



World Health Organization

SAFETY MONITORING *of* **MEDICINAL PRODUCTS**

Guidelines for setting up and running
a Pharmacovigilance Centre



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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 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 schemes 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 materials 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 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 purposes.
- 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 24 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 or 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
- pharmaceuticals
- 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 24).

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* 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* 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** 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** 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** 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 and departments.
- 9.7** *Media and consumer organisations*: 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 properties 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 are 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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