

# Safety of Medicines

A guide to detecting and reporting  
adverse drug reactions

Why health professionals need to take action



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## Introduction

The purpose of this Guide is to help health professionals to participate in the very important process of continuous surveillance of safety and efficacy of the pharmaceutical products which are used in their clinical practice. Continuous evaluation of their benefit and harm will help to achieve the ultimate goal to make safer and more effective treatment available to patients.

**The objectives of the Guide are to raise awareness of the magnitude of the drug safety problem and to convince health professionals that reporting of adverse reactions is their moral and professional obligation.**

**The ultimate goal of the Guide is to reduce drug morbidity and drug mortality by early detection of drug safety problems in patients and improving selection and rational use of drugs by health professionals.**

It is a model guide which can be translated into national languages and modified as the local situation may require.

WHO would be grateful to receive any comments on experience gained from the practical use of the Guide which would help in developing it further. Please contact the Department of Essential Drugs and Medicines Policy (EDM) with your comments:

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# Glossary

The terms are from “Safety Monitoring of Medicinal Products”<sup>4</sup>

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1. An *adverse drug reaction (ADR)* is ‘a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man’.

In this description it is of importance that it concerns the response of a patient, in which individual factors may play an important role, and that the phenomenon is noxious (an unexpected therapeutic response, for example, may be a side effect but not an adverse reaction).

2. An *unexpected adverse reaction* is ‘an adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation, or expected from characteristics of the drug’.
3. A *drug or medicine* is ‘a pharmaceutical product, used in or on the human body for the prevention, diagnosis or treatment of disease, or for the modification of physiological function’.
4. A *side effect* is ‘any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which is related to the pharmacological properties of the drug’.

Essential elements in this definition are the pharmacological nature of the effect, that the phenomenon is unintended, and that there is no deliberate overdose.

5. An *adverse event* or *experience* is defined as ‘any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment’.

The basic point here is the coincidence in time without any suspicion of a causal relationship.

6. A *serious adverse event* is any event that:
- ❖ Is fatal
  - ❖ Is life-threatening
  - ❖ Is permanently/significantly disabling
  - ❖ Requires or prolongs hospitalization
  - ❖ Causes a congenital anomaly
  - ❖ Requires intervention to prevent permanent impairment or damage
7. A *signal* refers to 'reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously'.

Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

## The magnitude of the problem

During the last decades it has been demonstrated by a number of studies that medicine morbidity and mortality is one of the major health problems which is beginning to be recognized by health professionals and the public. It has been estimated that such adverse drug reactions (ADRs) are the 4<sup>th</sup> to 6<sup>th</sup> largest cause for mortality in the USA,<sup>2</sup>. They result in the death of several thousands of patients each year, and many more suffer from ADRs. The percentage of hospital admissions due to adverse drug reactions in some countries is about or more than 10%<sup>3, 4, 5</sup>.

Norway	11.5%
France	13.0%
UK	16.0%

In addition suitable services to treat ADRs impose a high financial burden on health care due to the hospital care of patients with drug related problems. Some countries spend up to 15-20% of their hospital budget dealing with drug complications<sup>6</sup>.

Beside ADRs, medicine-related problems include also – drug abuse, misuse, poisoning, therapeutic failure and medication errors.

There is very limited information available on ADRs in developing countries and countries in transition. However, one may expect that the situation is worse rather than better. This problem is also caused by a lack, in some countries, of legislation and proper drug regulations, including ADR reporting, a large number of substandard and counterfeit products circulating in their markets, a lack of independent information and the irrational use of drugs.

## Why postmarketing surveillance and reporting ADR is needed

The information collected during the pre-marketing phase of drug development is inevitably incomplete with regard to possible ADRs. This is mainly because :

- ❖ Tests in animals are insufficient to predict human safety;
- ❖ Patients used in clinical trials are selected and limited in number, the conditions of use differ from those in clinical practice and the duration of trials is limited;
- ❖ By the time of licensing exposure of less than 5000 human subjects to a drug allows only the more common ADR to be detected;
- ❖ At least 30,000 people need to be treated with a drug to be sure that you do not miss at least one patient with an ADR which has an incidence of 1 in 10,000 exposed individuals<sup>7</sup>;
- ❖ Information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete or not available;

Thus, post-marketing surveillance is important to permit detection of less common, but sometimes very serious ADRs.

Therefore health professionals worldwide should report on ADRs as it can save lives of their patients and others.

## Why pharmacovigilance is needed in every country

There are differences among countries (and even regions within countries) in the occurrence of ADRs and other drug-related problems. This may be due to differences in e.g.:

- ❖ diseases and prescribing practices;
- ❖ genetics, diet, traditions of the people;
- ❖ drug manufacturing processes used which influence pharmaceutical quality and composition;
- ❖ drug distribution and use including indications, dose and availability;
- ❖ the use of traditional and complementary drugs (e.g. herbal remedies) which may pose specific toxicological problems, when used alone or in combination with other drugs.

Data derived from within the country or region may have greater relevance and educational value and may encourage national regulatory decision-making. Information obtained in one country (e.g. the country of origin of the drug) may not be relevant to other parts of the world, where circumstances may differ.

Therefore, drug monitoring is of tremendous value as a tool for detecting ADRs and specifically in relation to counterfeit and sub-standard quality products. ADR monitoring is to help ensure that patients obtain safe and efficacious products.

The results of ADR monitoring have also a very important educational value.

## How voluntary reporting on ADRs can prevent new medicine tragedies from developing

It took many decades before the deleterious effects of aspirin on the gastro-intestinal tract became apparent and almost as long before it was recognised that the protracted abuse of phenacetin could produce renal papillary necrosis; 35 years elapsed before it became clear that amygdopyrine could cause agranulocytosis; and several years before the association of phocomelia with thalidomide became obvious<sup>8</sup>.

### Withdrawals from the market as a result of spontaneous reporting

INN (brand name)	Reason for withdrawal	Year of marketing	Year of withdrawal
bromfenac (Duract <sup>®</sup> )	serious hepatotoxic effect	1997	1998
encainide (Enkaid <sup>®</sup> )	excessive mortality	1987	1991
flosequinan (Manoplax <sup>®</sup> )	excessive mortality	1992	1993
temafloxacin (Omniflox <sup>®</sup> )	haemolytic anemia	1992	1992
benoxaprofen (Oraflex <sup>®</sup> )	liver necrosis	1982	1982
mibefradil (Posicor <sup>®</sup> )	multiple drug interaction	1997	1998
terfenadine (Seldane <sup>®</sup> )	fatal cardiac arrhythmias	1985	1998

After the “thalidomide tragedy” many countries have established drug monitoring systems for early detection and prevention of possible drug-related morbidity and mortality. Their success depends on the cooperation of the medical profession in reporting suspected ADRs, especially to new drugs.

Some examples demonstrate how very astute, alert and observant medical doctors have been helped to prevent the development of drug morbidity and drug mortality by reporting on suspected ADRs which resulted in the withdrawal of dangerous drugs from the market or in restriction of their use.

## How voluntary reporting on ADRs can influence labelling

There are many examples of the importance of ADRs reporting in the improvement of information in labelling of many effective pharmaceutical products (new possible ADRs, contraindications, dosage etc.).

*Cyclophosphamide* has been on the market for several years in many countries. In January 2001 there were some new reactions included in the labels: Stevens Johnson syndrome and toxic epidermal necrolysis; they were not included in the Physician Desk Reference (PDR) 1995.

For example:

EPIDERMAL NECROLYSIS

ERYTHEMA MULTIFORME

STEVENS JOHNSON SYNDROME

*Losartan* was marketed in the USA since 1995. Some of the new reactions that have been discovered after launch and included in the PDR are:

VASCULITIS

PURPURA ALLERGIC

(incl. HENOCH-SCHOENLEIN PURPURA)

ANAPHYLACTIC SHOCK

ANAPHYLACTOID REACTION

*Levofloxacin* was launched in the USA in 1997. In February 2000 the label torsade de pointes was included.

## Why health professionals are in the best position to detect and report on ADRs

The effectiveness of a national postmarketing surveillance programme is directly dependent on the active participation of health professionals. Health professionals are in the best position to report on suspected ADRs observed in their every day patient care.

All healthcare providers (physicians, pharmacists, nurses, dentists and others) should report ADRs as part of their professional responsibility, even if they are doubtful about the precise relationship with the given medication.

You can reduce the suffering  
and save thousands  
of patients lives by doing  
one thing:

**Report suspected adverse  
drug reactions.**

## How to recognize ADRs

Since ADRs may act through the same physiological and pathological pathways as different diseases, they are difficult and sometimes impossible to distinguish. However, the following step-wise approach may be helpful in assessing possible drug-related ADRs:

1. Ensure that the medicine ordered is the medicine received and actually taken by the patient at the dose advised;
2. Verify that the onset of the suspected ADR was after the drug was taken, not before and discuss carefully the observation made by the patient;
3. Determine the time interval between the beginning of drug treatment and the onset of the event;
4. Evaluate the suspected ADR after discontinuing the drugs or reducing the dose and monitor the patient's status. If appropriate, restart the drug treatment and monitor recurrence of any adverse events.
5. Analyse the alternative causes (other than the drug) that could on their own have caused the reaction;
6. Use relevant up-to-date literature and personal experience as a health professional on drugs and their ADRs and verify if there are previous conclusive reports on this reaction. The National Pharmacovigilance Centre and Drug Information Centres are very important resources for obtaining information on ADR. The manufacturer of the drug can also be a resource to consult;
7. Report any suspected ADR to the person nominated for ADR reporting in the hospital or directly to the National ADR Centre.

## What should be reported?

- ❖ For “new” drugs - report all suspected reactions, including minor ones. (In many countries drugs are still considered “new” up to five years after marketing authorization);
- ❖ For established or well-known drugs - report all serious or unexpected (unusual) suspected ADRs;
- ❖ Report if an increased frequency of a given reaction is observed;
- ❖ Report all suspected ADRs associated with drug-drug, drug-food or drug-food supplements (including herbal and complementary products) interactions;
- ❖ Report ADRs in special fields of interest such as drug abuse and drug use in pregnancy and during lactation;
- ❖ Report when suspected ADRs are associated with drug withdrawals;
- ❖ Report ADRs occurring from overdose or medication error;
- ❖ Report when there is a lack of efficacy or when suspected pharmaceutical defects are observed.

**Thus, report all suspected adverse reactions that you consider of clinical importance as soon as possible!**

## How to report ADRs?

Local Case Report Forms (CRF) should be obtained from the National Drug Regulatory Authority. Some countries have included CRF in their National Formularies (British National Formulary, Formularies of South Africa, Zimbabwe etc.).

There are different Case Report Forms in different countries. But all of them have at least four sections which should be completed :

1. Patient information:
  - patient identifier
  - age at time of event or date of birth
  - gender
  - weight
2. Adverse event or product problem:
  - description of event or problem
  - date of event
  - date of this report
  - relevant tests/laboratory data (if available)
  - other relevant patient information/history
  - outcomes attributed to adverse event
3. Suspected medication(s):
  - name (INN and brand name)
  - dose, frequency & route used
  - therapy date
  - diagnosis for use
  - event abated after use stopped or dose reduced
  - batch number
  - expiration date
  - event reappeared after reintroduction of the treatment
  - concomitant medical products and therapy dates
4. Reporter:
  - name, address and telephone number
  - speciality and occupation

The completed Case Report Form should be sent to the national or regional ADR centre or to the manufacturer of the suspected product.

Addresses of National Drug Regulatory Authorities and other useful information can be found on the Website of the WHO Collaborating Centre for International Drug Monitoring ([www.who-umc.org](http://www.who-umc.org)) or requested from this Centre by e-mail: [info@who-umc.org](mailto:info@who-umc.org); by Fax : +46 18 65 60 80 or by Tel.: +46 18 65 60 60).

## References

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## Useful Websites

### WHO

[www.who.int/medicines/](http://www.who.int/medicines/)

Section: Quality Assurance and Safety: Medicines

*WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre)*

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

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