

# Viewpoint

*Watching for safer medicines*

*Part 1*

Second edition

Issues, controversies and science in the search for safer and more rational use of medicines



WHO Collaborating Centre for  
International Drug Monitoring

An account of the WHO Programme for International Drug Monitoring, the work of *the Uppsala Monitoring Centre* and the challenges of worldwide collaboration for improved patient care and public health.

# Watching the World the Uppsala Monitoring Centre

## Welcome...

... to Part 1 of this two-part account of the story of the science of the safety of medicines, known as *pharmacovigilance*, and of the important worldwide work of *the* Uppsala Monitoring Centre.

The two booklets in the series are intended for everyone. We hope they may alert our readers round the world to new issues and ideas, and that you will find interesting and useful – even provocative! – information in them. For those who want more, there are many references to printed material and electronic links. You can also ask for more information by contacting *the* UMC (see back cover for details).

## This booklet, Part 1

– raises and discusses the big issues:

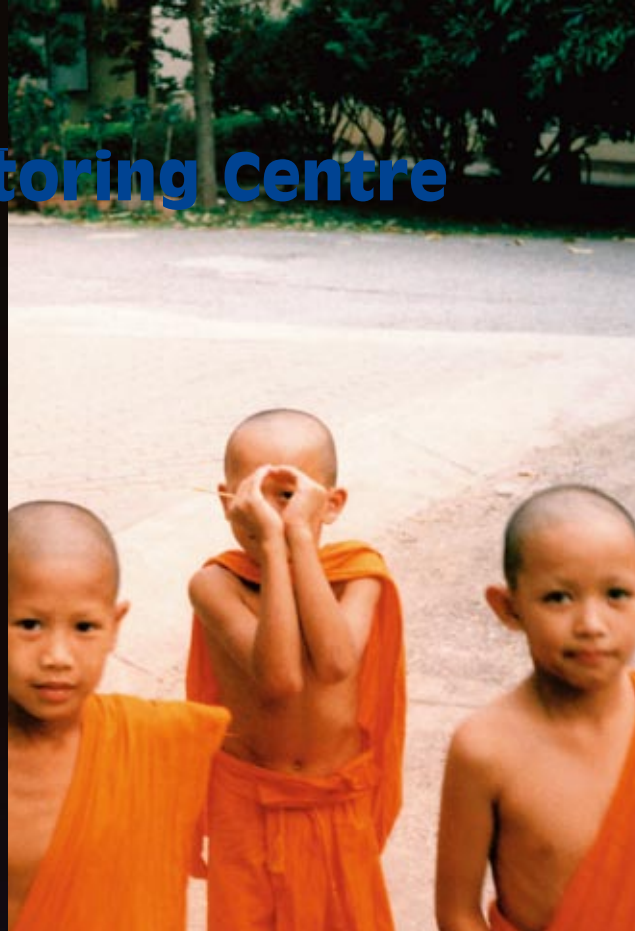
- How safe are medicines?
- What is risk?
- How can potential harm from medicines be identified and reduced?

The questions are important for *everyone*: from the most specialised scientist to current and potential patients everywhere.

## The companion volume, Part 2

– provides detailed, technical information about the activities, services and products of *the* Uppsala Monitoring Centre. This publication is intended more for specialists in the field, though there is much of interest to the general reader too. (Part 2 is available from *the* UMC.)

Please let us know your reaction by post, email or fax and help us improve the material next time.



## Alert: at the lookout tower

From: French – à l'airte; Italian – all'erta: alla: at the; erta: at the lookout or watch tower

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

Source: The Importance of Pharmacovigilance, WHO 2002

\* From:  
Greek *pharmakon* – drug  
Latin *vigilare* – to keep awake or alert, to keep watch



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## '...Take two tablets, three times a day for ten days...'

Apparently the simplest of instructions, these ordinary words alert us to many serious questions for doctors and patients alike. The answers are often not nearly as obvious as we may think.

- Has the disease been correctly diagnosed?
- Has the right dose of the right strength of the right formulation of the right medicine been prescribed?
- What are the risks of the treatment producing an adverse drug reaction (ADR) or side-effect?
- What is the potential seriousness and duration of possible harmful effects?
- Is the patient taking anything else which might interact badly with the medicine or prevent its working at all?
- Does the patient have any medical or genetic or allergic condition which might cause a bad reaction to the medicine?
- Is the manufacturing source of the medicine safe and reliable?
- Does the patient understand the instructions and will they comply with them?

These are some of the vital questions which are the concerns of pharmacovigilance, examined in these two booklets. Much is being done worldwide to deal with these questions but, as will become clear, we are far from having answers to many of them yet.

Read on!

Some of the specific challenges these questions raise are listed on page 18.

## Adverse Drug Reaction (ADR)

An ADR is officially described as:

'A response to a drug which is noxious and unintended, and which occurs at doses normally used... for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function.'

*International Drug Monitoring: The Role of National Centres. Geneva, World Health Organization, 1972 (WHO Technical Report, No 498).*

To this basic definition, the European Union adds the following:

'A reaction, contrary to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected, i.e. judged possible by the reporting or reviewing healthcare professional.'

'An adverse drug event that is judged to be caused by the drug.'  
*Strom BL, ed. Pharmacoepidemiology, 3<sup>rd</sup> edition, Wiley, 2000*



# Our Audience Everyone

has an interest in the safety of medicinal drugs and in their effects.

We hope the material in this brochure will be relevant and stimulating to:

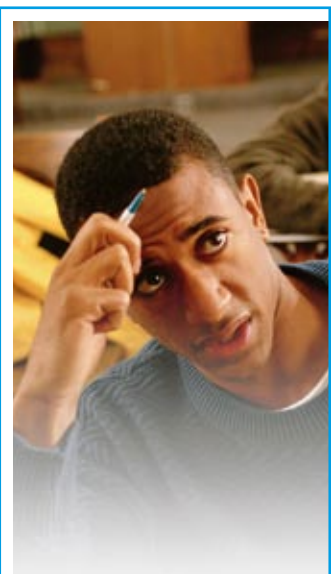


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*How to find out more:* See back cover.

There is a comprehensive glossary and list of technical definitions in Viewpoint Part 2.



### Aspirin

One of the world's most successful drugs, developed in 1897, is consumed in huge quantities: about 100 billion tablets in one year – 35,000 metric tonnes

[www.aspirin-foundation.com](http://www.aspirin-foundation.com)



# A very important message

Medicines are among the miracles of the age. They have helped to bring improved health and longer life to the human race. They affect the lives of hundreds of millions of people every day. But they are not without risk, and have caused, do cause and will continue to cause lesser or greater harm to many people, alongside the many who benefit. There are also large numbers of people who experience no evident effect at all from the drugs they take.

These booklets are about how we make sense of what we know about benefit, harm, effectiveness and risk in medicine, how little we really know and what is being done to advance knowledge.

## Finding the Balance

No human activity is absolutely safe or without some element of risk. This applies equally to medical care which is amongst the most complex of human enterprises. Like science itself, medicine is full of uncertainty and unresolved questions, though we do not often understand or admit this. Medical action or inaction always carry some risk.

High priorities for all societies are:

- understanding the balance of positive and negative effects for communities and for individuals in all areas of human activity
- reducing areas of uncertainty
- decreasing the risk of harm.

Such ambitions require:

- time
- resources
- expertise
- widespread collaboration
- a radical re-education in our understanding and expectations of the physical world and of science and medicine in particular.

## Living with Uncertainty

The urge to create a safer world is sometimes expressed in the form of the false hope that risk can be reduced to zero, or of the impossible demand for simple, unambiguous answers about complex and uncertain issues.

Only if expectations are more realistic can anxiety (sometimes crisis) in medicine be avoided. Expecting too much leads to disappointment, frustration and cynicism. Open debate and wide collaboration are essential to prevent such negative reactions. All stakeholders need to be involved, including:

- patients
- consumers
- manufacturers
- healthcare professionals
- politicians and public officials
- journalists
- teachers
- researchers
- lawyers

– in fact *everyone*, because everyone's life is touched by the issues in some way, at some point.

## Open Debate

This first booklet sets out to discuss these vital issues more openly and objectively than has been attempted before in a widely-available public document. It describes the leadership being exercised by the World Health Organization and in particular by its specialist subsidiary group, *the Uppsala Monitoring Centre*, in vital technical research, and in stimulating public debate.

It seeks the active engagement of the people of the world in understanding and tackling the issues and controversies through widespread partnership. Only through such a process will the best interests of patient care and public health throughout the world be advanced.

## the UMC

*the Uppsala Monitoring Centre (the UMC)* is the field-name of the WHO Collaborating Centre for International Drug Monitoring. The business of *the UMC* is:

- To co-ordinate the WHO Programme for International Drug Monitoring and its growing number of member countries
- To collect, assess and communicate information from member countries about the benefits, harms, effectiveness and risks of drugs and other substances used in medical care
- To alert the regulatory authorities of member countries about potential drug safety problems
- To collaborate with member countries in the development and practice of the science of pharmacovigilance.

The main focus and source of data in pharmacovigilance are reports of Adverse Drug Reactions (ADRs) from healthcare providers and patients in member countries of the Programme. (See Vision and Goals, p 7.)

## Recognised long ago...

The truth about the nature of medicines has long been understood by scientists, but the message has not reached the general public. In its report for 1969-70, the UK Committee on the Safety of Drugs included the following:

*No drug which is pharmacologically effective is entirely without hazard. The hazard may be insignificant or may be acceptable in relation to the drug's therapeutic action.*

*Furthermore, not all hazards can be known before a drug is marketed; neither tests in animals nor clinical trials will always reveal all the possible side effects of a drug. These may only be known when the drug has been administered to large numbers of patients over considerable periods of time.*

# The Risks of Being Alive

Living is not a safe occupation. There are potential hazards for each of us ranging from the activity of the tiniest micro-organisms to the threat of global or cosmic catastrophe. Even our homes are full of hazards and great numbers of accidents and misadventures happen in them. Driving a motor vehicle or being a passenger in one is amongst the most dangerous of everyday activities.

All of us engage in risky activity every day of our lives, but we willingly or unthinkingly live with risk. We knowingly accept risks if:

- the probability of something harmful happening is small or distant in time, or
- the possible harmful event is not serious
- the possible benefits are sufficiently strong.

We may well put caution aside and act in spite of possible or suspected risk.

However, most of us are less willing to live with risk if:

- the probability of harm is high, or
- the probable harm is serious, or
- we are not in direct control and the risk is officially assessed and managed by people we do not know, by criteria we may not know or share (drugs or food standards, for example).

For each of us those risk assessments are different and we each apply different criteria to different kinds of risks.

Perception of risk is affected by many variables from the tiny workings of individual psychology through to the sweeping influences of language and culture.

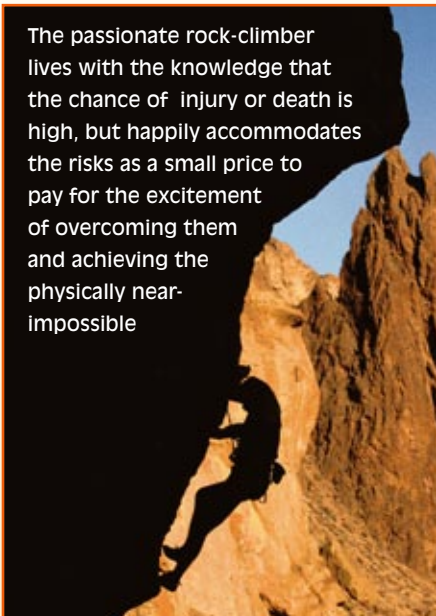
## Reducing Risk

In recent years there has been increasing public pressure to reduce risk and consequential harm and improve safety. Laws requiring the wearing of seat-belts and crash-helmets represent one kind of measure; standards for food and domestic power supplies are two others. No amount of legislation, of course, will

eliminate risk any more than litigation will eliminate human error.

Each of us is expected to take responsibility for the levels of risk we are willing to live with in areas over which we have control. Governments are expected to take responsibility for risks which we must live with in areas over which we do not have direct control (aircraft safety and food production, for example) and some areas which are within our control (permitted levels of alcohol in the blood of drivers, for example).

When we make decisions about our activities we do so on the basis of a calculation or an instinctive perception or judgement of the risks (and potential harm) as well as potential benefits. Some people do things even when they know



The passionate rock-climber lives with the knowledge that the chance of injury or death is high, but happily accommodates the risks as a small price to pay for the excitement of overcoming them and achieving the physically near-impossible

the odds are stacked against them, when the probability is high and the potential harm is great (smokers, for example).

## Risk-aversion

However, a social climate which is increasingly intolerant of risk, has created a tendency to seek absolute safety and security. This has led to a trend of blaming and punishing those who are seen to be the cause of accident or misadventure. Part of this results from an unwillingness to accept that it is natural for accidents to happen, and that there is always some uncertainty in all human activities, in spite of legislation or good intentions. Part of it results from the pressure on politicians and public servants to show that they are in control of the variables of existence.

## Risk in Medicine

So what about medicines? We are much less tolerant of risk in relation to medicines. Indeed, there is a common fantasy that medicine should be – can be – risk-free. We are particularly intolerant when we feel we may not be given the full information or when knowledge of risk emerges long after exposure. Demands that risk should conscientiously be reduced to absolute minimum are entirely proper, as is the expectation that information about risk should be openly and freely available.

What about the miraculous remedy, the ‘magic bullet’, the infallibility of doctors? What about the risks of medical treatment?

- While medicines have led to major improvement in the treatment and control of diseases, from the deadliest to the most trivial, they can also produce adverse effects on the human body
- While many drugs are precisely targeted to the causes and mechanisms of disease, and are brilliantly effective in that respect, they may also
  - have minor or major negative effects on other parts of the body, or



Should dangerous sports be regulated or licensed or prohibited to reduce or eliminate risk and costly accidents? Should the rights and freedoms of individuals be subject to considerations of social harm or cost, when only they are directly harmed?

–interact negatively with the systems of the particular individual or with other drugs or substances they are taking, or, of course,  
 –not work well or at all for some, many or all of those who take them

- No one really believes that doctors are perfect, though doctors, in the past, may have encouraged the idea. Patients have been willing to accept this – in some ways – comforting myth. But science is a complex and uncertain pursuit; doctors are fallible, may overestimate their knowledge and authority, and do, from time to time, make mistakes, sometimes very serious
- There is no such thing as a completely safe medicine. There are risks in any intrusion into the human body, whether chemical, surgical or psychological. Nothing in this field is entirely predictable – except that the interaction between science and the human body may produce surprises. If you test a medicine on many thousands of people you may find no evidence of problems. If subsequently someone does have a serious reaction to it, maybe even a fatal one, does this make the medicine a dangerous drug?

Well, it depends. It depends on many complicated issues. And we try to deal with those by putting them in perspective on the next page.

## Vision and Goals of *the* UMC

### Vision

'UMC improves worldwide patient safety and welfare by reducing the risk of medicines'

### Mission statement

The purpose of the UMC is to be recognised world wide as:

- a global centre of scientific excellence committed specifically to the reduction of risk in medication and to the safeguarding of patient health and welfare
- a leader in the research and development of tools and methodologies for pharmacovigilance and patient safety
- a prime resource for all stakeholders involved in international collection, coding, assessment, analysis, interpretation and communication of data relating to drug safety issues and patient safety concerns
- a preferred provider of high quality and cost-effective international drug and medical dictionaries, classifications, and terminologies
- an organisation with open, impartial and ethical values and performance.

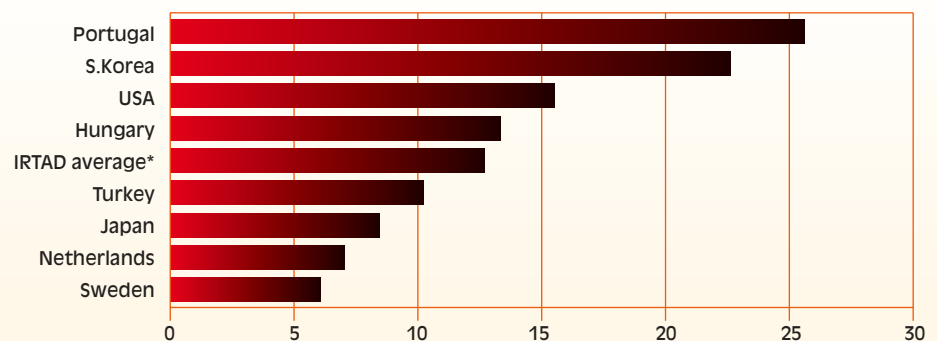
### Values

The underpinning aspirational value of UMC is to give service to the people of the world, especially patients, and all those who work for their safety and wellbeing. The corporate tag-line 'Safeguarding patients' reflects an extension of the previously known focus of the UMC relating to drug safety towards the end beneficiary.

Below are the operational values guiding us in our daily work and in all collaborations. We will:

- provide innovation and leadership in the area of patient safety
- conduct our operations within WHO principles and concepts
- constantly develop our knowledge and strive for scientific excellence
- deliver high quality products and services to all our customers
- always have a global focus, particularly considering the needs of developing and emerging countries
- seek and maintain active and fruitful collaboration with all stakeholders
- actively listen to all partners' views whilst maintaining the highest possible level of integrity and impartiality
- favour openness and transparency in our communications without sacrificing confidentiality and data security needs
- encourage creativity and intellectual adventurousness, amongst UMC staff and in our relationships
- endeavour to earn trust and respect, by applying the highest ethical and technical standards in everything we do
- defend the position of the UMC as a unique organisation, balancing income-generation and the public good in its products and services.

### Traffic deaths per 100,000 population in 1998



\*OECD International Road Traffic and Accident Database. Internet: [www.bast.de](http://www.bast.de)

**Risk:** the chance or likelihood of harm or danger. In science usually expressed as a probability in numbers: the extent to which an event is likely to occur measured by the ratio of particular events to the total number of events possible.

Example: numbers of car drivers killed while driving: total number of car drivers or total population.

From a bag containing 3 red balls and 7 white balls, the probability of a red ball being drawn first is 3/10; if the red balls are explosive, the risk is 3 in 10 or slightly less than 1 in 3 of being blown up.

# Benefit, Harm, Effectiveness and Risk

## in Medicine



When we think about the risks of medicines, we need to relate the discussion to our understanding of risk in our lives in general.

Tens of millions of people worldwide take part in national lotteries. The odds of winning are tiny (maybe 1:15,000,000 or less – comparable to the odds against a catastrophic collision between the earth and an asteroid\*); in other words the chances of not winning are utterly overwhelming.

Why do people do it? Because the dream of winning (someone wins, after all) is more pleasing than the almost certain loss of a few euros, dollars, or lire, ceddis, pesos or baht and the usually minor harm to one's personal finances. It's a perverse activity: the pleasure of taking part in something with enormous potential benefit, though the odds against winning are staggeringly huge (much, much higher than the odds against being killed in a car accident, which is relatively common).

We make these judgements or calculations all the time:

- what is the probability of benefit and how much can I expect?
- what is the probability of damage and how severe and of what duration?
- how do I feel about the balance between them?

## Tough Standards

We apply different criteria to medicines: we are much tougher in our demands for good odds against the occurrence of harm. Although the benefits of a medicine to a significant proportion of the intended patients may be clear, a major crisis can arise when a few dozen people out of perhaps hundreds of thousands receiving the drug suffer or die as a result of taking it.

\* The probabilities and timescales involved, are quite different, however: in a lottery there is almost certain to be a winner and quite certainly X million losers (depending on how many people buy tickets); with the asteroid it's the risk of a remotely possible event occurring during a very long period of time.

Thus, even when a medicine is known to provide significant benefits to a substantial portion of the treated population, a relatively infrequent occurrence of harm may give rise to demands for the drug to be restricted in use or withdrawn completely. The authorities make judgements on behalf of populations rather than individuals, usually on the basis of uncertain and incomplete information. Such action may leave individuals or groups of individuals significantly disadvantaged.

This behaviour has to do with the very proper concern – indeed the duty – of officials nationally and internationally to protect the population from harm. Their commitment is such that they may be panicked into radical action on the weakest of evidence. (On the other hand, even strong evidence sometimes takes years to lead to action of any kind – the harm caused by the drug piroxicam and the massacre caused by traffic accidents, for example.)

## Expressing Risk

Our reactions to risk are also related to our poor understanding of probability and how levels of risk are expressed. A magazine headline may say: 'Risk of blood clotting doubles in new study of drug X' – and national panic follows. But what is the reality behind the headlines?

## Absolute Risk

The absolute risk tells us the number of affected cases and the total number of people in the relevant population (e.g. for every 1,000 skiers X will break a leg in any one year). If the study group is 10,000 people, then a doubling of risk from one case to two cases is a very small numerical and percentage increase (from 1 in 10,000 to 2 in 10,000). If the study group is 1,000 people, then an increase in cases from ten to twenty is also a doubling, but is a larger increase in numbers and percentage (from 10 in 1,000 to 20 in 1,000). The use of words like 'doubling' or simple percentage figures can be very misleading unless the total numbers are also given.

**A recent and damaging controversy** concerned third generation oral contraceptives. This arose from (a) careless use of the phrase 'doubling of risk' (relating to a very small suggested rise in risk of venous thromboembolism) coupled with (b) various disputed statistics. The problems (particularly of women abandoning the drug and of a rise in abortions) were greatly increased by late or inadequate information and communications involving doctors, patients and journalists.

For an account of the issues, see: *Mills A, Edwards IR. Venous thromboembolism and the pill. The combined oral contraceptive pill – are poor communication systems responsible for loss of confidence in this contraceptive method? Hum Reprod 1999;14(1): 7-10.*

## Relative Risk

The relative risk provides a comparison in risk for the exposed population and for the non-exposed population.





## Benefit, Harm, Effectiveness and Risk...

(The exposed population could be those taking a new medicine; the non-exposed population those taking no drug at all, a placebo or another drug, for example.) This is calculated as a ratio.

If the problem affects 5 in 5,000 in the exposed population, and 5 in 10,000 in the non-exposed population, the relative risk is 2:1 – a doubling of relative risk – but the ratio makes sense only if the true extent of the risk is indicated by inclusion of the figures. In this case it is an increase in risk from 5 in 10,000 to 5 in 5,000 (or 1 in 2,000 to 1 in 1,000). As with absolute risk, ‘doubling’ or ‘100% increase’ can be misleading and dangerous expressions on their own.

### Attributable Risk

Our understanding of the risk of harm from a medicine must also be qualified by knowledge of the extent of the identified problem in the population not taking the drug. *Attributable* risk is the difference between the risk in an exposed population (the *absolute* risk) and an unexposed population (the *reference* risk).

Maybe a ‘background rate’ of thirteen in a thousand people with the disease get skin rashes when they’re not taking any drug. If there are thirteen patients experiencing skin rashes in a study group of one thousand it’s unlikely that most cases were caused by the drug. On the other hand, if there are twenty-two rashes in the study group, then there may be an increased *attributable risk*, in this case – around 9 in 1,000.

### Communicating Risk

Most people come across these matters through TV, newspapers, magazines and internet. Much of such material is written by people who do not necessarily know a lot about medicines, the nature of risk or medical practice. What they tell us may be true, but it may also be only a part of the whole picture and, therefore, potentially very misleading.

Relative risk (or risk ratios) tell us only the probability of an event occurring. They do not tell us about the seriousness or extent of the real event, nor do they provide sensitive information to allow patients to decide if they feel the harm they might endure is outweighed by the benefits they are likely to enjoy.

### Quality of Life

‘Benefits’ are often described in the medical literature only in relation to the likely pharmacological effectiveness of the medicine on the symptoms or the disease. They do not usually allow for

the subjective assessment of benefit by the patient, which may be very different, and will vary from patient to patient. (For more on this issue, please see page 19)

### Secrecy

But public concerns may also be justified: some medicines or interventions may well be suspect or unacceptably risky. In the past, there has been a tendency for some regulators and manufacturers to be secretive, and to disguise their sometimes inevitable uncertainty or ignorance. There may be incompatibility between the goals of manufacturers’ commercial interests and public health. The evidence and reasoning for regulatory action are very rarely made public. Such practices have contributed to lack of public confidence and have, sometimes, increased the risk of otherwise manageable events turning into crises.

Everyone – especially those who report these matters in the media – needs to have a very clear and accurate understanding of the complexity of the issues, and of the inherent elements of uncertainty in science. (See article on Communications and Education, page 16, for more on this.)

Formal definitions of the terms discussed in this article appear in the glossary on page 22.

### Don't be misled ...

...by statements like ‘Doubling of risk’ or ‘A relative risk of 2:1’ – what really matters is the number of people involved (‘increase from one to two people in a thousand...’)

### Defining the terms

- **Benefits** are commonly expressed as the proven therapeutic good of a product, but should also include the patient’s subjective assessment of its effects
- **Risk** is the probability of harm being caused, usually expressed as a percentage or ratio; the probability (chance, odds) of an occurrence
- **Harm** is the nature and extent of the actual damage that could be caused. It should not be confused with risk
- **Effectiveness** in pharmacovigilance expresses the probability of the medicine working as expected in the clinical setting (opposite to its risk)
- **Efficacy** is used to express the capacity of the medicine to work as intended in ideal experimental circumstances

### How common is common?

In pharmacovigilance the following terms represent the various probabilities of an occurrence:

**Common or frequent:** between 1 in 100 (1%) and 1 in 10 (10%)

**Uncommon or infrequent:** between 1 in 1,000 (0.1%) and 1 in 100 (1%)

**Rare:** 1 in 10,000 (0.01%) and 1 in 1,000 (0.1%)

Source: Guidelines for Preparing Core Clinical Safety Information on Drugs – Report of CIOMS Working Group III. Geneva, WHO, 1995.



# How do we find out about the risks of drugs?

**Clinical Trials:** Pharmaceutical companies are required by law in all countries to have tested new medicines on people before they are made generally available. They usually select a representative sample of patients for whom the drug is designed – at most a few thousand – along with a comparable control group. The control group may receive a placebo (sugar pill) or another medicine that is already marketed for the disease.

Clinical trials are full of medical, scientific, ethical and statistical complexities, though

the science of clinical research has become increasingly sophisticated to cope with them.

The declared purpose of pre-marketing\* clinical trials is to discover

- if a drug works and how well
- if it has any harmful effects
- if it does more good than harm, and how much more;
- if it has a potential for harm, how probable and how serious is the harm?

Pre-marketing trials rarely include other than a small number of healthy, male volunteers and highly selected patients. Post-marketing trials (one third of the total) may be carried out to clarify new aspects of drug effects and risk in specified patient groups.

Clinical trials do, in general, tell us a good deal about how well a drug works for a defined disease and what potential harm it may cause. They provide only limited information for larger populations with different characteristics from the trial group – age, gender, state of health, ethnic origin, and so on. If a drug were later tested on many more people, or on people of different ethnic origin, for example, there might be very different results.

A clinical trial can never tell you the whole story of the effects of a drug in all situations. In fact, there is nothing that could tell you the whole story, but a clinical trial must tell you enough about its acceptability; ‘enough’ being determined by legislation and statistics, and by contemporary judgements about the acceptable balance of benefit and harm.

**Pharmacoepidemiology:** This is the science of investigating the effects of medicines already on the market or of other medical interventions (such as vaccination) in large groups of the population.

Pharmacoepidemiological studies are usually carried out by academic scientists or commercial research organisations. It’s a powerful science but has its limitations: for example, it is very complex to carry out a useful study of the effects of a vaccination programme, not least because of the enormous numbers of people usually involved and the wide range of complicating and confounding factors.

\* Pre-marketing is the term used to describe the stage before a drug is available for prescription or sale to the public; post-marketing to describe the stage when a drug is generally available on the market

## Vaccines

Immunisation programmes have brought incalculable benefits to the human race, saving tens of millions of lives in recent decades, although some individuals are harmed in the process. It is argued that their dramatic benefits for public health far outweigh the occasional harm thought to affect very small numbers of people. Scares about speculative damage caused by vaccines have sometimes compromised immunisation programmes and led to new outbreaks of an epidemic disease, with far more dramatic damage to larger numbers of people than could have been harmed by the vaccine.

Monitoring the risks of immunisation programmes is exceptionally difficult, as is establishing a causal relationship with certainty between vaccination and concurrent or subsequent disease experienced by subjects.

For more information GO TO: [www.who.int/immunization\\_delivery/](http://www.who.int/immunization_delivery/)



Although one can determine whether there is any association between a drug and an event through pharmacoepidemiology, it cannot establish whether or not there is a causal relationship in each individual case, nor does it explain the nature or mechanism of an ADR.

**Pharmacovigilance:** This is the science and art of collecting, monitoring, researching and evaluating data on the effects of medicinal drugs, biological products, herbals and traditional medicines with a view to identifying new information about adverse reactions and preventing harm to patients.

Such data comes primarily from 'spontaneous reporting' of information by health care professionals. Sometimes these will be effects which were not picked up in clinical trials. While its primary concern is to alert the world to possible new safety hazards, it is also concerned with enhancing medical therapy with new information and thinking about benefit, harm, effectiveness and risk and such issues as rational prescribing and quality of life criteria. (How pharmacovigilance works is described in more detail on the next page.)

### Some of the problems...

These are the controversial concerns of researchers about some aspects of academic pharmacoepidemiology:

- Increasing secret work and non-sharing of data due to contractual obligations with the private sector
- Diversion of resources to 'fringe' medicine where no basis for rational study investigation has been presented
- In the desire to obtain funding, conducting studies where a predetermined outcome is desired and engineered as a service to the funding agency
- Neglect by pharmacoepidemiologists of the plight of Third World consumers, where drug markets are often unregulated and drug advertising grossly and dangerously misleading, and
- Increasing control and setting of research priorities in pharmacoepidemiology by the private sector to further its needs, which are not always congruent with public health goals

Stolley PD, Laporte JR. *The Public Health, the University, and Pharmacology*. In: Strom BL, ed. *Pharmacovigilance*, 3rd ed. Chichester, Wiley, 2000:82-83.

### Cost of ADRs

In the US, it has been estimated that each year 2.2 million hospitalised patients have serious ADRs; 106,000 patients have fatal ADRs. Interpretation of the data is problematic, but it seems likely that many of these ADRs are in the category of 'avoidable' and do not reflect the intrinsic qualities of the medicines.

Lazarou J, Pomeranz BH, Covey PN. *Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies*. *Journal of American Medical Association*, 1998, 279:1200-1205.

See also: Griffin JP. *The cost of adverse drug reactions*. *Adverse Drug React Toxicol Rev*, 1997, 16(2):75-78.

ADRs may be the 4<sup>th</sup> to 6<sup>th</sup> largest cause of death in the US. Hospital admissions due to ADRs may be more than 10% in some countries; up to 20% of healthcare budgets may be spent on drug complications.

Source: *Safety of Medicines – A Guide to detecting and reporting adverse drug reactions*. World Health Organization, 2002.

### Conclusions of an up-to-date study of US Drug-related Morbidity and Mortality

Overall the cost of medicine-related morbidity and mortality exceeded \$177.4 billion in 2000. Hospital admissions accounted for nearly 70% (\$121.5 billion) of total costs, followed by long-term admissions, which accounted for 18% (\$32.8 billion) ... Since 1995 the costs associated with drug-related problems (DRPs) have more than doubled... the total cost of drug-related morbidity and mortality exceeds the cost of the medications themselves. DRPs are increasingly recognised as a serious and urgent – but largely preventable – medical problem.

Ernst FR, Grizzle AJ. *Drug-related morbidity and mortality: updating the cost of illness model*. *Journal of American Pharmaceutical Association*, 2001, 41:192-9.

### International Reporting of ADRs

the UMC receives around 350,000 reports from member countries each year. Countries with the best reporting rates generate:

- over 200 reports per 1,000,000 inhabitants per year. The average is around 100/1,000,000
- over 150 reports per 1,000 physicians per year. The average is around 50/1,000

Source: Olsson S ed. *National Pharmacovigilance Systems*. Uppsala, the UMC, 1999.

### Clinical Trials

Around 6,400 clinical trials are thought to take place each year around the world, prior to new drugs being brought to market. Including trials run after drugs are on the market, the figure may be nearer 10,000 per year. Information based on Centre for Medicines Research International figures quoted by DrugDev123 Ltd 2000.

**Epidemiology:** From Greek *epidemia* among people. Usually referring to prevalence of disease in a population and Greek *logos* – word, speech, thought, and, hence theory or science

# Pharmacovigilance

## — The Great Challenge

**Thalidomide** In 1961 the world experienced the infamous ‘thalidomide disaster’. Thalidomide was marketed as a mild hypnotic (sleeping drug) and as a remedy against morning-sickness for pregnant women. About four years after its launch, a dramatic increase was seen in several countries in the frequency of phocomelia, a previously rare birth-defect which left babies without limbs or with serious deformities. Epidemiological studies established that the cause was exposure of the foetus to the drug during pregnancy. Had international data been collected at the time, the pattern of seriously harmful adverse effects might have been noticed earlier.

If hundreds of millions of people are taking drugs and other therapeutic substances every day, how on earth do you find out if any of those people are having problems as a result?

Medical vigilance is the key: every healthcare professional in the world should be constantly alert for adverse effects or potential new hazards and reporting them to their National Centres. Manufacturers should also receive such information.

### International Vigilance

This principle is the basis for the WHO Programme for International Drug Monitoring: all member countries have systems in place which encourage healthcare personnel to record and report adverse effects of drugs in their patients. These reports are assessed locally and may lead to action within the country. Through membership of the WHO Programme one country can know if similar reports are being made elsewhere. (The European Union also has its own collective international scheme.) Member countries send their reports to the Uppsala Monitoring Centre where they are processed, evaluated and entered into the WHO International Database. When there are several reports of adverse reactions to a particular medicine this process may lead



to the detection of a *signal* – a notice of a need for increased awareness of a possible hazard communicated to member countries. This happens after preliminary evaluation and expert review, prior to detailed work on the ground by individual authorities.

(Full details of this process of assessment are described in Part 2. There are also details of the Bayesian Confidence Propagation Neural Network (BCPNN) – a very sophisticated automated way of detecting if particular adverse reaction reports stand out from the background of the entire database.)

### Spontaneous Reporting

One of the problems with this voluntary system of ‘spontaneous reporting’, is that hard-pressed medical personnel don’t always see it as a high priority. If the effects are not serious, they may not get to know about them at all, and even if they are serious, they may not be recognised as the effect of drugs. Doctors may also worry that the adverse effects they report may be seen as the result of their bad practice and leave them open to criticism or even litigation.

Even so, spontaneous reports are a crucial element in the world-wide enterprise of pharmacovigilance and form the core of the WHO Database, which includes over five million reports, growing annually by more than 350,000. (See Part 2 for full technical details.)

### Special Measures

Some countries require spontaneous reporting by physicians by law. In most countries manufacturers are required to submit reports they receive from healthcare providers to the national authority. Others have intensive, focused programmes concentrating on new medicines, or on controversial medicines, or on

### SIGNAL...

...is notice of an early concern or hypothesis about a possible drug safety problem. Detecting SIGNALS is one of the primary objectives of member countries of the WHO Programme for International Drug Monitoring.



the prescribing habits of groups of doctors, or involving pharmacists in reporting. All of these generate potentially useful information. Such intensive schemes, however, tend to be the exception.

There is some controversy about how far patients should be involved in reporting adverse effects of drugs directly to their National Centres. There is no disagreement that all patients should report adverse effects to their doctors. Many people argue that there is a strong case for them to report direct to their national schemes. Their experiences may reflect different concerns from those of health professionals, and they may show up issues relating to compliance. In particular, patients are better able to give a picture of how the harm from the medicine has affected them and their lives.



This raises some questions of practice (consistency and quality control for example), but few in principle. Few countries have yet addressed this important challenge and established active patient participation.



## Watching the World *the* Uppsala Monitoring Centre

After the thalidomide disaster – before which there were no national or international schemes for collecting information about emerging drug hazards – the World Health Organization (WHO) set up its Programme for International Drug Monitoring at the same time as a number of countries set up their own schemes. Since 1978, responsibility for managing this Programme has been carried by *the* Uppsala Monitoring Centre (UMC) in Uppsala, Sweden.

*the* UMC has achieved a great deal in its more than thirty years in collaboration with the growing number of member countries in the Programme (representing over one third of countries in the world),

and with academic, scientific and medical experts and organisations throughout the world.

There is no other official body in the world which has a truly independent and global perspective on drug safety other than the WHO and its collaborating centre, *the* UMC. International harmonisation and standardisation are difficult to achieve without consensus. It is the WHO's general mandate to do this work, and the record of achievement in the field as a whole is now substantial, authoritative and widely-recognised.

Full details of *the* UMC's achievements appear in Viewpoint Part 2.

Go to: [www.who-umc.org](http://www.who-umc.org)

## Pharmacovigilance in the 19<sup>th</sup> Century

Over 150 years ago, on January 29, 1848, 15-year-old Hannah Greener from Winlaton, north-east England, had a routine general anaesthetic before treatment of an ingrowing toenail. The anaesthetic agent, chloroform, had only been introduced into clinical practice a year earlier by James Simpson, professor of midwifery at Edinburgh, since it produced less nausea and vomiting than ether. Unfortunately, Hannah Greener died during the anaesthetic from what was probably an episode of ventricular fibrillation. Because of the continuing concerns of the public and the profession about the safety



of anaesthesia, *The Lancet* set up a commission, which invited doctors in Britain and its colonies to report anaesthesia-related deaths. These findings were subsequently published in the journal in 1893. Thus, the forerunner of a spontaneous reporting system for suspected adverse drug reactions (ADRs) was established, at least for a time.

*Routledge PA. 150 years of pharmacovigilance. Lancet, 1998, 351:1200-01.*  
For a tabular History of Pharmacovigilance from around 2000 BC (!) to the present day, see Stephens MDB, Talbot JC, Routledge PA, eds. *Detection of New Adverse Drug Reactions, 4th ed. London, Macmillan, 1999: 2-4.*

# Why do Adverse Drug Reactions matter and how do they happen?

ADRs matter because pharmaceutical products and other substances taken for medical purposes have the potential for harming patients, even killing them. (A very small number of people have a serious or even fatal reaction to penicillin, for example.)

ADRs happen for many reasons, some inevitable and unavoidable, some preventable.

## The inevitable reasons are:

- The effects of any medical intervention cannot be predicted with absolute certainty
- There is no drug or medical intervention which will not have some negative and undesirable effect on someone, somewhere at some time
- Information about rare events may, by their very nature, not be available until they happen.

## The preventable reasons include:

- An error in diagnosing the disease
- Prescription of the wrong drug for the disease
- Prescription of the wrong dose of the right drug
- Choice of the right drug for the disease, but maybe the wrong drug for the patient, because of a genetic or ethnic predisposition, age, some other illness or medication, allergy or intolerance
- Choice of an appropriate drug but without taking into account the potentially harmful interactive effects with other drugs or substances being taken by the patient
- The full specification, indications, contraindications and risks of the drug may not have been read or fully understood

- The patient may not comply with the doctor's advice or with the manufacturer's advice in the patient information leaflet
- As long as people are choosing drugs and other substances for their own medication without professional advice, there may be problems
- The taking of many drugs (polypharmacy) or receiving treatment from more than one source (polytherapy) can contribute significantly to causing drug-related problems, particularly harmful drug interactions.

## The remedies for the preventable reasons are clear, if hugely challenging to achieve:

- A higher priority in all medical training in the knowledge and skills associated with diagnosing and treating disease – including taking case-histories, diagnostic skills, pharmacology, and the recognition and reporting of adverse effects
- Greater awareness by healthcare professionals and the general public about the complexities and safety profiles of medical interventions
- Much more effective communication and openness about the nature of drugs and their effects and the degree of uncertainty associated with them
- Comprehensive public education and debate about the benefit, harm, effectiveness and risk of medical interventions and agreement about the balance of benefit, harm, effectiveness and risk which is acceptable, given that there will always be some uncertainty.
- Wider discussion and education on the nature of risk in general and its communication, and in the individual variables affecting perception and acceptance of risk.



## Spontaneous Reporting

This is the core data-generating system of international pharmacovigilance, relying on healthcare professionals (and in some places consumers) to identify and report any suspected adverse drug reaction to their national pharmacovigilance centre or to the manufacturer.

Among the system's major weaknesses are under-reporting and variable quality of reporting, though the figures vary greatly between countries and in relation to minor and serious ADRs.

In the early 90s reporting rates were estimated to be around 10% at best, often much lower\*.

\*Fletcher AP. An Appraisal of Spontaneous Adverse Event Monitoring. *Adverse Drug Reaction Rev*, 1992, 11(4): 213-227.

## Package Inserts or Leaflets

In many countries, manufacturers are required by law to enclose information for patients about their products in the package (this includes information on the active drug substance itself as well as the 'excipients' – the materials included to bind the chemical into a tablet, to stabilise it, and so on).

While possible 'side effects' (adverse experiences) of products must be mentioned, there is usually little discussion of the probability of their occurrence, their seriousness or duration, though categories such as 'common' or 'rare' are used.

## Medical Error

Doctors and other healthcare providers make mistakes. There is evidence that excessive and inappropriate prescription of drugs contributes substantially to the occurrence of ADRs<sup>1</sup> and that hospital patients are particularly vulnerable to medication errors<sup>2</sup>. The FDA (US regulatory body) has a reporting system for medical error<sup>3</sup>

The Institute for Safe Medication Practices is an American non-profit organisation for reporting medical errors. Its mission is: *Educating the healthcare community about safe medication practices*. There

are contact organisations in several countries. Go to: [www.ismp.org](http://www.ismp.org)

<sup>1</sup> Leape LL et al. *The nature of adverse events in hospitalised patients: results of the Harvard Medical Practice Study II*. *New England Journal of Medicine*, 1991, 324:377-84.

<sup>2</sup> Bates DW et al; *Patient risk factors for adverse drug reactions in hospitalised patients*. *Archives of Internal Medicine*, 1999, 59:2553-60.

<sup>3</sup> *Medication Error Prevention Office of Post-Marketing Drug Risk Assessment*. Go to: [www.nccmerp.org](http://www.nccmerp.org)



## Quality Problems and Counterfeiting

There are large volumes of medicines on the world market which are either counterfeit (illegal copies) or sub-standard. Counterfeit medicines may also be sub-standard.

Sub-standard medicines may contain little or none of the labelled active ingredient. They may include other substances or include even contaminated or poisonous ingredients. Some medicines are sold and used after their expiry dates and some are stored in conditions which damage them.

Spontaneous reporting can help expose such hazardous medicines when healthcare personnel are alert to unexpected and apparently inexplicable adverse reactions, or to lack of effect.

These problems are relatively rare in developed countries where inspection and quality control regimes are rigorous, but they are not unknown.

## Generics or Multisource Pharmaceutical Products

These are copies or near-copies of branded medicines (usually drugs whose patent protection period has elapsed) made and sold legally and subject to the usual quality-testing procedures. Such products are usually intended to be interchangeable with the original product, but may be produced in different dosage forms and/or strengths. Widely available, they are favoured because they are usually much cheaper than the original products. They may or may not be sold under their own brand name.

As with branded drugs, there are instances of illegal manufacture and distribution.



# Communication and Education

*the* Uppsala Monitoring Centre has insisted for some years now that among the crucial issues to be addressed is the achievement of open and effective communication about benefit, harm, effectiveness and risk and about drug safety issues in general.

Technical and scientific issues clearly remain of fundamental importance, but unless healthcare professionals, patients, the public in general and journalists really understand the issues, and are much more critical and discriminating in their treatment of medical information, there will continue to be misunderstanding, mistrust, and crises which may damage patients and public health. Such problems may also damage the legitimate interests of pharmaceutical companies.

The *Erice Declaration*\* was an important statement of principle on these issues resulting from an international conference sponsored by *the* UMC and the Ettore Majorana Centre in Sicily in 1997.

Among the many challenges identified then and since are:

- A greater willingness among regulators and manufacturers to show openness and transparency in the communication of the information they have about drugs, especially in admitting uncertainty
- A commitment to public education, including materials in school courses about the nature of medicine, the effects of drugs and about being an intelligent, critical and empowered patient
- More open and mature relationships with the media and the briefing and training of journalists on the science and its complexities
- A commitment to include more extensive discussion of and training in benefit, harm, effectiveness and risk and drug safety issues (pharmacovigilance) in all medical education

- Efforts to ensure that all healthcare professionals are alerted to the importance of recognising and reporting ADRs and of encouraging their patients to do so as well.

*the* UMC has strongly argued the case that much greater imagination and professionalism is needed in the planning, design, composition and presentation of medical communications. 'Brilliant scientists are not necessarily brilliant communicators' is a truth not always acknowledged by people who are expert in their own specialism, but may be only amateurs in the business of communication. It's a huge challenge to compete for attention on equal terms in the crowded, noisy, modern world where communicators and their audiences are so very sophisticated. It's a challenge that requires expert skills.

[www.who-umc.org/DynPage.aspx?id=22690](http://www.who-umc.org/DynPage.aspx?id=22690)

## The Guardians of Drug Safety

Most countries have a regulatory authority which has legal responsibility for controlling the use of medicines and other substances for human consumption (food, food supplements and food additives, for example).

Various names...

- Philippines: The Bureau of Food and Drugs
- UK: Medicines and Healthcare products Regulatory Agency
- US: Food and Drug Administration
- Australia: The Therapeutic Goods Administration
- France: L'Agence du Médicament
- Japan: The Pharmaceutical and Food Safety Bureau.

These organisations have a legal duty to protect their populations from harm, and usually carry out the following statutory functions:

- receive applications from manufacturers for approval for new products
- examine the data for product efficacy and safety from clinical trials or other premarketing research
- decide if the potential benefits outweigh the harms and if so, approve the product on the basis of its risk profile and sometimes on the basis of its cost
- decide on the conditions for allowing the product on to the market and the information which must be provided for doctors, pharmacists and patients
- officially license the product for prescription only (POM) or for sale over the counter (OTC)
- keep watch over all products on the market
- respond to any evidence of a change in a product's safety profile or reports of problems
- withdraw, modify or confirm a product's licence after investigation of new concerns.

Many also receive periodic safety update reports (PSURs) from manufacturers on the latest information about their products. The regulatory authorities usually advise their governments and communicate with medical and pharmaceutical personnel, the media and the public on drug safety matters.

Often the same organisation manages the country's drug safety monitoring programme, including the receipt and processing of spontaneous reports of adverse drug reactions. There is a strong ethical and scientific case for these functions to be separated. An independent safety evaluation board is likely to have a more objective and balanced view of the issues. Such a system is run in New Zealand, for example.

Most countries with drug safety programmes are members of the WHO International Drug Monitoring Programme. (Full details appear in Viewpoint Part 2.)





# 'Patient Empowerment'



Consumers and patients in many countries are demanding a greater say in their medical treatment. This can only come about if there is a commitment to basic education in schools on health and medical matters, and if doctors and patients have access to comprehensive, reliable information about treatment options.

It requires doctors to take their patients seriously as participants or collaborators in the choice and use of therapy (still something of a radical proposal); and patients to assert their right to have as much of a part in decision-making as they want. Some countries have excellent educational and information programmes, as well as other printed and electronic resources.

There is a growing movement worldwide for greater lay involvement in medical matters. Patient liaison groups for professional societies and health institutions

and patient representation or groups for general or specific interests are increasingly common. These are sometimes independent pressure groups or officially-supported activities.

Some examples of resources for patients:

[www.haiweb.org](http://www.haiweb.org) – Health Action International (HAI) is a non-profit, global network of health, development, consumer and other public interest groups in more than 70 countries working for a more rational use of medicinal drugs. HAI represents the interests of consumers in drug policy and believes that all drugs marketed should be acceptably safe, effective, affordable and meet real medical needs. HAI also campaigns for better controls on drug promotion and the provision of balanced, independent information for prescribers and consumers.

Grant R, Which? Medicine, Consumers Association (UK), 2000

Patient FASS Farmaceutiska Specialiteter i Sverige A version of the manufacturers' organisation's (LIF) drug reference list produced specially for patients. Available in printed booklet or on the internet: [www.fass.se](http://www.fass.se)

SIGNAL, occasional newsletter produced by the Bureau of Food and Drugs, The Philippines

[www.healthtalkonline.org](http://www.healthtalkonline.org) – a database of patient experiences of medical treatment

[www.patientsorganizations.org](http://www.patientsorganizations.org) – an international database of patient organisations

[www.consumersinternational.org](http://www.consumersinternational.org)

– international organisation working for the interests of consumers

[www.quackwatch.com](http://www.quackwatch.com) – a fascinating and provocative (if occasionally controversial) account of a wide range of medical matters

<http://www.usp.org/audiences/consumers/resources.html> – Wide-ranging drug information from the United States Pharmacopeia (USP), including drugs on the market, for public review and comment

[www.nlm.nih.gov/portals/public.html](http://www.nlm.nih.gov/portals/public.html)

– Easily accessed information about 11,000 drugs from the USP (see previous item)



## Challenging issues

The impact of global pharmaceutical activity and consumption on world issues is huge – economic, political, social, ethical, as well as medical.

There is the suggestion that '...trade agreements reinforce justifications for commercial secrecy to the detriment of scientific openness and drug regulation,' and that '...Lack of access to essential

drugs and vaccines because of economic factors raises human rights issues.'<sup>1</sup>

Figures from WHO indicate that one third of the world's population does not have access to essential drugs. Pharmaceutical consumption in the top ten countries (including 17.5% of total world population) in the year ending 30 June, 1999 (amounting to 190 billion dollars) was around 60% of total world consumption in that year (amounting to 315 billion dollars).<sup>2</sup>

<sup>1</sup> Stolley PD, Laporte JR. *The Public Health, the University, and Pharmacology*. In: Strom BL, ed. *Pharmacoepidemiology*, 3rd ed. Chichester, Wiley, 2000:82-83.

<sup>2</sup> as above, page 81.



## Questions



# Questions and Answers



After covering so much ground in this booklet, here again are the questions from the opening page, this time with some of the challenges to which we should be alerted and the action we need to take:

### Has the disease been correctly diagnosed?

- The need for up-to-date refined and sophisticated diagnostic skills
- Increased awareness that symptoms may be caused by adverse reactions to medicines or other substances already being taken, as well as by disease.

### Has the right dose of the right strength of the right formulation of the right drug been prescribed?

- Provision of easy access to clear and comprehensive information about the drug and its use and about possible alternative therapies, for the prescriber and the patient.

### What are the risks of the treatment producing an adverse drug reaction (ADR)?

- Provision of comprehensive, accessible, up-to-date information about all known ADRs, the risk of their occurring generally and for this particular patient, their potential seriousness and duration.

### What is the potential seriousness and duration of possible harmful effects?

- Informed discussion with the patient about their particular view of the potential *benefit* and *harm* in relation to *effectiveness* and *risk* for them.

### Is the patient taking anything else which might interact badly with the drug or prevent its working at all?

- Public education in the way medicines work and on the way they interact with many other medical and non-medical substances
- Patient awareness of the critical nature of issues which may not seem immediately relevant to the present consultation: for example, patients may not regard all drugs they are taking as drugs, and may therefore not mention such products as aspirin, oral contraceptives, vitamins, herbal remedies.

### Does the patient have any medical or genetic or allergic condition which might cause a bad reaction to the drug?

- Training in the expert and thorough taking of case-histories and in effective interaction with patients
- Continuity of care or, at least, excellent communications between healthcare providers about their shared patients

### Is the manufacturing source of the drug safe and reliable?

- Universal requirement for adherence to WHO Good Manufacturing Practice (GMP), including strict inspection and quality control by manufacturers and regulators (this is a serious problem in some developing countries)
- Reliable and conscientious reporting by health providers and patients of occasions where drugs cause adverse reactions, or do not work at all (the medicine may be contaminated or contain no active substance).

### Does the patient understand the instructions and will they be followed exactly (the issue of *adherence*)?

- Much more sophisticated communications skills in health-care providers (and probably more time)
- Much greater understanding among patients about how drugs work and the necessity (for example) of completing a course of treatment even if symptoms appear to have gone.

Assessing benefit and harm (as opposed to effectiveness and risk) is both a scientific *and* sociological pursuit.

Scientists cannot judge how all patients, or some patients – or this patient – will assess the potential benefit and potential harm of a particular therapy. Only patients can tell us what they want, and how it contributes to their quality of life. Commonly, the term '*benefit*' has been defined only by scientists and usually refers only to technical, therapeutic effectiveness and not to emotional, social or psychological benefits which may be equally or more important.

# Quality of Life



A patient with terminal illness may be willing to tolerate radical and unpleasant therapy to prolong life – or may opt for a life-enhancing therapy which may give strength and energy for a short time. There are equally complex issues to be addressed for those with chronic disease which does not threaten life.

A patient with a minor ailment may be unwilling to take the risk of adverse effects of a drug that could be equal to or more serious than the original illness, or conversely, the patient may judge that the illness is sufficiently troubling to take the risk.

Quality of life issues are intensely personal and individual – and no one but patients can say what matters to them.

## Signal

... is an early alert of a possible drug safety hazard. Detecting SIGNALS is one of the primary objectives of member countries of the WHO Programme for International Drug Monitoring

# The Current State of Play



- The science of pharmacovigilance is relatively immature and is only now beginning to develop the theory and tools to have a significant impact on patient care and public health
- Since thalidomide, there has been no comparable drug disaster. Medicines causing serious harm have been identified and action has been taken before widespread damage occurred (examples include practolol, bromfenac and troglitazone).
- There has been little substantial, scientific evaluation of the outcomes and effects of pharmacovigilance worldwide
- Where there has been assessment, it has been on the basis of looking at regulatory action (number of drug withdrawals or label/package insert changes, for example) rather than on the ultimate impact on prescribing habits, rational drug use, patient treatment and public health



- Regulatory action is only an intermediate goal of pharmacovigilance, though it has sometimes been seen as the ultimate goal
- The evidence for the expected impact and outcomes from withdrawals and other regulatory action are not readily available for public scrutiny, if at all
- Assessment of the effect of issuing warnings about particular drugs (e.g. 'Dear Doctor' letters and other methods)

suggests that they have little effect, and much more imaginative communication approaches to change prescribing habits are required

- Studies on ADRs and hospital admissions over many years suggest little change in rates of illness and death attributable to drug complications in spite of warnings and advice
- There is some evidence that the wisdom of pharmacovigilance is influencing medical education, but it is still a very low priority in most professional health curricula
- Patients in some parts of the world are becoming more demanding and assertive and less willing simply to trust everything they are told.

## The Role of *the* UMC

- 'Never miss a signal' is a goal for the international collaboration of member countries in the Programme, supported by *the* UMC
- *the* UMC has drawn attention to matters of concern which have arisen from examination of the international data, but its primary role is to facilitate the pharmacovigilance of member countries by the provision of information and tools
- *the* UMC is not directly in control of ultimate end-points of action within the Programme as individual countries make their own decisions on the basis of information available
- *the* UMC has concentrated on the weakest elements in the science and systems of pharmacovigilance and provided significant development
- The Bayesian Confidence Propagation Neural Network tool (BCPNN), developed by *the* UMC, is a great advance which provides one of the best tools available internationally for signal detection. It has been assessed for

effectiveness. (See Part 2, for a detailed description of this process.)

- *the* UMC has raised and promoted discussion of the issues of benefit/effectiveness, harm/risk, essential to the achievement of the higher goals of pharmacovigilance
- *the* UMC has raised the question about the essence of the meaning of pharmacovigilance in the worldwide medical community ('What are the messages?') and the challenge of effective communication of them ('How are the messages to be conveyed?') to all audiences
- *the* UMC's concern with the central scientific issues of pharmacovigilance and the ultimate effects on patient care and public health may not fit easily with the way pharmacovigilance is going internationally: there is an increasing emphasis on regulatory action, rather than on open and reflective scientific progress, learning from experience and rational use of drugs
- *the* UMC has had a significant impact on the thinking and practice of the staff of the National Centres of member countries, on the growth of pharmacovigilance activities around the world, and on the establishment of new National Centres
- *the* UMC's 'success' must be judged largely by the effectiveness of the drug safety activities of the community of National Centres and on their impact on patient therapy and public health in their own countries. Research in this area remains an important priority.

# Herbals and Traditional Medicines

While enormous quantities of modern medicines (known as allopathic medicines) are consumed worldwide, there are certainly much greater quantities of herbals (and traditional medicines and modern phytotherapeutic and homeopathic medicines) being taken by large numbers of people in every country.

In many developing countries there are far more traditional practitioners than medically qualified doctors. In these countries the great majority of the population rely largely on traditional remedies, since they are relatively cheap and readily available.

In developed countries, where medical services are comparatively comprehensive, the popularity of non-allopathic remedies has soared in recent years.

## Why Monitor Herbals?

- Few traditional remedies are today subject to any regulation, inspection or quality-control in their collection, production or distribution.
- The ingredients of traditional remedies are sometimes uncertain. *the UMC* is taking a major role in serious work being done to make it possible to classify their sources and standardise references to plant names and parts. (See Herbals in Viewpoint Part 2.)



Traditional practitioners learn their profession through apprentice systems and not through text books. Little is known by health professionals about this process and the knowledge it imparts. Very little is known about the interactions between allopathic and herbal-based medicines whether traditional or modern. Monitoring herbals in the same way as allopathic remedies is beneficial both to the populations of developing countries that depend on traditional remedies for their health care, and to developed countries where herbal remedies are a more and more important element of modern life.

Another aim of promoting the monitoring of herbals it to make the two sciences more mutually understood and accepted.

## The widening arena of pharmacovigilance

Pharmacovigilance is changing! In the past it has been seen as a relatively limited – though important – technical activity concerned with the identification of adverse drug reactions from pharmaceutical products. Its uses have been more or less confined to regulatory deliberations and decisions.

Increasingly, it is now seen as the starting point for the consideration of larger and more radical questions:

- the benefit, harm, effectiveness and risk of medicinal products as they affect individual patients and public health
- the safety of all substances used in medical or alternative practice – herbals, vaccines, blood products and so on
- the rational use of drugs in collaborative relationships with patients
- the communication of complex issues among healthcare professions and with the media, patients and the public.

# Glossary

The following list contains the majority of words used in specialised ways in pharmcovigilance and which appear in the text in this publication

Word	Meaning
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<b>Absolute risk</b>	The probability of an event affecting members of a particular population (e.g. 1 in 1,000)
<b>Adverse drug reaction (ADR)</b>	Negative effects or lack of effect, from taking a drug at normal dose
<b>Allopathy</b>	The treatment of disease by conventional (Western) means, usually in opposition to the disease (allo- = other, different, opposite). Compare Homeopathy, below
<b>Association</b>	Events associated in time but not necessarily linked as cause and effect
<b>Attributable risk</b>	The difference from the absolute risk in the probability of an event happening, directly attributable to a drug or other variable
<b>Benefit</b>	The proven therapeutic good of a product; should also include the patient's subjective assessment of its effects
<b>Causal relationship</b>	Where there is a cause-effect relationship between two events
<b>Common</b>	In pharmacovigilance, an event with a probability between 1 in 100 and 1 in 10
<b>Compliance</b>	Faithful adherence by the patient to the prescriber's instructions
<b>Control group</b>	The comparison group in drug-trials not being given the studied drug
<b>Effectiveness</b>	The probability of the drug working as expected in the clinical setting
<b>Efficacy</b>	The intrinsic capacity of the drug to work as demonstrated in ideal experimental circumstances
<b>Epidemiology</b>	The study of disease in large populations
<b>Event</b>	A specific, identifiable happening or occurrence, e.g. the taking of a drug; the experience of an ADR
<b>Excipients</b>	All materials included to make a pharmaceutical formulation (e.g. a tablet) apart from the active drug substance
<b>Generics</b>	Copies or near-copies of branded drugs
<b>Harm</b>	The nature and extent of the actual damage that could be caused
<b>Homeopathy</b>	The treatment of disease by means with similar effects to the disease. Compare Allopathy, above
<b>Member countries</b>	Countries which comply with the criteria for, and have joined the WHO Programme for International Drug Monitoring
<b>National Centres</b>	Organisations recognised by government to represent their country in the WHO Programme for International Drug Monitoring
<b>Over the counter (OTC)</b>	A medicine available for sale without a prescription
<b>Pharmacoepidemiology</b>	Branch of epidemiology (see above) dealing with the effects of drugs in large populations
<b>Pharmacology</b>	Study of the uses, effects and modes of action of drugs
<b>Pharmacovigilance</b>	The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.
<b>Phocomelia</b>	Characteristic deformity caused by exposure to thalidomide in the womb, also very rarely occurring spontaneously. Means: limbs like a seal
<b>Phytotherapy</b>	Western-style, scientific treatment with plant-extracts or materials
<b>Placebo</b>	An inactive substance (often called a sugar pill) given to a group being studied to compare results with the effects of an active drug
<b>Pre-marketing</b>	The stage before a drug is available for prescription or sale to the public
<b>Post-marketing</b>	The stage when a drug is generally available on the market
<b>Prescription only medicine (POM)</b>	A drug licensed only for prescription
<b>Prophylaxis</b>	Prevention or protection
<b>Rare</b>	In pharmacovigilance, an event with a probability between 1 in 10,000 and 1 in 1,000
<b>Regulatory authority</b>	The legal authority in any country with the responsibility for regulating all matters relating to drugs
<b>Rational drug use</b>	A visionary concept implying the achievement of rational, intelligent, critical prescribing and use of drugs
<b>Reference risk</b>	The probability of an event happening in the non-exposed population ('background' risk)
<b>Relative risk</b>	A comparison of the probability of an event happening for the exposed and non-exposed population, expressed as a ratio
<b>Risk</b>	The probability of harm being caused; the probability (chance, odds) of an occurrence
<b>Signal</b>	Notice of an early concern or hypothesis about a possible drug safety problem
<b>Spontaneous reporting</b>	The core data-generating system of international pharmacovigilance, relying on healthcare professionals (and in some places consumers) to identify and report any suspected adverse drug reaction to their national pharmacovigilance centre or to the manufacturer
<b>Thalidomide</b>	Drug prescribed in 1950s as a mild sleeping pill and remedy for morning-sickness for pregnant women. Led to serious birth defects. Returning to favour as a treatment for leprosy.

# Watching the World the Uppsala Monitoring Centre



## Greetings from Marie Lindquist, UMC Director

This booklet has been welcomed and widely read and I do hope you too have found it stimulating and enjoyable! This is a revised and updated version of the original 2002 publication and the 2005 reprint.

Most people are not familiar with pharmacovigilance, yet it is of great importance to the health and welfare of everyone. Our concerns go well beyond the issues of drug safety to the critical and much broader questions of patient safety. Viewpoint represents our first effort to present these issues in print for a wide, general audience.

The science – however good – is no use if it is not available, understood, and used by everyone concerned with safer use of medicines – healthcare professionals, regulators, politicians and, of course, patients. Effective education and communication are critical to these goals and Viewpoint is one of our contributions to achieving them.

We hope this booklet will:

- Provoke comment and debate
- Educate
- Widen the audience informed about and involved in the issues
- Provide useful technical information about UMC's activities and about pharmacovigilance
- Promote the interests of patient safety and public health worldwide

UMC's mission is to provide information and service: please tell us how we can help you. If you haven't seen the companion volume, Viewpoint Part 2 (a more technical, scientific account of the work), please contact us and ask for a copy. And please let me and the UMC team know what you think of these publications and of our work.

Best wishes from all of us in Uppsala!

A handwritten signature in black ink that reads "Marie Lindquist". The signature is written in a cursive, flowing style.

Marie Lindquist

Now you've reached the end – please let us have your opinion of this first part of Viewpoint. We're very keen to have your feedback so we can do better next time.  
Email: [info@who-umc.org](mailto:info@who-umc.org), or  
Fax: Cecilia Biriell on +46 18 65 60 88

## The companion booklet, *Viewpoint Part 2*, contains the following material:

A full description of the WHO Programme for International Drug Monitoring, and detailed scientific and technical accounts of

- Adverse Drug Reaction Reporting Systems, Evaluation and Quality Control (including the Bayesian Confidence Propagation Neural Network for signal detection)
- Core Products and Services (including the WHO Drug Dictionary and much else)
- Publications
- Collaborations
- Communications
- Issues in Pharmacovigilance
- Training
- Consumer and Patient Groups
- Bibliography of UMC academic publications – and considerably more, including a list of acronyms, a specific glossary and scientific definitions. Copies obtainable from *the* UMC.

### How to find out more:

The website of *the* UMC – [www.who-umc.org](http://www.who-umc.org) – contains *Viewpoint* Parts 1 and 2 (including summaries in English, French and Spanish) and much more, including links to related sites of interest.

For more copies of this booklet or of the companion volume, or summary versions in English, French or Spanish or for any other enquiries or information, please contact us:

Fax: +46 18 65 60 88

Email: [info@who-umc.org](mailto:info@who-umc.org)

Contact from you will be very welcome!



WHO Collaborating Centre for  
International Drug Monitoring



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