance centre have been published (*3*). It might be advantageous to establish the centre in a tertiary care hospital or an academic institution (medical or pharmacy school).

6.8 Training and capacity building

Public health staff will not have received the training or have the expertise necessary to deal with serious medicine-induced disease, unexpected adverse reactions, adverse reactions to new medicines or adverse reactions in vulnerable groups such as pregnant women, the very young or the very old.

Training and capacity building in pharmacovigilance are required for staff working at peripheral health facilities because adverse reactions are not well understood and, in many countries are seldom detected and reported. Monitoring is often neglected or absent, and staff therefore need to be made aware that ADR monitoring is a part of good professional practice. The identification of ADRs, the completion of reporting forms and procedures for patient referral all need to be taught. Clinical teaching in the diagnosis of adverse reactions is essential. Competence will need to be achieved in assisting investigations by the district investigation team. Motivation to continue monitoring over a longer period of time may diminish and the pharmacovigilance system may require the introduction of training to sustain activities. Common concerns and barriers to reporting by health care personnel will need to be addressed during such training activities. Communication issues also need to be addressed in training courses.

It is recognized that countries need to develop and tailor their own national training materials to ensure relevance. Materials are best developed with the collaboration of the end-user to encourage ownership and facilitate the process of updating. Steps in the development of training materials include: assessment of needs, preparation of the first draft, revision, pilot-testing, finalization, printing, distribution, implementation, evaluation and updating. Staff in peripheral health facilities in rural and remote areas should be included in training schemes. These health workers have to deal with a high burden of disease, but receive minimal supervision.

In most disease-endemic countries, public health-care providers and professionals have now been exposed to modern concepts of disease management. Most of those who have used standard medicines are familiar with some of the common medicine-related problems such as nausea following treatment with chloroquine.

Public health staff may have been made aware of vaccine-related adverse events and systems for reporting them. However none of them will have the training and expertise to deal with serious medicine-induced disease, unexpected adverse reactions, adverse reactions to new medicines, or adverse reactions in vulnerable groups such as pregnant women, the very young and the very old.

Training and capacity building of staff will be needed to help them carry out their duties against the changing scenario of greater use of medicines, wider coverage of programmes, use of new medicines and the prophylactic use of medicines. Training for these special needs can be integrated with the training for other programme-related activities and will help reinforce this training.

Training and capacity building are required to ensure that staff understand new prescribing practices for new medicines, the correct dosage regimens and how treatment failures are defined. In conjunction, they need to be taught the reaction profile of the medicines they are to use, how to identify ADRs, how to manage them, when to refer patients, the basic data elements required in an ADR report, how to report, to whom and when. Clinical guidance for improving the recognition of serious adverse reactions is required. Staff will need to feel confident in reporting and assisting in the reviewing process. The ESRPs, the national pharmacovigilance coordinator and district health officer/programme manager should all be focal points in training programmes.

Timing of training is all-important. Training, distribution of treatment guidelines and quality reference materials for monitoring ADRs should precede the distribution of new medicine, but only by a short time. Long delays between training and deployment of a new medicine cause confusion and frustration. Refresher courses, reinforcement through newsletters, posters and publications in local medical journals are good ways of ensuring that the message is assimilated and can be recalled when required. Certification of training of personnnel employed in retail outlets would facilitate compliance with prescribing guidelines.

The national pharmacovigilance centre could give general training in pharmacovigilance. Pharmacovigilance training for a specific programme should involve both pharmacovigilance and public health staff. The pharmacovigilance training material could become part of the programme manual.

Capacity building of pharmacovigilance centre staff and the national pharmacovigilance coordinator would be required to set up the pharmacovigilance component of a public health system, develop a reporting form and database, and enable analysis of adverse reaction data and decision-making.

Training in communication skills is vital. The pharmacovigilance programme involves communication with the public and patients about the risks involved in using medicines and the need to report any adverse experiences that are treatment-related. Explaining to the media and elected government representatives the details of the pharmacovigilance system will build public confidence. Training in the preparation of a media statement on adverse reactions that have become headline news is essential so that a balanced and well-reviewed report that justifies any action taken can be presented.

Motivation to continue monitoring may diminish over time and methods need to be developed for sustaining a reporting culture. Common concerns and barriers to reporting by health care personnel will need to be addressed during training (e.g. fear of blame).

Training should be given to the entire team involved in the initial identification, investigation, management and reporting. Training and update programmes should involve the experts who are members of the ESRP.

6.9 Evaluation of the system

Evaluation and assessment should be built into the monitoring system. This will assist in achieving the goals of the programme.

6.9.1 Assessment of the pharmacovigilance system

Evaluation and assessment should be built into the monitoring system. The national pharmacovigilance centre, coordinator and review panel should periodically evaluate whether, or to what extent:
— the reporting is complete, timely and accurate;
— response has been swift enough;
— case management has been appropriate; and
— action has been appropriate to avoid programme error.

Ideally, a set of criteria should be identified by which the performance of the pharmacovigilance system may be evaluated. Such criteria may include:
— distribution of reporting by professional category, specialization or patient reporting;
— reporting quality, e.g. completeness of information, precision of description, contributory value to decision-making;
— proportion of reports, describing reactions that are serious or previously unknown;
— promptness of reporting;
— reporting rate, e.g. the number of case reports per unit of population or number of health workers; and
— evaluation of the impact of adverse reactions on morbidity, mortality and health care costs (often done by analysing hospital admissions due to ADRs).

6.9.2 Impact of the pharmacovigilance system on the public health programme

The pharmacovigilance system adopted may be comprehensive, or may be restricted to a specific medicine or programme. It is envisaged that whatever system is used, it will undoubtedly help in the early detection and prompt management of adverse reactions, but will also assist in achieving the goals of the programme. The pharmacovigilance training given should result in a better understanding of the medicine being used in the PHP, better compliance by health workers with prescribing guidelines and better adherence of patients to dosing regimens, fewer drop-outs and the early detection of counterfeit medicines. There is a need to conduct studies to evaluate the impact of pharmacovigilance in public health, including comparative studies.

CHAPTER 7

CONCLUSIONS AND RECOMMENDATIONS

Pharmacovigilance can strengthen dedicated national programmes such as those for the control and treatment of tuberculosis, malaria, HIV/AIDS, schistosomiasis, human African trypanosomiasis and immunization coverage. It is important that the traditional division between medicine safety on the one hand and PHPs on the other should be removed.

It is nearly 40 years since the World Health Assembly and WHO committed themselves to developing the necessary scientific and clinical infrastructure to provide for surveillance and monitoring of the safety of medicines in general use. Much has been achieved since then. Pharmacovigilance, as the discipline has come to be known, is supported by the WHO Collaborating Centre for International Drug Monitoring, based in Uppsala, Sweden (the Uppsala Monitoring Centre), and a network of 78 countries that are now affiliated as contributing centres. The MRAs have come to depend increasingly on their national pharmacovigilance centres for the continuous review of the safety of medicines that they approve after licensing for general use, and for support of rational use of medicines — particularly those in use in the public sector.

Pharmacovigilance provides invaluable underpinning, or has the potential to do so, to dedicated national programmes such as those for the control and treatment of tuberculosis, malaria, HIV/AIDS, schistosomiasis, human African trypanosomiasis and immunization coverage. It is also essential in providing the necessary infrastructure for essential drugs programmes. Health ministries, health professionals and the public can all be reassured by knowing that there is a competent and functional system in place that focuses on the safety of medicines used in the prevention and treatment of disease, including vaccines and pharmaceuticals for family planning. It is all the more important that there should be dependable monitoring of the safety of medicines as they become increasingly potent and more widely available.

Experience has shown that for a country to be able to rely on its own pharmacovigilance programme a number of elements need to be in place. These are as follows:

— a dedicated pharmacovigilance centre, independently funded (usually by the state), and staffed by a person or persons with expert knowledge of drug safety and of the evaluation of reports of adverse events;
— links, electronic and personal, between the pharmacovigilance centre and WHO, specifically with the Uppsala Monitoring Centre;
— close operational ties with the national MRA that fulfil the mutual needs of the MRA and the pharmacovigilance centre for the evaluation and continuous monitoring of the safety of medicines;
— access to comprehensive and unbiased drug information relevant to the medicines available in the country; and,
— a firm ethical underpinning of the operations of the pharmacovigilance programme as enshrined in the Erice Declaration (Annex 4).

Many of the 78 or so contributing national centres meet most of these requirements. Currently, national centres are expected to respond to the special needs of programmes such as national immunization programmes, HIV/AIDS programmes and introduction of new antimalarials and anti-tuberculosis drugs for treatment and prophylaxis. No MRA, however competent and sophisticated it may be, can fully anticipate and meet the need to address the safety and rational use of the new medicines prior to their introduction for general use.

It has been argued in this document that because medicines are central to PHPs, but have the potential to cause morbidity and even mortality through adverse effects, and accepting the imperative that the use of medicines should be rational and cost-effective, pharmacovigilance is an indispensable public health activity. It is a crucial weakness in pharmacovigilance programmes that they are not fully integrated into national and regional PHPs and it does not make sense that the latter should function in isolation from the former. This report has explored the requirements for integrating the systems of pharmacovigilance with national or regional PHPs. The benefits would be mutual, and considerable, in particular where resources are limited.

To achieve the objective of integrating pharmacovigilance with public health systems the following are necessary. (What follows applies to countries with a minimum national pharmacovigilance system in place. Countries without such a national system will be covered later in this section.)

— The national pharmacovigilance programme should have clinical underpinning, and should be known to and be actively supported by the ministry of health, health professionals and the academic sector. The programme should have ready access to sound and independent drug information (particularly information on drug safety) and it should serve as a robust and dependable reference centre. The public should know of its existence, and have trust in the judgement and expertise of its professional staff. There should be adequate financial support from the state to enable the programme to perform these functions.
— The national pharmacovigilance centre may be based physically (but not necessarily so) at the ministry of health, within the national MRA, within a leading state hospital, or at an academic school of pharmacy, medicine or health sciences. Whatever arrangement is made, there should be close collaboration, exchange of information, and mutual technical support between the centre and the MRA.
— A national medicines safety review committee (ESRP) for adverse reactions that advises both the MRA and the national pharmacovigilance centre, and that has strong clinical representation in its membership, should provide support and focus for the work of the national centre, and for the MRA.
— The scientific and clinical disciplines and methods that underpin PHPs — epidemiology, systematic review and outcomes measurement — are vital for the future successful operation of pharmacovigilance centres and for their integration into the mainstream of public health. Outcomes analysis should be regarded as an inherent part of the work of the national centre, so that its impact on the national disease profile can be readily evaluated and demonstrated. The safe and rational use of medicines needs to be considered in conjunction with epidemiological profiles of disease if sound medicines policy is to be made.
— Pharmacovigilance centres, jointly with current PHPs, should address the special needs of the vulnerable regarding the safety of medicines (i.e. the very young, the

elderly, pregnant women and patients with other diseases, e.g. renal, cardiac or hepatic disease), and of dedicated PHPs such as those for malaria, tuberculosis, HIV/AIDS, schistosomiasis, national immunization programmes and family planning. For this purpose, they should have ready access to dedicated national and international databases in which safety reports on medicines are compiled and managed, and they should themselves be contributing to such information resources.

— Finally, there should be regular opportunities for the professional staff of pharmacovigilance centres to upgrade their knowledge and experience through training, study and research — ideally in conjunction with colleagues in public health.

The World Health Organization has historically played a seminal and vital role in promoting the safety of medicinal products as a clinical and public health issue. The success of WHO, in conjunction with the WHO Collaborating Centre for International Drug Monitoring, in having established 78 national pharmacovigilance centres for the purpose has been remarkable. In addition the signals that have been produced from the centre have to a large extent led to changes in the labelling of medicines. An even greater challenge lies ahead — those countries that do not have the necessary facilities, expertise and resources for pharmacovigilance arguably need them the most. In working to achieve this it will be important that the traditional division between medicine safety on the one hand and public health on the other should cease to exist. Technological advances in information capture, storage and retrieval, improved systems and resources for financing public health and medicine safety initiatives, specialization in medicine safety, and a growing awareness of the importance to the public good of medicines that are safe and rationally used, in addition to their efficacy and good quality, should make these objectives realizable.

To explain how that might happen, and why, has been the purpose of this report.

REFERENCES

1. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalised patients: a meta-analysis of prospective studies. *Journal of the American Medical Association*, 1998, 279:1200–1205.
2. Pirmohamed M, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *British Medical Journal*, 2004, 329:15–19.
3. *Safety monitoring of medicinal products — WHO Guidelines for setting up and running a pharmacovigilance centre.* Stora Torget 3, Uppsala, Sweden, The Uppsala Monitoring Centre, 2000.
4. Potkar CN, Kshirsagar NA, Kathuria R. Resurgence of malaria and medicine resistance in *Plasmodium falciparum* and *Plasmodium vivax* species in Bombay. *Journal of Association of Physicians of India,* 1995, 43:336–338.
5. Mengue SS, et al. Medicine use by pregnant women in six Brazilian cities. *Revista de Saude Publica*, 2001, 35:415–420.
6. *Counterfeit medicines: guidelines for the development of measures to combat counterfeit medicines.* Geneva, World Health Organization, 1999 (WHO/EDM/QSM/99.1).
7. Csillag C. Epidemic of counterfeit drugs causes concern in Brazil. *Lancet*, 1998, 352:553.
8. Singh J, et al. Diethylene glycol poisoning in Gurgaon India 1998. *Bulletin of the World Health Organization*, 2001, 79:88–95.
9. *WHO Guidelines for Good Donation Practices Revised 1999*. WHO/EDM/PAR/99.4. World Health Organization, 1999.
10. St John's Wort (*Hypericum perforatum*) interactions with medicines: EMEA, Canada, Malaysia, Netherlands, Sweden UK, USA . *WHO Drug Alert* 96, 3 March 2000.
11. Solomon AW, et al. Pilot study of the use of community volunteers to distribute azithromycin for trachoma control in Ghana. *Bulletin of the World Health Organization*, 2001, 79:6–14.
12. *Report of the WHO Informal Consultation on the use of praziquantel during pregnancy/lactation.* Geneva, World Health Organization, 2002 (WHO/CDS/CPE/PVC/2002.4).
13. *The importance of pharmacovigilance: safety monitoring of medicinal products*. Geneva, World Health Organization, 2002.
14. *Effective communications in pharmacovigilance containing The Erice Declaration on communicating medicine safety information.* Uppsala, Sweden, Uppsala Monitoring Centre, 1998.
15. *Dialogue in pharmacovigilance — more effective communication*. Uppsala, Sweden, Uppsala Monitoring Centre, 2002.
16. *Surveillance of adverse events following immunization (AEFI) — Field guide for managers of immunization programmes* (WHO/EPI/TRAM/93.02 Rev.1)
17. Mann R, Andrews E., eds. *Pharmacovigilance*. Chichester, Wiley & Sons, 2002.
18. Bénichou Ch. ed. *Adverse drug reactions — a practical guide to diagnosis and management*. Chichester, Wiley & Sons, 1994.
19. Council for International Organisations of Medical Sciences. *Benefit-risk balance for marketed drugs: evaluating safety signals*. *Report of CIOMS Working Group IV.* Geneva, CIOMS, 1998. No. 762.
20. Shakir S. PEM in the UK and Coulter D. PEM in New Zealand. In: Mann R, Andrews E. eds. *Pharmacovigilance.* Chichester, Wiley & Sons, 2002, p. 333–362.

ANNEX 1

SUMMARY OF ROLES AND RESPONSIBILITIES FOR PHARMACOVIGILANCE IN PUBLIC HEALTH PROGRAMMES

Patient, public	— to follow prescribed treatment and report adverse reactions to health-care provider
Primary health-care worker	— diagnose adverse reactions — manage adverse reactions — refer patients with serious and severe ADRs to district hospital for investigation and management — make basic causality assessment — take action (stop medicine, stop use of batch, stop programme in area) if deemed necessary in consultation with DHO — send ADR reports to DHO — patient education — prevent programmatic errors — promote rational drug use — follow treatment guidelines — communicate with patients and public — attend meetings to receive feedback from DHO
Health-care provider outside government system	— all of the above — may refer patient to primary health-care provider for further action
District investigation team	
(a) District hospital members: physician, nurse	— assess relationship/causality — investigate and manage ADRs, as advised by expert safety review committee — take action as advised by DHO — educate patients — be part of resource team for training primary health workers
(b) DHO/district programme manager (as part of the public health programme)	— lead the DIT — coordinate and complete the investigation of ADRs — report the ADRs and follow-up details to the public health pharmacovigilance coordinator or the national pharmacovigilance coordinator — take interim action on continuation of the medicine or programme — take action as advised by the expert safety review panel — training, supervision of primary and district level health-care teams
National pharmacovigilance coordinator	— receives ADR reports from DIT — works under the national centre — coordinates the national pharmacovigilance programme — develops and adapts procedures; develops and maintains the national database for data processing, collection and storage of ADR records and signal generation; provides advice (especially if an

	international agency is initiating the programme); maintains a supply of and distributes reporting forms — is a member/secretary for expert safety review panel; assists with assessment of case reports — develops training modules — liaises with public health, expert safety review panel, national centre, MRA, international agency — submits recommendations to public health, national pharmacovigilance centre, MRA
Expert safety review panel	— reviews ADRs, checks and finalizes causality assessments and possible signals — recommends additional investigations if needed — submits conclusions and recommendations to public health, national pharmacovigilance centre, MRA — provides resource person for training, education and awareness — advises pharmacovigilance coordinator
National pharmacovigilance centre	— supervises work of national coordinator — provides technical, training and managerial support for all pharmacovigilance activities — develops pharmacovigilance in the public health system and jointly decides on the specific goals for pharmacovigilance — serves as a resource for the MRA on a regular and continuing basis — submits expert safety review panel recommendations with comments to public health and MRA — contributes to decision-making by MRA — liaises with UMC, WHO — liaises with sponsoring agency
Public health programme	— supervises work of DIT and programme manager — provides technical, training and managerial support for all functions of DIT and programme manager — takes programme-related decisions — liaises with national pharmacovigilance centre and decides jointly on the pharmacovigilance goals
MRA	— receives reports from expert safety review panel and national pharmacovigilance centre — takes regulatory decisions — liaises with MRAs from other countries — liaises and consults with UMC and WHO
WHO Collaborating Centre for International Drug Monitoring (Uppsala)	— provides guidance, technical support and training for national pharmacovigilance centres or national pharmacovigilance coordinators — receives and processes ADR reports from national programmes or pharmacovigilance centres — provides regular feedback and specific services on request
WHO Headquarters, Geneva, Switzerland	— provides the formal framework for collaboration in international pharmacovigilance — provides funding and secretariat for the Advisory Committee on the Safety of Medicinal Products

Advisory Committee on the Safety of Medicinal Products	— advances and promotes the future developments of pharmacovigilance as a discipline — examines policy needs and their implications with respect to drug safety and pharmacovigilance for WHO and countries — responds to identified needs of a country that may be beyond the capability of the country or countries themselves; such responses should be made within an appropriate timeframe, taking into account any existing information and the urgency of the issue; and/or — provides advice to national and international programmes when drug safety issues have the potential to adversely affect them

ADR, adverse drug reactions; DHO, district health officer; MRA, medicines regulatory authority; DIT, district investigation team; UMC, Uppsala Monitoring Centre; WHO, World Health Organization.

ANNEX 2

VACCINES EXAMPLE

There are several aspects of the experience gained with vaccines and their safety monitoring that have relevance to pharmacovigilance in general.

It is as important for medicines as it is for vaccines to understand that adverse events might arise from errors or deficiencies in transport or storage. Maintaining appropriate conditions for the preservation of the quality of the medicine is the equivalent of maintaining the cold chain for vaccines. Faulty dispensing or administration may also occur, e.g. as a result of dispensing from contaminated multi-dose vials. These potential risks with their consequent adverse effects are the equivalent of the "programmatic errors" seen in vaccine programmes. An appreciation of the frequency of programmatic errors is important.

The World Health Organization has developed, within the Department of Vaccines and Biologicals, and under the framework of the Global Training Network, a comprehensive training programme for the identification and reporting of adverse events following immunization. The training curriculum includes a component on communication to the public with a full explanation of safety issues that might be linked with vaccines. Details of this training programme can be obtained from the department's web site (http://www.who.int/immunization_safety/en/) and in reports published in the WHO publication, *Weekly Epidemiological Records*. At the time of writing this report (May 2004), more than 140 senior health professionals from 52 countries had been trained within this programme. A network of vaccine safety experts within participating countries has been established, and a number of individuals trained within the programme have subsequently served as facilitators. It is anticipated that in this way a new leadership in the special issues of vaccine pharmacovigilance will be established in the foreseeable future.

A further initiative of the Department of Vaccines and Biologicals at WHO that lends itself to more general application in pharmacovigilance, was the establishment (in 1999) of a Global Advisory Committee for Vaccine Safety. This Committee, which includes experts in paediatrics, internal medicine, epidemiology and statistics, public health, virology and vaccinology, pharmacology and toxicology, provides independent and authoritative advice to the director of the Department of Vaccines and Biologicals. The Committee allows no special advocacy considerations for vaccine programmes to influence its decisions regarding vaccine safety. The procedure of enquiry of the Advisory Committee is open, and all parties who might have an interest in the detail and the outcome of its deliberations are invited to participate, and to make formal or informal representation. (This does not apply to the decision-taking of the Committee, which is confined, *in camera* to the members of the committee, to ensure its complete impartiality.) The Vaccine Safety Advisory Committee has met twice yearly since 1999. The issues considered by the Committee are generally of major potential national or international importance (real or perceived) that are likely to have implications for immunization programmes and where, either proactively or reactively on the part of the advisory committee, the authority of WHO is sought for arbitration of vaccine safety issues.

ANNEX 3

WORLD HEALTH ASSEMBLY RESOLUTIONS

WHA18.42 Adverse Drug Reaction Monitoring System
The Eighteenth World Health Assembly
Handb. Res., 7th ed., 1.3.2.3 Twelfth plenary meeting, 20 May 1965
(Committee on Programme and Budget, sixth report)

WHA19.35 International Monitoring of Adverse Reactions to Drugs
The Nineteenth World Health Assembly
Handb. Res., 8th ed., 1.3.3 Fourteenth plenary meeting, 20 May 1966
(Committee on Programme and Budget, fourth report)

WHA20.51 WHO Pilot Research Project for International Monitoring of Adverse Reactions to Drugs
The Twentieth World Health Assembly
Handb. Res., 8th ed., 1.3.3 Twelfth plenary meeting, 25 May 1967
(Committee on Programme and Budget, ninth report)

WHA 23.13 International Monitoring of Adverse Reactions to Drugs
The Twenty-third World Health Assembly
Handb. Res., 10th ed., 1.10.1;7.1.6.3 Twelfth plenary meeting, 16 May 1970
(Committee A, first report)

ANNEX 4

ERICE DECLARATION

The following declaration was drawn up at the International Conference on Developing Effective Communications in Pharmacovigilance, Erice, Sicily, 24–27 September 1997. It was attended by health professionals, researchers, academics, media writers, representatives of the pharmaceutical industry, drug regulators, patients, lawyers, consumers and international health organizations.

Preamble

Monitoring, evaluating and communicating drug safety is a public-health activity with profound implications that depend on the integrity and collective responsibility of all parties — consumers, health professionals, researchers, academia, media, pharmaceutical industry, drug regulators, governments and international organizations — working together. High scientific, ethical and professional standards and a moral code should govern this activity. The inherent uncertainty of the risks and benefits of drugs needs to be acknowledged and explained. Decisions and actions that are based on this uncertainty should be informed by scientific and clinical considerations and should take into account social realities and circumstances.

Declaration

Flaws in drug safety communication at all levels of society can lead to mistrust, misinformation and misguided actions resulting in harm and the creation of a climate where drug safety data may be hidden, withheld, or ignored.

Fact should be distinguished from speculation and hypothesis, and actions taken should reflect the needs of those affected and the care they require. These actions call for systems and legislation, nationally and internationally, that ensure full and open exchange of information, and effective standards of evaluation. These standards will ensure that risks and benefits can be assessed, explained and acted upon openly and in a spirit that promotes general confidence and trust.

The following statements set forth the basic requirements for this to happen, and were agreed upon by all participants from 34 countries at Erice:

1. Drug safety information must serve the health of the public. Such information should be ethically and effectively communicated in terms of both content and method. Facts, hypotheses and conclusions should be distinguished, uncertainty acknowledged, and information provided in ways that meet both general and individual needs.
2. Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large, as well as for patients and health care providers. Such education requires special commitment and resources. Drug information directed to the public in whatever form should be balanced with respect to risks and benefits.

3. All the evidence needed to assess and understand risks and benefits must be openly available. Constraints on communication parties, which hinder their ability to meet this goal must be recognized and overcome.
4. Every country needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated and made accessible to all. Adequate nonpartisan financing must be available to support the system. Exchange of data and evaluations among countries must be encouraged and supported.
5. A strong basis for drug safety monitoring has been laid over a long period, although sometimes in response to disasters. Innovation in this field now needs to ensure that emergent problems are promptly recognized and efficiently dealt with, and that information and solutions are effectively communicated.

These ideals are achievable and the participants at the conference commit themselves accordingly. Details of what might be done to give effect to this declaration have been considered at the conference and form the substance of the conference report.

Erice, 27 September 1997

The Conference was organized by: the Uppsala Monitoring Centre; the Clinical Pharmacology Unit, Institute of Pharmacology of Verona University; the Ettore Majorana Centre for Scientific Culture, International School of Pharmacology; the World Health Organization and supported by EQUUS Communications, London.