Malaysian Guidelines for the Reporting & Monitoring

Preface

These guidelines have been developed to outline the requirements and procedures to be followed for submission of reports of adverse drug reactions to the Drug Control Authority (DCA).

Under current arrangements, the National Adverse Drug Monitoring Centre and the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) Secretariat are located within the National Pharmaceutical Control Bureau, which in turn acts as the Secretariat to the DCA.

Although these guidelines and certain stipulations are not obligatory, registration holders and health professionals are encouraged to comply in the spirit of cooperation towards establishing the safety profile of drugs which may be under evaluation as well as for products already registered by the DCA.

The DCA hopes that the recommendations in this document will help to improve the quality and standard of safety monitoring of products used in Malaysia.

CHE MOHD ZIN CHE AWANG
DIRECTOR, PHARMACEUTICAL SERVICES DIVISION and
CHAIRMAN
MALAYSIAN ADVERSE DRUG REACTIONS ADVISORY COMMITTEE

MINISTRY OF HEALTH MALAYSIA, KUALA LUMPUR, MARCH 2002

PART 1

1. INTRODUCTION

Before a product is marketed, experience of its safety and efficacy are limited to its use in clinical trials. The conditions under which patients are studied pre-marketing do not necessarily reflect the way the product will be used in hospital or in general practice once it is marketed. No matter how extensive the pre-clinical work in animals and the clinical trials in patients, certain adverse effects may not be detected until a very large number of people have received the product.

Pharmacovigilance is the process of

- monitoring products as used in everyday practice to identify previously unrecognised adverse reactions or changes in the patterns of their adverse effects
- assessing the risks and benefits of products in order to determine what actions, if any, is necessary to improve their safe use
- providing information to users to optimise safe and effective use of products
- monitoring the impact of any action taken.

Information from the spontaneous adverse drug reaction (ADR) reporting schemes, clinical and epidemiological studies and literature are used to aid in decision-making. Information from all these sources can lead to changes such as restrictions in use, refinement of dosage instructions and strengthening of specific warnings that allow products to be used more safely. Occasionally, when a risk is considered unacceptable, a product may have to be withdrawn from the market.

2. LEGAL BASIS

In accordance with Section 28 of the Control of Drugs And Cosmetics Regulations 1984, Sale of Drugs Act 1952 (revised 1989) it is mandatory for registration holders of all products registered by the DCA to submit reports of all adverse reactions encountered to the DCA.

Although, ADR reporting by health professionals is on a voluntary basis, submission of reports of all adverse reactions encountered to the Drug Control Authority is highly encouraged.

3. CONFIDENTIALITY

THE DRUG CONTROL AUTHORITY WILL MAINTAIN STRICT CONFIDENTIALITY WITH REGARDS TO THE IDENTITY OF PATIENTS AND REPORTERS. REPORTERS ARE NOT REQUIRED TO DISCLOSE THE IDENTITY OF THE PATIENTS IN REPORTS.

4. SCOPE OF ADR REPORTING

Adverse drug reactions encountered should be reported for all products registered by the Drug Control Authority i.e. pharmaceutical products as well as traditional medicines

A reaction is suspected if either the reporting health-care professional or the registration holder believes that there is a possible causal relationship between the reaction and the drug in question. Spontaneous reports of suspected adverse drug reactions received from health-care professionals should be reported even if the product registration holder does not agree with the reporters' assessment of a possible causal association or if the reporter has not provided a causal assessment.

Adverse events which are not suspected of being product-related by the health-care professional attending the patient should not be reported unless the registration holder has reason to believe that there is a causal relationship.

Product registration holders should validate and follow-up all serious reactions reported by them to the authorities. All available clinical information relevant to the evaluation of the reaction should be provided. After the initial notification, further correspondence should be cross-referenced to the ADR reference number given to minimize duplication of reports.

All adverse reactions should be considered reportable according to the requirements outlined in these guidelines regardless of whether or not the product was used in accordance with the product information provided by the company marketing the product.

5. OBJECTIVES OF ADR MONITORING

The primary objectives of ADR monitoring are as follows:-

- To detect adverse reactions to drugs as early as possible especially serious, unknown and rare reactions
- To establish the frequency and incidence of adverse reactions, both the well-recognised and newly discovered reactions
- To identify risk factors that may predispose/induce/influence the development, severity and incidence of adverse reactions e.g. genetic/racial factors, drug interactions, underlying conditions, etc.
- To maintain a database for sharing of information with regards to ADRs in this country

6. IMPACT OF ADR MONITORING

Achievement of the primary objectives will allow for the following actions to be taken:

- Product registration holder can initiate steps to make changes to the product dossier/information leaflets/labels to create awareness on these findings
- Regulatory authority can take appropriate action in the interest of public health to minimise risk of ADRs to consumers
- Health professionals prescribe drugs rationally
- Public use products in an appropriate manner
- Make data available to analogous systems in other countries (via the WHO) to promote the growth of knowledge in this field worldwide.

7. PROCEDURES FOR REPORTING

7.1. GENERAL PRINCIPLES

7.1.1 All ADR reports should be sent to:

The National Adverse Drug Monitoring Centre
National Pharmaceutical Control Bureau
Ministry of Health Malaysia
P.O. Box 319, Jalan Universiti
46730 Petaling Jaya

7.1.2 Reporting Forms

The National ADR Centre has a preferred format for reporting of ADRs which is a pre-paid "blue-card". Reports may also be submitted via the Internet using the reporting form found on the MADRAC website (www.madrac.gov.my/madrac).

7.1.3 Content of suspected serious ADR reports

The minimum information required for the submission of an initial report is

- a named suspected drug
- a suspected reaction
- an identifiable patient
- an identifiable reporter

If the data submitted in the report lacks essential information, the report cannot be assessed objectively and will not be entered into the ADR database

Where possible, the trade name of the suspected product should be used. If it is not known, the generic name and the product registration number should be given. Terminology used to describe the adverse reaction should be standard medical terminology and the use of vague terms should be avoided.

In cases where the registration holder is informed of the occurrence of a serious ADR, the registration holder is expected to follow-up on the report and obtain comprehensive information where available. Additional information not available at the time of the initial report, should be provided to the DCA in the form of follow-up reports.

Registration holders may comment on whether they consider there is a causal association between the suspected product(s) and reactions(s) reported and should provide the criteria on which they have made the assessment for reports which they obtain directly from health professionals before submission to the DCA.

7.1.4 Route of Notification

All reports should be sealed and mailed and not faxed except in cases of perceived urgency.

7.1.5 Time-lines for Reporting

Refer to Appendix 2

7.1.6 Follow-up reports

After initial notification of an adverse reaction, a letter of acknowledgement will be sent to the reporter citing an adverse reaction number assigned to that case report in the MADRAC database.

Any follow-up correspondence relating to the same case report should be cross- referenced, where possible to the ADR database number (if one has already been assigned) or to an appropriate unique number assigned by the reporter (relating specifically to the initial notification). This in the only reliable way to minimise the duplication of reports submitted to the DCA by the applicant.

7.2 REPORTING REQUIREMENTS IN SPECIAL SITUATIONS

7.2.1 Reporting in the period between the submission of the application and the granting of the registration

In the period between the submission of the application for registration but prior to registration, information which has an impact on the benefit/risk evaluation based on information from use on a compassionate basis or from countries where the drug is marketed must be submitted. This information should be immediately submitted by the applicant to the DCA when the application is under assessment (Refer Appendix 2).

What constitutes a change to the benefit to risk balance is a matter of judgment for the company submitting the dossier but an applicant may be required to justify a decision not to report. For example, normally another report of a well-known adverse reaction would not be considered significant, but a report of an unexpected/new, serious suspected reaction with good evidence of causal relationship, or reports of a group of cases of such a reaction where there is a possible relationship, or where there is suspicion of a change in the frequency or severity of a known effect would be considered relevant to the evaluation. Similarly, results from studies which impact on the assessment of efficacy would be significant.

7.2.2 Reporting of outcomes of use during pregnancy and breast-feeding

Registration holders must establish surveillance systems of pregnant or breast-feeding patients for the purpose of collating experience on the usage and outcome of drugs used in these groups.

Registration holders must report adverse drug reaction reports related to pregnancy and breast-feeding regardless of whether or not the drug is contraindicated in pregnancy. Reports on pregnancy should not be forwarded before the outcome is known unless unintended pregnancy is suspected as an adverse drug reaction.

Registration holders & health professionals are expected to follow up all reports of pregnancies where the foetus could have been exposed to medicinal products. When an active substance, or one of its metabolites has a long half-life, this should be taken into account when considering whether a foetus could have been exposed (i.e. medicinal products taken before the gestational period need to be considered).

If, a registration holder becomes aware of a signal of possible teratogenic effect (e.g. a cluster of similar abnormal outcomes) the DCA should be informed immediately.

7.2.3 Reporting from other post-marketing initiatives: surveys, registries

A registration holder may be involved in post-marketing initiatives, which result in the collection of information related to its products. Only those events which are specifically reported as suspected serious adverse reactions to a particular product must be reported.

7.2.4 Compassionate use/named patient supplies

Compassionate or named patient use of a drug should be strictly controlled by the company responsible for providing the drug and should ideally be the subject of a protocol. The protocol should ensure that the patient is registered and adequately informed about the nature of the product. Both the prescriber and the patient must be provided with the available information on the properties of the product with the aim of maximizing the likelihood of safe use.

The protocol should encourage the prescriber to report any adverse reactions suspected of being related to use of the product to the company and to the DCA. Companies should continuously monitor the balance of benefit and risk of drugs used under such conditions.

The prescriber of the product, as approved by the DCA, must report any serious adverse drug reaction occurring with the use of the product, in the specified patients within 15 calendar days of first knowledge by such individual.

7.2.5 Lack of efficacy

Reports of lack of efficacy should also be reported to the DCA. Judgment should be used in reporting. For example, antibiotics used in life-threatening situations where the medicinal product was not, in fact, appropriate for the infective agent should not be reported. However, life-threatening infections where the lack of efficacy seems to be due to the development of newly resistant strain of a bacterium previously regarded as susceptible should be reported.

7.2.6 Reporting of overdoses

The registration holder should report cases of overdose (accidental or intentional) that lead to suspected serious and unexpected adverse reactions.

Reports of overdose with no associated adverse reactions should not be reported as adverse reactions. They should be routinely followed up to ensure that information is as complete as possible with regards to early symptoms, treatment and outcome of the overdose.

7.2.7. Consumer Reports

If a registration holder receives a report from a consumer, the consumer should be advised to report this reaction through his or her doctor or pharmacist. If this approach fails, the registration holder should attempt to obtain as much information as possible from the patient.

If the minimum information for reporting has been met, and the report is deemed to be relevant by a health care professional within the company, the case is considered reportable.

8. RISK - BENEFIT EVALUATION

The approval for registration for a medicinal product indicates that it is considered to have a satisfactory balance of benefits and risks under the conditions defined in the dossier on the basis of the information available at that time of application.

During the post-registration period the product will be used in a setting different from clinical trials and larger populations are likely to be exposed. More new information will be generated which may impact on the benefit or risk of the product, and evaluation of this information needs to be an on-going process, both within pharmaceutical companies and the regulatory agencies where the drug is in use.

Both, registration holders and the regulatory agencies must keep abreast of all relevant information in order to fulfill the following responsibilities:

- Ensuring that appropriate action is taken in response to new evidence which impacts on the balance of benefit to risks,
- Keeping prescribers and patients informed through changes to authorised product information and by direct communication.

In the event of any new or changing information becoming available which may influence the overall benefit-risk assessment of a medicinal product, the registration holder should immediately inform the DCA. A comprehensive report evaluating the issue and the risks in the context of the benefits should be submitted at the earliest opportunity.

8.1 PRINCIPLES OF BENEFIT-RISK ASSESSMENT

Overall benefit-risk assessment should take into account and balance all the benefits and risks referred to below. Benefit-risk assessment should be conducted separately in the context of each indication, which may impact on the conclusions and actions.

8.1.1 Assessment of risks

Assessment of risk involves a stepwise process requiring identification, confirmation and characterization (including identification of risk factors), and quantification of product safety hazards in the exposed population. Multiple sources of data should be used, principally the following:

- National and international spontaneous ADR reports
- ADR-data from observational experimental clinical studies which may or may not be company-sponsored
- In vitro and in vivo laboratory experiments
- World-wide scientific literature
- Investigations on pharmaceutical quality
- Data on sales and product usage

When possible product safety hazards are identified which have an impact on, or may influence the overall benefits to risk of medicinal product, the registration holder should propose appropriate studies. Such studies should investigate further the nature of the hazard(s) and their frequency of occurrence, provided that such studies would not cause unacceptable risk to the patients involved.

Overall assessments of risk should be made using all the available information. Important issues, which should be addressed in the assessment of risk include:

- evidence for causal association
- seriousness
- absolute and relative frequency
- factors which may allow preventative measures

8.1.2 Assessment of benefits

Where a new or changing hazard is identified, it is important to re-evaluate the benefit of the medicinal product using all available data. The benefit of a medicinal product can be seen as the decrease in disease burden associated with its use.

Benefit comprises of three main parameters:

- the extent to which the drug cures or improves the disease, or relieves the symptoms
- the responder rate

- the duration of response.

The quality of the different types of evidence of benefit should be taken into account. Efficacy and benefit should, as far as possible, be expressed in quantitative terms in a way that makes them comparable to the expression of risks.

8.1.3 Benefit-risk assessment

Both benefit and risk that may be considered acceptable is dependent on the seriousness of disease being treated. For example:

- the treatment of a disease with high mortality, a high risk of serious or fatal adverse reactions may be acceptable providing the benefits associated with treatment have been shown to be greater
- for products used in chronic diseases or in the prevention of disabling diseases, if there is a substantial improvement in the prognosis or quality of life, a higher risk may be acceptable.
- in situations where the main benefit is symptom relief for minor illnesses in other wise healthy individuals or where individuals are treated not only for their own benefit but also for the benefit of the community (e.g. vaccination) safety standards must be exceptionally high.

8.2 IMPROVING THE BENEFIT TO RISK BALANCE

The registration holder should aim to achieve as high as possible "benefit to risk balance" for an individual product and to ensure that the adverse consequences of a product do not exceed the benefits within the population treated. The benefit-risk profile of a product cannot be considered in isolation but should be compared with those of other treatments for the same disease.

The "benefit to risk" ratio can be improved either by increasing the benefits or by minimising risk factors (e.g. by contra-indicating the use in patients particularly at risk, lowering dosage, recommending pre-treatment investigations for patients at risk or monitoring during treatment for early diagnosis of hazards that are reversible.)

When proposing measures to improve the benefit to risk of a product (e.g., restricting use to a patients group most likely to benefit or where there is no alternative) their feasibility in normal conditions of use should be taken into account.

The following types of action may be necessary and can be undertaken voluntarily by registration holders or compulsorily by the DCA:

- Making changes to the indications, dosage recommendations, contraindications, special precautions, warnings or adverse effects and in consequence
- Amendments to the products dossier and the product information material
- Modification of advertising material
- Direct provision of important safety information to health-care professionals (e.g., through letters and/or bulletins).

When any significant alteration to the safety information is made, the appropriate health-care professionals must be informed promptly and provided with the new product information materials. The product inserts should also be updated and means found to draw the prescribers and patients attention to important warnings.

8.3 WITHDRAWAL OF A PRODUCT FROM THE MARKET ON RISK-BENEFIT GROUNDS

In the event that the overall benefit to risk balance is judged to be unacceptable after the implementation of appropriate action is taken into account, the product should be withdrawn from the market and the appropriate health-care professionals informed. Such action may be taken voluntarily by registration holders or on the directive of the DCA.

8.4 COMMUNICATION

The content of the agreed communication to health-care professionals and the time-scale for the distribution of that communication should be agreed between the registration holder and the DCA.

9. GUIDELINES FOR REGISTRATION HOLDERS

9.1 REPORTING OBLIGATIONS

The legal provisions regarding the conduct of pharmacovigilance is set out in the Sales of Drug Act, Control of Drug and Cosmetic Regulation 1984, Section 28 which states that:

"A licensed manufacturer, a licensed wholesaler, a licensed importer or the holder of a registration certificate in respect of any product shall inform the Authority of any adverse reactions arising from the use of the registered product immediately after he receives notice of such adverse reactions".

9.2 RESPONSIBILITIES OF THE REGISTRATION HOLDER

All registration holders must ensure that an appropriate system of pharmacovigilance is in place in the company in order to accept responsibility and liability for its products on the market and to ensure that appropriate action can be taken, when necessary. It is recommended that the registration holder have permanently and continuously at its disposal in Malaysia, a qualified person responsible for pharmacovigilance. This person should have experience in all aspects of pharmacovigilance. If the identified person is not a health care professional, he/she should have access to a medically qualified person.

Registration holders should inform the Surveillance Pharmacovigilance Division, National Pharmaceutical Control Bureau, in writing of the contact person(s) responsible for all matters pertaining to pharmacovigilance. The postal address, email address, telephone and fax numbers of this person should be submitted in this correspondence as well.

The role of the qualified person responsible for pharmacovigilance are as follows.

- To establish a system for monitoring ADRs encountered by health professionals associated with the use of products marketed by the company
- To ensure that information pertaining to suspected adverse reactions which are reported to the staff of the company or organisation, including medical representatives, is collected and collated so that it is accessible at a single point
- To ensure that all local adverse drug reaction reports are submitted to the DCA in a timely manner
- To submit Periodic Safety Updated Reports (PSUR), company-sponsored post-registration study reports, etc to the DCA
- To ensure that any request for additional risk-benefit information from the DCA is reported to the DCA promptly and fully.

9.3 REPORTING ADRS TO THE DCA

9.3.1 Adverse Drug Reactions Occurring Within Malaysia

i. ALL reports of adverse reactions associated with the use of registered products occurring in Malaysia must be reported to the DCA within the stipulated timelines as outlined in Appendix 2.

ii. New Chemical Entities
Registration holders of New Chemical Entities are required to actively monitor for adverse reactions occurring as a result of the use of the compounds registered. Registration holders are required to report all ADRs in accordance to the stipulated timeliness. The registration holder is also obliged to submit a "NULL" report at six-monthly intervals for the first two years should there be no ADR reports submitted to them.

9.3.2 Adverse Drug Reactions Occurring Outside Malaysia

i. Foreign individual case reports need not be forwarded to the DCA on a routine basis, but should be reported in the context of a specific safety issue or on specific request by the DCA.
ii. The DCA should be advised of any significant safety issue or action which has been taken by a foreign agency, including the basis for such action, no later than 3 days of first knowledge by the applicant.
iii. Information on withdrawal of the registration status in any country must be notified to the DCA within 24 hours of first knowledge by the registration holder.

9.4 PERIODIC SAFETY UPDATE REVIEWS (PSUR)

i. Registration holders who have registered a product containing a new chemical entity after 1 January 2002 must routinely submit PSURs on that product 6 monthly for the first 2 years after approval in Malaysia and annually for the subsequent 3 years.
ii. This time frame may be varied in order to harmonize periodic safety updates internationally. However, the periodic safety update should be submitted no later than 6 months after the date of approval.
iii. The registration holders should inform the DCA of any steps which are to be taken with regards to safety concerns raised in the PSUR.
iv. A copy of the most updated relevant package insert/s should be submitted together with the PSUR.
v. The registration holder should submit any consequential variations (e.g. package insert changes) simultaneously with the PSUR at the time of its submission, in order to prevent any unnecessary duplication of effort.
vi. Registration holders may, in addition, be requested to submit PSURs in the following circumstance - new indications, dosage form, routes of administration or use in populations beyond the registration for the active ingredient.

9.5 CASE REPORTS FROM PUBLISHED SCIENTIFIC LITERATURE

i. Registration holders should report published suspected adverse drug reactions related to the active substance(s) of its registered products, as relevant. A copy of the relevant published article should be provided to the DCA.

ii. If multiple drug products are mentioned in the literature report, only the registration holder whose drug is the suspect drug is required to submit a report. The suspect drug is usually that mentioned as such by the author or stated in the article's title.

9.6 REPORTS FROM POST-REGISTRATION STUDIES

i. All adverse reactions from post-registration studies taking place in Malaysia must be reported to the DCA in accordance to the timelines given in Appendix 2 based on the seriousness of the adverse reactions. This applies to reports from any type of clinical or epidemiological investigation, independent of design or purpose.
ii. Investigators involved in post-registration studies should be aware of the definition of what constitutes a serious adverse drug reaction as well as the distinction between 'reactions' and 'events'.
iii. In the case of post-marketing studies, adverse "events" are usually systematically solicited. In cases where there is uncertainly as to whether or not an event is a reaction, it is better to report the case as an adverse reaction. Events that are clearly unrelated to the product should not be reported.

iv. If the registration holder receives a report of a serious adverse drug reaction from the investigator who is blinded to individual patient treatment, the guidelines outlined in Section 10.3 below should be adhered to. Blinded cases should not be routinely submitted.

9.7 ON-GOING PHARMACOVIGILANCE EVALUATION

i. Registration holders must inform the DCA within 3 calendar days of first knowledge by the registration holder, whether new evidence becomes available which may significantly impact on the benefit/risk assessment of a product or which would be sufficient to consider changes in the conditions of registration of the product.
ii. Additional pharmacovigilance data such as actual case reports, drug usage figures, the regulatory status of the product in other countries, independent pharmacoepidemiology studies, pre-clinical studies or significant product quality data may be requested by the DCA as the situation warrants. This must be submitted within a time period specified by the DCA.

10. GUIDELINES FOR REPORTING ADVERSE DRUG REACTION FROM CLINICAL TRIALS

[PART 3 OF THIS PAGE HAS BEEN REMOVED]

11. GUIDELINES FOR HEALTH PROFESSIONALS

11.1 SCOPE OF ADR MONITORING

Adverse drug reaction reporting by health professionals is not mandated by the law but health professionals are encouraged to report adverse reactions encountered to the Drug Control Authority (DCA). The reporter should bear in mind that he would often be reporting suspicions, where he thinks that a drug has caused a particular adverse event. He should not wait until he feels certain that a causal link can be considered proven or disproven. In doubtful cases, it is better to report than not to report.

The DCA would especially like health professionals to monitor newly registered drugs and also reactions encountered with generic products which are not commonly associated with the equivalent market leader products.

Health professionals should also report any adverse reactions encountered in patients where the drug was used for off-label indications and in doses differing from the recommended doses as this information will also serve to provide a better understanding of the drug safety profile of the products concerned.

Reactions to food products and unprocessed herbs should not be reported as these products are beyond the jurisdiction of the DCA.

11.2 WHAT TO REPORT

The World Health Organisation encourages reporting of ALL adverse drug reactions. Health professionals are requested to report adverse reactions to all identifiable drugs including traditional medicines.

However, if health professionals feel that it is cumbersome to report trivial, common and well documented adverse reactions, they should report reactions which are serious, unexpected or unlabelled to the DCA.

11.2.1 Serious ADRs

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization of prolongation of existing hospitalisation,
- is a congenital anomaly/birth defect.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

When using cytotoxic drugs or other preparations of a highly toxic nature it will not be necessary to report those serious reactions which are well known to be frequent.

11.2.2 Unexpected/Unlabelled ADR

In many cases, the event will be surprising because it is one in which the reporter did not expect the drug to cause; e.g. use of chlorothiazide associated with causing jaundice (icterus).

When it is analysed at the National Centre and compared with other evidence it may be found that:-

- The drug and the event probably were associated, and that this is a new finding. In such case, the report is an element in a new discovery.
- An association between the drug and the event is well known from the literature, even though it may be rare. In this case the fact that the reporter did not know this will indicate the need for better information on this point to be given.
- No conclusion can be drawn and further data on other cases must be sought
- The drug and the event were probably not associated.

Whatever the case, health professionals should report any case where it is suspected that the ADR is related to the drug used.

11.3 CONFIDENTIALITY

All reports submitted to the DCA are treated as being confidential and reporters are not required to divulge the identity of the patients involved. The sole purpose of soliciting adverse drug reactions is for monitoring the safety profile of products and for formulating regulatory actions to minimise risks to the patients and consumers.

11.4 ADR REPORTING MECHANISM

Health professionals may report directly to the DCA or through the product registration holder who is then obliged, under the law, to report to the DCA.

Reports may be submitted by using the pre-paid ADR forms which are supplied free of charge by the DCA or by letter. Reporting may also be done through the internet by using the MADRAC website at www.madrac.gov.my/madrac.

11.5 REPORTING FROM GOVERNMENT / PRIVATE HOSPITALS

Every hospital may decide for itself how the reporting systems should be operated and by whom. The arrangements will depend on the hospital's own organization and traditions. Ideally, the hospital's Drugs and Therapeutics Committee should be informed of all adverse drug reactions occurring within the establishment.

The two types of arrangement which may be considered for reporting ADRs are as follows:

11.5.1 Physician Reporting

The physicians act as reporters, completing the reporting forms themselves. There should preferably be a central point for collecting the forms, keeping a record, and sending them to the Drug Control Authority. The hospital pharmacy is the obvious central point for this work. In this arrangement, the pharmacy can also play the role of providing the DCA with information on the brand name of the product used, the outcome of the patients and to provide feedback received from the DCA back to the reporter.

11.5.2 Pharmacy Reporting

The hospital pharmacist acts as the reporter, completing the ADR forms in consultation with the reporting physician. In this situation, the hospital pharmacist retains all the tasks listed as above but in addition, he collects the data, either when the physician reports that an adverse event seems to have occurred or by himself checking patient records. The pharmacist should discuss the information in the reporting form prior to submitting it to the DCA.

11.6 GOVERNMENT HEALTH CENTRES

The prescriber or other health professional who comes in contact with the drug can act as reporter, completing the reporting forms and sending them directly to the DCA.

11.7 PRIVATE CLINICS

The General Practitioners and Private Specialist Clinics should report the adverse reactions encountered directly to the DCA by completing the ADR forms and sending it through the post or by using the on-line reporting form available through the internet. The private practitioner may also provide the information on the ADR encountered to the product registration holder who will then report it to the DCA. However, the registration holder must ensure that all the necessary information for submission of the report to the DCA is obtained.

11.8 RETAIL PHARMACIES

All retail pharmacists should send in any adverse reactions encountered or reported to them by their clients either directly to the DCA or via the product registration holders.

12. BASIC PRINCIPLES OF EFFICIENT REPORTING

i. Report the event soon after it occurs. A recent event is easier to report upon and the report is more likely to be accurate.
ii. If possible, take the decision to report whilst the patient is still with you, so that he/she can easily be questioned about the event and the details filled in at once on the report form.
iii. Ask the patient particularly about other products taken which may contribute towards the causing the event e.g. other concomitant drugs, herbal products, food supplements, chemicals, etc. Ask the patient particularly about other products taken.
iv. If any additional data is available later e.g. if the same patients develop the effect again or if something happens which increases your suspicions or seems to exclude the effect, send in a supplementary note.
v. In cases where a foetus or suckling infant sustains an ADR, information on both the parent and the child/fetus should be provided.
vi. Always write legibly.
vii. All reports must have the following four data elements
    a. an identifiable patient
    b. am identifiable reporter
    c. a suspected drug
    d. an adverse event

If any of these basic elements remain unknown, a report on the incident should not be submitted because reports without such information make interpretation of their significance difficult, at best, and impossible, in most instances.

APPENDIX 1

DEFINITIONS AND TERMINOLOGY

SIDE EFFECT
Any unintended effect occurring at doses used in man which is related to the pharmacological properties of the product

ADVERSE DRUG REACTION (ADR)
A response to a product which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of a disease or for the modification of physiological function.
Any significant hazards to patients, such as lack of efficacy with contraceptives, vaccines and products used in life-threatening diseases may also be included as an adverse reaction.

ADVERSE EVENT
Any untoward medical occurrence that may present during treatment with a product but which does not necessarily have a causal relationship with this treatment.

In pre-marketing studies and clinical trials, adverse events are usually systematically solicited and monitored as it is not yet known whether the event is related to the product under study or not.

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

SERIOUS ADVERSE DRUG EVENT OR ADVERSE DRUG REACTION
A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose

- results in death,
- is life-threatening
- requires inpatient hospitalization of prolongation of existing hospitalisation,
- results in persistent or significantly disability/incapacity
- is a congenital anomaly/birth defect.

NOTE:

i. The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.
ii. Medical and scientific judgment should be exercised in deciding whether other situations that may not be immediately life-threatening or result in hospitalisation or death but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above classify as being serious.
iii. The term "severe" is not synonymous with serious.

UNEXPECTED ADVERSE REACTION
An "unexpected" adverse reaction is an adverse reaction, the nature, specificity, severity and outcome of which is not consistent with the product information.

UNLABELLED ADVERSE REACTION
An adverse reaction which is not specifically included in the product information.

SPONTANEOUS ADR REPORTING

A report to a the regulatory agency of an adverse drug reaction in a patient given one of more products obtained through the use of a product not resulting from a study.

SIGNAL

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 on the seriousness of the event and the quality of the information.

PERIODIC SAFETY UPDATE REPORTS (PSUR)

A periodic safety update is an update of the world-wide safety experience of a product obtained at defined times post-registration.

HEALTH CARE PROFESSIONAL

For the purposes of reporting suspected adverse reactions, "health care professionals" includes medical practitioners, pathologists, dentists and pharmacists. This definition is extended to include pharmacy assistants, nurses and medical assistants in government health clinics.

When reports originate from pharmacists or other allied health professionals, a medically qualified doctor responsible for the patient should be able to supply information about the case whenever possible.

APPENDIX 2

TABULATED SUMMARY OF REPORTING REQUIREMENTS
FOR REGISTRATION HOLDERS

1. POST-REGISTRATION ADR REPORTING

	Type of Adverse Reaction	Time Frame for Reporting
LOCAL REPORT	Life-threatening or fatal	As soon as possible but no later than 7 calendar days after first knowledge by registration holder, followed by as complete a report as possible within 8 additional calendar days. This report should include an assessment of the importance and implications of the findings including relevant previous experience with the same or similar products.
	Serious, Expected	As soon as possible but no later than 15 calendar days after first knowledge by registration holder.
	Serious, unexpected but that are no life-threatening or fatal	As soon as possible but no later than 15 calendar days after first knowledge by registration holder
	Non-serious unexpected	Within 15 calendar days
	Non-serious expected	Within 15 calendar days
FOREIGN REPORTS	Not required on a routine basis	
LOCAL & FOREIGN	Notification of changes in nature severity, frequency or risk factors	Within 15 days after first knowledge by registration holder
	New information impacting on risk-benefit profile of product including international regulatory decisions	3 days
	Withdrawal of registration in any country	24 hours after first knowledge by registration holder
Periodic Safety Update Reviews (PSUR)	For NCEs only	6 monthly for first two years Annually for subsequent 3 years.