LEADING ARTICLE

Drug Safety 1999 Dec; 21 (6): 429-447
0114-5916/99/0012-0429/$09.50/0

Pharmacovigilance in Perspective

Ronald H.B. Meyboom,[1] *Antoine C.G. Egberts,*[2] *Frank W.J. Gribnau*[3] and *Yechiel A. Hekster*[4]

1 Netherlands Pharmacovigilance Foundation LAREB, 's-Hertogenbosch, The Netherlands
2 Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, Utrecht, and TweeSteden Ziekenhuis, Tilburg, The Netherlands
3 Department of Clinical Pharmacology, Nijmegen University Hospital St Radboud, Nijmegen, The Netherlands
4 Department of Clinical Pharmacy, Nijmegen University Hospital St Radboud, Nijmegen, The Netherlands

Abstract

Pharmacovigilance is more than spontaneous reporting alone, and the evaluation of marketed medicines is more than just pharmacovigilance. The positioning of a drug usually takes place during the years following introduction, when worldwide experience has accumulated. Originally a modest appendix of drug regulation, pharmacovigilance has become a major activity. The provision of the information needed for the evaluation of the benefits and risks of drugs is in the first place a scientific challenge. In addition, there are important ethical, logistical, legal, financial and commercial constraints. Good pharmacovigilance practice needs to be developed to ensure that data are collected and used in the right way and for the right purpose.

Pharmacovigilance, and more generally the study of the benefits and risks of drugs, plays a major role in pharmacotherapeutic decision-making, be it individual, regional, national or international. In addition, pharmacovigilance is becoming a scientific discipline in its own right.

A variety of changes are taking place in the complex system of drug development, regulation and distribution. Pharmacovigilance should be proactive in monitoring their possible consequences.

1. History

Pharmacovigilance aims at the detection, assessment and prevention of adverse effects or of any other possible drug-related problems.[1,2] Its principles and procedures are reviewed in a guideline soon to be published by the World Health Organization (WHO).[3]

The ultimate goal of pharmacovigilance is to foster the rational and safe use of medicines. During the 1960s, in the aftermath of the thalidomide disaster, national pharmacovigilance centres were established in a number of countries around the world. New centres continue to be established, now mainly in developing countries. Originally, spontaneous reporting – a countrywide system for the reporting of suspected adverse effects of drugs – was the only conceivable early warning system for possible future drug-induced disasters. Spontaneous reporting has since proved to be the main

source of information for pharmacovigilance and drug regulation, in addition to any findings published in the literature.

National pharmacovigilance centres were usually established in connection with (equally new) drug regulatory agencies, responsible for granting marketing authorisations for medicinal products. Spontaneous reporting developed largely within the governmental legislative environment.

Granting a marketing authorisation is an official decision, based on legal rules and criteria, and secondary to the integral results of a series of scientific studies encompassing pharmaceutical quality, experimental pharmacology and toxicology, and controlled clinical trials. These studies are performed according to the established rules for 'good practice'.[4] After approval is granted for a medicine, case reports of suspected adverse drug reactions are direct evidence – both scientifically and legally – in further regulatory decision-making. However, because of variable underreporting and a doubtful causal relationship in most case reports, these data are often difficult to interpret and may not suffice as legal evidence.

Through the years, doubt has been expressed on several occasions regarding the validity of spontaneous reporting.[5-7] From the outset, many countries kept secret the data and arguments underlying postmarketing regulatory decisions. As a consequence, the contributions of spontaneous reporting to regulatory changes could pass unnoticed by scientists and healthcare providers, i.e. the potential reporters. In the 1980s a number of publications revealed, however, that spontaneous reporting had become a major routine in postmarketing drug regulation.[8-12] At the time, spontaneous reporting was mainly regarded as an instrument of drug policy. Many of the scientific and logistical problems inherent to its use had not yet been explored, or not fully so.

2. The Present Situation

The experience from many countries makes it clear that spontaneous reporting is a prolific source of information.[13-17] It thus plays an important role in postmarketing drug regulation, even in arriving at difficult and extreme decisions such as withdrawal from the market.[18] The principles and procedures, and the strengths and weaknesses, of spontaneous reporting are now taking shape. Current developments suggest that there is consolidation and professionalisation of spontaneous reporting, and are indicative of increased governmental interest in pharmacovigilance. Worldwide reporting rates have increased steadily over the years. There are now several countries where the number of case reports per year exceeds 200 or 300 per 10 million inhabitants.[19,20] National centres are also expanding: several European countries have teams of 20 to 50 people working full-time in pharmacovigilance, i.e. about 1 to 2 staff members per 10 million inhabitants.

Documents issued by the European Commission now include pharmacovigilance and spontaneous reporting as a formal part of the basis for drug legislation and regulation.[21,22] Several countries demand that pharmaceutical companies report suspected adverse effects to the regulatory authority and have qualified pharmacovigilance staff. In addition, an increasing number of countries have made reporting of adverse drug effects mandatory for physicians and other healthcare providers,[19] although there are usually no penalties for noncompliance. Pharmacoepidemiology units have now been established at many universities and special postgraduate courses in pharmacovigilance are offered in an increasing number of countries.

There are many variations on the theme of spontaneous reporting.[23] Reporting may be intensified, may concentrate on selected drugs or adverse effects (e.g. skin reactions, liver injury or eye disorders), and can be regional, national or international. All these forms are valuable enrichments of pharmacovigilance, provided they are linked to the national pharmacovigilance database. Undoubtedly, further improvements and refinements of spontaneous reporting are foreseeable.[14] Structured collaboration between pharmacists and physicians may quantitatively and qualitatively improve the reporting of adverse reactions.[24] Direct

Table I. Advantages of spontaneous reporting

Very wide spectrum: includes many different adverse effects (although mainly type A and B), interactions and other problems (e.g. pharmaceutical defects) and countrywide (in principle, coverage of all drugs and all patients)
Effective
Rapid
Continuous
Comparatively cheap

reporting by patients themselves has been found to accelerate the detection of adverse effects.[25]

In addition to spontaneous reporting, 'prescription event monitoring' and 'record linkage' are major general approaches used in pharmacovigilance.[26-28] Furthermore, case-control surveillance and cohort follow-up studies are finding their place.[29] Case-control surveillance is useful for the study of rare but characteristic disorders which are relatively frequently of drug-induced origin, especially when there is not a suggestive time relationship. In theory a follow-up study is the method of choice for the evaluation of a treatment. In the practical situation, however, there are many difficulties and its use is often restricted to diseases that are both frequent and serious, e.g. diabetes mellitus, rheumatoid arthritis or epilepsy. When such diseases are treated by specialists in a standardised (protocol-driven) way, computerised database cohorts can be formed without much effort. An example of this approach, which might be called 'cohort surveillance', is the Arthritis, Rheumatism and Ageing Medical Information System (ARAMIS).[30]

3. What Spontaneous Reporting Can Do

Experience gained internationally shows that spontaneous reporting is effective in providing information about a wide range of different adverse effects and other drug-related problems.[13,14] In The Netherlands, a modest rate of reporting of only about 1000 cases per year (70 per million inhabitants) could still yield a continuous stream of useful information.[14] When the number of reporting physicians increases, the quantity of information (number of topics) and its quality (evidence per topic) are likely to improve. Since there is a critical minimum number of case reports needed for a signal,[31] increased reporting by a greater proportion of physicians is also likely to accelerate the detection of rare (but serious) adverse effects. In the light of international experience, it is reasonable for a developed system to aim at receiving a steady annual input of up to 300 reports per 1 million inhabitants, including 30% or more of the serious adverse effects occurring in the country, originating from more than 10% of practitioners.[19,20,32-34] When such levels are reached, the community may be reasonably confident that unexpected adverse effects will be detected within an acceptable period of time.

The primary role of spontaneous reporting is signal generation. It has proved to be particularly effective in detecting type A and type B adverse effects, (see Meyboom et al.[35] for a description of type A, B and C adverse effects) especially when there is a clue for the physician to recognise the possible drug involvement (e.g. a characteristic event and a suggestive temporal relationship) [see table I].[14,31,35]

On the other hand, spontaneous reporting is of less use for the study of adverse effects with a relatively high background frequency and occurring without a suggestive temporal relationship, e.g. the heterogeneous group of type C effects (table II).[14] In most case reports the involvement of the drug is uncertain and in many it is even doubtful. As a consequence, spontaneous reporting may not be expected to provide the necessary evidence to confirm the connection between a drug and a suspected adverse reaction. Standardised case causality assessment has not been able to change this situation fundamentally. Furthermore, there is a substantial, variable but usually unknown extent of underreporting. As a result, spontaneous reporting cannot

Table II. Limitations of spontaneous reporting

Causal relationship in case reports usually uncertain
Underreporting and reporting bias
No quantitative measurement (comparison of drugs is often difficult)
Insensitive to type C adverse effects

Table III. Determinants of the level of performance of a spontaneous reporting system

Reporting rate (e.g. number of case reports/million inhabitants/year)
Reporting distribution, i.e. the proportion of physicians reporting, reporter characteristics (e.g. general practitioners, specialists, pharmacists), geographic distribution, reporting rates in specific populations
Reporting quality (documentation and follow-up, e.g. The Uppsala Monitoring Centre's documentation grading)
Reporting efficiency (the proportion of relevant case reports, e.g. concerning unknown or serious adverse effects)

measure the frequency of an adverse reaction and a comparative assessment of the safety of different drugs is usually not possible. If a consistently high reporting rate and adequate data on drug consumption are available in a particular country, however, spontaneous reporting may give a useful impression of the frequency of adverse drug effects.

When a signal is detected, further study is usually needed to test the hypothesis. Obviously, the source of the signals, spontaneous reporting, should not as a rule be also expected to confirm and quantify the association. For this purpose different – notably pharmacoepidemiological – approaches may be indicated.

The success of a spontaneous reporting system depends, in addition to the reporting rate, on the quality and relevance of case reports (see table III).[36] A variety of other factors may influence the success of spontaneous reporting, e.g. the numbers of drug users, drug registration policy, training of physicians and other healthcare providers, and feedback and other services provided by the centre. Drug utilisation data are useful as a reference, for instance for assessment of reporting rates and differences or changes in reporting. The more drugs there are on the market for a given indication, the smaller are the numbers of users of each individual drug, and consequently monitoring will be less effective. For small countries, international collaboration may be a means of obtaining data for large populations. An increase in reporting can only be expected to improve the results of pharmacovigilance if it is associated with a proportionate increase in assessment capacity (e.g. number and training of staff, quality of computer facilities). Pharmacovigilance is only likely to give good results if the system is well organised and is acceptable to the medical community. Sufficient staff is needed for intensive communication with practitioners and follow-up of reports. Important new information is only likely to be harvested as part of a much larger (and therefore expensive) mass of data of less interest. Even when the reporting rate is high in general, some groups of drugs (e.g. anticancer agents) may escape monitoring as a result of selective underreporting.[14]

4. Is This All We Need?

Spontaneous reporting primarily serves the aim of early detection of serious and unexpected adverse effects of new drugs. Undoubtedly, this was the cardinal issue in the early 1960s. In future decades, however, there will be more emphasis on the rational, safe and cost-conscious use of drugs, and on the precise evaluation of the merits and appropriate use of established treatments. These purposes require a much wider spectrum of information (summarised in table IV) which, in turn, implies a variety of additional activities. Notwithstanding the importance of many of these topics,

Table IV. Topics of interest for the study of medicines after approval

Fine tuning of dosage recommendations
Reappraisal of indications (extension or restriction)
Assessment of side effects
detection of unexpected adverse effects and interactions
identification of risk factors
quantitative measurement of (un)safety
long term safety/toxicity
study of potential risk groups (e.g. children, the elderly, pregnancy, etc.)
Detection of unexpected beneficial effects
Detection of pharmaceutical defects and counterfeit drugs
Further kinetic, pharmacological and mechanistic studies
Assessment of long term efficacy (e.g. when surrogate end-points used for approval)
Characteristics of drug use and drug users
Inappropriate drug use (addictions, noncompliance, medication error, intentional and accidental intoxications)
Quality of life and utility assessment
Collection of data needed for cost assessment

the pharmacovigilance budget is only a modest part of total expenditure on drug regulation and marketing.

The 'real life' conditions of drug use after introduction are quite different from those during the trials before approval. Indication, duration of use and patient characteristics may not be the same. Once a drug is on the market, exact quantitative knowledge is needed of both its short and long term efficacy and safety in different situations, relative to other drugs and treatments, and to the untreated condition. Further information is often needed about dosage and pharmacokinetics in special populations and situations, and about the parameters for therapeutic monitoring (e.g. blood concentrations, warning signs, risk factors). Methods for acquiring information are still under development and face a number of scientific, ethical and logistical difficulties. In addition, there is uncertainty both about the appropriate ways of funding this research and about the size of the funds that will be needed. Ideally, systems should be developed that measure simultaneously, quantitatively and comparably the efficacy and the safety of drugs; this is particularly important for long term use when initial approval involved surrogate endpoints. In the foreseeable future, however, there remain pressing issues, such as the unravelling of the delayed and complex influence of oral contraceptives on carcinoma of the breast, as major challenges to postmarketing drug evaluation.

5. Current Developments

5.1 Progress in Automation

Case reports contain detailed information concerning patients, including medical and medication histories. From the start, the administration, processing and utilisation of such complex data posed serious problems for pharmacovigilance centres, especially with regard to signal detection and to presentation of the aggregated data. Modern, powerful and flexible, computer systems have fortunately solved many of these difficulties.

The WHO Adverse Reaction Terminology (WHO-ART), a preferred and high level system, was designed in the 1960s as a fixed and hierarchical system of key words and diagnostic codes, consistent with the state of computer technology at the time. New computer technology has meanwhile been developed and different approaches may now be tried. Complete event descriptions can be stored as free text, and case reports can be processed and retrieved by using plain words, parts of words, and combinations. The specific role of a preferred adverse reaction terminology such as WHO-ART or the Medical Dictionary for Regulatory Activities (MedDRA) in data processing and signal and syndrome recognition may need to be reconsidered.

In many countries, the introduction of automation into medical and pharmaceutical practice has drastically changed administrative routines in family practices, hospital wards and pharmacies. These changes open promising possibilities for pharmacovigilance. In a computerised medical administration system, electronic reporting of suspected adverse drug effects may become an easy and routine activity. The generation of databases by linking individual computers, and the resolution of incompatibilities between different software systems, are now mainly technical problems rather than the utopia of 10 years ago. The collection of up-to-date data on drug prescribing and (subsequent) medical events in vast populations seems to be within reach. Concrete and useful results such as those achieved in Scotland indicate that, after the experiments of pioneers such as Doll and Skegg 25 years ago, there is now a breakthrough in the use of 'record linkage' in pharmacovigilance.[28]

An improvement, both quantitatively and qualitatively, in national reporting will contribute to improved international pharmacovigilance, for example by the Uppsala Monitoring Centre. Further advances in computer technology will lead to further improvements in international collaboration. The notorious delay in international data transmission may be decreased and lack of harmonisation may become a soluble problem. The new Eudra-

watch system of the European Medicines Evaluation Agency (EMEA) will enable swift data transmission in the European Union.

To combine spontaneous reporting with drug utilisation data has long been a goal. Advancements in computer technology have also spurred work on this issue. On an international scale, the Uppsala Monitoring Centre and International Medical Statistics (IMS) are collaborating in the Adverse Drug Reaction Signal Analysis Project (ASAP) which combines reporting and prescription data.[37]

The barriers now will probably be new legislation regarding privacy protection and medical ethics rather than insurmountable technical challenges.[38] However, as pharmacovigilance is of the utmost importance for users of medicines, the question of privacy as a barrier can be expected to be solved.[36]

5.2 Synthesis of Spontaneous Reporting and Population Studies

Each method in pharmacovigilance (e.g. spontaneous reporting, prescription event monitoring, record linkage or case-control surveillance) follows a more or less individual approach to signal generation. In spontaneous reporting, new adverse effects are often signalled through a fairly small number of eye-catching case reports.[13,14] In population studies, unexpected associations are traced through statistical disproportionality.[39,40] Promising results have occasionally followed the application of a technique from one method to another method, e.g. calculation of odds ratios in a spontaneous reporting database.[41,42] The establishment of new and very large databases covering large parts of national populations, with the use of powerful computers, flexible software and scanning techniques, will open unprecedented possibilities for statistical assessment in pharmacovigilance and pharmacoepidemiology. Hopefully, pharmacovigilance may then be extended to type C adverse effects. Nested case-control studies can be promptly done to address specific questions whenever they arise.[43]

Concepts in attributing causality in medicine are changing.[44] This may also influence approaches towards attributing events to drug exposure in populations. As elsewhere in medicine,[45-47] novel statistical systems are used in pharmacovigilance for signal generation in large databases, e.g. the Bayesian neural network of the Uppsala Monitoring Centre.[48] Computerised systems for automated signal generation are also currently under development at national centres in several countries, combining statistical, medical and regulatory criteria.[40,49-51] These systems are being tested in different situations, for example for the identification of drug interactions,[52] and may be applicable to spontaneous reporting as well as to other databases.

A scenario like this one, with integration of population exposure-event databases, spontaneous reporting and case-control assessment, could result in a synthesis of existing approaches. Statistical signal generation may overcome the Achilles' heel of spontaneous reporting: the physician's limited ability to recognise unknown and unexpected adverse effects. Uncertainty as regards the background frequency of various medical events – another notorious problem in pharmacovigilance – may also be dealt with (except for events that give no reason to consult a physician). With ever-expanding numbers of patients, automated population databases may ultimately be used for signal testing as well as for signal generation.

These optimistic views are tempered somewhat by the fact that there remain expected and unexpected limitations and errors to be envisaged. Obviously, a medical history is much more than a diagnosis, an administrative note or a laboratory finding. Diagnostic codes may not be identical to the clinical diagnostic descriptions. Self-medication is not usually stored in databases, is therefore excluded from vigilance, and may be a major confounder. It may be difficult to translate statistical findings for populations to risk estimation for individual patients.

Although in the future spontaneous reporting may be of less importance, it is expected to continue to serve as a direct and rapid monitoring sys-

tem for urgent and serious problems, especially during the first few years following the introduction of a new drug.

6. Pharmacovigilance and Drug Regulation

6.1 Confidentiality and Transparency

In most countries, adverse reaction reporting started as a spontaneous, voluntary and confidential activity. Since a case report is essentially a medical history, it is subject to the constraints deriving from medical secrecy and privacy regulations. A basic principle is the right of patients to refuse to allow the use against their wish of data originating from their medical histories (with the exception of designated contagious diseases or insurance accounting purposes).[53] Originally, confidentiality concerned the report as a whole, including the association of drug and adverse event involved. This was expected to decrease the reluctance of reporters to submit doubtful or incomplete observations.

The registration dossier is the best-informed data source for a drug. It is in its entirety the property of the company and may only be used by the competent authority for the purpose of registration of the drug. After approval, the only public part of a registration file is the Summary of Product Characteristics. In several countries, including The Netherlands, drug regulation is excluded from freedom of information legislation; in other countries it is not. Often, the pharmacovigilance database was regarded as part of the drug's secret registration file.

Recently, the concept of confidentiality has in many countries become less strict, e.g. because of the introduction of freedom of information legislation, resulting in diversity in the availability of data (see table V). It has now become usual in many countries that numerical data, and often also case report summaries, are available to healthcare professionals and frequently to the public, with the restriction that any data that could possibly lead to the disclosure of the identities of persons or institutes involved must be removed. In some countries (e.g. France), on the other hand, access to the spontaneous reporting database is difficult or impossible.

Although it originally reported only to regulatory authorities, the Uppsala Monitoring Centre has, after consultation with participating countries, changed its policy and now releases numerical data to third parties on request. In addition, 30 countries have agreed to routinely disclose case details as stored in the international system.

Pharmacovigilance is incontestably a general public health interest. The data acquired through spontaneous reporting are supplied voluntarily by real patients and should thus be regarded as the property of the community at large. All those involved with medicines benefit from accurate and timely information.[54] Ideally, all persons or parties with an interest in medical drug use, drug information and drug policy should have access to the national spontaneous reporting database (with the exception of personal identifiers). The spontaneous reporting system is, however, based on the willingness of patients and of healthcare professionals to contribute. If these groups, for one reason or another, no longer trusted the system, the process as a whole might collapse.

In spontaneous reporting, data are usually based on suspicion, and may be preliminary, ambiguous, doubtful or wrong. Premature or erroneous conclusions may be reached and lead to unbalanced publicity, unnecessary anxiety, patient noncompli-

Table V. Parties having access to pharmacovigilance databases in 45 countries. In 8 countries, case details are not made available to any outside party (from Olsson,[19] with permission)

Category of user	Type of access		
	on demand	periodic standard listing	on-line connection
Health professionals	31	3	1
Drug manufacturers	29	11	4
Researchers	29	2	
General public	10		
Drug information centres	1		1
Medical libraries		1	

ance, public mistrust and unwarranted decisions. It is the responsibility of a pharmacovigilance centre to give instructions for use of the data and to provide assistance regarding their interpretation. A data management code, explaining which data may be used for which purpose, is desirable. 'Good communications practice', and not concealment of the data, will be the appropriate way of preventing unnecessary drug-safety scares.[55]

6.2 Science May Not Keep Pace with Drug Policy Needs

New medicines are usually developed as the property of a pharmaceutical company. Once a medicine has become an established treatment, its efficacy, safety and cost are of interest to the community as a whole. The decision as to whether or not a new drug may be put on the market rests solely with the regulatory authority. After registration, however, drug policy is formulated by a variety of organisations: e.g. hospital or regional formulary committees, governmental and non-governmental medicines reimbursement systems (insurance), professional medical and pharmaceutical associations, university teachers and information officers, consumer and patient organisations, as well as scientific and educational journals and books. Ultimately, patients and prescribers set their own therapeutic policies, based on the information within their reach.

Many adverse effects are detected or fully evaluated only after the introduction of a drug. The course of events leading to the discovery and understanding of an adverse drug effect frequently follows an S-shaped curve, with 3 major phases: a latent period during which a suspicion arises at some point, followed by the often sudden accumulation of data (signal strengthening) and, finally, a usually lengthy phase of evaluation during which the adverse effect is confirmed (signal testing), explained and quantified.[56] The steep middle part of the curve, during which a weak hypothesis changes into a strong suspicion (i.e. signal detection), is crucial in pharmacovigilance. Many 'known' adverse effects, e.g. those included in Summaries of Product Characteristics and in textbooks, are still somewhere early in the third phase. Knowledge is often incomplete as regards frequency, mechanism and risk factors. The existence of the effect is legally acknowledged but full evaluation and scientific proof are still missing.

Once marketing authorisation is granted, the company cannot usually be required to perform further studies. As a result, there may be a vacuum with respect to the funding and performance of the scientific study of approved medicines. The recent introduction in the European Union of the possibility of provisional approval of selected new drugs (e.g. for the treatment of HIV infection) seems to have changed this situation, but experience is still limited. Additional studies can be demanded before approval of such drugs is made definitive. Also, the new rule in the European Union that marketing authorisation needs to be renewed every 5 years may be a stimulus in cases when further study is needed. Some countries are currently considering the introduction of various categories of marketing authorisation, linked to different levels of monitoring activity.

The detection and scientific evaluation of an adverse drug effect is a gradual process and may take a long time. Once a serious suspicion has arisen, however, a conclusion must be reached on the basis of the limited information available. For the protection of public health a decision must often be arrived at, and measures taken, while the scientific verdict is still pending. In other words, science and policy may not be developing at the same pace. Questions have to be answered when they arise and decisions must often be reached ad hoc. Regulators and companies, educators and prescribers, and journalists and patients, often cannot wait to make up their minds until the final truth has been established. As a consequence, in drug regulation a decision is often a compromise. Good data and reasonable arguments foster sensible compromises. Decisions are more likely to be accepted by the company and appreciated by the community when the arguments are reasonable and transparent.

Premature action – whether publicity or regulatory measure – may destroy a product commercially and lead to the undesirable disappearance of a valuable treatment. Delayed action, on the other hand, may lead to an unacceptable number of victims, compromise both government and company, and arouse public anxiety. Once a measure is applied, an indication dropped or the drug withdrawn, scientific evaluation may never be completed. A decision may often be considered to have been made both too early and too late, depending on the individual point of view. In such cases, there may be attempts to sift the available evidence. Public concern and undue publicity may urge stronger action than is scientifically justified. Commercial interests, on the other hand, may lead to attempts to minimise a problem. The natural solution would be to allow pharmacovigilance the time, means and independence needed for the unbiased collection and verification of the necessary evidence.

6.3 Rational Drug Use and the 'Information Turmoil'

The ultimate goal of pharmacovigilance is the rational and safe use of medicines.[3] In other words, the findings are intended to influence physicians, pharmacists and patients in their choice of medicines (including self-medication) and the precautions to be taken. Prescribers are under assault in several ways by different parties attempting to influence their preferences, e.g. pharmaceutical companies, drug bulletins, formulary committees, health authorities and insurance funds. The intentions and priorities of the various parties – for example rational prescribing, market share increase or cost-containment – may differ, however, and even conflict (see the next paragraph). Unfortunately, rationality in prescribing may be a fairly subjective notion. Drug utilisation data are difficult to interpret. Overprescribing and underprescribing may both be disadvantageous. Seemingly simple questions, such as whether a promising new drug really is better than its predecessor, may pose problems that are not answerable objectively.

Information produced by pharmacovigilance may change the position of a drug. The data so obtained are often preliminary and open to different interpretations, however, and different views and backgrounds may influence the judgements or decisions. The importance of an adverse effect depends upon its seriousness, frequency and preventability, and must be seen in the context of the indications for use and efficacy of the drug. Therapeutic truth may be hard to extract from the usual turmoil of information.

To assess safety, communicate risk and influence prescribing are all difficult. The scientific assessment of the quality of drug prescribing and of the impact of pharmacovigilance on the improvement of prescribing is an additional issue with its own methodology, difficulties and challenges.

6.4 The Pharmacovigilance Arena

Medicines are both powerful healthcare instruments and profitable commercial products. This dualism applies throughout the process of drug regulation. Different parties in the community have an interest in pharmacovigilance and drug regulation; the bases for these interests may differ and be in conflict.

Several ministries within a government are involved in drug policy in different ways. The pharmaceutical industry is an important economic factor, especially in drug-exporting countries, where it yields employment and foreign currency. Trade ministries ensure that there are no undue obstacles to the selling and exportation of medicinal products. Health authorities are committed to ensure the pharmaceutical quality, efficacy and safety of the drugs in the country concerned, and also to restrict the budgets spent on pharmaceuticals. Cheap drugs, however, may not necessarily be safe. One of the reasons for relaxation of the self-medication regime may be that this relieves the drug reimbursement budget.

The regulatory authority plays a key role with regard to the conditions of use and marketing of a medicine. The location of the regulatory authority

within the health department and names such as 'Committee on the Safety of Medicines' or 'Medicines Evaluation Board' may suggest a wide interest in the promotion of rational prescribing and the education of physicians. Usually, however, the primary responsibility of the regulatory authority is to deal with pharmaceutical companies. This is to be achieved within the scope of the law, with regard to the marketing authorisation of drugs and to the approved indications for use and other information contained in the Summary of Product Characteristics. Appeals against regulatory decisions can only be made by the company concerned and not, for example, by a healthcare fund or consumers' council. The economic background of drug regulation may be illustrated by the fact that the EMEA is part of the directorate of trade of the European Commission (Directorate III).

The quality of pharmacotherapeutic training of healthcare professionals is the responsibility of the ministry of education. Those involved in training need to have up-to-date knowledge of the adverse effects of medicines.

Healthcare insurers share with the government the interest in drug safety as well as in containment of the costs of drugs (especially of new expensive treatments of, for instance, cancer or HIV infection).

For pharmaceutical companies, the involvement in pharmacovigilance is a complex matter. Greater safety is a major argument for the promotion of many new drugs. For a company is of vital importance to know as much as possible about the adverse effects of its products. Sales managers and pharmacovigilance experts may disagree, however, with regard to the implications of a given adverse effect. Even the mere rumour of an adverse effect may endanger the commercial value of a drug and even decrease the share value quoted for the company. A decline in confidence in a drug may be to the advantage of the competition. Except for the obligation of informing (in confidence) the authorities, companies often keep information on adverse effects secret. Medical secrecy and privacy protection are other reasons why data on adverse effects may remain secret. Proposed new legislation in Europe regarding privacy and the confidentiality of personal health data is a real threat to future pharmacovigilance.[38]

Impartial information providers – such as national bulletins, university teachers and medical journalists – and pharmaceutical companies compete for the attention of the medico-pharmaceutical audience. Scientific journalists are committed to the provision of well balanced information, while the popular press searches for sensation. The precise data and considerations underlying regulatory decisions are often not made public, other than as an occasional announcement or press release. National drug bulletins depend, apart from published articles, on what company and regulator are willing to reveal.

Vast amounts of money are paid out to victims of adverse effects of drugs. In litigation cases (claims for compensation), the data collected through pharmacovigilance may play a crucial role and be of great interest to lawyers.[57] Often legal actions are settled out of court and the inclusion of a secrecy clause in the settlement is common. As a result, other people who have suffered a similar injury may remain unaware of it and lose the opportunity to obtain redress. This is an injustice and a public mischief.[58]

6.5 International and National Developments May Interact

International trade agreements may interfere with national restrictive actions. The WHO and nongovernmental organisations such as Health Action International pursue global transparency and harmonisation in drug policy, and promote the use of 'essential' drugs. Reinsurance companies may discourage pharmaceutical companies from selling drugs that carry a high risk of litigation for compensation.

Economic factors, scientific uncertainty in the data, secrecy in decision-making and the political consequences of unsafe drugs are all aspects that may mobilise lobbies and pressure groups. This

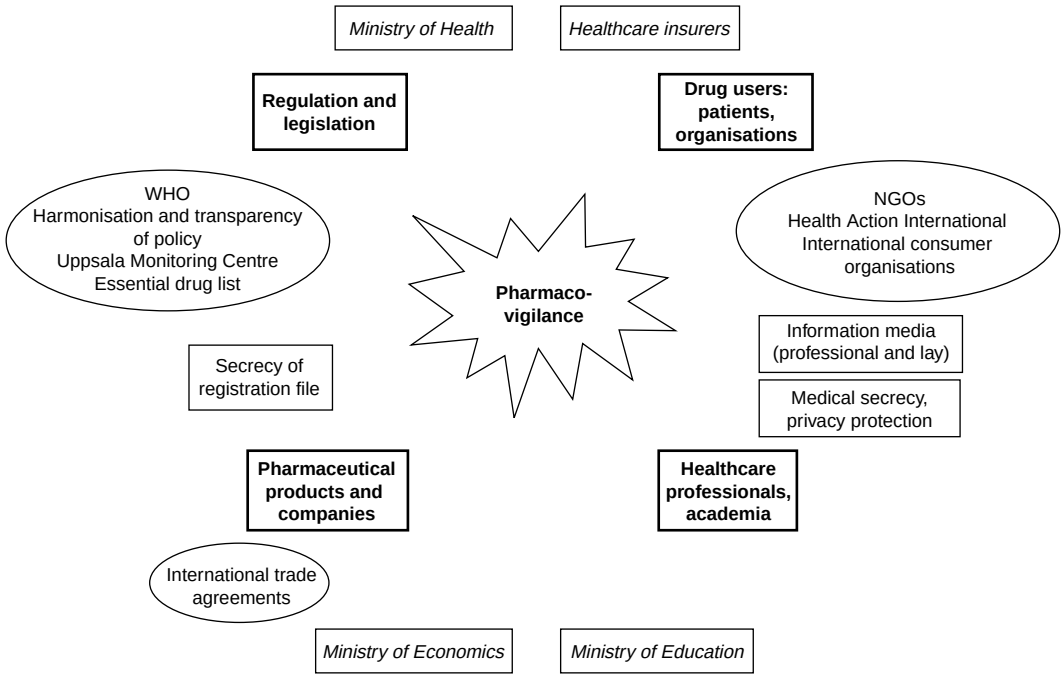

Fig. 1. A pharmacovigilance arena. **NGOs** = nongovernmental organisations; **WHO** = World Health Organization.

complex of direct and indirect, and more or less conflicting, interests places pharmacovigilance at the centre of a sort of arena (see fig. 1).[59,60]

Within this interplay of forces, secrecy or lack of transparency can lead to unbalanced conclusions, confusion of both patients and physicians, and public mistrust.[58] Herxheimer and others have recently criticised the undue secrecy prevalent in pharmacovigilance and drug regulation.[61-64]

7. Trends That May Affect Pharmacovigilance

7.1 Consolidation and Good Practice

Recent initiatives in various countries have announced the formulation of rules for 'good pharmacovigilance practice', as has happened in the past with 'good clinical trial practice'. Good pharmacovigilance practice aims to ensure appropriate procedures for the collection, processing, assessment and distribution of data, and to protect the interests of individual patients as well as of public health.[36]

7.2 'Privatisation' of Pharmacovigilance

In the past 25 years, spontaneous reporting has become a mainstay of pharmacovigilance. The various procedures and requirements for spontaneous reporting are well recognised and are expected soon to be codified as 'good practice'.[3,36] The level of performance of a national spontaneous reporting system can be evaluated by using international experiences as a standard (e.g. as regards the number, quality and source of case reports). The primary governmental responsibility is to ensure that an appropriate pharmacovigilance system is in place in the country, providing the regulatory agency with the necessary information. It may be disputed, however, whether a national pharmacovigilance organisation should itself be a government agency. What is needed in the first place is

that pharmacovigilance should be able to thrive in an environment of independence and be somewhat protected from possible influences relating to the interests discussed in section 6. Some distance between the pharmacovigilance system and the government may favourably influence the problem of underreporting.

In the UK, prescription event monitoring – as an additional countrywide pharmacovigilance system – has been developed as a private initiative, in the form of a trust.[65] In The Netherlands, the national spontaneous reporting system has recently been contracted out to an autonomous foundation [the Netherlands Pharmacovigilance Foundation (Stichting Landelijke Registratie Evaluatie Bijwerkingen; LAREB)], subsidised by the government.[66] With these examples in mind, and in line with current political views, it may be deemed appropriate to delegate the processes of collection, assessment and distribution of pharmacovigilance data to a separate organisation, e.g. a foundation or a trust. This could foster both the advancement of pharmacovigilance and its integration in the healthcare and academic communities. Whatever the case may be, scientific independence, accessibility of the data and continuity of financial resources must be guaranteed.

7.3 Integration of Pharmacovigilance, Drug Regulation and Drug Information in the Rationalisation of Drug Use

Traditionally, drug regulatory authorities were responsible for the assessment for approval of drugs. Usually there was no 'need' clause: a new drug had to be approved when the legal criteria were met, even if there were a number of equivalent drugs already available. Legal requirements were focused on the efficacy and safety of the drug when taken according to the instructions for use. In The Netherlands, for example, problems relating to overdose or abuse were not legally the concern of the Medicines Evaluation Board. Regulators neither had a role in the price or cost-effectiveness of drugs, nor in the education of prescribers or in influencing their choices.

In recent years health authorities have shown, for quality and financial reasons, increased interest in rational drug use and improving prescribing practices. For these purposes, pharmacovigilance data are a powerful instrument. Also, poisoning and abuse are increasingly recognised as important factors in drug regulation and the traditional separation of pharmacovigilance and poison control centres is lessening. Regulators show growing interest in acting as a 'centre of excellence' and extending their responsibilities to the provision of information and education. Hopefully, new legislation may open the possibility of using the data in the secret registration files for such purposes, perhaps by making the data available for meta-analysis. In some countries regulators may be able to include medical need as an approval criterion. In other countries additional bodies are charged with deciding if a drug is needed and should be included in the coverage of the healthcare costs insurance system.

7.4 Cost Containment

As part of a movement to maintain healthcare of good quality for the less affluent majority of the population at reasonable cost, governments are committed to decrease the expenditure on pharmaceuticals. However, new drugs are usually expensive and often intended for the treatment of common disorders. In addition to attempts to directly influence the price of drugs, there are various possible measures to decrease governmental expenditure on drugs, e.g. the encouragement of generic drug use, restrictions regarding the reimbursement of drugs and expansion of self-medication.

7.5 Marketing Activities of Companies

Although the benefit/risk evaluation of established drugs and rationalisation of prescribing are major commitments of governments, pharmaceutical companies seem to be inclined to further increase the marketing activities of their or-

ganisations. Emphasis is put on early registration, rapid market penetration, high profits and tough competition. These developments may have consequences with regard to pharmacovigilance.

7.6 The Data, the Study, the Money

The data in pharmacovigilance – e.g. reporting systems or population databases – are derived from real patients. These data are neither sold nor bought and should be considered public property. 'Good practice' should regulate their use and a pharmacovigilance ethics committee should ensure that the data are used appropriately, e.g. as regards availability, methods or purpose. The collection, storage, retrieval and study of data is costly, and medical data have potentially great commercial and political value. In other words, information can be big business. There may be uncertainty with regard to the ownership and accessibility of databases. The UK General Practice Database, for example, was set up by a commercial company, VAMP, and later on given to the Department of Health.[67] It is now being run by the UK Medicines Control Agency.[68] It will be run on a nonprofit basis, with access fees, and will be revived both technically and organisationally. Another major data collecting system, IMS, has been commercial from the outset. Governmental and scientific pharmacovigilance institutes need additional resources to involve medical databases in their activities; database holders should collaborate on a nonprofit basis.

7.7 Globalisation of Drug Marketing

Through the years, new drugs were often registered at different times in different countries. A step-wise, country by country, increase in the use of a drug has the advantage that the total population exposed is only gradually increased and that experience gained in one country can be incorporated into the approval procedure in other countries. The creation of large supranational markets (for example the European Union), or even of a global market, may well affect pharmacovigilance. The greater the number of users of a new drug, the greater the number of victims of an unforeseen adverse effect will be.

Globalisation of drug registration increases the importance of effective international pharmacovigilance.

8. New Interests and Problems that May Arise

The entire pharmaceutical process – from drug development, production and promotion to dispensing or buying – constitutes a very complex system. A change anywhere in this system, even a change in trend or policy, may – sometimes indirectly and unexpectedly – have consequences for safety and pharmacovigilance. Pharmacovigilance is continuously developing, improving and searching for new ways. A number of fields of possible interest are reviewed in the following sections.

8.1 Self-Medication

In the European Union and other countries, changes in regulations have eased the availability without prescription of 'over-the-counter' (OTC) drugs and the advertising of these drugs. Drugs that would previously have been excluded from self-medication may in The Netherlands and other countries nowadays be considered for OTC status once they have been on the market for 5 years.[69] Increased self-medication may have consequences with regard to pharmacovigilance. Experience has shown that many self-medication drugs can cause significant adverse effects.[70] Several major drug-related problems (e.g. analgesic nephropathy, bismuth encephalopathy, clioquinol-induced subacute myelo-optic neuropathy) concerned self-medication. Release for self-medication may lead to heavy advertising and to a steep increase in the use of the drug. Such increases may not replace prescription drug use, but represent new additional markets.[71] Many OTC drug advertisements are of dubious informative value, and the increased use of OTC drugs may be far from rational. Increased use proportionally increases the occurrence of adverse ef-

fects (in absolute numbers). In addition, changed conditions of use may influence the risk of adverse experiences. OTC and prescription drugs containing the same active ingredient often bear different names and may have somewhat different data sheets. Patients may overlook the fact that the drug they take because it is promoted on television has the same active principle as that prescribed by their physician and they therefore may unknowingly take too high a dosage.

For the above reasons, a drug that appeared reasonably safe when used on prescription may not necessarily be safe after its release for self-medication. Healthcare professionals are often ill-informed with regard to OTC drug use by their patients. This is probably why adverse effects of OTC drugs are relatively rarely reported. In addition, unrecognised self-medication is a potential confounder for practically all current methods used in pharmacovigilance. Increased self-medication may require additional pharmacovigilance activities under difficult conditions.

8.2 Generics

Generic and 'parallel' products have the advantage of being cheap and are – in countries such as those of the European Union – of good quality. It is a rule of thumb in medicine not to make changes to a satisfactory treatment unless there is a medical indication. A consequence of generic dispensing is that the same patient may receive different preparations one after another, depending on a pharmacy's or a wholesaler's purchasing policy. It is now common practice in The Netherlands, for example, that a treatment is started in hospital using a particular product in the form of the patented preparation, which after discharge of the patient is routinely replaced by the generic used in the patient's local pharmacy. Different generic or parallel products may contain different colouring agents or other excipients that may elicit hypersensitivity reactions.[72] For some drugs with a small therapeutic window, even small differences in bioavailability could be clinically relevant. Also, manufacturing errors may occur and be more difficult to detect when many different products circulate. The information in the data sheets of generic products may not be the same. For these reasons, spontaneous reporting needs to pay more attention to the precise identity of the suspected drugs. However, reporting physicians are often not aware of the actual generic or parallel product the patient is taking.

Patients recognise their drug by its size, shape, colour or some characteristics of the packaging. This may play a role in the prevention of medication error, especially in the case of polypharmacy, impaired vision or in the elderly. A change of product may have emotional effects, e.g. decrease trust, induce placebo adverse effects and cause noncompliance. Another possible disadvantage of generic dispensing concerns litigation for compensation in the case of a serious adverse effect. If a patient took different products and the offending product and its manufacturer cannot be identified unambiguously, the patient's position may be weakened. Thanks to new legislation such problems will not occur in countries of the European Union, but this is less obvious in other parts of the world.

8.3 Counterfeit Drugs, Contamination and Production Error

Accidental contamination or production error occurs around the world, because of adulteration [e.g. diethylene glycol-contaminated paracetamol (acetaminophen)] but also at reputable companies (e.g. a recent case of accidental replacement of glucose by potassium chloride in a parenteral solution). The penetration into the market of counterfeit drugs is now a worldwide phenomenon. The WHO has collected information on 751 cases of counterfeiting in the period 1982 to 1997; 25% occurred in developed countries and 65% in developing countries.[73] Besides random laboratory testing, counterfeit drugs and medication error can be discovered through spontaneous reporting (e.g. through the reporting of visually recognisable deviations, therapeutic failure or toxic symptoms).

8.4 Resistance Development

Effective treatment of infectious diseases is one of the most spectacular achievements of modern pharmacology. However, the worldwide expansion of resistance in major infectious diseases – e.g. 'hospital infections' (multidrug resistance of bacterial strains), tuberculosis and malaria – is a major concern. Monitoring of resistance and the validation of active strategies against resistance development (e.g. through the selective use of new antibacterials) is one of the future fields of interest for pharmacovigilance.

8.5 Affordability, Availability and Costs of Drugs

The price of new patented drugs may be very high. Whereas companies are primarily concerned with profit, governments concentrate on cost containment. Only the very rich can afford to pay privately the costs of healthcare. It may occur in developing and also in developed countries that a drug is not within the reach of patients who need it and are dependent on (private or social) healthcare insurance. With the gap between the poor and the rich increasing worldwide, pharmacovigilance should include the monitoring of when and where drugs cannot be taken because of economic or infrastructural reasons.

8.6 Monitoring of Drug Promotion

A medicine is not just a chemical, it is a product with a shape, a package and a data sheet, a promotional campaign and a reputation. The performance of a drug is influenced by the expectations of prescribers and patients. The acceptance of a drug, by the professional and the lay communities, is influenced by the promotional campaign and the expectations raised. Modest deviations from the approved indications for use may be commercially attractive. If the improvement of the safe and rational use of drugs is truly an aim of pharmacovigilance, monitoring of the promotional activities of pharmaceutical companies, as regards their compliance with the approved conditions, can be seen as a natural part of pharmacovigilance.

8.7 Seeding Trials

There is increasing interest from pharmaceutical companies in performing further studies after a drug has been approved. The purposes of a company may not coincide with the public health interest. Increase in market share may be an underlying incentive for a postmarketing study. The scientific and ethical aspects of studying approved drugs are still under development. Simultaneous postmarketing studies may be mutually disturbing and there may not be enough patients for more than one such large scale study at a time. Regulations are needed to ensure that commercial studies do not interfere with independent pharmacovigilance.

8.8 Polypharmacy and Drug Interactions

The number of drugs being taken is an established risk factor for developing adverse drug reactions. For various reasons, polypharmacy is a common phenomenon, e.g. because of self-medication, advancing age of the population and preventive regimens such as anticoagulation. There is much evidence that drug-drug or food-drug interactions are a frequent and important cause of adverse outcomes. On the other hand, polypharmacy is a major confounder in spontaneous reporting, and interactions may be difficult to detect and study with this method. The automated detection of unexpected drug interactions in databases is still in an experimental phase and is one of the fields of current interest in pharmacovigilance.

8.9 Planned Pharmacovigilance

In addition to the provision of the data requested for approval of the drug, any registration file is likely to contain a number of unsubstantiated suspicions or clues of possible interest. Although published data are sparse, it is our impression that few serious drug-related problems are entirely unexpected. Pharmacovigilance centres should actively

search the registration files of new drugs for possible signals, however uncertain. Planning of pharmacovigilance may increase efficiency, i.e. enable a more rapid acquisition of the relevant data.

8.10 Hospital Pharmacovigilance

Patients with serious adverse drug reactions are likely to be admitted to hospital. Polypharmacy, adverse drug reactions and interactions are common in the hospital environment, and often pose difficult diagnostic and therapeutic questions. In a recent working group of the European Society of Pharmacovigilance it was emphasised that pharmacovigilance is essentially a clinical specialism concerned with the diagnosis and treatment of patients. The proper study, documentation and reporting of such cases would be a natural part of this setting. The successful French national vigilance system, with its network of pharmacovigilance centres at about 30 major hospitals, is based on this principle. In the US the accreditation committee has adopted the presence of a specialised pharmacovigilance consultant in the hospital as one of the criteria for acceptance of the hospital.

The establishment of pharmacovigilance centres in hospitals will at the same time improve the care of patients with drug-induced diseases and increase, qualitatively and quantitatively, adverse reaction reporting.

8.11 Monitoring of Risk Groups

Several subgroups of patients can be recognised that may have been insufficiently studied in clinical trials, but are likely to use pharmaceuticals. Complementary approaches are needed to collect the information needed for safer and more effective treatments of these patients.

8.11.1 The Elderly

Pharmacokinetic and pharmacodynamic changes in the elderly may make these patients more susceptible to adverse effects. Both overtreatment and undertreatment may be a cause of problems. Elderly patients often have several serious disorders simultaneously and the use of multiple drugs is common. Likewise, interactions are frequently encountered in these patients. Polypharmacy is a major difficulty in attributing causality in adverse event case reports.

8.11.2 Children

Children are often not included in clinical trials, and information regarding metabolism, dosage and efficacy may be lacking. Children may develop similar adverse reactions as adults and may, in addition, be especially vulnerable to certain effects, e.g. on the central nervous system.[74] In children drug hypersensitivity may be difficult to distinguish from a viral infection. A group of drugs which are typically used in children are the vaccines.

8.12 Special Drugs May Need Special Attention

8.12.1 Vaccines

Vaccines are pharmacologically and ethically a special group of medicines, and this also applies to their adverse reactions. In several countries special monitoring schemes have been established as part of the national vaccination programme.[75] The need for intensive monitoring of vaccines, and the profound dilemma that may arise regarding vaccine safety, can be illustrated by a recent signal in France and the US regarding the possible induction of autoimmunity by hepatitis B vaccination.[76,77]

8.12.2 Anti-HIV drugs

Because of the high prevalence and poor prognosis of HIV infections, there is a great interest in the early introduction of new drugs. All available drugs have substantial toxicity, however, and new drugs need active follow-up for unexpected or more frequent adverse effects. Adverse reactions may occur with increased frequency in AIDS patients. Whenever HIV-infected patients are treated in a structured setting, long term safety follow-up should be included in the protocol.

8.12.3 Biopharmaceuticals

Because of the particular nature of biopharmaceuticals and of their production processes, special

attention needs to be given to the monitoring of possible unexpected risks.

8.12.4 Gene Therapy

Although still largely experimental, the various forms of gene therapy will require special attention as regards adverse effects and risks.

8.12.5 Non-Orthodox Drugs

The increased interest worldwide in the use of non-orthodox drugs (e.g. phytotherapy, traditional remedies) is associated with additional difficulties for pharmacovigilance. Such products may contain large numbers of poorly or unidentified drugs, several of which may cause serious adverse effects, or be fortified with potent drugs such as corticosteroids or nonsteroidal anti-inflammatory drugs. These products largely escape the official system of approval and quality control. The coding of such products, analysis of their contents and identification of toxic ingredients pose new and difficult problems. In the case of adverse effects, it may be very difficult to expose the causative agent. The Uppsala Monitoring Centre has started a special project to address the problems related to these drugs (Dr M.H. Farah, personal communication).

9. Conclusions

In the early 1960s, in the aftermath of the thalidomide tragedy, spontaneous reporting was the only conceivable early warning system for possible new drug-induced disasters. In spite of early scepticism, spontaneous reporting has proved to be a continuing source of useful information on adverse effects and other drug-related problems. The principles, procedures, strengths and weaknesses of spontaneous reporting have by now largely taken shape. Professionalisation and formalisation, both as a scientific method and as an instrument in drug regulation, are currently taking place.

In addition to spontaneous reporting, population studies are in increasing use in pharmacovigilance, e.g. prescription event monitoring, case-control surveillance and the use of large linked automated data resources. Additional funds are needed for their further development and structural use in pharmacovigilance.

The introduction of automation into medical and pharmaceutical practice administration and progress in computing technology are likely to lead to drastic changes in the routines of pharmacovigilance. The setting up of databases encompassing very large populations may allow the integration of different methods and the synthesis of signal detection strategies.

In coming years, the following issues may become of special interest in the development of pharmacovigilance.

(i) Improvement of national spontaneous reporting systems through:

- an increase in the proportion of medical practitioners participating in spontaneous reporting;
- the development of software for electronic reporting in automated medical and pharmaceutical administration systems;
- the development of automated signal generation;
- the establishment of rules for ‘good practice’ in spontaneous reporting, with special reference to the ethical and legal basis of reporting, improvement of data availability and transparency in pharmacovigilance, and the development of criteria for the assessment of the performance of a pharmacovigilance centre.

(ii) The development or improvement of additional methods in pharmacovigilance, especially with regard to the study of type C adverse drug effects.

(iii) Intensification of the scientific study of medicines after approval, e.g. for signal testing, frequency estimation of adverse reactions, identification of risk determinants and elucidation of reaction mechanisms. Such studies are needed for careful and integrated assessment of the benefits and risks of drugs, which, in turn, is the basis of well considered drug regulation (for example, the periodic renewal of marketing authorisations) and, more generally, rational drug use.

(iv) In the midst of different and possibly conflicting interests, pharmacovigilance needs a cli-

mate of independence, whether scientific, political or financial, to allow for due collection and assessment of the data. On the other hand, the system must be as transparent as possible to ensure public confidence. Also, information must be readily available and distributed. However, the possibility that preliminary or ambiguous data may lead to erroneous conclusions, drug scares and commercial damage poses a dilemma. 'Good practice' in pharmacovigilance and in communications may be an appropriate solution.

(v) The ultimate aim of pharmacovigilance is that new information be rapidly and effectively incorporated into therapeutic decision-making by physicians, pharmacists and patients, by drug information professionals and formulary committees, by regulators and by pharmaceutical companies. More comprehensive and efficient pharmacovigilance should further improve the safe introduction of new medicines and foster rational pharmacotherapy.

References

1. International drug monitoring: the role of national centres: report of a WHO meeting. World Health Organ Tech Rep Ser 1972; 498: 1-25
2. Stephens M, Talbot JCC, Routledge PA. Detection of new adverse drug reactions. 3rd ed. London: Macmillan Reference Ltd, 1998
3. World Health Organization. Safety monitoring of medical drugs: guidelines for setting up and running of a pharmacovigilance centre. Geneva: World Health Organization. In press
4. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. World Health Organ Tech Rep Ser 1995; 850: 97-137
5. Dollery CT, Rawlins MD. Monitoring adverse reactions to drugs. BMJ 1977; 1: 96-7
6. New strategies for drug monitoring. BMJ 1977; 1: 861-2
7. Venning GR. Validity of anecdotal reports of suspected adverse drug reactions: the problem of false alarms. BMJ 1982; 284: 249-51
8. Griffin JP, Weber JCP. Voluntary systems of adverse reaction reporting: part 1. Adverse Drug React Acute Poisoning Rev 1985; 4: 213-30
9. Griffin JP, Weber JCP. Voluntary systems of adverse reaction reporting. Part 2. Adverse Drug React Acute Poisoning Rev 1986; 5: 23-55
10. Mann RD. The yellow card data: the nature and scale of the adverse drug reactions problem. In: Mann RD, editor. Adverse drug reactions. Carnforth: Parthenon Publishing, 1987: 5-66
11. Rawlins MD. Spontaneous reporting of adverse drug reactions. Br J Clin Pharmacol 1988; 26: 1-11
12. Nordic Council on Medicines. Drug monitoring in the Nordic countries: an evaluation of similarities and differences. Uppsala: Nordic Council on Medicines, 1989
13. Mann RD. Drug safety alerts – a review of 'current problems'. Pharmacoepidemiol Drug Saf 1992; 1: 269-79
14. Meyboom RHB, Gribnau FWJ, Hekster YA, et al. Characteristics of topics in pharmacovigilance in The Netherlands. Clin Drug Invest 1996; 4: 207-19
15. XIII Journées Françaises de Pharmacovigilance. Therapie 1992; 47 (5): 359-453
16. 4th Annual Meeting of the European Society of Pharmacovigilance (ESOP): 1996 Sep 18-20; Lisbon
17. Fucik H, Edwards IR. Impact and credibility of the WHO adverse reaction signals. Drug Inform J 1996; 30: 461-4
18. Spriet-Pourra C, Auriche M. Drug withdrawal from sale: an analysis of the phenomenon and its implications. Richmond: PJB Publications, 1988
19. Olsson S, editor. National pharmacovigilance systems: country profiles and overview. Uppsala: The Uppsala Monitoring Centre, 1997
20. Belton KJ. European Pharmacovigilance Research Group [oral communication]. Meeting Mar 21 1996, Amsterdam-Schipol Hilton Hotel
21. Notice to marketing authorisation holders: pharmacovigilance guidelines. European Agency for the Evaluation of Medicinal Products (EMEA). London, 1999 Jan 29, CPMP/PhVWP/108/99 Corr
22. Committee for Proprietary Medicinal Products (CPMP). Note for guidance on procedure for competent authorities on the undertaking of pharmacovigilance activities. European Agency for the Evaluation of Medicinal Products (EMEA). London, 1998 Feb 25, CPMP/PhVWP/175/95 Rev. 1
23. Inman WHW, editor. Monitoring for drug safety. Lancaster: MTP Press, 1986
24. Koning GPH. A regionalized spontaneous surveillance program for adverse drug reactions as a tool to improve pharmacotherapy [academic thesis]. Utrecht: Utrecht University, Faculty of Pharmaceutical Sciences, 1993
25. Egberts TCG, Smulders M, De Koning FHP, et al. Can adverse drug reactions be detected earlier?: a comparison of reports by patients and professionals. BMJ 1996; 313: 530-1
26. Mann RD. Prescription-event monitoring – recent progress and future horizons. Br J Clin Pharmacol 1998; 46: 195-201
27. Mackay FJ. Post-marketing studies: the work of the Drug Safety Research unit. Drug Saf 1998; 19: 343-53
28. Evans JMM, MacDonald TM. Record-linkage for pharmacovigilance in Scotland. Br J Clin Pharmacol 1999; 47: 105-10
29. Strom BL, editor. Pharmacoepidemiology. 2nd ed. Chichester: John Wiley, 1994
30. Fries JF. ARAMIS and toxicity measurement. J Rheumatol 1995; 22: 995-7
31. Edwards R, Lindquist M, Wiholm BE, et al. Quality criteria for early signals of possible adverse drug reactions. Lancet 1990; 336: 156-8
32. Anon. Yellow card reporting by doctors. Curr Probl Pharmacovigilance 1997; 23: 6
33. Bötiger LE, Westerholm B. Drug-induced blood dyscrasias in Sweden. BMJ 1973; 3: 339-43
34. Lumley CE, Walker SR, Hall GC, et al. The under-reporting of adverse drug reactions in general practice. Pharm Med 1986; 1: 205-12
35. Meyboom RHB, Egberts ACG, Edwards IR, et al. Principles of signal detection in pharmacovigilance. Drug Saf 1997; 16: 355-65

36. Meyboom RHB. Good practice in the postmarketing surveillance of medicines. Pharm World Sci 1997; 19: 187-90
37. Lindquist M, Pettersson M, Edwards IR, et al. Omeprazole and visual disorders: seeing alternatives. Pharmacoepidemiol Drug Saf 1996; 5: 27-32
38. Mann RD. Databases, privacy, and confidentiality - the effect of proposed new legislation on pharmacoepidemiology and drug safety monitoring. In: Aronson JK, Van Boxtel CJ, editors. Side effects of drugs: annual 18. Amsterdam: Elsevier, 1995: xxi-xxxv
39. Finney DJ. Statistical logic in the monitoring of reactions to therapeutic drugs. In: Inman WHW, editor. Monitoring for drug safety. Lancaster: MTP Press, 1986; 423-42
40. Egberts ACG, Van der Hofstede JW, Meyboom RHB, et al. Transformation of a data base of spontaneously reported suspected adverse drug reactions and its use as tool in signal detection [academic thesis]. In: Egberts ACG, editor. Pharmacoepidemiologic approaches to the evaluation of antidepressant drugs. Utrecht: Utrecht University, Faculty of Pharmacy, 1997: 112-24
41. Stricker BHCh, Tijssen JGP. Serum sickness-like reactions to cefaclor. J Clin Epidemiol 1992; 45: 1177-84
42. Egberts ACG, Meyboom RHB, De Koning FHP, et al. Non-puerperal lactation associated with antidepressant drug use. Br J Clin Pharmacol 1997; 44: 277-81
43. Suissa S. Novel approaches to pharmacoepidemiology study design and statistical analysis. In: Strom BL, editor. Pharmacoepidemiology, 2nd ed. Chichester: John Wiley, 1994: 629-45
44. Charlton BG. Attribution of causation in epidemiology: chain or mozaic? J Clin Epidemiol 1996; 49: 105-7
45. Goldberger AL. Non-linear dynamics for clinicians: chaos theory, fractals, and complexity at the bedside. Lancet 1996; 347: 1312-4
46. Cross SS, Harrison RF, Kennedy RL. Introduction to neural networks. Lancet 1995; 346: 1075-9
47. Rikken F, Kiers HAL, Vos R. Mapping the dynamics of adverse drug reactions in subsequent time periods using INDSCAL. Scientometrics 1995; 33: 367-80
48. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol 1998; 54: 315-21
49. Davis S, Evans S, Wark S, et al. Signal generation: procedures for identification, evaluation and tracking. Pharmacoepidemiol Drug Saf 1998; 7: S97
50. Evans SJW, Waller P, Davis S. Proportional reporting ratios: the uses of epidemiological methods for signal generation. Pharmacoepidemiol Drug Saf 1998; 7: S102
51. Gross TP. The analysis of postmarketing drug surveillance data. In: Strom BL, Velo G, editors. Drug epidemiology and postmarketing surveillance. New York: Plenum Press, 1992: 1-7
52. Van Puijenbroek EP, Egberts ACG, Meyboom RHB, et al. Signalling possible drug-drug interactions in a spontaneous reporting system: delay of withdrawal bleeding during concomitant use of oral contraceptives and itraconazole. Br J Clin Pharmacol 1999; 47: 689-93
53. Roscam Abbing HDC. Informatie en toestemming in de gezondheidszorg; recente ontwikkelingen. Ned Tijdschr Geneeskd 1994; 138: 2561-4
54. Editorial. Time to act to avoid drug-safety scares. Lancet 1997; 350: 1041
55. Edwards IR, Hugman B. The challenge of effectively communicating risk-benefit information. Drug Saf 1997; 17: 216-27
56. Meyboom RHB, Hekster YA, Egberts ACG, et al. Causal or casual? The role of causality assessment in pharmacovigilance. Drug Saf 1997; 16: 374-89
57. Dukes MNG, Mildred M, Swartz B. Responsibility for drug-in duced injury. A reference book for lawyers, the health professions and manufacturers. Amsterdam: IOS Press, 1998
58. Herxheimer A. Secret out-of-court settlements in drug-injury cases. Lancet 1999; 353: 517-8
59. Meyboom RHB. Observations with regard to pharmacovigilance in the Netherlands and in the European Community. RAD-AR Meeting, 1991 Mar 1, London
60. McNamee D. Speaking about pharmacovigilance. Lancet 1996; 348: 908
61. Medawar C. Secrecy and medicines. Int J Risk Safety Med 1996; 9: 133-41
62. Dukes MNG. Drug regulation and the tradition of secrecy. Int J Risk Safety Med 1996; 9: 143-9
63. Herxheimer A. Side effects: freedom of information and the communication of doubt. Int J Risk Safety Med 1996; 9: 201-10
64. Statement of the International Working Group on transparency and accountability in drug regulation. Int J Risk Safety Med 1996; 9: 211-7
65. Inman WHW. 30 years in postmarketing surveillance: a personal perspective. Pharmacoepidemiol Drug Saf 1993; 2: 239-58
66. Broekmans AW, Lekkerkerker JFF, De Koning GHP, et al. Nieuwe regels voor het melden van bijwerkingen in Nederland na 1995. Ned Tijdschr Geneeskd 1996; 140: 1166-7
67. Walley T, Mangani A. The UK General Practice Research Database. Lancet 1997; 350: 1097-9
68. McNamee D. Pharmacovigilance into 2000. Lancet 1999; 354: 1406
69. Wijziging Besluit U.R.-geneesmiddelen. Staatscourant 107; 10 Juni 1993
70. Meyboom RHB. Side effects of self-medication drugs. J Social Admin Pharmacy 1984; Suppl. 1: 173-80
71. Temin P. Costs, benefits, and politics in switching drugs from prescription to over-the-counter in the United States. J Social Admin Pharmacy 1984; Suppl. 1: 189-200
72. Napke E. Stevens DG. More on excipients and additives [letter]. Can Med Assoc J 1985; 132: 509
73. Report of the international workshop on counterfeit drugs, Geneva, 26-28 Nov 1997. Geneva: World Health Organization, WHO/DRS/CFD/98.1
74. Meyboom RHB. Adverse reactions to drugs in children, experiences with 'spontaneous monitoring' in the Netherlands. Bratisl Lek Listy 1991; 92: 554-9
75. Dittmann S. Immunobiological preparations. In: Dukes MNG, editor. Meyler's side effects of drugs. 13th ed. Amsterdam: Elsevier Science, 1996: 919
76. Anon. French studying hep B vaccine ADRs. Scrip 1999 Jan 20; 2404: 3
77. Anon. Hepatitis B vaccine safety under attack by US patient advocacy group. Reactions 1999 Jan 30; 736: 3

Correspondence and reprints: Dr *Ronald Meyboom,* The Uppsala Monitoring Centre, Stora Torget 3, S-75320 Uppsala, Sweden.