Pharmacovigilance in a changing world

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Pharmacovigilance is concerned with the set of activities and actions that take place after the approval of a medicine and aims at expanding knowledge and encouraging safe and rational pharmacotherapy. Halfway through the last century, in an attempt to monitor the safety of medicines and in the absence of other options, practising physicians were called on to report to the health authorities their experiences with suspected adverse drug reactions. Today, 50 years later, this 'spontaneous monitoring' system, be it in a changed and regulated way, still plays a central role in pharmacovigilance. The core data of spontaneous monitoring typically are case reports of patients with disorders that are suspected to be related to the use of medicines. Straightforward as it may seem, the use of medical histories is complex and difficult – scientifically, technically and ethically – and the interpretation of such data is often ambiguous and uncertain. Drug safety is a shared concern of various parties – notably patients, clinicians, companies, insurers and governmental agencies. While the main goal of pharmacovigilance is the generation and dissemination of additional clinically helpful knowledge, enabling a better or safer use of a drug, its findings are often regarded as bad news, as something negative. Different parties may have different interests and priorities, and news about a medicine is often a cause of tension or trouble. For the success and effectiveness of pharmacovigilance a fair amount of independence – scientifically and financially – is necessary. In the past few decades, the possibilities for the scientific study of medicines, before as well as after approval, have improved tremendously as regards methodology as well as technical feasibility. Likewise the execution of pharmacovigilance, in the widest sense of the word, has changed and continues to change. In a time of continuing changes, it is important to reconsider what the expected – current and future – contributions of spontaneous monitoring are and what the most appropriate form of organisation of the reporting system will be, in order to enable and to ensure that these data – derived from real patients – will be used effectively and efficiently and to their best advantage. Whatever methods and tools come into use in future pharmacovigilance, the original function of the spontaneous monitoring system – the early detection of new and unexpected drug-related problems – is likely, at least in part, to continue.

Key words: **pharmacovigilance, adverse drug reactions, reporting.**

Klin Farmakol Farm 2011; 25(3): 102–111

Introduction and background

During the unprecedented pharmacotherapeutic revolution which took place halfway through the 20th century, the thalidomide disaster and a series of other worrying experiences (Figure 1) showed that medical drugs can paradoxically cause serious adverse reactions that are unexpected and unknown, and that such reactions may be unrelated to the drug's known pharmacological effects. Around the world, society has responded with the creation of governmental regulatory agencies responsible for the approval of medicines before their release for use in patients and for continued monitoring of their safety afterwards.

Figure 1. Early adverse drug reactions (< 1970)

Streptomycin	deafness
Isoniazid	hepatitis
Chloramphenicol	aplastic anaemia
Phenacetin	chronic nephropathy
Thalidomide (prenatal exposure)	phocomelia
Procainamide	systemic lupus
Chloroquine	retinopathy
Reserpine	Vital depression
Clioquinol	myeloptic neuropathy
Methyldopa	haemolytic anaemia
Aminorex	pulmonary hypertension
Diethylstilbestrol (prenatal exposure)	vaginal carcinoma

In that time the controlled clinical trial has further been improved and become the paradigm for demonstrating a drug's efficacy and tolerability. It also became understood, however, that clinical trials were of little use for the discovery of additional adverse effects, in particular when rare, occurring after prolonged use, or in types of patients that had not been included in clinical trials (e.g. childhood, pregnancy, the elderly). In the absence of established scientific methods for this purpose and following the example of the monitoring of infectious diseases, medical practitioners were called upon to report to the health authorities suspected adverse drug reactions occurring in their patients. The primary aim of this was to serve as an early warning system, enabling the prompt detection of any possible adverse reactions that had not yet been identified at the time of approval, in order to minimise possible harm to patients. While the reporting of infectious diseases was mandatory, overruling medical secrecy and privacy protection, the reporting of adverse drug reactions was to be voluntary and confidential.

Pharmacovigilance

Pharmacovigilance has recently been defined as: *The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems*[1]. This description illustrates the characteristic task of tackling something that is needed in practice in the scientifically best possible way. Pharmacovigilance aims at complementing and expanding the body of knowledge of a medicine that is available at the time of approval. The various interests and concerns regarding medicines in the post approval period can be summarised as follows[2]:

- Fine tuning of dose recommendations
- Reappraisal of indications (extension or restrictions)

Figure 2. Characteristics of clinical or epidemiological studies and of pharmacovigilance

Investigation	Vigilance
Defined aim (identified problem)	Open question: *'looking for the unknown'*
Hypothesis testing (problem solving)	Hypothesis generation ('problem generating')
Established methods (clinical trial, case control, cohort follow-up study)	Exploratory, under development (Spontaneous monitoring, Prescription-event monitoring, Case control surveillance)
Comparison	Often no (good) comparison
Limited (in duration, drugs, population characteristics, study parameters, place)	Use in real environment (e.g. elderly, pregnancy, children, co-medication (interactions, co-morbidity,)
Valid findings	Findings are preliminary; further study needed

- Assessment of side effects
  - Detection of unexpected adverse effects and interactions
  - Identification of risk factors
  - Quantitative measurement of safety (or lack of it)
  - 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 effectiveness and long-term efficacy (e.g. when surrogate end-points were used for approval)
- Characteristics of drug use and drug users
- Drug promotion control
- Inappropriate drug use (addiction, noncompliance, medication error, intentional and accidental intoxications)
- Quality of life and utility assessment
- Collection of data needed for cost-benefit assessment

About science and vigilance

Pharmacovigilance differs in several respects from clinical trials and other established study methods[3]. Some of the principles of a trial or case control study may not apply to the methods used in vigilance (monitoring), while the typical aims of vigilance would be inappropriate for study in a clinical trial (figure 2). These differences explain why misunderstandings and disagreements between experts in these fields are not uncommon and may lead to controversy.

Clinical drug investigation and pharmacovigilance are complementary, are different parts of clinical pharmacology, and are both needed.

Different types of adverse drug reactions

Around 1970 a simple but meaningful definition of an adverse drug reaction was agreed by a WHO expert committee: 'a response to a medicine which is noxious and unintended and occurs at doses normally used in man[4]. From this definition, it follows that there are countless different disorders and phenomena that can occur as an adverse reaction and through a large variety of mechanisms, actions and interactions. Also, the drugs and products that are in use as a medicine are heterogeneous and large in number. Likewise, adverse drug reactions are not a group of related diseases but are a very large and heterogeneous group of 'responses' that have only in common that in some way a drug has contributed to their occurrence. The other commonly-used notion in pharmacovigilance – an 'adverse drug event' – has a fairly different meaning: any event that occurs during (or after) the use of a drug *irrespective of its cause* (i.e. with or without a suspicion of a possible relationship) is an adverse event[4].

It does not come as a surprise that there are several more or less different classification systems of various adverse drug reactions, ranging from two to 10 or so different classes. Some may be superior from the theoretical point of view, while others may be more helpful in the practical situation.

For the planning of pharmacovigilance as well as for training and education a pragmatic and useful approach is to distinguish three basic groups of adverse effects, Types A, B and C, on the basis of clinical, pharmacological and epidemiological characteristics (see Figure 3)[5]. Each of these groups needs different methods for detection and evaluation. Special types such as drug interactions, dependence, congenital malformations and neoplasms can be placed in a logical way within this basic structure.

Spontaneous monitoring as a method

The early warning function is the primary aim of spontaneous monitoring. In this context a case report is a "confidential notification from a physician or other health care professional concerning a (possibly anonymous) patient with a disorder that is *suspected* to be drug-induced".

Figure 3. Three main categories of adverse drug reactions[5]

Types	Features	Methods (examples)
Type A: 'Drug actions' Pharmacological side effects	■ Common ■ Dose-response relationship ■ Suggestive time relationship (pharmacological) ■ Experimentally reproducible	■ Clinical trial ■ Prescription event monitoring ■ Spontaneous monitoring
Type B: 'Patient reactions' Hypersensitivity	■ Rare ■ Unexpected ■ No obvious dose relationship ■ Mechanism uncertain ■ Connection uncertain ■ Not experimentally reproducible ■ Characteristic, serious ■ Often typical drug-reactions ■ Suggestive time relationship (immunological) ■ Low background frequency	■ Spontaneous monitoring ■ Case control surveillance ■ Prescription event monitoring
Type C: 'Statistical connections' More frequent in exposed population	■ Significant background frequency ■ No suggestive time relationship ■ Mechanism uncertain ■ Not reproducible	■ Follow-up study ■ Prescription event monitoring *Challenge to pharmaco-epidemiology and data mining*

From this it follows that there is inherent uncertainty in the data and that the consequences of medical secrecy and privacy legislation apply.

The principle underlying the early warning function is simply that when several physicians in a country independently report the same unknown suspected adverse reaction to a drug this may be a valuable signal, with the emphasis on 'may'[6].

Practical instructions for the creation and maintenance of a pharmacovigilance centre (mainly based on spontaneous monitoring) have been given in the 'Guidelines for setting up and running of a Pharmacovigilance Centre', developed by the Uppsala Monitoring Centre in Sweden and WHO Headquarters in Geneva[7]. This blueprint for a – hospital, regional or national – centre can be easily downloaded from the website of the UMC at:

www.who-umc.org > Publications > UMC material.

In this guide the main aims are described as the:

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

To this is added that the ultimate goals of a centre 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 patients

Figure 4. Characteristics of pharmacovigilance topics in the Netherlands[9]

Often small numbers of reports	< 10 in 70 %
Often new drugs	39 %
Also old drugs	56 %
Often new adverse reactions	46 %
Also established reactions	51 %
Also new reactions to old drugs	41 %
Mainly Type B adverse reactions	62 %
Also Type A adverse reactions	33 %
Predominant adverse reactions:	Together 62 %
Anaphylactic reactions	
Hepatitis	
Blood dyscrasias	10 %
Nervous system	
Interactions	
Drug removed from the market	17 %

How 'spontaneous' is reporting?

At the time of the introduction of the reporting system, physicians were earnestly requested (or required) – by government and medical associations together – to report any suspected adverse drug reactions encountered in practice, and especially when unknown, serious and in connection with a new drug (for instance 'black triangle' drugs in the UK). More recently in many countries, including those of the European Union, it has been made mandatory for pharmaceutical companies to report cases of suspected adverse reactions to their products to the regulatory agency.

Obviously there is not much spontaneity in requested or mandatory reporting. It may be more appropriate to talk about 'spontaneous monitoring' than 'spontaneous reporting'. With hindsight perhaps 'joint monitoring' (as a collective medical responsibility) might have been a better name.

Early experiences with spontaneous monitoring

One reason why the results and successes of spontaneous monitoring may be difficult to assess and to objectify is that the data are usually part of the regulatory system and are kept confidential in the registration files. In addition, pharmacovigilance centres often communicate directly with the medical-pharmaceutical community and disseminate and publish information on safety issues.

In the 1990s a few retrospective studies reviewed the information that had been distributed by national pharmacovigilance centres, for example in the United Kingdom[8] and The Netherlands[9]. These studies presented a useful picture of the functioning of the spontaneous monitoring system in that period and of the nature of the information it had generated.

In the Dutch study a prominent finding was that during a study period of 18 years (1973–1990) the system had served as a continuous source of valuable information of different kinds, ranging from a pharmaceutical defect or lack of effectiveness to life-threatening adverse reactions or drug interactions (see figure 4). Typically, the information was often based on only a handful of case reports, illustrating that just small numbers of reports may have great value and concerned new as well as old drugs (i.e. 7 or more years on the market). The latter observation that in practice pharmacovigilance is also concerned with old drugs, was similarly found in a more recent study regarding the Uppsala Monitoring Centre's Vigimed e-mail discussion group[10].

The majority of the published topics concerned 'Type B' adverse reactions. There were a number of adverse reactions that dominated: anaphylaxis, liver injury, blood dyscrasias, nervous system toxicity, and drug interactions (mostly with cumarine anticoagulants). Only 17 % of the registered drugs involved had been withdrawn from the market (non-orthodox drugs excluded) because of the adverse reaction or for other reasons. This illustrates that in pharmacovigilance drug withdrawal is the exception rather than the rule.

Another study in the Netherlands, on the reporting of anaphylactic reactions, revealed that at that time underreporting had been about 93 %[11], which was presumably also true for other serious adverse reactions.

A fairly similar picture was seen in the study in the UK, which focussed on the Committee on the Safety of Medicine's Current Problems (and similarly only including published actions connected with spontaneous monitoring)[8]. These studies showed that, besides being a safeguard for possible major safety calamities, spontaneous monitoring can be a continuous source of useful information for prescribers.

Data assessment

Data assessment in pharmacovigilance takes place in two steps:

- The assessment of each individual case report (i.e. patient history) upon arrival at the centre or before storing in the database.
- Processing and interpretation of aggregated data, i.e. selected case reports or subsets of the data, for example for signal detection, case series studies, nested case control studies, case non-case studies and other ways of generating knowledge.

Case report assessment

A case report usually contains information about the following items:

- ***The patient:*** age, sex, medical history, current diseases and reasons for drug use. Case reports are kept confidential and may be anonymous, but the possibility of requesting additional information can be helpful.
- ***Drug exposure, suspect and other:*** product name (batch), active ingredients, route, dose, dates.
- ***Adverse event:*** clinical description, severity, lab values, histology, dates, outcome;

Figure 5. Standardised case causality assessment

What causality assessment *can* do	What causality assessment *cannot* do
Decrease disagreement between assessors	Give accurate quantitative measurement of relationship likelihood
Categorise uncertainty	Distinguish valid from invalid cases
Mark individual case reports	Prove the connection between drug and event
Education; improvement of scientific quality	Quantify the contribution of the drug to the development of the event
	Change uncertainty into certainty

diagnosis. One adverse event may contain several event terms (MedDRA, WHO-ART). It is advisable to record two unrelated adverse events that occurred in one patient as two case reports (with a cross reference).

- ***Timing:*** time to onset, course, outcome, dechallenge, rechallenge.
- ***The source of the case report*** (confidential).

In the assessment of a case report the central question can be summed up as: *"How surprised am I that this happened in this patient"*. Basic criteria and considerations in the assessment of case reports are:

- Possible relevance of the observation:
  - New adverse reaction (unknown, 'unlabelled'; unexpected or expected; previously reported similar cases in the database)?
  - New drug?
  - Serious event?
  - Important drug?
  - Public health issue?
  - Scientific or educational value?
- Documentation quality
- Coding of the report
  - Drugs (products) (WHO Drug Dictionary, ATC classification)
  - Adverse event term (MedDRA, WHO-ART)
- Consideration of other possible causes (differential diagnosis; presence or absence of an alternative explanation)
- Estimation of the likelihood of the connection ('case causality assessment')
- Follow-up (e.g. laboratory data, long-term recovery)

Signal detection may already begin during the routine assessment upon arrival of a case report. In the discovery of a new adverse reaction there is always one patient who is the first.

Case causality assessment

The primary aim of spontaneous monitoring is the detection of unknown problems. For this purpose a pharmacovigilance centre deliberately collects case reports of *suspected* adverse drug reactions. It is therefore somewhat paradoxical that the uncertainty contained in the case reports, inherent as it is in the system, continues to be a cause of confusion and controversies.

In the early 1970s the pathologist Nelson Irey gave an enlightening review of the criteria and arguments involved in diagnosing an adverse drug reaction, and also proposed a categorisation of patients or case reports into different levels of relationship likelihood. Subsequently many others have tried to go a step further and to design systems for estimating 'causality' in a standardised, objective and reliable way[12, 13]. In these systems the question of relationship is split up in a number of sub (and sub-sub) questions, which usually need to be answered with yes/no/don't know, and at the end the verdict follows automatically. None of these systems, however, has been validated, and for several reasons none probably will (figure 5).

Uncertainty is common in medical practice and is often hard to measure. Trying to categorise the amount of uncertainty in a case report, however, can be a sensible thing to do, in particular within a given context or study aim.

Using a structured way of classifying the uncertainty in case reports – for instance with the use of the WHO-UMC causality categories[4] or the French assessment system[14] – may be helpful in the following:

- *In practical pharmacovigilance routines*. Nowadays there are huge flows of case report data around the world. Data that today have lost much of their original secrecy and are fairly easily accessible also by the media, outsiders, etc. Attaching a 'causality' flag to these reports can serve as a caveat and prevent misunderstanding and inappropriate use of the data (and misuse may harm the reputation of spontaneous monitoring as a system). When used for this purpose, it is important that the various causality classes have been well defined and described and are also understandable to outsiders. Without proper explanation, for example, case reports that have been designated as 'possible' by the government may be taken for 'likely' by a journalist or the public.
- *In the (routine) exchange and communication of data sets or early signals*. With the help of case causality grading, differences in relative credibility between such data collections can often be easily seen.
- Also in the context of a more elaborate and planned *scientific study*, for example one on the occurrence of adverse reactions in a given hospital or ward, such a tool can be a useful part of the study protocol.
- Last but not least, the *educational value* of causality assessment tools has been, and still is, substantial. It has increased the understanding of what *suspected* adverse reactions are and has improved the expertise of pharmacovigilance professionals to assess and interpret these seemingly simple but in fact often very complex matters. Today such schemes continue to serve as an educational tool for under- and postgraduate students and serve as a welcome structure for young professionals in this field, for example at clinical pharmacy units, regional pharmacovigilance centres, companies and national centres.

More valuable than the classification of individual case reports, on the other hand, is the assessment of the evidence and credibility contained in a series of reports, as for example in signal detection or in a case series study, by focussing on aggregated data (see below): *a handful of 'possible' case reports may constitute a 'probable' signal*.

Signal detection[6, 15]

Signal detection in the spontaneous monitoring system is like searching for diamonds somewhere in a field in the wild: which stone is just another stone and which is perhaps a raw diamond? Any time when in clinical practice the question arises as to whether a patient's disorder is possibly drug-related, the event may be the first observation leading to a new adverse reaction: signal detection may already start during the assessment of case reports before storage into the database. At centres where the input process has been automated, however, this mechanism may no longer be functioning.

A signal in pharmacovigilance can be defined as: *a set of data constituting a hypothesis that is relevant to the rational and safe use of a drug*[6].

A signal consists of a hypothesis, together with data and arguments – arguments in favour and arguments against a connection. The considerations that play a role in the assessment of a signal are usually clinical, pharmacological, pathological and epidemiological in nature, although their importance may differ. In the context of spontaneous monitoring these data come from case reports, i.e. observations in patients. A signal usually has a qualitative and a quantitative aspect and there are roughly two first approaches towards signal detection: either clinical-pharmacological or quantitative/epidemiological.

Clinical-pharmacological approach

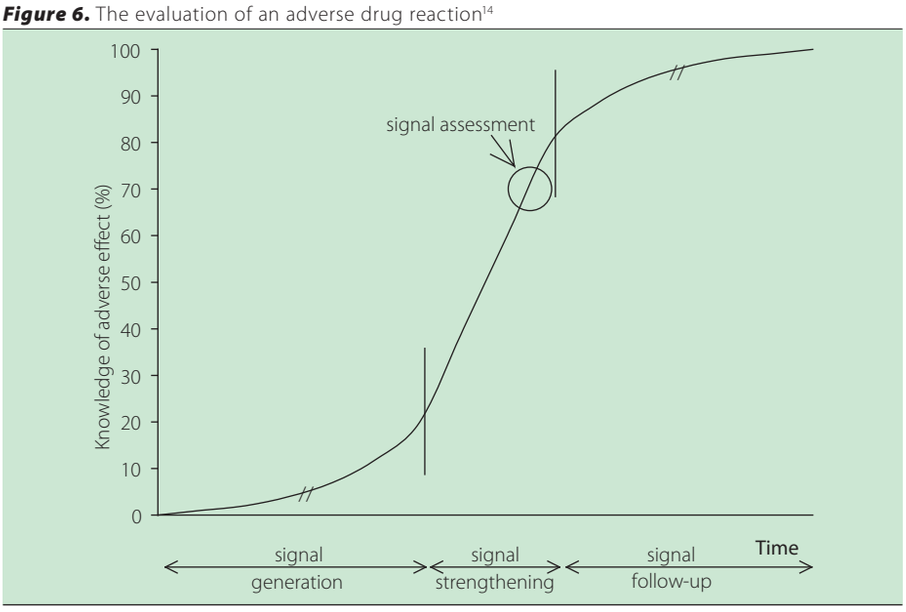
In spontaneous monitoring a signal may typically first catch the eye through observations in a fairly small number of reports that stand out because they are remarkable, often in clinical, pharmacological or quantitative respects. The fact that similar observations – that were unexpected, unusual or unknown – were made by different physicians in the country adds to the strength of the suspicion; other supportive situations may be the presence of distinctive, characteristic and objective signs and symptoms that occur in a consistent pattern and a suggestive temporal relationship and without any other likely explanation. When more similar reports come in, the signal can rapidly be strengthened. In particular Type B adverse reactions have been discovered in this way. On the other hand, a signal is at any point in time a snapshot; it is a suspicion, which is dynamic and may change over time: what is today a weak hypothesis, may be a credible suspicion next week or be refuted next month (see figure 6).

Quantitative approach

Besides eye-catching case reports, an unexpectedly large number or high reporting rate of a particular drug-event combination can also be the first pointer to a previously unnoticed connection. When a pharmacovigilance centre has built up a large database, data-mining strategies can be used for the detection of disproportional reporting rates. Such quantitative signals have the advantage that (clinically) unremarkable connections between drugs and adverse events can also be identified, independently of the views and experiences of assessors and of the investigator's bias. Importantly, Type C adverse reactions, which are often otherwise difficult to detect, can also be identified through quantitative signal detection.

Today quantitative signal detection strategies are operational at many pharmacovigilance centres, notably also at the WHO Uppsala Monitoring Centre[16–18] and the FDA in the US. Promising and ingenious as these approaches are, they are still under development and have not yet been fully evaluated and validated[19].

Figure 6. The evaluation of an adverse drug reaction[14]



Signal assessment and follow-up[6, 15]

By definition a signal is a hypothesis which, if credible and pressing enough, needs to be put to the test – be confirmed or refuted – by using the appropriate research methods. As illustrated in figure 6, the acquisition of full knowledge of an adverse drug reaction is a lengthy process, with three phases: 1. signal generation, 2. signal exploration and strengthening (or refutation), and 3. signal confirmation, quantification and explanation (taken from reference 15, page 460, figure 1). The proof of the connection can come from clinical data, pharmacological findings and epidemiological evidence.

For many of the adverse reactions mentioned in the product information of drugs in current use, however, the evaluation is more or less incomplete and proof is still lacking. Though designated as such via the legal and regulatory process, many adverse reactions remain scientifically unproven.

Making up the preliminary balance of evidence in a signal from the available and usually inconclusive evidence is a characteristic and often tricky task of pharmacovigilance professionals. Regulators, companies or the media and all parties involved wish to have certainty, but often science cannot provide it fast. For use in such situations, which may occur suddenly, an adapted version of the historical criteria put forward by Sir Austin Bradford Hill has been proposed[6]. These criteria, which are a combination of quantitative and qualitative considerations, are shown in figure[7]. For obvious reasons there are similarities with the criteria already mentioned above in the context of case causality assessment and signal selection.

Often signals remain uncertain, which may lead to confusion, indecisiveness, disagreement and drug scares. Under such pressures, the reporting system is often – wrongly – forced to try to eliminate uncertainty and give firm answers to questions it had itself put forward. As a rule, however, a hypothesis needs to be tested in appropriate, planned studies, usually with other methods. World-wide more attention and funds need to be given to the establishment of effective strategies for the further study of questions and uncertainties occurring in the field of pharmacotherapy, ranging for 'rapid responses' (quick efforts for preliminary assessmend of a signal using existing and available data of various kinds) to formal and comprehensive scientific evaluations.

In practice, in countries where the reporting of adverse reactions is reasonably well-established the number of reports of a particular combination, also taking into account the estimated exposure to the drug, may often provide a useful impression of the frequency of the reaction and enable decisions by regulators and prescribers alike.

Underreporting; the reporting of known adverse drug reactions; a reporting optimum?

Underreporting is an important but hard to influence feature of the spontaneous monitoring system; while usually but not necessarily huge, it is also unknown and variable and therefore diffi-

Figure 7. Balancing the evidence in a pharmacovigilance signal (adapted from A.B. Hill)[6]

- The quantitative strength of the association,
  - number of case reports
  - drug exposure
  - reporting-disproportionality (e.g. ROR, IC value)
- Consistency of the data (characteristic and consequent pattern)
- Exposure-response relationship: site, timing, dose, reversibility
- Biological plausibility of hypothesis: pharmacological, pathological
- Experimental findings, e.g. dechallenge, rechallenge, blood/tissue levels, unusual metabolites, drug-dependent antibodies
- Previous analogies (for example avascular necrosis of the jaw unexpectedly developing today in patient on high dose biphosphonates and 100 years ago in workers in the phosphorus industry, e.g. matches).
- Nature and quality of the data; objectivity, documentation quality, case causality assessment

cult to adjust for. Roughly speaking, underreporting is likely to be more profound for unknown adverse reactions than for known ones, since physicians tend to see (and to report) what they know and less so what they don't know, while at the same time publicity may stimulate reporting. On the other hand the unexpectedness of an event may for a physician be a valid reason for concern and a trigger for reporting.

The effectiveness of the early warning system depends first of all upon the proportion of physicians who are aware of the reporting system, contribute to it with some regularity and understand when reporting is needed. If this proportion is small, the monitored population of users of a drug may be too small to yield the minimal number of case reports needed for a timely and credible signal. At the same time signal detection is dependent on the prompt recognition and reporting by physicians of the cases that count: *new and possibly interesting or important suspected drug-related problems*.

In addition to unknown or unexpected adverse drug reactions the reporting is also requested – or mandatory – of cases of (suspected) established adverse reactions, especially when serious. Of course such reports don't play a role in the early warning function of the system, but there are several reasons for reporting known adverse reactions, for instance:

- The number of case reports can give an impression of the rate of occurrence of a reaction, of the size of the problem. This can very helpful when, as is often the case, the frequency of an adverse reaction is still unknown.
- Collecting a number of patients with a given adverse reaction for further study, e.g. in a clinico-pathological case series study.
- Educational purposes.

The consequences of underreporting and the difficulties in adjusting for it are well recognised. A disadvantage of underreporting at a regional or hospital pharmacovigilance centre is that it impairs local therapeutic safety studies and interferes with educational and preventive activities.

The other extreme, that most (suspected) adverse reactions would go reported, on the other hand, may paradoxically also lead to problems. Preparing a good case report takes a fair amount of time; first for the collection and documentation of the data of the patient and subsequently for the assessment of the case before storage into the database. If, say, 10 times as many case reports were received than today this would dramatically increase the workload and also the costs of the pharmacovigilance centre. Many pharmacovigilance centres in the world are understaffed and have limited resources[20] and a steep increase in reporting might paradoxically lead to delay or impairment of signal detection. Uncertainty would still continue, because not all drugs and not all reactions will be equally well reported; underreporting may for instance still be somewhere between for instance 10 % and 50 % of the total and will still be variable and uncertain.

There is probably a reporting optimum: Below the optimum the system is slow, insensitive and unreliable in particular as regards the early warning function. Above the optimum a sharper image is obtained, but the picture remains the same and at exceedingly higher cost and probably loss of efficiency. My feeling is that such an optimum may (in a medium size country) be in the range of 10 % or more of reporting physicians and about 25 % reporting of serious adverse reactions[1], provided that there is a stable input of reports coming from a sufficiently large part of the country (see below, Assessing a centre). Case reports from other sources, including patients, can have great value and also deserve to be studied seriously. They are different collections of data, however, and are complementary to the professional reporting system.

It needs to be repeated that for several reasons the reporting system is inherently not the right instrument for measuring the frequencies of infrequent or rare adverse reactions or for comparing drugs.

Advantages and limitations of spontaneous monitoring

On the basis of the practical experiences with spontaneous monitoring and also taking into account its original aims, the strengths and weaknesses of the system can be summarised as shown in figure 8.

A shift from qualitative to quantitative in pharmacovigilance

In various countries around the world, national pharmacovigilance centres have in many respects developed somewhat differently, e.g. in respect of procedures, practical solutions and priorities. In the course of the 1990s drug regulators showed an increasing interest in post-approval safety problems, and pharmacovigilance became more actively integrated in regulatory routines, with also more emphasis on the quantitative aspects of safety, such as the frequency of a rare serious adverse reaction or the comparative safety of drugs in a group. No longer would the mere discovery of agranulocytosis or hepatic necrosis in itself be reason for considering withdrawal, but its frequency would.

Also the role of epidemiological reasoning and the importance of quantitative evidence for the proof of a connection became more prominent. The safety issues that emerged in that period were often of a different nature, for example 'Type C' adverse reactions such as myocardial infarction or rhabdomyolysis, and underreporting became more strongly felt as a major shortcoming. Reporting was more vigorously stimulated and made mandatory for companies, while pharmacists and patients were also invited to contribute. Year by year the numbers of case reports have continued to increase. In addition the nature and heterogeneity of case reports have changed, the handling of large numbers of data profited from new computerised databases, and also the interest in quantitative and automated strategies for signal detection and data evaluation has increased.

1. With few exceptions (e.g. oncology) in everyday practice serious adverse drug reactions are infrequent. The annual proportion of reporting physicians gives an impression of the awareness of physicians of the pharmacovigilance centre. There is some evidence that measured over a longer period the number of reporters increases. In the case of an emergency the fraction of reporting physicians is likely to be larger than the basic annual number.

Figure 8. Advantages and limitations of spontaneous monitoring

Advantages	Limitations
Effective	Mainly signal detection
Rapid	Mainly Type B adverse effects
More than disaster monitoring: continuous source of practically useful information	Causality uncertain
All drugs, all patients, many different adverse effects, interactions, and other possible problems	Underreporting (vast, variable, unknown)
Permanent	No frequency measurement
Cheap	Comparison of drugs difficult
	Need for signal testing

Additional groups of drugs: vaccine vigilance, haemovigilance, phytovigilance and 'biopharmacovigilance'

In many countries the responsibilities of drug regulators have also extended to other types of drugs and products, such as vaccines, blood-derived medicines, paediatric drugs, orphan drugs, and phytotherapeutics and other 'nature-derived' products. These groups may differ much from the 'small molecule drugs' and in the monitoring of, for example, vaccines (in- or outside a country's national vaccination programme) and blood products (haemovigilance), the reporting system may need to be used in different ways and may have a somewhat different role to play. The increase in drugs available for self-treatment (OTC status) has also influenced the way these drugs are used, which in turn has consequences for pharmacovigilance. For example the use by patients of OTC drugs is often unknown by physicians and these products are notoriously poorly reported.

The newcomers in the medical armamentarium, biopharmaceuticals (biologicals, or protein drugs) are now revolutionising pharmacotherapy. In addition to problems such as anaphylaxis and serum sickness – which had already been encountered by pioneers such as Ehrlich and Landsteiner over 100 years ago – these protein drugs have novel profiles of adverse reactions and require intensified monitoring and planned safety evaluation studies after as well as before their approval. A few years ago Pichler reviewed the types of adverse reactions due to biopharmaceuticals and proposed a useful novel classification system[21].

Until now, many biopharmaceuticals have been in use as immune suppressants or oncolytics, but the therapeutic targets are currently expanding. In recent years the knowledge of neoplastic diseases has increased enormously and the mechanisms of action of biopharmaceuticals and other novel oncolytics (for instance nature-derived drugs such as trabectedin) may differ much from, and be far more selective than, those of traditional cytotoxic drugs.

All these changes and developments may have substantial consequences as regards drug safety and may require additional and different efforts for the follow-up of their safety. Pharmacovigilance is dynamic and how it should be planned and performed may change over time and may differ for various types of drugs.

Monitoring the monitors: assessing a pharmacovigilance centre

The success of a spontaneous reporting system depends upon the quantity and quality of adverse reaction reporting, the organisation of the system, and the utilization of the collected data. With regard to the level of reporting *(input)* the following criteria may be used[22]:

- Reporting rate (e.g. number of case reports/100 inhabitants/year).
- Reporting distribution, i.e. the percentage of practicing physicians reporting, reporter characteristics (e.g. general practitioners, specialists, pharmacists, nurses, dentists), sources of reports (hospital or family practice, various parts of the country), etc.
- Reporting quality.
- Reporting efficiency (the proportion of relevant case reports, e.g. concerning unknown, serious or otherwise interesting reactions).

Drug utilization data are useful as a reference, for instance when assessing reporting rates and differences or changes in reporting. Regarding the organisation of a pharmacovigilance centre it is of interest how the system for data acquisition is structured. The professional expertise of assessors and the mean assessment time per case report (or the number of staff members per 1000 case reports) may be used as parameters of the quality of data assessment at a centre. The budget available for pharmacovigilance and the sources and continuity of funding indirectly give information regarding organisational development. The yearly numbers and the content of publications and changes in data sheets in connection with the reporting system *(output)* in a country, may be used as indicators of the utilization of pharmacovigilance data.

International pharmacovigilance[23]

As an initiative of the World Health Organization in 1968. Ten such 'national monitoring centres' agreed to work together in a Collaborating Programme for International Drug Monitoring. This international system has its roots in the thinking of scholars such as David Finney, Bill Inman and Jan Venulet. Czechoslovakia was one of the founding countries of the WHO Programme, thanks to the pioneers Professors Jiří Ellis, Otakar Šmahel and Milan Kriska. An informative review of the present situation of pharmacovigilance in the Czech Republic has recently been presented by Kopečná and colleagues[24].

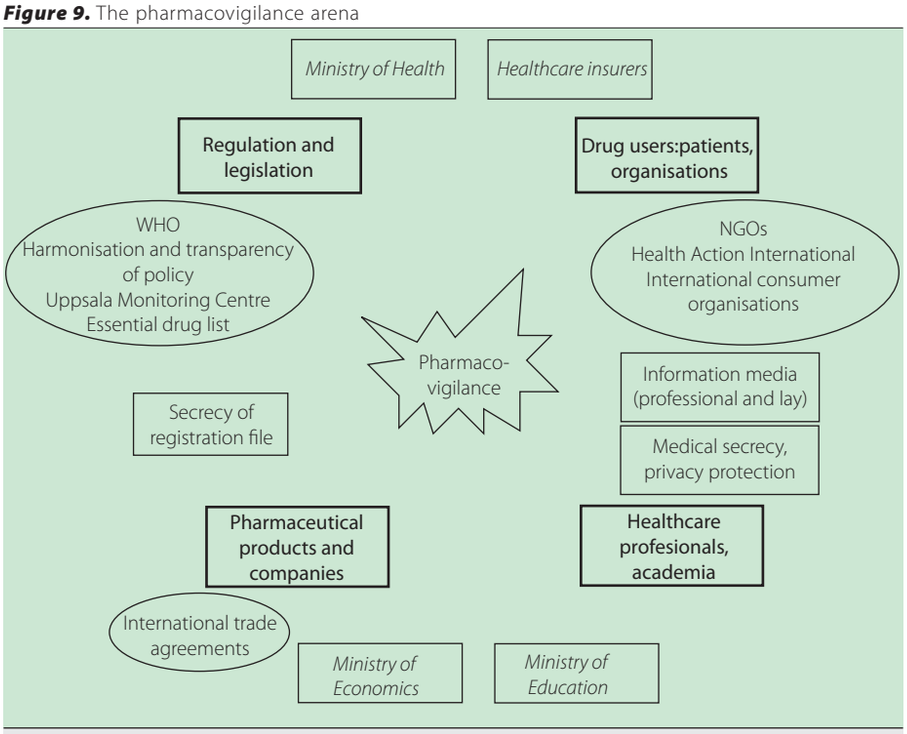
In 1978 the international system moved from Geneva to Uppsala after an agreement between the Swedish government and the WHO and has become known as 'the Uppsala Monitoring Centre' (UMC)[23]. It is a non-profit self-financing foundation and has an international administrative board, while WHO Headquarters is responsible for the Centre's policy.

The aims and activities of the UMC include world-wide collection, analysis and distribution of data through collaboration with national pharmacovigilance centres around the world. The focus is on pooling of data for the detection and analysis of signals and comparing experiences in various parts of the world. In addition to communication and the exchange of information, the centre provides technical support, invests in the development and improvement of methods and tools, and aims at global pharmacovigilance and the stimulation of safe and rational use of medicines. Today the Centre has over 100 participating countries and its database, Vigibase, now contains over 6 million case reports.

In a recent review of 55 low- and middle income countries participating in the WHO Programme for International Drug Monitoring, unfortunately shortage of staff and resources was found to be common around the world[20].

Much information about the UMC and its international pharmacovigilance programme can be found on the Internet: http://www.who-umc.org/.

Figure 9. The pharmacovigilance arena



Other methods developed for the use in pharmacovigilance[25, 26]

Prescription Event Monitoring (PEM) refers to another basic method used in pharmacovigilance which is only operational in two countries: New Zealand (the Intensive Medicines Monitoring Programme IMMP) and the United Kingdom (at Southampton's Drug Safety Research Unit, DSRU). In PEM large cohorts of users of selected drugs are formed with the use of prescription data and through questionnaires at intervals all events that have happened are recorded. In different ways various comparisons can be made. In addition to signal detection this method enables early signal testing as well as quantitative assessments. A prominent feature of PEM is that explicitly adverse events, irrespective of their possible causes, are recorded and therefore it is independent from the clinicians' views.

In Case Control Surveillance all patients with a particular study disease (usually rare and serious, for instance Stevens-Johnson syndrome) in a large delineated area are captured and studied in detail. At the same time in the same area control patients are acquired and studied for drug-exposure and any other differences with the cases, in order to identify like causative agents, drugs and otherwise. Often using a multi-centre and multi-country network of hospitals, CCS is an excellent method for providing clinicopathological information of the study disease, identifying likely causes and risk determinants and measuring its absolute (!) frequency and the drug-related fractions. Unfortunately it is rarely used.

In Intensive Hospital Monitoring, developed in the time before the automation of hospital administration, there is comprehensive registration of all or selected drugs given during hospitalisation and all clinical events occurring in patients, with or without a suspected drug relationship. This system gives complete information on what happens during hospitalisation, and likewise mainly concerns short-term adverse reactions. In the past the famous network of hospitals participating in the Boston Collaborative Drug Surveillance Program (BCDS) produced a treasure of information on the qualitative and quantitative aspects of adverse reactions in the hospital environment. Still active today, the website of the BCDS is: http://bcdsp.net/.

Record Linkage and other observational studies

Originally introduced by Doll and Skegg, linking the records of patients in different databases and linking exposure data with outcome data, this was one of the first effective quantitative study methods used in pharmacovigilance[27]. The recent enormous progress in Information Technology and the building of very large comprehensive medical databases have revived the original record linkage principle. The utilisation of these automated databases is widely under development, exploring data mining, performing nested case control studies, case non-case studies, and other established and novel epidemiological approaches, for signal detection as well as for signal testing and exploration. As discussed above, computerised quantitative data mining strategies are intended to lead to innovations in pharmacovigilance, including the early warning strategies in pharmacovigilance; as yet results are still limited[19].

Changes in medicine, information technology and legislation, and the influences on future pharmacovigilance

In the past 50 years medical and pharmaceutical science and practice has changed tremendously. Advances in pathology, pharmacology and epidemiology, and in the understanding of their complex interactions, have been immense, and progress in information technology and automation have in a fairly short period of time drastically changed healthcare administration and opened research possibilities that had previously been impossible if not in unimaginable.

Detailed and comprehensive data concerning millions of patients – medical histories, laboratory values, treatments, outcomes – are now stored in huge automated databases, enabling the formation of large and lasting cohorts of all kinds and linking countless variables.

Of course the scientific use of these rich data resources, freed from so many previous limitations, will introduce new pitfalls and possible false tracks in the collection and interpretation of data and will also raise new questions – ethically, scientifically and technically. It is remarkable that in this changed and changing world, in pharmacovigilance the old spontaneous reporting system – be it with many changes – still plays a key role.

When drug laws were introduced there was a sharp distinction made between the two phases: between what happens before approval and what happens after. In scientific, ethical and legal respects there were fundamental differences between the pre- and post-approval phases. After approval, for example, the 'burden of proof' (in the case of new questions or uncertainty) moved from the company to the regulator. Another characteristic legal restriction was that decision-making had to be restricted to the use of a product according to its 'approved instructions for use'. Licensing was an all or nothing decision; there was for

Figure 10. Regulatory- or macro-pharmacovigilance

- Legislative
- Licensing, product information, distribution
- National policy making
- General benefit / harm (public health)
- Focus on risk management
- Communication of safety information based on regulatory requirements
- Pricing and reimbursement

example no place for conditional approval. Before a drug has been approved (in a clinical trial) patients are first carefully informed and asked for their 'informed consent' and their data are recorded in detail and closely studied. After release the main information for is in the product's SPC and the data of the patients remained hidden in medical dossiers and behind medical secrecy.

Up-to-date information regarding Eudravigilance and the procedures and requirements in pharmacovigilance in the EU is given on the website of the European Medicines Agency (EMA):
http://eudravigilance.ema.europa.eu/
http://www.ema.europa.eu/
http://eudravigilance.ema.europa.eu/human/docs/19263206en.pdf

The EMA Template for a European Risk Management Plan provides advice to Marketing Authorisation Holders (MAHs) on which data need to be collected and how the data should be presented[27]. Less attention is paid to scientific methodology and it has no ethics paragraph.

In the Good Pharmacovigilance Practice Guide compiled by the Medicines and Healthcare products Regulatory Agency (MHRA) a detailed description is given of the collection, storage and presentation of pharmacovigilance data by MAHs as required in the United Kingdom[29].

In recent years legislation is becoming less rigid and regulatory policies are changing and the possibilities for provisional, conditional and monitored release have improved. In the years to come further changes may take place that will stimulate post-approval studies of good scientific quality and perhaps more active involvement and responsibility of medical specialists and patient organisations.

With ever increasing prices of new drugs, in particular of biopharmaceuticals, there are also increasing governmental concerns regarding cost-containment and affordability of pharmacotherapy. Pharmacoeconomic research will further develop and improve and data on benefit, harm and cost will be taken together in future regulatory decision-making. In practice it may often be the safety component that will influence the outcomes of cost-benefit decisions of medicines.

All these developments are likely to change the entire landscape of pharmacovigilance and also to affect the specific contributions of the spontaneous monitoring system. Progress in IT will stimulate the further exploration and use of epidemiological approaches in the study of approved medicines. Electronic patient dossiers will enable comprehensive 'planned pharmacovigilance', for example of new biopharmaceuticals, and innovative data mining strategies are likely to take over a part of the early warning function of spontaneous monitoring. The future will show which roles spontaneous monitoring will continue to play and how it can be organised to be used to its best advantage.

The pharmacovigilance arena and the need for scientific and financial independence

Medicines are both powerful healthcare instruments and profitable commercial products. This dualism applies throughout the complex process of the development, approval, marketing, distribution, reimbursement and evaluation of medicinal products. Patients want the best possible treatments, drug companies intend to gain as much profit as possible, and governments are increasingly concerned with cost containment. Neither regulators, nor doctors and companies wish to be criticised, and the media are all too often interested in sensational news. As a consequence of this tangle of potentially conflicting interests, one might speak of a 'pharmacovigilance arena' (figure 9)[2].

Pharmacovigilance aims at increasing knowledge, enabling better use of medicines; it is essentially something positive. Nevertheless new information concerning adverse effects, interactions, risk factors, contraindications and the like are often regarded as bad news, and bad news is usually not welcome (and does not raise money). Pharmacovigilance centres and their experts may be put under pressure from various sides and also job security may be at risk. Because of differences in interests and priorities, the uncertainty commonly encountered in pharmacovigilance signals may lead to disagreement, controversy and worse. This is the more so because a structure and the necessary funds for a prompt independent scientific investigation of such signals are often missing.

It is important that pharmacovigilance centres are sufficiently independent – as regards science and freedom to publish – from all parties shown in Figure 9, and that the funding of pharmacovigilance is sufficient, permanent and secure.

Spontaneous monitoring and macro- and micro-pharmacovigilance[3]

Rooted in legislation, major responsibilities of drug regulation are the approval for licensing and the text of the formal product information (e.g. SPC, EPAR) of pharmaceutical products. The focus is on the quality, efficacy and safety of products, on national policy- and decision-making from a general perspective, and on the protection of public health. Pharmacovigilance can in this context be regarded as *regulatory- or macro-pharmacovigilance* (figure 10).

At the same time up-to-date safety information is of utmost importance to prescribers and patients, but at the clinical level priorities and interests may differ. Here the emphasis of pharmacovigilance is on personalised treatment and individual risks, preferences and choices. Here the focus is on the interaction with prescribers, on education, increasing awareness of current safety issues, improving rational prescribing and reporting of adverse reactions, and patient safety. For these functions health care practitioners should be familiar with and close to pharmacovigilance: *therapeutic- or micro-pharmacovigilance* (figure 11). Likewise, pharmacovigilance centres should be nearby and operate in a personal way and for instance be localised in a teaching hospital that also provides drug information service and are a regional reference point, or in a large dispensing pharmacy with a regional function.

Figure 11. Therapeutic- or micro-pharmacovigilance

- Personalised treatment (individual preferences and benefit/risk decisions)
- Therapeutic choices
- Patient safety
- Prescriber awareness
- Increasing knowledge; rational prescribing
- Local / regional: Regional pharmacovigilance centres
  - Individual communication & feedback to practitioners
  - Hospital formulary
  - Guidelines by professional groups (e.g. paediatricians, oncologists)
  - Education / information bulletin

Making, as well as possible, a diagnosis in a patient is the central professional activity of a physician. Prescribing or advising about a particular medicine or other treatment to the patient is the next professional step. Suspecting that a medicine may have been the cause of the disease in a particular patient is part of making a diagnosis. The reporting, in reasonable detail, of such a suspicion to the national pharmacovigilance centre in the country is also a part of the professional relationship between a physician and a patient. Also in the future the participation of medical practitioners and other health care professionals will be a fundamental part of pharmacovigilance. The medical community will continue to have a role to play and to have a say in pharmacovigilance.

I wish to ackowledge the review of this paper by Geoffrey Bowring

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