WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems

World Health Organization
Geneva
2004

Contents

Foreword

The use of herbal medicines continues to expand rapidly across the world. Many people now take herbal medicines or herbal products for their health care in different national health-care settings. However, mass media reports of adverse events tend to be sensational and give a negative impression regarding the use of herbal medicines in general rather than identifying the causes of these events, which may relate to a variety of issues. The safety of herbal medicines has become a major concern to both national health authorities and the general public.

The World Health Organization (WHO) received an urgent request from its Member States, through the national pharmacovigilance centres participating in the WHO International Drug Monitoring Programme and drug regulatory authorities, to assist Member States to strengthen national capacity in monitoring the safety of herbal medicines and in analysing the causes of adverse events, and to share safety information at national, regional and global levels. These guidelines have been developed as WHO's immediate response to this request, and to support Member States' efforts in this area in the context of the WHO International Drug Monitoring Programme, which has been in operation since the 1970s. Thus, development of the guidelines has been carried out as a joint project between the Traditional Medicine Team (TRM) and the Quality, Safety: Medicines Team (QSM) in the Department of Essential Drugs and Medicines Policy (EDM) at WHO headquarters.

The recommended approach is to include herbal medicines in existing national pharmacovigilance systems or, where such systems have not yet been developed, to establish comprehensive national pharmacovigilance systems which incorporate coverage of herbal medicines. As described in the Introduction to the guidelines, it is not WHO's intention to suggest that different systems should be instituted for this purpose. However, in view of the unique characteristics of the provision and use of herbal medicines, there are several technical issues that need to be addressed if adequate and effective monitoring is to be introduced. The guidelines therefore identify the particular challenges posed in monitoring the safety of herbal medicines effectively and propose approaches for overcoming them. Special attention is also given to the reporting system for adverse reactions to herbal medicines, and to the analysis of the causes of the reported adverse reactions.

In order to handle herbal medicines, in particular, to analyse the causes of adverse events, national pharmacovigilance centres (or equivalent institutions) will need to acquire specific technical expertise. This will include trained personnel in relevant technical areas and facilities to analyse the products concerned, for which there is often insufficient information and lack of access to reliable information support. Many countries currently lack this expertise, in particular, access to suitable analytical laboratories. Member States have therefore recommended the establishment of regional laboratories specializing in

the analysis of herbal products. WHO encourages Member States to explore the feasibility of this proposal.

To further the implementation of these guidelines, WHO plans to organize a series of training workshops for Member States, in collaboration with the WHO Collaborating Centres for International Drug Monitoring and for Traditional Medicine. National capacity in monitoring the safety of herbal medicines will be further strengthened through national training workshops on topics such as, broadening reporting schemes, acquiring technical expertise at national pharmacovigilance centres, and promoting awareness. Training of practitioners who provide herbal medicines will also be crucial.

The guidelines also articulate technical issues relating to data management and communication. The Uppsala Monitoring Centre, Uppsala, Sweden (UMC) has proposed the herbal anatomical-therapeutic-chemical classification (HATC) as a coding tool to permit the inclusion of individual herbal products in the global WHO database of adverse drug reaction (ADR) reports for pharmacovigilance purposes. The summary explanation of the proposed system by UMC is annexed to the guidelines. Although the system represents a valuable attempt at coding herbal medicines, it may not be perfect for covering all types of herbal products, in particular, traditional medicines that are used under unique concepts and with unique terminologies. Member States are encouraged to offer suggestions, on the basis of their national experience in the day-to-day operation of national pharmacovigilance, as to how classification could be approached in a more comprehensive manner and in a way that meets their national circumstances. WHO, in collaboration with UMC, will work with Member States to continue development of the system.

Currently, the majority of adverse events related to the use of herbal products and herbal medicines that are reported are attributable either to poor product quality or to improper use. Inadequate regulatory measures, weak quality control systems and largely uncontrolled distribution channels (including mail order and Internet sales) may have been contributing to the occurrence of such events. In order to expand knowledge about genuine adverse reactions to herbal medicines, and to avoid wasting scare resources for identifying and analysing adverse events, events resulting from such situations will need to be reduced or eliminated. Member States are therefore encouraged to strengthen national regulation, registration and quality assurance and control of herbal medicines. In addition, national health authorities should give greater attention to consumer education and to qualified practice in the provision of herbal medicines.

WHO has welcomed the active participation of drug regulatory authorities and national pharmacovigilance centres, among others, in the development of these guidelines. This has provided a useful starting point for strengthening communication between these authorities, which will be needed to ensure progress towards the common goal – the safety of herbal medicines.

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Acknowledgements

The World Health Organization (WHO) wishes to express its sincere appreciation to Health Canada, in particular the Natural Health Products Directorate, for kindly hosting the WHO Consultation on Safety Monitoring of Herbal Medicines in Vancouver, Canada, in February 2004 (Annex 1), with its financial support.

WHO also wishes to thank the Ministry of Health, Welfare and Sports, Netherlands for its generous financial contribution to WHO in support of the WHO Working Group Meeting on Safety Monitoring and Pharmacovigilance of Herbal Medicines held in Amsterdam, Netherlands in October 2002, and the WHO Consultation on Safety Monitoring of Herbal Medicines held in Vancouver, Canada, in February 2004. Special thanks are extended to Dr Kees van Grootheest, Director, Netherlands Pharmacovigilance Foundation (LAREB), and his team, for their assistance in organizing the 2002 meeting.

WHO acknowledges the valuable contribution of Dr Ralph Edwards, Director, WHO Collaborating Centre for International Safety Monitoring at the Uppsala Monitoring Centre, Uppsala, Sweden, and his team, and Professor David Coulter, Intensive Medicines Monitoring Programme, Department of Preventive and Social Medicine, School of Medicine, University of Otago, Dunedin, New Zealand, to the preparation of the draft guidelines.

The Organization is grateful to the participants in the two consultative meetings for their work in reviewing the draft guidelines. Thanks are also due to the more than 400 experts in over 102 countries, including those at the national pharmacovigilance centres participating in the WHO International Drug Monitoring Programme, national drug regulatory authorities, poisons centres and national health authorities, as well as, WHO Collaborating Centres for Traditional Medicines, and members of WHO Advisory Panel on Traditional Medicines, who reviewed and provided comments and advice on the draft guidelines. Preparation of the guidelines has also benefited from technical support from relevant international and nongovernmental organizations, including associations of health professions and of manufacturers of herbal medicines, and consumer associations.

Finally, WHO expresses its appreciation to The Council for International Organizations of Medical Sciences and the Uppsala Monitoring Centre, Uppsala, Sweden for permission to reproduce the material included in Annexes 3 and 4, and Part II of the guidelines, respectively.

Part I

WHO Guidelines on safety monitoring of herbal medicines in pharmacovigilance systems

1. General introduction

1.1 Introduction

Safety is a fundamental principle in the provision of herbal medicines and herbal products for health care, and a critical component of quality control. These guidelines provide practical technical guidance for monitoring the safety of herbal medicines within pharmacovigilance systems. The safety monitoring of herbal medicines is compared and contrasted with that of other medicines currently undertaken in the context of the WHO International Drug Monitoring Programme. While there are regulatory and cultural differences in the preparation and use of different types of medicines, they are all equally important from a pharmacovigilance perspective.

The guidelines were developed with the view that, within current pharmacovigilance systems, monitoring of the safety of medicines should be enhanced and broadened in ways that will allow the successful monitoring of herbal medicines. It is not the intention to suggest that different systems should be instituted for this purpose. The guidelines should therefore be considered in conjunction with the publication entitled, *Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre (1)*, which is reproduced as Part II of this publication.

The inclusion of herbal medicines in pharmacovigilance systems is becoming increasingly important given the growing use of herbal products and herbal medicines globally. For example, in the United States of America, some US$ 17 billion was spent by more than 158 million Americans in 2000 *(2)*. Further, a recent study indicated that more than 70% of the German population reported using "natural medicines" and that, for most of them, herbal medicinal products were the first choice in the treatment of minor diseases or disorders *(3)*. The worldwide consumption of herbal medicines is enormous, so that, in terms of population exposure alone, it is essential to identify the risks associated with their use. Safety of herbal medicines is therefore an important public health issue. Herbal medicines are frequently used in conjunction with other medicines, and it is essential to understand the consequences of such combined use and monitor whether any adverse effects are arising. This can be achieved most readily within existing pharmacovigilance systems.

1.2 Background

Problems

Among consumers, there is a widespread misconception that "natural" always means "safe", and a common belief that remedies from natural origin are harmless and carry no risk. However, some medicinal plants are inherently toxic.

Further, as with all medicines, herbal medicines are expected to have side effects, which may be of an adverse nature. Some adverse events reported in association with herbal products are attributable to problems of quality. Major causes of such events are adulteration of herbal products with undeclared other medicines and potent pharmaceutical substances, such as corticosteroids and non-steroidal anti-inflammatory agents. Adverse events may also arise from the mistaken use of the wrong species of medicinal plants, incorrect dosing, errors in the use of herbal medicines both by health-care providers and consumers, interactions with other medicines, and use of products contaminated with potentially hazardous substances, such as toxic metals, pathogenic microorganisms and agrochemical residues.

The following examples demonstrate the range of problems encountered with the use of herbal medicines and products.

- Some herbal products were found to contain 0.1–0.3 mg of betamethasone per capsule after some patients developed corticosteroid-like side effects.
- Owing to misidentification of the medicinal plant species, plant materials containing aristolochic acid were used for manufacturing herbal products, which caused severe kidney failure in patients in several countries.
- Reports have been received by drug safety monitoring agencies of prolonged prothrombin times, increased coagulation time, subcutaneous haematomas and intracranial haemorrhage associated with the use of *Ginkgo biloba*.
- One of the most well known traditionally used herbal medicines caused severe, sometimes fatal cases of interstitial pneumonia when used in conjunction with interferon.

Adverse events thus far reported in relation to herbal products are frequently attributable either to poor quality or to improper use, and it is therefore difficult to distinguish genuine adverse reactions to herbal medicines and herbal products until the cause of such events has been identified.

Current situation

Despite the growing interest in the safety of herbal medicines, national surveillance systems to monitor and evaluate adverse reactions associated with herbal medicines are rare, even among the more than 70 Member States participating in the WHO International Drug Monitoring Programme. Moreover, there is a lack of effective communication on this subject at all levels, from international to local. A recent WHO survey showed that around 90 countries, less than half of WHO's Member States, currently regulate herbal medicines, and an even smaller proportion has systems in place for the regulation/qualification of providers of herbal medicines. Moreover, there are disparities in regulation between countries, and this has serious implications for international access to and distribution of such products.

National pharmacovigilance systems should be closely linked to national drug regulatory systems. To function properly, a national safety monitoring programme for herbal medicines should be operated alongside an effective national drug regulatory system with the will and the potential to react to signals emanating from reports of adverse effects of herbal medicines and to take proper regulatory measures.

At the national level, the capacity for reporting adverse events on herbal medicines, analysing their causes and learning from past experience is seriously hampered in many Member States by the lack of methodological uniformity in identification and measurement, the lack of information on adverse effects of herbal medicines, inadequate reporting schemes, fear of professional liability, and inadequate information systems relating to the use of herbal medicines. Current knowledge of the epidemiology of adverse reactions to herbal medicines, such as frequency of occurrence and causes, is very limited.

Action required

For the safety of those using herbal medicines, four complementary actions are needed:

- clear identification of the nature of adverse events
- management of the risks
- institution of measure to prevent adverse events
- good communication of the risks and benefits of herbal medicines.

These require:

- increased ability to learn from identified adverse events through better reporting systems, skilful technical investigation of incidents and responsible sharing of data
- greater capacity to anticipate adverse events and to probe systemic weaknesses that might lead to problems
- identification of existing knowledge resources, within and outside the health sector
- improvements in the health-care delivery system, so that structures are reconfigured, incentives are realigned, and safety and quality are placed at the core of the system

In 2000 and 2001, the annual meetings of national pharmacovigilance centres participating in the WHO International Drug Monitoring Programme requested WHO to provide urgent support to Member States in developing national systems for the safety monitoring of herbal and traditional medicines. This was echoed by a recommendation made at the Third WHO Consultation on Selected Medicinal Plants, and at the WHO Informal Meeting on Methodologies for Quality Control of Finished Herbal Products, both held in Ottawa, Canada, in July 2001. The International Conference of Drug Regulatory Authorities (ICDRA) also made recommendations to WHO in 1999 and 2002 that it should support Member States in strengthening their capacity in these areas. In addition, resolution WHA56.31 on traditional medicine, adopted at the Fifty-Sixth World Health Assembly in May 2003, urged Member States to set up or expand and strengthen existing national drug safety monitoring systems to monitor herbal medicines and other traditional practices.

Action needed by WHO to respond to these requests includes:

- provision of technical guidance to facilitate the expansion of existing systems to monitor and report adverse drug reactions to herbal medicines or the establishment of comprehensive national drug safety monitoring systems that

incorporate the safety monitoring of herbal medicines, where these do not yet exist
- support to countries in strengthening their pharmacovigilance system for herbal medicines, allowing for the involvement of health-care providers, consumers and manufacturers.

WHO has taken the lead in tackling the need for drug safety monitoring since 1970 (resolution WHA23.13 on international monitoring of adverse reactions to drugs, 1970). The WHO International Drug Monitoring Programme, together with the WHO Collaborating Centre in Sweden, the Uppsala Monitoring Centre (UMC), has instituted a coherent programme of action for pharmacovigilance, which includes the establishment of a programme for exchange of safety information, maintenance of the global WHO database of adverse drug reaction (ADR) reports (hereafter referred to as the global WHO database), and the provision of numerous guidelines on monitoring drug safety. It also seeks to bridge the gap between industry and regulatory authorities. As an immediate response to the need for pharmacovigilance for herbal medicines, WHO has increased its efforts to promote their safety monitoring within the context of the WHO International Drug Monitoring Programme.

Where there is a national drug safety monitoring system in place, there is a clear need to expand its scope to include herbal medicines. If no such system exists, there is an urgent need to establish such a system, which should include monitoring of herbal medicines. However, adding herbal medicines to a list of target substances for a national drug safety monitoring activities is not enough in itself. Because of the particular nature of the distribution and use of herbal medicines, adequate and effective monitoring demands special requirements, including:

- expanding the source of case reports, for example by:
  - involving all providers of herbal medicines, including providers of traditional medicine and complementary/alternative medicine, according to national circumstances
  - strengthening the role of providers, such as pharmacists and health-care professionals, working in the community
  - involving manufacturers of herbal medicines
  - facilitating consumer reporting
  - developing systems of information exchange involving drug information centres, poisons centres, consumer organizations and manufacturers
- establishing a system for the exchange of regulatory and quality information on herbal medicines among national pharmacovigilance centres and national drug regulatory authorities
- strengthening capacity to carry out monitoring of herbal medicines at national pharmacovigilance centres by:
  - training staff in relevant technical areas
  - ensuring access to facilities for analysing products suspected of causing adverse reactions
  - providing access to reliable information
- developing a standard classification and/or coding system for herbal medicines, with standardized terms and definitions
- strengthening communication and awareness at all levels (global, regional, national, local and community) and among key players (international bodies,

regulatory authorities, national pharmacovigilance centres, health-care providers and consumers).

In response to these needs, WHO has developed these guidelines. It also plans to organize a series of training workshops to strengthen national capacity in safety monitoring of herbal medicines within pharmacovigilance systems in Member States.

1.3 Objectives

The objectives of these guidelines are to:

- support Member States, in the context of the WHO International Drug Monitoring Programme, to strengthen national pharmacovigilance capacity in order to carry out effective safety monitoring of herbal medicines
- provide technical guidance on the principles of good pharmacovigilance and the inclusion of herbal medicines in existing national drug safety monitoring systems; and where these systems are not in place, to facilitate the establishment of an inclusive national drug safety monitoring system
- provide standard definitions of terms relating to pharmacovigilance, and safety monitoring of herbal medicines
- promote and strengthen internationally coordinated information exchange on pharmacovigilance, and safety monitoring of herbal medicines among Member States
- promote the safe and proper use of herbal medicines.

The regulation of herbal medicines and their place in national health-care systems differs from country to country, and these guidelines will therefore need to be adapted to meet the needs of the local situation.

1.4 Glossary

The terms used in Part I of these guidelines are defined below.

Terms relating to herbal medicines

These terms and their definitions have been selected and adapted from other WHO documents and guidelines that are widely used by the WHO Member States, such as the *General guidelines for methodologies on research and evaluation of traditional medicine (4)*. These definitions may differ from those included in national regulations, and are therefore, for reference only.

Herbal medicines include *herbs, herbal materials, herbal preparations* and *finished herbal products*. In some countries herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (e.g. animal and mineral materials).

Herbs include crude plant material, such as leaves, flowers, fruit, seeds, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.

Herbal materials include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting or stir-baking with honey, alcoholic beverages or other materials.

Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.

Finished herbal products consist of herbal preparations made from one or more herbs. If more than one herb is used, the term "mixture herbal product" can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture herbal products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal.

Traditional use of herbal medicines refers to the long historical use of these medicines. Their use is well established and widely acknowledged to be safe and effective, and may be accepted by national authorities.

Therapeutic activity refers to the successful prevention, diagnosis and treatment of physical and mental illnesses. Treatment includes beneficial alteration or regulation of the physical and mental status of the body and development of a sense of general well-being as well as improvement of symptoms.

Active ingredients refer to ingredients of herbal medicines with therapeutic activity. Where the active ingredients have been identified, the preparation of the finished herbal product should be standardized to ensure that it always contains a defined amount of the active ingredients, providing adequate analytical methods are available. In cases where it is not possible to identify the active ingredients, the whole herbal medicine may be considered as one active ingredient.

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

Terms relating to safety monitoring of medicinal products

The terms and definitions below have been adopted by the national pharmacovigilance centres participating in the WHO International Drug

Monitoring Programme. Different medical paradigms may view clinical events differently in their relationship to herbal medicines, whether they are expected therapeutic outcomes or adverse reactions.

Side effect. Any unintended effect of a pharmaceutical product occurring at doses normally used in humans that is related to the pharmacological properties of the drug.

Adverse event/experience. Any untoward medical occurrence that may present during treatment with a pharmaceutical product but that does not necessarily have a causal relationship with this treatment.

Serious adverse event. Any untoward medical occurrence that, at any dose:

- results in death
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is life-threatening.

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

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

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

Spontaneous reporting. A system whereby case reports of adverse drug events are voluntarily submitted by health professionals and pharmaceutical manufacturers to the national regulatory authority.

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems (see also section 2).

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

2. Pharmacovigilance and the WHO International Drug Monitoring Programme

2.1 What is pharmacovigilance?

The WHO publication entitled *The importance of pharmacovigilance: safety monitoring of medicinal products (5)*, describes pharmacovigilance as follows.

> Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects of drugs or any other possible drug-related problems.
> Recently, its concerns have been widened to include:
> - herbals
> - traditional and complementary medicines
> - blood products
> - biologicals
> - medical devices
> - vaccines.
>
> Many other issues are also of relevance to the science:
> - substandard medicines
> - medication errors
> - lack of efficacy reports
> - use of medicines for indications that are not approved and for which there is inadequate scientific basis
> - case reports of acute and chronic poisoning
> - assessment of drug-related mortality
> - abuse and misuse of medicines
> - adverse interactions of medicines with chemicals, other medicines and food.
>
> The specific aims of pharmacovigilance are to:
> - improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions
> - improve public health and safety in relation to the use of medicines
> - contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use
> - promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

These aims of pharmacovigilance can be achieved *(1)* by:

- early detection of hitherto unknown adverse reactions and interactions
- detection of increases in frequency of (known) adverse reactions

- identification of risk factors and possible mechanisms underlying adverse reactions
- estimation of the quantitative aspects of benefit/risk, and analysis and dissemination of the information needed to improve the prescription, dispensing, provision and regulation of medicines.

The ultimate goal of pharmacovigilance is the safe and proper use of effective medicines of all types.

2.2 How does pharmacovigilance operate?

It must be emphasized that there is no difference in principle between the safety monitoring of herbal medicines and that of other medicines.

The WHO International Drug Monitoring Programme
Under the WHO International Drug Monitoring Programme, national pharmacovigilance centres designated by the competent health authorities are responsible for the collection, processing and evaluation of case reports of suspected adverse reactions supplied by health-care professionals (mainly spontaneous reporting by physicians of reactions associated with the use of prescribed medicines). The Programme is described in two publications: *Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre (1)*, chapters 7 and 8; and *The importance of pharmacovigilance: safety monitoring of medicinal products (5)*, especially chapters 3 and 4.

The Programme currently comprises a network of more than 70 national pharmacovigilance centres that operate independently, but whose functions are coordinated and facilitated by WHO and UMC. UMC manages the global WHO database to which all case reports received by the national pharmacovigilance centres are sent. UMC uses the global WHO database to identify/detect signals of new adverse reactions from the cumulative data and to communicate risk assessments back to the national pharmacovigilance centres and to others concerned with drug safety.

The core functions in this collaborative international programme can be summarized as follows.

Functions of national pharmacovigilance centres
- Continuous collection of reports of suspected adverse reactions for medicines on the market
- Assessment of case reports in respect of:
  - quality of documentation
  - causality assessment
  - coding to international standards using the appropriate medicine classification (the anatomical-therapeutic-chemical (ATC) classification), adverse reaction classification (WHO Adverse Reaction Terminology (WHO-ART)) and the Medical Dictionary for Drug Regulatory Activities (MedDRA)
  - clinical relevance
  - quality control, in particular identification of duplicate reports

- Transmission in suitable format of the assessed reports to UMC
- Generation of hypotheses or the identification of signals. These activities may be strengthened by a search of the global WHO database (managed by UMC) for similar reports
- Communication of relevant safety information to the national and regional regulatory authorities, health professionals, pharmaceutical companies and other players as appropriate
- Further investigation of signals, risk factors or pharmacological mechanisms
- Receipt and communication as appropriate of safety information resulting from analyses by UMC and from regulatory agencies, case reports and the literature
- Provision of feedback to reporters
- Timely advice to health-care professionals and consumers on drug safety issues
- Education and training
- Information sharing at regional and global levels.

Functions of UMC

- Receipt and storage of reports from national pharmacovigilance centres
- Provision of facilities to enable national pharmacovigilance centres to search the global WHO database
- Generation of signals from the global WHO database
- Communication of signal analyses to national pharmacovigilance centres and clinical review of the analyses by experts
- Provision of technical assistance to national pharmacovigilance centres
- Facilitation of communication between countries
- Maintenance and development of WHO-ART and the use of MedDRA within the WHO International Drug Monitoring Programme
- Training of national pharmacovigilance centre personnel
- Standardization of procedures relating to pharmacovigilance activities
- Publication of relevant documents
- Provision of data as appropriate to other parties.

Among the many players that need to be involved in pharmacovigilance systems at different levels are: qualified health professionals such as providers of medicines (physicians, dentists, pharmacists) and nurses, researchers and academics, media writers, the pharmaceutical industry, national and regional drug regulatory authorities, patients/consumers, lawyers, poisons centres, drug information centres, and international and regional health organizations *(6)*.
In collaboration with UMC, national pharmacovigilance centres have already achieved a great deal in the following areas *(5)*:

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

The framework of values and practice for the collection, analysis and subsequent communication of drug safety issues is provided by the Erice Declaration (Annex 2). Issues of privacy and confidentiality in relation to personal health data are covered in Annex 3.

3. Challenges in monitoring the safety of herbal medicines

3.1 Regulation, quality assurance and control

Regulation

National regulation and registration of herbal medicines vary from country to country. Where herbal medicines are regulated, they may be categorized as either prescription or non-prescription medicines. Herbal products may also be categorized other than as medicines. Moreover, the regulatory status of a particular herbal product may differ in different countries. The national regulatory framework usually also includes involved qualified providers and distributors of respective substances. Regulatory status consequently determines the access to or distribution route of these products.

If trade in a particular herbal product is made between countries where different regulatory status is given, reclassification of the regulatory status in the importing country depends not on the nature or characteristics (medical or therapeutic value) of the product itself, but on the regulatory framework of the importing country. Further, herbal products categorized other than as medicines and foods are becoming increasingly popular, and there is potential for adverse reactions due to lack of regulation, weaker quality control systems and loose distribution channels (including mail order and Internet sales).

National regulatory information on herbal medicines is not fully shared among national regulatory authorities, and is often not shared between national regulatory authorities and national safety monitoring/pharmacovigilance centres.

Almost all new medicines are introduced to the market as prescription medicines, and a significant volume of post-marketing safety data from spontaneous reporting will have been realized over time. At some stage, some of these medicines will subsequently be reclassified as non-prescription medicines and will become major sources of self-medication. However, in many countries, a significant proportion of herbal products enters directly into the non-prescription medicines category rather than by reclassification from the prescription medicines category.

Quality assurance and control

Quality assurance and control measures, such as national quality specification and standards for herbal materials, good manufacturing practices (GMP) for herbal medicines, labelling, and licensing schemes for manufacturing, imports and marketing, should be in place in every country where herbal medicines are regulated. These measures are vital for ensuring the safety and efficacy of herbal

medicines. Weak regulation and quality control may result in a high incidence of adverse reactions attributable to poor quality of herbal medicines, in particular resulting from adulteration with undeclared potent substances and/or contamination with potentially hazardous substances and residues.

Requirements and methods for quality control of finished herbal products, particularly for mixture herbal products, are far more complex than for other pharmaceuticals. The quality of such products is influenced by the quality of the raw material used. Good agricultural and good collection practices (GACP) for medicinal plants, including plant selection and cultivation, are therefore important measures *(7)*.

National/regional pharmacopoeias
National and regional pharmacopoeias define quality specifications and standards for herbal materials and some herbal preparations, such as essential oils and powdered herbal materials. Use and inclusion of herbal materials in such pharmacopoeias are based on local availability of these products. Availability is dependent on the original medicinal plants, which have ecologically and environmentally specific habitats. Therefore, even if the same pharmacopoeial monograph name is given to a herbal material, its listing in one pharmacopoeia may refer to a different original medicinal plant and/or processing method from that defined in another (see also section 4.3, Reporting of suspected adverse reactions, under Recording and coding the identity of herbal medicines).

Action required
As with other medicines for human use, herbal medicines should be covered by a drug regulatory framework to ensure that they conform to required standards of safety, quality and efficacy.

3.2 Appropriate use

Providers of herbal medicines
A variety of health-care professionals serve as qualified providers of herbal medicines, according to each country's national health-care delivery system and legislative framework. In those countries where herbal medicines are classified as prescription medicines, prescribers and dispensers other than physicians, dentists and pharmacists are sometimes excluded from current reporting systems.

In many countries, prescriptions are not required to obtain herbal medicines since these are categorized as non-prescription medicines or products suitable for self-care. Providers of herbal medicines in this category are not normally physicians. They include providers of traditional and complementary or alternative medicine as well as community pharmacists and nurses.

Action required
All providers of herbal medicines should play a role in monitoring the safety of non-prescription herbal medicines. Nurses are becoming increasingly involved in this area and are making a valuable contribution to safety monitoring. For

providers of herbal medicines to be effectively involved, it is essential to create an atmosphere of trust to enable the sharing of knowledge about the use and safety of herbal medicines.

Lack of proper knowledge of herbal medicines

Providers of medicines, such as physicians, nurses and pharmacists, may have little training in and understanding of how herbal medicines affect the health of their patients, who are often also taking other medicines, prescription or non-prescription. An appropriate knowledge base is also relevant to diagnostic and treatment decision-making. Other health-care professionals who are not providers of herbal medicines are also likely to be poorly informed about these products and how they are being used. If they see patients who are taking herbal medicines, they should ask about their use. Health professionals who work in poisons centres and health information services also need to be informed about herbal medicines.

The use of medicinal plants is the most common form of traditional medication, worldwide. Herbal medicines are used within many different healing traditions with different knowledge bases and so there is still a question as to the suitability of the categories defined in section 4.2.

Traditional medicines are increasingly being used outside the confines of traditional cultures and far beyond traditional geographical areas without proper knowledge of their use and the underlying principles. They are also being used in different doses, extracted in different ways and used for non-traditional indications. The concomitant use of traditional medicines with other medicines, which is now quite frequent, is quite outside the traditional context and has become a particular safety concern.

Patient/consumer attitudes to herbal medicines

As mentioned in section 1, there is often a misconception that "natural" means "safe" and many consumers believe that remedies of natural origin carry no risk. Patients who use herbal medicines and other medicines together, as is often the case, will often not mention the use of herbal medicines to their physician. Likewise, patients commonly fail to mention the use of other medicines to their providers of herbal medicines.

Health-care professionals and providers of herbal medicines should ask patients directly, respectfully and persistently what other medicines they are taking, including prescription medicines, herbal medicines and other health products for self-care.

Action required

The education of health-care professionals, providers of herbal medicines and patients/consumers is vital for the prevention of potentially serious risks from misuse of herbal medicines.

4. Safety monitoring of herbal medicines

4.1 Sources of reports

The Council for International Organizations of Medical Sciences (CIOMS) Working Group V has recommended that, as a general guiding principle, emphasis should be placed on the quality of a report and not on its source. Thus, the value of a report lies not in who made it, but in the care and thoroughness with which it is prepared, documented, received, recorded, followed-up, clarified and analysed (8). However, the source of a report can be an important factor in evaluating the report as it may affect the quality and value of the information. The nature, degree and even feasibility of any follow-up will also be highly dependent on the source.

The most common sources of information on adverse events and reactions to medicines are clinical trials and spontaneous reports (voluntary, unsolicited communications on marketed medicinal products). The latter ordinarily far exceed the former in numbers and type, especially serious reports, over the lifetime of a product. In some countries, adverse reaction reporting by physicians is mandatory; such reports are regarded as spontaneous.

In many countries, providers of herbal medicines other than physicians, dentists, pharmacists and nurses are excluded from reporting systems. If adequate coverage of herbal medicines is to be achieved, national reporting schemes should be developed to include all providers of herbal medicines (both prescribers and dispensers), and providers of traditional, complementary and alternative medicine, according to national circumstances.

Reports from health-care professionals

Internationally, adverse drug reaction reporting systems in the post-marketing safety surveillance setting depend primarily on voluntary reporting by health-care professionals, preferably those directly associated with the care of the patient/consumer (i.e. the patient's primary health-care provider or specialist). This is appropriate, since the understanding of adverse drug reactions depends on medical knowledge and such professionals should be aware of the patient's medical history and attuned to the subtleties of clinical differential diagnosis.

A substantial proportion of herbal medicines are non-prescription medicines, and many come directly into this category without prior post-marketing safety monitoring as prescription medicines. It is therefore most important to take measures to strengthen pharmacovigilance activity in the non-prescription medicines setting. Community pharmacists and nurses can play a particularly useful role in monitoring the safety of non-prescription medicines, although many such products are sold outside pharmacies.

Reports from consumers

The involvement of consumers in the use of herbal medicines and herbal products in health care, and their concern regarding possible adverse effects should be valued positively. Consumer reports on adverse reactions should be accepted as a serious source of information, which can contribute to the identification of signals for unknown effects of herbal medicines.

For non-prescription medicines, often taken without health professional involvement, reports received directly from consumers may provide the only source of signals. With herbal medicines in the non-prescription medicines setting, there is clearly an essential role for consumer reporting.

Consumer reporting, in one form or another, is therefore an essential development if adequate information on risk is to be obtained. However, only a few national regulatory authorities currently explicitly require collection of direct reports from consumers. The CIOMS Working Group proposes several policy approaches and practices aimed at ensuring that consumer reports are treated with appropriate respect and that there is a rational approach for handling them (Annex 4).

Manufacturers[1]

Manufacturers of herbal medicines could be a source of information on adverse events associated with their products. Some countries include reporting of adverse events by manufacturers as part of their regulatory framework.

Consumers may report directly to companies or their representatives. However, there are reasons other than concern about an adverse effect that might prompt a consumer to contact a company. These include legal concerns and, most frequently, requests for further information about the product. Another source of consumer reports derives from a variety of industry programmes in which adverse reaction information may be solicited; such cases are not regarded as spontaneous reports.

Reports from other sources

Problems associated with herbal medicines may be reported as toxicity to the following.

- *National poisons centres*. Where resources are very limited in the national situation and where no pharmacovigilance centre has been established, a poisons centre could play a core role in pharmacovigilance for and safety monitoring of herbal medicines.
- *Drug information centres* may also be a first point of contact and may provide a wealth of clinical information. National pharmacovigilance centres should have a good level of communication with such centres.
- *Consumer organizations* receive complaints about any type of product in the marketplace and may obtain relevant information about herbal medicines
- *Clinical trials and studies* can also be a source of information (see section 4.2).

[1] For the purpose of these guidelines, the term "manufacturer" refers to the producer, importer, distributor or marketer of a finished herbal product and, where applicable, to the holder of the marketing authorization or registration for that product in the country in question.

4.2 Herbal products targeted for safety monitoring

In order to obtain comprehensive coverage, it is useful to think of herbal products in the following categories:

- according to their regulatory status
  - herbal medicines in the prescription medicines category
  - herbal medicines in the non-prescription medicines category
  - other herbal products intended for use in health care
- according to their registration/marketing status
  - herbal medicines undergoing the new drug development process: in clinical trials prior to national drug regulatory approval
  - herbal medicines undergoing the new drug development process: under post-marketing safety surveillance
  - herbal medicines undergoing re-evaluation under the current protocol: in clinical trials
  - herbal medicines undergoing re-evaluation under the current protocol: under post-marketing safety surveillance
  - herbal medicines on the market: under post-marketing safety surveillance
  - other herbal products marketed for health care, such as dietary supplements.

Recommendations on how to record and report adverse events occurring during clinical trials should be covered by national guidelines on good clinical practice for trials on pharmaceutical products (GCP) *(9)*.

4.3 Reporting of suspected adverse reactions

Who should report and to whom?
The setting (see section 4.2) in which an adverse reaction is noted and the status of the person noting the reaction will determine the most appropriate means of reporting. Although the term "national pharmacovigilance centre" has been used in these guidelines, it is recognized that in some countries the national pharmacovigilance system consists of a network of national and regional centres. Reports should be sent to the appropriate centre in accordance with the particular national reporting scheme. The following should provide reports.

- *Health professionals who are providers of herbal medicines*, including physicians, pharmacists and nurses, should report to the national pharmacovigilance centre.
- *Patients/consumers* should normally report to their physicians or providers of herbal medicines. They may also report directly to the national pharmacovigilance centre, consumer organizations or manufacturers.
- *Manufacturers* should report directly to the national pharmacovigilance centre or national regulatory authority.

What information should be requested?

Any suspected adverse reaction associated with the use of a herbal medicines should be reported. A case report should contain information on the following elements:

- where it is permitted by the country health information privacy code, and with appropriate confidentiality, some form of identification of the patient/consumer in order to avoid duplications and facilitate follow-up
- age, sex and a brief medical history of the consumer/patient (when relevant); in some countries, ethnicity may need to be specified
- details of suspected herbal product(s) if known: species name (Latin binomial name and common vernacular name of medicinal plant) and/or brand or ingredient name(s), including the part of medicinal plant used, preparation methods; manufacturer, country of origin, batch number, expiry date and provider
- administration details: dose and quantity supplied, dosage form, route, start/stop dates
- indication or reason for use
- adverse reaction data: date of onset (or duration from first administration to onset of event), description with symptoms and signs, severity and seriousness, results of clinical investigations and tests, course and outcome, and dechallenge/rechallenge with the same product, where appropriate
- all other medicines used (including self-medication), with administration details
- risk factors, e.g. age, impaired renal function, previous exposure to the herbal medicine(s) concerned, previous allergies, drug misuse or abuse, the social use of drugs
- name and address of reporter (to be considered confidential and to be used only for data verification, completion and case follow-up).

Details of the factors to consider when developing a report are provided in Annex 5, together with an example of a reporting form.

How to report

A single reporting form covering all medicines, including herbal medicines, should be used. For health-care providers already included in a national pharmacovigilance system, a familiar form will facilitate reporting; the introduction of a second type of reporting form may cause confusion. It is desirable to use a standard printed or electronic reporting form and to ensure that forms are widely available. It should also be acceptable to receive reports by telephone, letter or e-mail. If possible, a sample of the herbal product and its packaging should be submitted with the report.

Consideration should be given to the distribution of reporting forms to those involved in the provision of herbal medicines, such as providers of traditional medicine and of complementary/alternative medicine, who may not previously have been part of the national pharmacovigilance system. It may be necessary to design a special reporting form for those not familiar with the reporting of suspect reactions to medicines. Educational materials, including a list of simple terminology that can be understood by all parties, should be developed to inform and assist those not familiar with reporting.

Recording and coding the identity of herbal medicines

Use of a standardized classification and identification for transmitting reports to UMC is desirable. Coding of adverse events/adverse reactions to herbal medicines should be compatible with that for other medicines. UMC therefore proposes the use of the WHO Drug Dictionary (WHO-DD) *(10)*, as it has been developed to store structured, classified information on the names of herbal products and their ingredients in the same way as similar information on other medicines. For the therapeutic classification of herbal products, UMC proposes the herbal anatomical-therapeutic-chemical (HATC) classification, which is structurally equivalent to the anatomical-therapeutic-chemical (ATC) classification used for chemical substances in other medicines. HATC is being implemented within the WHO-DD structure as part of the global WHO database. A combination of the use of the HATC classification and the expanded global WHO database structure can manage all levels of data input, however imprecise (Annex 6). In addition, UMC also proposes a system checklist for cross-referencing of botanical and vernacular names used as names of ingredients. UMC suggests that the WHO-DD, the HATC classification and the checklist should prove useful tools for national pharmacovigilance centres when asking questions of the reporter to increase the clarity and accuracy of reports.

Herbal medicines usually contain multiple ingredients and it is not always possible to identify them all. In such cases, the product name should be recorded and referred to UMC, which will assist with identification. If the product is not already in the global WHO database, it will be added, together with the available information. A particular herbal product may have a number of indications and therefore appear in several places in the HATC classification.

Local input by the reporter as to the precision or otherwise of the information on the product is most useful. This can be provided in free text, as a commentary on the report, or by the submission of manufacturer's information or the original packaging. A national inventory or catalogue of medicinal plants may also serve as a reference on medicinal plants and their use in the community. In many countries, however, knowledge of medicinal plants and their medicinal use has not been documented. The establishment of a national inventory or catalogue should therefore be encouraged.

If the finished herbal product concerned or its raw materials were imported from other countries, the drug regulatory authority of the exporting country may be able to provide helpful information.

The precise Latin binomial botanical name (genus, species, author; as well as name of family) of the medicinal plants concerned should be used whenever possible, together with information about the plant parts used and the extraction and preparation methods employed. This information allows accurate comparison with other reports. A common vernacular name may be used in order not to delay or cancel submission of a report. National pharmacovigilance centres should collaborate with the pharmacognosy departments of universities and with botanists, zoologists and botanical garden staff regarding taxonomic (botanical and chemical) identification and botanical and vernacular nomenclature.

Further classification systems may need to be specially developed in order to cover additional products used in traditional medicine.

Other reporting issues
Under no circumstances should information obtained during pharmacovigilance activities be divulged for commercial purposes. The identity of both the patient and the reporter should remain confidential unless their written permission to reveal this information is obtained (Annex 3).

Reporting on herbal medicines should be as accurate and complete as possible. On the other hand, that fact that information is less than optimal should not deter reporting.

4.4 Assessment of case reports

Individual case reports
Assessment of reports on adverse reactions to herbal medicines should be undertaken by national pharmacovigilance centres in the same way as for other medicines. Each data element in the report should be considered and a causality assessment made using a standard approach. The assessment is usually based on:

- the association in time between administration of the herbal product and the event
- the outcome of dechallenge and rechallenge
- known pharmacology (including current knowledge of the nature and frequency of adverse reactions)
- medical or pharmacological plausibility (the sequence of symptoms, signs and laboratory tests and also pathological findings and knowledge of mechanisms)
- likelihood of other causes or their exclusion
- testing for adulterants or contaminants that could be the source of adverse events.
- inappropriate use.

The WHO causality categories benefit from long and extensive use and have the advantage of being internationally agreed and easy to use. The causality categories are listed in Table 1 *(1)*.

It is most important to determine whether a reaction is caused by the way a herbal medicine has been used or prepared. Particular attention to these factors should be given when an adverse reaction is suspected in connection with the use of herbal medicines usually employed in a traditional medicine. Misdiagnosis and use outside an established tradition by poorly trained providers and practitioners can be unsafe and may lead to overdose and adverse reactions. A change in the procurement sources of herbal materials, misidentification of the medicinal plant(s) and/or herbal material(s) used, or a change in the mode of preparation may lead to entirely preventable and sometimes serious adverse reactions. This should be taken into account when assessing individual cases. The best evidence should be sought to determine the established standards of practices.

Table 1. Causality categories

The causality categories described by the Uppsala Monitoring Centre		
1	***Certain:***	a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drugs (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
2	***Probably/Likely:***	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
3	***Possible:***	a clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
4	***Unlikely:***	a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
5	***Conditional/Unclassified:***	a clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment, or the additional data is under examination.
6	***Unassessable/Unclassifiable:***	a report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.
As a step towards harmonization in drug regulation in the countries of the European Union (EU), three causality categories were proposed by the EU pharmacovigilance working parties		
Category A:	"Reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable".	
Category B:	"Reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain and may be even doubtful, e.g. because of missing data, insufficient evidence or the possibility of another explanation".	
Category C:	"Reports where causality is, for one or another reason, not assessable, e.g. because of missing or conflicting data".	

Feedback to reporters

The receipt of each report should be acknowledged and a new reporting form supplied to the reporter. The reporter will also appreciate receiving further information about the reaction concerned, for example, on experience held at the national pharmacolovigilance centre or that may be helpful in further use of the medicines, unless the provision of such information is in conflict with regulatory policy. Such feedback will motivate the reporter to send in further reports.

Detection of signals at national level

The national pharmacovigilance centre should, at regular intervals, analyse the case reports in its database by class of organ system and in smaller groups of clinically related events. This may reveal case series of similar events that could constitute a signal and/or indicate the need for further study or regulatory action. Such signals should be communicated to UMC. Weak signals may be

strengthened by examination of reports from other countries held in the global WHO database.

Detection of signals at international level
The major aim of pharmacovigilance is the early detection of signals of previously unrecognized adverse reactions. Early signals may be strengthened by combining the experiences reported in various countries. Regional studies may be of particular value in the monitoring of herbal medicines. Data-mining techniques can be helpful in individual countries, but are most effective in the global WHO database managed by UMC.

Use of an advisory committee
Each national pharmacovigilance centre should have an advisory committee composed of experts to give advice on:

- maintaining quality standards in data collection and assessment procedures
- data interpretation
- publication of information
- follow-up action required.

The committee should be selected according to the expertise available but it should not be too large, so that it may not be possible to have all of the relevant disciplines represented. A committee might be selected from the following disciplines: general medicine, pharmacy, pharmaceutics, clinical pharmacology, clinical toxicology, pharmacogenetics, epidemiology, pharmacoepidemiology, pathology, drug regulation and quality assurance, drug information, information science, medical anthropology, communications, ethnopharmacology, pharmacognosy, phytochemistry, traditional medicine and/or complementary/alternative medicine.

Investigation and analysis of the cause of suspected adverse reactions
Some adverse reactions, particularly serious ones should be further investigated scientifically. The investigations may include the following:

- medical investigation of the adverse reactions: pathology, clinical pharmacology, clinical toxicology, pharmacogenetic studies
- pharmaceutical investigation of the adverse reactions: pharmacokinetics, pharmaco-dynamics and pharmaceutical, pharmacological and toxicological analysis
- pharmacognosical/phytochemical investigation (including authentification) of the herbal medicines
- physicochemical analysis to identify the constituents of the herbal medicines
- pharmacoepidemiology.

Technical expertise and basic equipment
Where possible, national pharmacovigilance centres should have the necessary technical expertise to handle herbal medicines. This might include:

- access to reliable information support on herbal medicines
- trained personnel in relevant technical areas (e.g. pharmacognosy, phytochemistry, ethnobotany, ethnopharmacology) and in the use and provision of herbal medicines

- access to facilities for analysis of potentially causative products about which there is often insufficient information.

Not all countries have access to suitable analytical laboratories. The establishment of regional laboratories specializing in the analysis of herbal products should be considered.

4.5 Data management

- *Data quality*. Strenuous efforts should be made to ensure that there are quality controls on data processing and that the data elements of reports are as complete and accurate as possible. Mechanisms to check for duplications should be instituted.
- *Data storage*. Computer databases should be managed to as high a standard as possible to facilitate access to and use of the data. Software should be selected with expert advice so that analytical needs can be met.
- *Data analysis*. Programmes should be developed to provide for regular analyses and data output appropriate for local needs.
- *Analysis of the global WHO database*. The global WHO database managed by UMC is being improved on the basis of the proposed "Database management and classification for coding of herbal medicines", of which the previously mentioned HATC is one part (Annex 6). Data-mining techniques that have proved effective on the very large numbers of reports for other medicines will be used for signal detection on reports for herbal medicines. The success of these techniques depends on the volume and quality of data submitted by national pharmacovigilance centres.
- *Support on technical and data management* is available from the WHO Collaborating Centre for International Drug Monitoring, UMC (http://www.who-umc.org/).

5. Communication

5.1 General

The successful safety monitoring of herbal medicines depends on good communication (Annex 2). There are many barriers to be broken down if all the players in this field are to be involved. There is distrust between some and ignorance of the work and function of different groups. Transparent communication is essential to overcome these problems and ensure that all players collaborate to meet the goal of the safe and effective use of herbal medicines.

National pharmacovigilance centres should ensure that manufacturers receive timely information so that they can take appropriate action regarding their products. Effective communication of the results of monitoring is also essential so that pharmacovigilance activities can have a positive impact on the health of the people.

If there is no national pharmacovigilance centre, consideration should be given to designating other relevant organizations, such as the national regulatory authority, poisons centres, drug information centres and consumer complaints authorities as the focal point.

Communication should be established at many different levels, for example, between:

- the national pharmacovigilance centre and health professionals
- the national pharmacovigilance centre and providers of herbal medicines
- health professionals and providers of herbal medicines, and consumers and patients
- providers of herbal medicines and those for other medicines
- the national pharmacovigilance centre and consumers
- the national pharmacovigilance centre and the regulatory authority
- the national pharmacovigilance centre and such centres in other countries, within the region or in other regions
- the national pharmacovigilance centre and UMC
- the national pharmacovigilance centre and the mass media.

The development of effective communication needs to be adequately resourced. It is likely that this most important part of the safety monitoring programme for herbal medicines will require proportionately greater resources than is the case for other medicines.

5.2 Risk communication

Communication strategies should be established to effectively reach all relevant target audiences, such as providers of herbal medicines, other health professionals, manufacturers and patients/consumers.

Communication of safety information is a shared responsibility between national pharmacovigilance centres, national regulatory agencies, manufacturers and health professionals. Different risk communication vehicles can be considered, including:

- adverse reaction bulletins or articles distributed in reputable journals
- public advisories or warnings
- "Dear Health Professional" letters.

Various methods of information dissemination can be considered, such as:

- Internet posting
- direct mass mailing to providers of herbal medicines and health professionals
- briefings to the mass media
- briefings to patient/consumer associations
- education sessions at health professional society meetings.

In order to reach consumers and the wide range of providers of herbal medicines successfully, messages should be tailored to suit the recipients, including translation into local languages where appropriate.

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Annex 2: The Erice Declaration on Communicating Drug Safety Information, 1997

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.

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 30 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 with 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 evaluation 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 September 29, 1997

Annex 3: Privacy and the confidentiality of personal health data[2]

Legislation or rules recently enacted or in progress in the EU, US and elsewhere in many countries have introduced new data subject rights and the need for strong safeguards in the collection, processing and transfer (especially across country borders) of personally identifiable data handled via any media, electronic or physical (paper, film, etc.). It has particular relevance to health information, among the more sensitive types of data, and certainly applies to adverse events reports, which often include data that directly identify the subject and/or the reporter with name, address, national health number, or other overt identifiers. Within some legal systems, *indirect* information that might allow determination of an individual's identity must also be protected (i.e. reference to one or more factors specific to a person's physical, physiological, mental, economic, cultural or other characteristics that could facilitate determination of his/her identity).

Although current practices throughout the pharmaceutical industry and by regulatory authorities reflect a commitment to protection of personal data, new laws in many countries necessitate some changes in personal-data handling practices. Increased rights for data subjects include notification on who is processing their data, for what purpose, and with whom the data may be shared, as well as the ability to access their own data and make corrections. Under appropriate circumstances, this may require enhancement of the ordinary informed consent process for activities, such as clinical trials. The use of secondary databases, so important to pharmacoepidemiology and retrospective studies in general, may also be affected.

There is no intention to cover this complicated topic here in more detail and those working in pharmacovigilance, and clinical research generally, should familiarize themselves with applicable data protection laws and regulations. However, it is important to explain that the term "identifiability" does not have the same meaning under one of the CIOMS V topics, "Assessing Patient and Report Idntifiability", as it does within the context of data protection legal regimes. For adverse event reporting, an identifiable patient of reporter relates to the existence of a real person that can be verified/vaiadated in some way. Under data protection schemes, the term refers to an ability to associate a data set with a particular person ("trace" a person from the data available).

[2] Reproduced, by permission, from *Current challenges in pharmacovigilance: pragmatic approach. Report of CIOMS Working Group V*. Geneva, The Council for International Organizations of Medical Sciences, 2001.

Annex 4: Spontaneous reports from persons other than health-care professionals[3]

The CIOMS Working group proposes several policy approaches and practices which aim to ensure that consumer reports are treated with appropriate respect and that there is a rational approach for handling them. In general, because the treating healthcare professionals remain vital partners in understanding and managing treatment emergent adverse events, their involvement in the confirmation process should take place whenever possible. Because much time and effort are expended on the management of consumer reports, international alignment of expectations regarding the handling of consumer-cases is also needed to assure proper focus on efforts likely to add public health value. Therefore the following principles and practices are recommended:

Definition of medical confirmation

A situation in which a healthcare professional, preferably one directly involved in the care of the patient (primary healthcare provider), confirms (i.e., agrees) that the circumstances as reported by or on behalf of the patient occurred and that the facts, as amended or updated in the confirmation process, constitute an adverse event case for which there is a suspicion by that healthcare professional of drug causality (thus, it should be considered an adverse drug reaction).

The important point in this context is to distinguish between verification of the facts by the healthcare professional (things did or did not happen as described by the patient) and the professional's confirmation that a drug-related adverse event (i.e., an adverse drug reaction) occurred.

General policy issues

- Consumers should be encouraged to report personal adverse experiences to healthcare providers, but primarily to their treating physician. Companies and regulators should convey this message through educational materials or in the course of responding to consumer inquiries or complaints. Consumer advocacy groups and disease-specific patient support groups should also be encouraged to foster this practice among their constituents.
- Neither a company nor a regulator should refer a consumer/patient to a specific healthcare professional.
- Physicians and other healthcare professionals, as part of any medical education, should be sensitized to the importance of listening to their patients for circumstances which might constitute a reportable adverse drug reaction. When reports about consumers are received from a third party who is not a healthcare professional (e.g., a relative or other patient advocate, traditional healer, lawyer), that party should be encouraged to have the patient contact his/her physician and request that the physician report the case, if appropriate, or alternatively (or in addition) to encourage the consumer to authorize the sponsor/authority to contact the doctor directly.

[3] Reproduced, by permission, from *Current challenges in pharmacovigilance: pragmatic approach. Report of CIOMS Working Group V*. Geneva, The Council for International Organizations of Medical Sciences, 2001.

Case management practices for companies and regulators:

- Regarding all reports directly from consumers or from their non-healthcare-professional representatives:

  During all contacts, attempts should be made to obtain information sufficient to ascertain the nature and seriousness of the complaint. Based upon this understanding, the strategy for documentation and follow-up will be determined (see below).

  Permission should be sought to contact the consumer's primary healthcare provider in order to obtain additional medical details when relevant; such permission should be documented. If the patient prefers to obtain and forward supporting/confirmatory medical records, attempts should still be made to obtain physician-contact permission.

  All such reports should be documented as for any other types of cases and should be taken into consideration when overall safety assessments are conducted.

  As with the handling of all other individual case reports, patient-specific information (personal data) should be treated confidentially[4]. Identification of the case should be sufficient to permit recall and cross-linkage with any subsequently obtained medical information, with all requisite steps to assure protection of patient privacy.

In addition to these general practices, some special considerations apply that depend on the perceived serious or non-serious nature of the case. The information provided in the initial consumer report will usually permit a judgement as to whether the case is "apparently" serious or on-serious; this may be the only judgement possible in the absence of subsequent medical confirmations.

- When the event is apparently non-serious and already labeled/expected:

  No additional effort (follow-up or medical confirmation) is required by the company or regulatory recipient as long as the minimum criteria for a case are satisfied[5].

- When the event is apparently serious, or is non-serious unlabeled/ unexpected:

  Special effort should be made to obtain permission to contact the consumer's physician. If the patient refuses, attempts should be made to encourage the consumer to provide relevant medical records on his/her own.

  If permission is obtained to contact the patient's physician or other healthcare professional, who in turn is unwilling to respond to company

[4] See Annex 3, Privacy and the confidentiality of personal health data.

[5] An identifiable reporter; an identifiable patient; a reaction/event; a suspected medicinal product.

attempts at follow-up for confirmation, it is possible that regulators in some countries may be in a better position to obtain the requisite follow-up or confirmatory data.

Even in the absence of medical confirmation, any report containing suspected adverse drug reactions with possible implications for the medicine's benefit-risk relationship should be submitted to regulators on an expedited and/or periodic basis.

Although the US and Canadian regulatory authorities appear to be the only ones currently requiring submission of consumer reports, consideration should be given to submitting such important cases to regulators.

Considerations on periodic safety reporting

- To satisfy current European, Japan and other countries' requirements, medically unconfirmed consumer reports should not be routinely included in official international summary reports, such as ICH Periodic Safety Update Reports (PSURs). It should be recognized, however, that others (such as the US and Canadian regulators) may require that a listing or summary of such reports be provided as an appendix to a PSUR.
- Nevertheless, all consumer reports regarded as adverse drug reactions should be regularly scrutinized for new "signals" or to confirm or extend the safety experience derived from all other sources. A statement should be made in the PSUR that such unconfirmed reports have been reviewed and either add no important new information or, conversely, suggest new findings.
- It is possible that unconfirmed consumer reports could contribute new, important information; if so, a separate tabulation and comment within the formal PSUR should be included.

Annex 5: Model reporting form

General considerations

- The reporting form for herbal medicines should be the same as that used for other medicines.
- Countries should modify their national reporting forms to facilitate the reporting of suspect reactions to herbal medicines or interactions between herbal medicines and other medicines.
- Only basic and important information should be requested. A request for great detail will result in fewer reports.
- The form should have a simple format.
- The form should look simple; a design with plenty of "white space" is helpful.
- The form should be designed in such a way that it is self-evident how it should be filled in. Any instructions for use should be simple; detailed instructions may discourage those with little training. Simplicity will encourage the recording of the best information available in the circumstances.
- The form should include instructions on how it should be completed and where it should be sent (i.e. a return address).
- The use of reporting forms should be seen as a screening process designed to reveal evidence of problems that need further investigation. The information supplied should be perfectly adequate, in most cases, to permit adequate identification and evaluation of a problem.
- Follow-up forms should be available for use when further details are required. These should be designed for use by district investigation teams or hospitals.
- Several types of follow-up forms may be needed for the investigation of specific problems, e.g. liver toxicity, death, inefficacy.
- Accurate identification of the patient/consumer is important for follow-up purposes and to avoid duplication. Essential information includes: name (or unique health facility number), date of birth (if unknown, then approximate age) and sex.

An example of a reporting form on suspected adverse reactions to medicines, including herbal medicines and vaccines, is shown on the following page. It is designed to support Member States in establishing a national drug monitoring system for the first time or in revising their reporting form to include herbal medicines.

Example of Reporting form for suspected adverse reaction to medicines, including herbal medicines and vaccines

PLEASE NOTE: all consumer/patient and reporter information will remain confidential.

Patient/consumer identification (please complete or tick boxes below as appropriate)

Last name	**First name(s)**	**Patient/record number**
Ethnicity		
Address (place and region, or health facility may be used)		**Date of birth**
		Sex □ M □ F

List of all medicines/vaccines/herbal medicines used by the patient. Please indicate suspected medicines with an asterisk (*) (please complete boxes below)

Medicine(s)Vaccine(s) + batch no.	**Daily dose**	**Route of administration**	**Date started**	**Date stopped**	**Reason for use**

For herbal medicines please give detailed information on the product
Product name:

How was the product obtained?

List of product ingredients; attach product label if available:

Name and address of the manufacturer;

Name and address of the distributor:

Other relevant information:

Description of the suspected adverse reaction (please complete boxes below)

Date of onset of reaction (dd/mm/yy):
Description of reaction (please include results of laboratory tests if available):

Outcome of the suspected adverse reaction (please tick boxes as appropriate)

Recovered □	**Not yet recovered** □	**Unknown** □	**Fatal** □	**Date of death**
Severe? Yes □ No □		**Rechallenge? Result:**	Yes □	No □
Was the patient admitted to hospital? If yes, give name and address of hospital:			Yes □	No □

Other factors (please tick box or describe as appropriate)

Kidney disease □	**Liver disease** □	**Allergy** (please describe) ....
Other illnesses (please describe):		**Malnutrition** □

Reporter identification

Type (please circle): nurse/doctor/pharmacist/other health worker /manufacturer/ distributor/supplier
Name:
Address: **Telephone:**
E-mail address:

Signature of reporter: ..... Date: .....

Please send completed form to: .....

Annex 6: Proposed database management and classification for coding herbal products (the Uppsala Monitoring Centre, Uppsala, Sweden)

Database management structure

With the aim of capturing data about adverse drug reactions (ADRs) to herbal products in the same system as ADRs to other medicines, the WHO Collaborating Centre for International Drug Monitoring in Uppsala (the Uppsala Monitoring Centre; UMC) has restructured the management of data relating to herbal products. This has mainly involved the structure of information held in the substance register of the WHO Drug Dictionary (WHO-DD). The register identifies the "preferred names" of ingredients of products mentioned on all ADR reports in the global WHO database. The logic for identifying "preferred names" for herbal substances follows, as far as possible, that for identifying preferred chemical substance names in the WHO-DD.

The validity of any scientific name (botanical names) that may be used as a "preferred name" for herbal products is problematic, since such names may be revised during taxonomic review. It is important to stress that the use of valid Latin binomial (scientific) names in the substance register of the WHO-DD is not for the purpose of providing a botanical reference work. They are the names that UMC has decided to use in order to provide unique names for herbal ingredients equivalent to international non-proprietary names (INN) for chemical ingredients in the global WHO database. The Royal Botanic Gardens, Kew, United Kingdom, has collaborated in ensuring that these names represent unique species. If there are other scientific names, they are regarded as synonyms. The scientific names comprise the Latin binomial (a genus name and a species epithet), the name of the author who described the specific species, and the publication source.

To determine which botanical names were synonyms, and to find further information on each medicinal plant, its major chemical constituents/entities and medical uses, the major reference publications that UMC considers relevant were examined. For information on ingredients of reported herbal products, a variety of sources was consulted, including the scientific literature, summaries of product characteristics (SPCs) from national pharmacovigilance centres, and direct input from national pharmacovigilance centres.

In addition to the preferred name, the list of ingredients should identify which part of the plant is used and give an indication of how the "active substances" have been extracted. This provides a more complete identification of the "active herbal ingredient". For conventional drugs, all preferred names of single ingredient medicines are either bases or salts. For all salts there must be a link to a base, e.g. omeprazole sodium is linked to omeprazole. Herbal products are treated in a similar way, in that the "mother herbs" (medicinal plants) will be the equivalent of bases and the different plant parts (herbal materials) and/or types of extract/herbal preparations are equivalent to the salts.

As shown in the herbal substance data links (Fig. 1), the herbal ingredients given as valid scientific names of medicinal plants are linked to common names of the plants and also to plant parts and the extracts or other herbal preparations used. So when retrieving information about a specified medicinal plant, starting from any scientific botanical name, vernacular, or common name, it will be easy to find all related substances (chemical

entities) including those where different parts/herbal materials and/or extracts or other herbal preparations are specified, and vice versa.

Herbal anatomical-therapeutic-chemical classification

The herbal anatomical-therapeutic-chemical classification (HATC) is a classification primarily based on those herbal products that have adverse drug reactions reported in the global WHO database and therefore appear in the WHO-DD. They are not necessarily categorized in a medicines category in any particular country. The HATC classification, unlike the regular ATC system, is based on botanical science, pharmacognosy, phytochemistry, literature search and documented traditional use rather than chemistry and evidence-based medicine. It is linked to botanical synonyms and vernacular names via the substance register of the WHO-DD, which contains all ingredients, herbal and chemical, of medicinal products mentioned on reports in the global WHO database.

In addition to the identification by preferred name and information on the plant parts used and methods of preparation, the HATC classification as used in the global WHO database, indicates:

- the suggested anatomical site of pharmaceutical action
- the range of intended medical uses including traditional therapeutic uses.

The HATC classification is mainly used as an administrative tool for placing groups of herbal products in the coding systems, and to group-related products in signal work and other congregated searches

The storage and management of safety monitoring information on herbal medicines

Principles of the system

It is often impossible to obtain information on both the traditional product composition and the use of such products by patients. No data management system can capture more than is known, but the combination of the HATC classification and the current global WHO database structure allows any and all information to be entered.

The basic philosophy behind the data management of herbal products and traditional medicines is to achieve a system that is capable of handling all levels of information, at the same time being utterly transparent to users over any imprecision, missing data and the links that are built into the hierarchies in the system. Precision versus uncertainty, for example, can be considered as occurring along several axes:

- identification of the medicinal plant
- itemization of the medicinal plant part (herbal material)
- stipulation of preparation methods (processing including extraction procedures)
- definition of the major chemical constituents extracted
- definition of the major ingredients/herbal materials (name and proportion) in mixture herbal products (complex preparations and products)
- note of any variations in product composition (and dosage form)
- intended medical use, indicating diseases or symptoms that can be treated.

Detailed descriptions of the HATC classification and the global WHO database system are available from UMC.

Adverse drug reaction terms, and indications, used in ADR reports on herbal products and traditional medicines will often be those recommended for other medicines. However, additions to WHO-ART and MedDRA may be needed to capture differences in expressing ADRs caused by the use of herbal products, especially in the case of traditional medicines, in accordance with particular treatment concepts and/or principles. For example, "increased/decreased Yin" are possible states of diseases within the Chinese medicine system, a concept unique to this particular type of medicine. Such details will be added to WHO-ART, as required.

It is clear that other systems can be devised to accomplish the same ends. The purpose of the data management system described above is specifically for pharmacovigilance, and is specially designed to allow its use alongside pharmacovigilance activities for other medicines. This is an important consideration in view of the increasing likelihood that patients/consumers may use both forms of treatment concurrently. Other systems developed and used for pharmacovigilance should function in a similar way and it should be possible to link them with the global WHO database, to ensure that all international data are pooled for global benefit.

Data analysis

The new structure and classification of herbal substances (entities) within the global WHO database will facilitate finding information about finished herbal products containing a specified medicinal plant or just a specific part, herbal materials, or extract or other herbal preparation of the specified medicinal plant. This is crucial in finding and evaluating signals concerning herbal medicines and traditional medicines (more complex than for other medicines), as the following example shows.

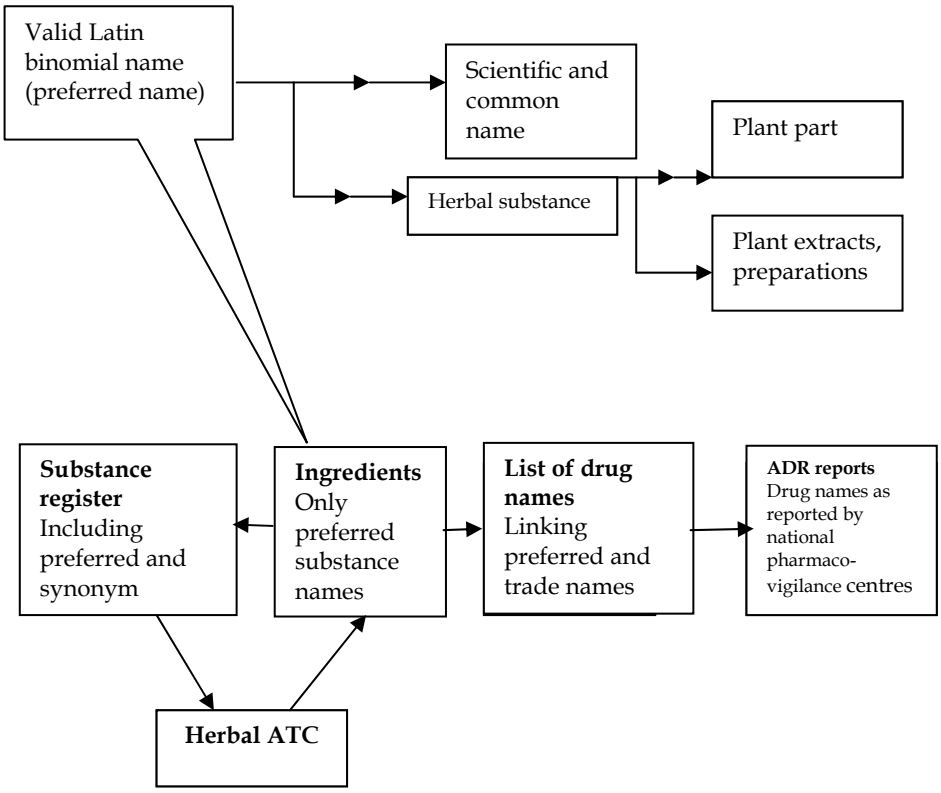
> A company has for years produced a product containing Senna alexandrina Miller, which in the labelling is called "Cassia". Another company markets a product that also lists "Cassia"' as active ingredient but the product is derived from Senna armata Wats, a different botanical species. Then reports of serious ADRs associated with "Cassia" appear and they are so serious that a withdrawal from the market is considered. It may be that only Senna armata Wats is causing these problems. In this case the other species, Senna alexandrina Miller, risks being wrongly accused because there is no distinction between the labelled names: "Cassia" is the suspected cause.

While the use of the global WHO database and, in particular, the proposed HATC classification does not solve the problem of missing or inaccurate information, it is hoped that it will facilitate proper classification of all herbal product information and, most importantly, show where there is a potential for confusion and/or error.

Another linked benefit is that it will be possible to produce a checklist of common and vernacular names covering several different languages, which will be valuable for all those seeking to identify the contents of herbal remedies used nationally. It may also prove useful at poisons centres and probably also for pharmaceutical companies in labelling their herbal products. In the end all involved with herbal products should use the valid scientific names, to avoid any confusion.

The use of data-mining tools on pooled international data will be particularly valuable in trying to find useful patterns within such a large volume of heterogeneous data. Much consideration will need to be given to the development of such tools and to the use of international expertise in the interpretation of information. As always, epidemiological studies, where they can be undertaken, will aid the quantification and validation of early signals. However, epidemiological studies on herbal products are difficult because of the problems of ascertaining precise information.

Fig. 1. Data links for herbal substances



Part II

Part II of these guidelines reproduces, in its entirety, the publication 'Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre', issued by the Uppsala Monitoring Centre, Uppsala, Sweden, in 2000, by kind permission of the Centre. WHO acknowledges the Uppsala Monitoring Centre (namely Dr David Coulter, Dr Ralph Edwards, Dr Jenny Ericsson and Dr Mohamed Farah) for their contribution in this respect.

Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre
(The Uppsala Monitoring Centre, Uppsala, Sweden, 2000)

CONTENTS

INTRODUCTION

This booklet aims to provide practical guidelines and information for the setting up of new Pharmacovigilance Centres.

The history of international pharmacovigilance goes back as much as thirty years, when the twentieth World Health Assembly adopted a resolution to start a project on the feasibility of an international system of monitoring adverse reactions to drugs. This resolution was the basis of WHO's Programme on International Drug Monitoring.

At this moment more than fifty countries participate in this Programme. The world of today no longer is as it was at the time the Programme was established. New developments challenge our attention, require adequate reaction, and raise new questions in adverse drug reaction monitoring.

A few examples may illustrate this: The current financial climate forces national authorities to find ways to contain the cost of pharmaceutical care. In some countries a strong tendency to self-medication can be seen, and many pharmaceuticals that used to be on prescription only are now available over the counter. The question arises: Does this have consequences for the safety of the patients?

Traditional medication is increasing in the Western world, but the use of herbal medicines risks escaping control. Nonetheless several herbal medicines are quite active, and may be associated with adverse effects. Continuing vigilance is needed.

A phenomenon that has received the attention it deserves, in only the last few years, is the prevalence of counterfeit drugs on the market. Instances of calamities, claiming the lives of numerous children due to the use of a toxic solvent have been documented. Drug monitoring programmes may well be instrumental in detecting such products.

The way drugs are being monitored has changed, both internationally as well as on the national level. The WHO Programme was established with ten countries, all of them highly developed. Gradually more countries showed interest and eventually joined the Programme, once they felt that their national systems were sufficiently developed.

Criteria for this development are not only the functioning of the centre in question itself, but also the presence of an effective drug regulatory body in the country that has the will and the potential to react to signals emanating from the centre and to take proper regulatory measures. WHO considers this point as vital: ***a pharmacovigilance system must be backed up by the regulatory body.***

In particular the last five years have seen an increasing number of countries expressing the wish to participate in the Programme, and several countries are in contact with WHO and the WHO Collaborating Centre, the Uppsala Monitoring Centre in Sweden, to receive support with the development of their national programmes. Practically all industrialised countries already participate; new countries now are all coming from the developing world. In several cases new countries have requested WHO's collaboration and assistance in setting up a monitoring system.

At national level also many changes have been taking place. In the original model a pharmacovigilance system is strongly centralised, and consists of one national centre collecting reports from health professionals in the country. Many countries, however, now prefer a more

decentralised system, with a national centre functioning as a focal point for some regional or local centres. Several countries are in the process of starting their systems (conforming to this model), and countries with a long-standing experience in drug monitoring are changing their programmes into a decentralised organisation. Both situations are similar in many aspects.

Monitoring Centres always start on a very small scale, often with only one enthusiastic (part-time) professional. These pioneers in their field need help and guidance. There is a need to provide such emerging centres with some information:

- the material and resources required,
- how to operate
- what kind of support is needed
- where to find adequate literature sources
- what kind of assistance can be expected
- what is the relationship to be sought with drug information centres and poison information systems, and so on.

WHO has reacted to this perceived need by holding a consultative meeting that was asked to share experience and competence through discussion of a draft guideline, prepared by Dr Ronald Meyboom. On the basis of this discussion this document has been produced, that is intended to be used by new monitoring centres, in order to prevent them from losing time and money as a consequence of the lack of experience. It discusses practical aspects of how to run a pharmacovigilance centre at the technical level, with down-to-earth recommendations. We hope that this guideline booklet helps people on the way to a well-organised and well-run pharmacovigilance centre.

This Guideline booklet is based on the proceedings of a Consultation on Setting up and Running of a Pharmacovigilance Centre, World Health Organization, Geneva, 26-27 June 1996.

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1. WHY PHARMACOVIGILANCE?

The information collected during the pre-marketing phase of a medical drug is inevitably incomplete with regard to possible adverse reactions (for definition see Glossary):

- tests in animals are insufficiently predictive of human safety
- in clinical trials patients are selected and limited in number, the conditions of use differ from those in clinical practice and the duration of trials is limited
- information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete or not available.

Pharmacovigilance is needed in every country, because there are differences between countries (and even regions within countries) in the occurrence of adverse drug reactions and other drug-related problems. This may be because of differences in:

- drug production
- distribution and use (e.g. indications, dose, availability)
- genetics, diet, traditions of the people
- pharmaceutical quality and composition (excipients) of locally produced pharmaceutical products
- the use of non-orthodox drugs (e.g. herbal remedies) which may pose special toxicological problems, when used alone or in combination with other drugs.

Data derived from within the country or region may have greater relevance and educational value and may encourage national regulatory decision-making. Information obtained in a certain country (e.g. the country of origin of the drug) may not be relevant to other parts of the world, where circumstances may be different. When information from a region itself is not available, it may take longer before a problem becomes known to drug regulatory authorities, physicians, pharmacists, patients and pharmaceutical companies.

On the other hand, international monitoring such as the WHO International Drug Monitoring Programme may provide information on possible safety issues which may not yet have emerged within the country's data. Pharmacovigilance is needed for the prevention of drug-induced human suffering and to avoid financial risks associated with unexpected adverse effects. In conclusion, medicines on the market need continuous monitoring in every country.

2. DEFINITION AND AIMS

Pharmacovigilance is concerned with the detection, assessment and prevention of adverse reactions to drugs. Major aims of pharmacovigilance are:

1. Early detection of hitherto unknown adverse reactions and interactions
2. Detection of increases in frequency of (known) adverse reactions
3. Identification of risk factors and possible mechanisms underlying adverse reactions
4. Estimation of quantitative aspects of benefit/risk analysis and dissemination of information needed to improve drug prescribing and regulation.

The ultimate goals of pharmacovigilance are:

- the rational and safe use of medical drugs
- the assessment and communication of the risks and benefits of drugs on the market
- educating and informing of patients.

Spontaneous reporting – a regional or country-wide system for the reporting of suspected adverse drug reactions – is the primary method in pharmacovigilance. In addition, other methods of data-collection exist or are under development (see § 8.5 and 10).

3. HOW TO START A PHARMACOVIGILANCE CENTRE

A new pharmacovigilance centre can start operating very quickly. The development of a pharmacovigilance system, however, from the first and uncertain stage to becoming an established and effective organisation, is a process that needs time, vision, dedication, expertise and continuity. The most promising location for a new pharmacovigilance centre may depend on the organisation and development of the healthcare system in the country and other local issues.

A governmental department (health authority, drug regulatory agency) can be a good host for a pharmacovigilance centre. However, any department in a hospital or academic environment, working in clinical pharmacology, clinical pharmacy, clinical toxicology or epidemiology, may be a suitable starting point for pharmacovigilance. The reporting of adverse drug reactions may start locally, perhaps in one hospital, then extend to other hospitals and family practices in the region, and progress step by step into a national activity. In some countries professional bodies such as the national medical association may be a good home for the centre.

When the centre is a country-wide organisation from the start, it should be remembered that much effort, especially in effective communications, will be needed before a substantial proportion of practitioners are contributing.

When a centre is part of a larger organisation (for example, a poison control unit, a clinical pharmacology department, or a hospital pharmacy) providing administrative continuity, it can get going as long as there is one professional (e.g. a physician or pharmacist) available who is primarily responsible for pharmacovigilance.

Whatever the location of the centre, pharmacovigilance is closely linked to drug regulation. Governmental support is needed for national co-ordination. Pharmacovigilance is nobody's individual privilege. Good collaboration, co-ordination, communications and public relations are needed for a coherent development and for the prevention of unnecessary competition or duplication.

3.1 Basic steps in setting up a Pharmacovigilance Centre

Prepare a plan according to the points below for the establishment of the pharmacovigilance system.

1. Make contacts with the health authorities and with local, regional or national institutions and groups, working in clinical medicine, pharmacology and toxicology, outlining the importance of the project and its purpose.
2. Design a reporting form (see § 4.1) and start collecting data by distributing it to hospital departments, family practitioners, etc.
3. Produce printed material to inform health professionals about definitions, aims and methods of the pharmacovigilance system.
4. Create the centre: staff, accommodation, phone, word processor, database management capability, bibliography, etc.
5. Take care of the education of pharmacovigilance staff with regard, for example, to:

    - data collection and verification
    - interpreting and coding of adverse reaction descriptions
    - coding of drugs
    - case causality assessment
    - signal detection
    - risk management.

6. Establish a database (administrative system for the storage and retrieval of data; see also § 7.1).
7. Organise meetings in hospitals, academia and professional associations, explaining the principles and demands of pharmacovigilance and the importance of reporting.
8. Promote the importance of reporting adverse drug reactions through medical journals, other professional publications and communications activities.
9. Maintain contacts with international institutions working in pharmacovigilance, e.g. the WHO Department of Essential Drugs and Medicines Policy (Geneva), and the Uppsala Monitoring Centre, Sweden (see page 17 for all contact details).

4. REPORTING OF ADVERSE DRUG REACTIONS

Spontaneous reporting – a regional or country-wide system for the reporting of suspected adverse drug reactions – is currently the major source of information in pharmacovigilance.

4.1 Reporting form

A case report in pharmacovigilance can be defined as: ***A notification relating to a patient with an adverse medical event (or laboratory test abnormality) suspected to be induced by a medicine.***

A case report should (as a minimum to aim at) contain information on the following elements:

1. The patient: age, sex and brief medical history (when relevant). In some countries ethnic origin may need to be specified.
2. Adverse event: description (nature, localisation, severity, characteristics), results of investigations and tests, start date, course and outcome.
3. Suspected drug(s): name (brand or ingredient name + manufacturer), dose, route, start/stop dates, indication for use (with particular drugs, e.g. vaccines, a batch number is important).
4. All other drugs used (including self-medication): names, doses, routes, start/stop dates.

5. Risk factors (e.g. impaired renal function, previous exposure to suspected drug, previous allergies, social drug use).
6. Name and address of reporter (to be considered confidential and to be used only for data verification, completion and case follow-up).

Reporting should be as easy and cheap as possible. Special free-post or business reply reporting forms, containing questions 1-6 mentioned above, can be distributed throughout the target area to healthcare professionals at regular intervals (for example, four times a year).

It may take the yearly distribution of hundreds of thousands of forms to harvest only some hundreds of case reports. It may be effective to include reply-paid reporting forms in the national formulary, drug bulletin and professional journals. Also telephone, fax and electronic mail or internet may be easy means of reporting where reliable technology is available and accessible.

4.2 Reporting by whom?

Professionals working in healthcare are the preferred source of information in pharmacovigilance, for example family practitioners, medical specialists and pharmacists. Dentists, midwives, nurses and other health workers may also administer or prescribe drugs and should report relevant experiences.

In addition pharmacists and nurses can play an important role in the stimulation of reporting and in the provision of additional information (for example, on co-medication and previous drug use).

Pharmaceutical manufacturers, being primarily responsible for the safety of their products, have to ensure that suspected adverse reactions to their products are reported to the competent authority. If adverse reactions are reported directly by patients to the national or local centre, it is useful to consider the possibility of communication with their physicians for additional information and data verification.

4.3 What to report?

In the early stages of any pharmacovigilance system, reports on all suspected adverse reactions - known or not, serious or not - are welcome and useful, because it is necessary to create a *notification culture* in which the instinctive response to any suspected adverse drug reaction is to report it. Healthcare professionals need to learn how and what to notify, and the staff of the pharmacovigilance centre need to gain experience in assessment, coding and interpretation.

In established pharmacovigilance systems it is common practice to request the reporting of all suspected reactions, including minor ones for new drugs. For established drugs the reporting of serious or unusual suspected adverse reactions is of particular importance, whereas known and minor reactions are of less interest. (See Glossary for the definition of a *serious reaction*.) If an increased frequency of a given reaction is suspected this is also a reason for reporting.

Although pharmacovigilance is primarily concerned with pharmaceutical medicines (including radiologic contrast media, vaccines and diagnostics), adverse reactions associated with drugs used in traditional medicine (e.g. herbal remedies) should also be considered. Special fields of interest are drug abuse and drug use in pregnancy (teratogenicity) and lactation.

In addition, the reporting of lack of efficacy and suspected pharmaceutical defects is recommended, especially when there is the possibility of manufacturing problems, counterfeit pharmaceuticals or of the development of resistance (e.g. antibiotics). Pharmacovigilance and

poison control are closely related activities, since the problems encountered with accidental or intentional overdose may cast doubt on the safety of a medical drug.

Also adverse reactions to cosmetics may need to be reported, especially when cosmetics contain obsolete or toxic ingredients (e.g. mercury compounds or corticoids in bleaching creams). If there is no other organisation in the country dealing with the issues, a pharmacovigilance centre may also cover problems related to medical devices and equipment, although different expertise may be needed.

The reporting of adverse events occurring during clinical trials are not covered by these guidelines. Recommendations on how to record and report such events are included in guidelines on good clinical practice for trials on pharmaceutical products (GCP).

4.4 Mandatory or voluntary reporting?

In many countries the reporting of adverse drug reactions is voluntary, but in an increasing number of countries some legal reporting obligations on healthcare professionals have been established (although a penalty is not usually associated with failure to report). Little information is available regarding the advantages and disadvantages of such obligations. In addition, in many countries it is mandatory for pharmaceutical companies to report suspected adverse drug reactions to the health authorities.

5. SPECIAL ISSUES IN REPORTING

5.1 Central or decentralised reporting ?

As a rule spontaneous monitoring aims at country-wide reporting and the use of one central pharmacovigilance database to obtain a national overview. The collection of data may nevertheless be more successful in number and quality if reporting is organised regionally, especially when countries are large or have regional cultural differences. Regional centres with short lines of communication to healthcare professionals may improve communications and feedback. When regional centres are used, good collaboration and data-exchange with the national centre needs to be ensured. Regionalisation requires more staff and facilities and can therefore be more expensive.

5.2 Stimulation of reporting

The reporting of adverse reactions needs continuous stimulation. It is important to achieve the development of a positive attitude towards pharmacovigilance among healthcare professionals so that adverse reaction reporting becomes an accepted and understood routine. In summary, the following may stimulate reporting:

- easy access to pre-paid reporting forms and other means of reporting
- acknowledging the receipt of adverse drug reaction reports by personal letter or phone call
- providing feedback to reporters in the form of articles in journals, adverse drug reaction bulletins or newsletters
- participation of the centres staff in pre- and postgraduate education and scientific meetings
- collaboration with local drug or pharmacovigilance committees
- collaboration with professional associations
- integration of pharmacovigilance in the (further) development of clinical pharmacy and clinical pharmacology in a country.

5.3 Under-reporting

Under-reporting is a common phenomenon in all countries. Correcting for under-reporting is difficult, however, because its extent is unknown and very variable. Even at established centres the reported proportion of serious reactions may not be more than 10%. Several of the countries participating for many years in the WHO Drug Monitoring Programme receive 200 or more adverse reactions per million inhabitants annually from about 10% of physicians. In many other countries, however, the reporting rates are much lower.

Under-reporting may delay signal detection and cause underestimation of the size of a problem. However, in signal detection not only the quantity but also the relevance of case reports and the quality of data are important.

There are also a number of more elusive issues which require attention. Sometimes healthcare professionals fear that the acknowledgement of adverse reactions may reflect negatively on their competence or put them at risk of litigation. Some are reluctant to report adverse reactions because of doubts regarding the causal role of the drug (although, of course, it is essential that suspected reactions are reported). Under-reporting is both a technical and a psychological issue. Clarity of criteria for reporting, simple procedures and good motivational practice are all influential in addressing the problem.

6. PRACTICALITIES IN THE ORGANISATION OF A PHARMACOVIGILANCE CENTRE

6.1 Staff

The expertise desirable in the routines of a pharmacovigilance centre includes (see also § 7):

- clinical medicine
- pharmacology
- toxicology, and
- epidemiology.

However, a new pharmacovigilance centre often starts with only a part-time expert - usually a physician or a pharmacist - and some secretarial support. It may soon become necessary to have one expert who is responsible for pharmacovigilance for most of his/her time and for secretarial assistance to be expanded (see § 6.3, Continuity). When the reporting of adverse reactions increases, staff resource requirements may be calculated by assuming that the average assessment time per case report is about one hour.

6.2 Useful equipment (includes):

- multi-connection telephone
- computer (database, see § 7.1; word processor)
- printer (computer linked)
- fax
- e-mail
- photocopier.

6.3 Continuity

Continuity in accessibility and service is a basic feature of a successful pharmacovigilance centre. The centre therefore needs a permanent secretariat, for phone calls, mail, maintenance of the database, literature documentation, co-ordination of activities, etc. Secretarial continuity may be achieved through collaboration with related departments, provided there is sufficient capacity.

6.4 Advisory Committees

A multi disciplinary advisory committee is desirable, to support the pharmacovigilance centre with regard to the quality of the procedures in:

- data collection and assessment
- the interpretation of the data
- the publication of information.

An advisory committee may represent the following disciplines:

- general medicine
- pharmaceutics
- clinical pharmacology
- toxicology
- epidemiology
- pathology
- drug regulation and quality assurance
- drug information
- phytotherapy.

In addition a network of experienced advisors in various specialisations is helpful. When the centre is located in a hospital, specialised expertise is usually within easy reach.

6.5 Information service

The provision of a high quality information service to healthcare professionals is a basic task of a pharmacovigilance centre and a major instrument in the stimulation of reporting. For this purpose and for the assessment of case reports the centre should have access to a comprehensive and up-to-date literature information database (a list of relevant literature references may be obtained from *the* Uppsala Monitoring Centre).

Location of the centre in a large hospital usually has the advantage of a library within reach. National pharmacovigilance centres can have on-line access to the database of *the* UMC and be on the mailing lists of adverse drug reaction and drug bulletins produced by the World Health Organization and many national or regional centres throughout the world (ask *the* UMC for addresses or see WHO contacts on page 17).

6.6 Communications

A bulletin or newsletter distributed to all healthcare professionals or a regular column in reputed (medical and pharmaceutical) journals are good means for the dissemination of information. Prompt data-sheet amendments are important, but data-sheets may be printed infrequently and their educational impact may not be large. In urgent cases of sufficient importance "Dear Doctor" letters may alert the profession.

6.7 Poison control and drug information centres

Poison control and drug information centres have much in common with pharmacovigilance centres, both in organisation and from a scientific point of view. If pharmacovigilance is started in a country where a poison control or drug information centre is already in place it may be efficient to develop the pharmacovigilance system in conjunction with it. Expensive facilities such as secretariat, computer resources and library services can be shared.

In any case close collaboration between these organisations is desirable.

7. ASSESSMENT OF CASE REPORTS

The assessment of adverse reaction case reports needs combined expertise in clinical medicine, pharmacology and toxicology, and epidemiology. This expertise can be developed by training the centre's staff and by the use of specialised consultants. In the assessment of case reports the following elements can be recognised:

1. ***Quality of documentation*** (e.g. completeness and integrity of data, quality of diagnosis, follow-up). The basic elements of a case report are listed in § 4.1.
2. ***Coding***. Drug names should be registered in a systematic way, for example by using the WHO Drug Dictionary (which is based on the INN nomenclature and the ATC classification). For the coding of the adverse events the WHO Adverse Reaction Terminology (WHOART), or another internationally recognised terminology (e.g. MedDRA) should be used.
3. ***Relevance*** with regard to the detection of new reactions, drug regulation, or scientific or educational value. The following questions especially may be asked:
    - ***New drug?*** Products on the market less than five years are usually considered new drugs
    - ***Unknown reaction?*** (i.e. not included in the approved Summary of Product Characteristics or 'unlabelled'). Also important is whether the reaction is described in the literature, e.g. national drug formulary, Martindale, Meyler's Side Effects of Drugs. (Ask the Uppsala Monitoring Centre for books and other information sources)
    - ***Serious reaction?*** (See Glossary).

4. ***Identification of duplicate reports***. Certain characteristics of a case (sex, age or date of birth, dates of drug exposure, etc.) may be used to identify duplicate reporting.

5. Causality assessment or imputation. With few exceptions, case reports describe suspected adverse drug reactions. Various approaches have been developed for the structured determination of the likelihood of a causal relationship between drug exposure and adverse events, for example by the WHO Drug Monitoring Programme (see Glossary), the European Commission, and the French national pharmacovigilance programme. These systems are largely based on four considerations:

    - the association in time (or place) between drug administration and event
    - pharmacology (including current knowledge of nature and frequency of adverse reactions)
    - medical or pharmacological plausibility (signs and symptoms, laboratory tests, pathological findings, mechanism)
    - likelihood or exclusion of other causes.

The WHO causality categories have the advantages of being internationally agreed and easy to use. Definitions for selected adverse reactions have been worked out and reached by

international agreement. For some of these reactions special causality algorithms have also been developed (Bénichou, 1994).

7.1 Data-processing

In the early stages case-reports can be managed manually. When reporting increases, a computer system enabling the processing and retrieval of cases according to suspected drugs and adverse reactions is generally advisable.

The computer system used should include a hierarchical drug file allowing drugs to be recorded according to product name, generic name and therapeutic category. Similarly a hierarchical adverse reaction terminology should be employed. Hierarchical systems for the recording of drugs and adverse reactions are necessary to allow for specific recording of detailed case information while still permitting retrieval of information at higher levels.

As far as possible internationally recognised terminologies and classifications of drugs (ATC, INN) and adverse reactions (e.g. WHOART, MedDRA) should be used, to facilitate international comparisons of results and international transfer of data. Special care should be taken to attain compatibility with the reporting requirements of the WHO Drug Monitoring Programme. Detailed instructions on how to organise computerised data for submission to the WHO database are obtainable from the Uppsala Monitoring Centre. It may not be cost-effective to design a computer system for the management of adverse reaction reports from scratch. Commercial programmes are available which have been appropriately tested and can be customised according to local needs including local languages.

8. USE OF THE DATA

Data collected in pharmacovigilance can be used in a variety of ways.

8.1 Hypothesis generation and strengthening

A major aim of pharmacovigilance is the early detection of hypotheses or signals (see Glossary) with regard to possible adverse reactions. Early signals may be too uncertain, however, to justify firm conclusions and regulatory action, and may need further study (see § 8.5). A signal may be strengthened by combining the experiences reported in various countries. Therefore international collaboration is important.

8.2 Drug regulation

After approval of a medicinal product, all available domestic and international safety information is continuously monitored by the drug regulatory authority and the pharmaceutical company concerned. Often problems can be solved by adaptation of the approved product information (inclusion of new adverse effects, warnings, or indication changes). Sometimes stronger restrictive actions are needed, with withdrawal of the marketing authorisation as the extreme. For the approval of a given drug in a given country, it may be very helpful to have information on the experiences with the drug in countries where it is already in use (e.g. through collaboration with *the* Uppsala Monitoring Centre).

8.3 Information

For the dissemination of information of current importance or interest to healthcare practitioners, an adverse drug reactions bulletin or a column in medical and pharmaceutical journals may be very helpful. In the case of an emergency, a letter directly to all doctors and pharmacists may be needed. Usually such actions take place in collaboration with the regulatory authority and the pharmaceutical company's experts.

8.4 Education and feedback

Continuous pre- and postgraduate education of healthcare professionals is an important aspect of pharmacovigilance. Appropriate educational activities will improve knowledge and awareness of adverse drug reactions and stimulate reporting. Drug information officers and local or national Formulary Committees may benefit from close collaboration with the pharmacovigilance centre.

8.5 Limitations regarding the use of the data

Usually case reports of suspected adverse reactions may be influenced by all sorts of bias. The interpretation of pharmacovigilance data may be difficult. Often signals are unsubstantiated and require further study for confirmation or refutation (hypothesis testing) and for the assessment of the reaction frequency, for example, as needed for drug regulatory decision-making.

On the one hand a pharmacovigilance centre has the task to stimulate the use of the collected data by healthcare professionals, and on the other hand to ensure that the heterogeneous and largely unproven data are used in a careful and scientifically (and socially) responsible way.

The spontaneous reporting system is especially helpful in the detection of adverse reactions that are specific or occur in a suggestive time-relationship with drug use (e.g. anaphylactic shock), but may be less effective in studying other sorts of adverse reactions (e.g. cancer development). The potential of the spontaneous reporting system to determine the true frequency of adverse reactions is limited.

The detailed reporting of histories of patients with iatrogenic injury and the subsequent use of the reports are to a variable extent subject to rules regarding privacy and medical secrecy. Confidentiality of personal data is needed. The complex of details in a patient history may be as personal as a finger print and therefore a potential identifier. It is advisable for a pharmacovigilance centre to establish data-management protocols, identifying legitimate data-users and describing which data elements are available to whom and for which purpose and which uses are excluded. Confidentiality primarily concerns the secrecy of the identity of all individuals (patient, reporter, doctor) and institutions (hospital) involved. In many countries case report summaries are not considered confidential.

Besides legal obligations, the basis of spontaneous monitoring is the commitment of healthcare practitioners and patients together to make information available. If pharmacovigilance data were used against the wish of reporters, the system as a whole might collapse.

9. RELATIONS WITH OTHER PARTIES

9.1 The Drug Regulatory Authority

The Drug Regulatory Authority in the country needs to be informed about suspected adverse reactions without delay, especially when unusual (e.g. reactions not included in the approved Summary of Product Characteristics) or serious. In addition, a pharmacovigilance centre should inform the regulatory authority about any cluster of case reports that is of possible interest, or when an adverse reaction is reported in high or increasing frequency.

9.2 Pharmaceutical companies

Pharmaceutical companies need the same information as the regulatory authority. It will depend on the local situation whether companies are to be informed directly or via the regulatory authority.

9.3 Professional medical and pharmaceutical associations

A pharmacovigilance centre should seek the support of ***professional medical and pharmaceutical associations***. In the case of an emergency, these associations should be informed in good time.

9.4 World Health Organization and WHO Collaborating Centre for International Drug Monitoring

A new pharmacovigilance centre should make contact with the **World Health Organization** in Geneva and the **WHO Collaborating Centre for International Drug Monitoring** (*the* UMC) in Uppsala, Sweden.

9.5 National pharmacovigilance centres

In addition it may be helpful to make contacts with ***national pharmacovigilance centres*** in nearby countries. When more experienced, such centres may be helpful with staff training.

9.6 Academia

The need for pharmacovigilance and the nature of its procedures are a natural part of the curriculum of pre-graduate training. In addition a pharmacovigilance centre may contribute to and participate in postgraduate educational programs. Findings or hypotheses from the pharmacovigilance system may be of potential interest for further study with regard to mechanisms, reaction frequency, and so on, to academic pharmacological or epidemiological institutions.

9.7 Media and consumer organisation

Support from national associations of consumers and patients may add to the general acceptance of pharmacovigilance. Good relations with leading journalists may be helpful, e.g. for general public relations and as part of the *risk management* strategy whenever an acute drug problem arises. Special attention may be needed to explain to journalists the limitations of pharmacovigilance data (see § 8.5)

10. OTHER SOURCES OF INFORMATION

Spontaneous Reporting is especially useful in picking up signals of relatively rare, serious and unexpected adverse reactions. For less rare adverse reactions several other methods may be used, e.g. clinical trials or cohort studies. In addition to spontaneous reporting several other methods have become available to provide data relevant to pharmacovigilance. Examples are: Prescription Event Monitoring, Case-Control Surveillance and linkage of records from multipurpose databases. In addition, drug utilisation data is of value in safety assessment.

11. FUNDING

An estimation of the amount of money needed for pharmacovigilance can be calculated as a function of the rate of reporting required and the size of the population (see § 5.3 and 6.1). The collection of quantitatively and qualitatively good data and the careful assessment and distribution of such information obviously have a price. A pharmacovigilance centre should have some basic, regular source of funding in order to ensure continuity in its work. Such funding may be obtained as part of the drug registration fee, or through a special mandatory pharmacovigilance contribution. Both can be included in the budget of the drug regulatory authority.

Apart from the basic resources, the centre may try to get additional funding from various parties with an interest in pharmacovigilance. Institutions that may be approached include:

- health insurance companies and health insurance funds
- university departments
- professional associations
- governmental departments with an interest in drug safety.

In view of the great commercial and public health consequences of adverse reactions, the continuity of the funding of pharmacovigilance should be guaranteed and not be susceptible to possible pressure groups, political changes or economic factors.

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GLOSSARY

A ***drug*** or ***medicine*** is 'a pharmaceutical product, used in or on the human body for the prevention, diagnosis or treatment of disease, or for the modification of physiological function'.

An ***unexpected adverse reaction*** is 'an adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation, or expected from characteristics of the drug'. Here the predominant element is that the phenomenon is unknown.

A ***side effect*** is 'any unintended effect of a pharmaceutical product occurring at doses normally used in man, which is related to the pharmacological proprieties of the drug'. Essential elements in this definition are the pharmacological nature of the effect, that the phenomenon is unintended, and that there is no overt overdose.

An ***adverse reaction*** is 'a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man'. In this description it is of importance that it concerns the response of a patient, in which individual factors may play an important role, and that the phenomenon is noxious (an unexpected therapeutic response, for example, may be a side effect but not an adverse reaction).

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

In these definitions drug or drug food interactions are also included. It should be added that many patients have only suspected adverse reactions in which the causal role of the drug is unproven and may be doubtful, and that pharmacovigilance data usually refer to only suspected adverse reactions and side effects.

An ***adverse event*** or ***experience*** is defined as 'any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment'. The basic point here is the coincidence in time without any suspicion of a causal relationship.

Serious adverse events can be defined as those that:

a. are life threatening or fatal
b. cause or prolong hospital admission
c. cause persistent incapacity or disability; or
d. concern misuse or dependence.

Type A effects ('drug actions') are those which are due to (exaggerated) pharmacological effects. Type A effects tend to be fairly common, dose related (i.e. more frequent or severe with higher doses) and may often be avoided by using doses which are appropriate to the individual patient. Such effects can usually be reproduced and studied experimentally and are often already identified before marketing.

Interactions between drugs, especially pharmacokinetic interactions, may often be classified as Type A effects, although they are restricted to a defined sub-population of patients (i.e. the users of the interacting drug).

Type B effects ('patient reactions') characteristically occur in only a minority of patients and display little or no dose relationship. They are generally rare and unpredictable, and may be serious and notoriously difficult to study. Type B effects are either immunological or non-immunological and occur only in patients, with - often unknown - predisposing conditions. Immunological reactions may range from rashes, anaphylaxis, vasculitis, inflammatory organ injury, to highly specific autoimmune syndromes. Also non-immunological Type B effects occur in a minority of predisposed, intolerant, patients, e.g. because of an inborn error of metabolism or acquired deficiency in a certain enzyme, resulting in an abnormal metabolic pathway or

accumulation of a toxic metabolite. Examples are chloramphenicol aplastic anaemia and isoniazid hepatitis.

Type C effects refer to situations where the use of a drug, often for unknown reasons, increases the frequency of a 'spontaneous' disease. Type C effects may be both serious and common (and include malignant tumours) and may have pronounced effects on public health. Type C effects may be coincidental and often concern long term effects; there is often no suggestive time relationship and the connection may be very difficult to prove.

Confidentiality: Maintenance of the privacy of patients, healthcare providers and institutes, including personal identities and all personal medical information.

Verification: The procedures carried out in pharmacovigilance to ensure that the data contained in a final report matches the original observations. These procedures may apply to medical records, data in case-report forms (in hard copy or electronic form), computer printouts, and statistical analyses and tables.

Validation: The action of proving that any procedure, process, equipment (including the software or hardware used), material, activity or system used in pharmacovigilance actually leads to the expected results.

CAUSALITY CATEGORIES

The causality categories described by the Uppsala Monitoring Centre are as follows:

1. ***Certain***: a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
2. ***Probable/Likely***: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
3. ***Possible***: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
4. ***Unlikely***: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
5. ***Conditional/Unclassified***: a clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment, or the additional data is under examination.
6. ***Unassessable/Unclassifiable***: a report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

As a step towards harmonisation in drug regulation in the countries of the European Union, the EU pharmacovigilance working parties proposed the following three causality categories:

- ***Category A***: 'Reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable'.
- ***Category B***: 'Reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain and may be even doubtful, e.g. because of missing data, insufficient evidence or the possibility of another explanation'.
- ***Category O***: 'Reports where causality is, for one or another reason, not assessable, e.g. because of missing or conflicting data'.

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