PHARMACOVIGILANCE GUIDELINES

THIRD EDITION 2017
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I. INTRODUCTION:

Since drugs are intended to relieve suffering, patients find it peculiarly offensive that drugs cause disease, which are often unexpected. A simple account of unwanted effects as inherent to the drug is erroneous. In addition to the inherent factors, adverse effects are promoted or even caused by numerous non-drug factors.

Adverse Drug Reaction reporting and monitoring system is important to collect, collate and analyze data as a means of establishing new knowledge and generate early signals of possible drug complications not reported through clinical trials. Output from such adverse drug reaction-reporting systems compliment the information appearing in the published literature and from other studies.

Collection, tabulation, and analysis of suspected adverse reaction on the national level is of paramount importance. The Drugs Regulatory Unit has prepared an easy to fill in reporting form which will be available for all healthcare professionals at each health facility for voluntary and spontaneous reporting. The success of the ADR monitoring depends on the cooperation of the healthcare professionals in reporting suspected adverse reactions, especially to new drugs.

This guideline is prepared with the intention to make the reporting of ADR consistent, regular and complete. Hence, it gives information on what, when, how and whom to report.
II. DEFINITIONS AND TERMINOLOGIES:

1. **Medicine**: means any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in the diagnosis, treatment, alleviation, modification or prevention of disease, illness, abnormal physical or organic condition or the symptoms thereof restoring, correcting or modifying any somatic or psychic or organic condition.

2. **Side effects**: any unintended effect of a pharmaceutical product occurring at doses normally used in humans which is related to the pharmacological properties of the drug.

3. **Adverse Drug Reactions**: [ADR]

   Noxious and unwanted reaction to drugs that occurs at a dose used in human for diagnosis, treatment or prophylaxis. The term adverse reaction should be considered for harmful or seriously unpleasant effects occurring at doses intended for therapeutic, prophylactic or diagnostic effect and which calls for reduction of dose or withdrawal of the drug and/or forecast hazard from (not clear)future administration.

4. **Signal**: refers to “reported information on a possible casual relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously”.

   Usually more than one report is required to generate a signal depending on the seriousness of the event and the quality of the information.

5. **Applicant**: means a company or individual who applies for the registration of a product or a medicine or who has applied for the use of a medicine or product in a clinical trial in Botswana.

6. **Clinical trial**: a systematic study in human beings or animals in order to establish the efficacy of or to, or to discover the or verify the effects or adverse reactions a medicine or product and includes a study of the absorption, distribution, metabolism and excretion of medicines.

7. **Pharmacovigilance**: Pharmacovigilance is concerned with the detection, assessment, prevention of adverse reactions of medicines and any related problems.

8. **ADR Case Report**: A notification relating to a patient with an adverse medical event (or laboratory test abnormality) suspected to be induced by a medicine.

9. **Lack of Efficacy**: Defined as a failure to produce the expected pharmacological action.

   An unexpected adverse reaction is “an adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug”. Here the predominant element is that the phenomenon is unknown.

   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.
Serious adverse events can be defined as those that:
- are life-threatening or fatal
- cause or prolong hospital admission
- cause persistent incapacity or disability; or
- concern misuse or dependence.

Verification: The procedures carried out in pharmacovigilance to ensure that the data contained in a final report matches the original observations. These procedures may apply to medical records, data in case-report forms (in hard copy or electronic form), computer printouts, and statistical analyses and tables.

Validation: The action of proving that any procedure, process, equipment (including the software or hardware used), material, activity or system used in pharmacovigilance actually leads to the expected results.

III. RATIONALE OF ADR MONITORING
Reporting ADR is essential to obtain the necessary information on safety of different subgroups such as children, pregnant women, elderly and patients with complicated disease or multiple conditions, which are not normally exposed during the clinical trial. It is also essential for the early detection of unknown reactions and interactions between medicines, detection of increase in ADR frequency, identification and quantification of risk factors, detection and removal of counterfeited and substandard drugs in the market.

IV. PHARMACOVIGILANCE:
1. AIMS:
- The rational and safe use of medical drugs
- To increase the trust of patient on medication and health care personnel
- Assessment and communication of the risks and benefits of drugs in the market
- To reduce the cost of treatment
- To increase patient compliance
- To educate and inform patients
Through
- Early detection of unknown adverse reactions and interactions
- Detection of increase in frequency of unknown adverse reaction
- Identification of risk factors and possible mechanisms underlying adverse reactions
- Estimation and quantification of benefits and risks
- Distribution of information needed to improve drug prescribing and regulation.

2. IMPORTANCE OF PHARMACOVIGILANCE:
Pharmacovigilance is important or required because,
- The information collected during the pre-marketing phase of a drug is inevitably incomplete with regard to possible adverse reactions.
- Tests in animals are insufficiently predictive of human safety.
- During clinical trials, the patients selected are limited in number, the conditions of use differ from those in clinical practice and the duration of trials is limited.
- Information about rare but serious adverse reactions, chronic toxicity, use in special groups (like children, elderly, pregnant women etc) or drug interactions is often incomplete or not available.

Pharmacovigilance is needed in every country, because there are differences in efficacy between populations (even regions within the countries) and also in occurrence of adverse reactions and other drug-related problems. This may be due to differences in
Drug distribution and use (e.g. indications, dose, availability etc)
Genetics, diet, traditions of the people
Pharmaceutical quality and composition (excipients) of locally produced pharmaceutical products.
The use of herbal medicines which may pose special 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 can encourage national regulatory decision-making. Information obtained in a certain country (e.g. the country of origin of the drug) may not be relevant to other parts of the world, where circumstances may be different. When information from a region itself is not available it may take longer before a problem becomes known to drug regulatory authorities, physicians, pharmacists, patients and pharmaceutical companies.

On the other hand, international monitoring centers such as the WHO International Drug Monitoring Program may provide information on possible safety issues which may not yet have emerged within the country’s data. Pharmacovigilance is needed for the prevention of drug-induced human suffering and to avoid financial risks associated with unexpected adverse effects.

In conclusion, medicines used in the country need continuous monitoring to assess its benefits and adverse effects.

V. REPORTING OF ADVERSE DRUG REACTIONS
1. ADR Case Report
An ADR case report should (as a minimum to aim at) contain information on the following entries:

✓ The patient: Age, sex and brief medical history (when relevant). In some countries ethnic origin may need to be specified.
✓ Adverse event: Description (nature, localization, severity, characteristics), results of investigations and tests, start date, course and outcome.
✓ Suspected drug(s): Name (brand or ingredient name + manufacturer), dose, route, start/stop dates, indication for use (with particular drugs, e.g. vaccines, a batch number is important).
✓ All other drugs used (including self-medication): Names, doses, routes, start/stop dates.
✓ Risk factors (e.g. impaired renal function, previous exposure to suspected drug, previous allergies, social drug use).
✓ Name and address of reporter (to be considered confidential and to be used only for data verification, completion and case follow-up).

ADR reporting forms are available on the website (www.moh.gov.bw)

2. RESPONSIBILITY OF REPORTING ADRs
Health professionals working in healthcare facilities are the preferred source of information in Pharmacovigilance. E.g., family practitioners, doctors, specialists pharmacists, dentists, midwives, nurses and other health workers who may also administer or prescribe drugs should report relevant experiences.

In addition pharmacists and nurses can play an important role in the stimulation of reporting and in the provision of additional information (for example, on co-medication and previous drug use). If adverse reactions are reported directly by patients to the national or local centre, it is useful to consider the possibility of communication with their physicians for additional information and data verification.
3. RESPONSIBILITY OF PHARMACEUTICAL MANUFACTURERS
Pharmaceutical manufacturers being primarily responsible for the safety of their products, have to ensure that suspected adverse reactions to their products are reported to the Drugs Regulatory Unit. The applicant for a medicine or pharmaceutical product is legally responsible for the reporting of the all known adverse drug reactions of the product or medicine for which the applicant is responsible.

4. GENERAL DETAILS OF REPORTING
In the early stages of development of any Pharmacovigilance system, reports on all suspected adverse reactions whether known or unknown, serious or mild are useful, because it is necessary to create a notification culture in which the instinctive response to any suspected adverse drug reaction is to report it.

In established Pharmacovigilance systems it is a common practice to request the reporting of all suspected reactions, including minor ones for new drug products.

For established drugs the reporting of serious or unusual suspected adverse reactions is of particular importance, whereas known and minor reactions are of less interest. If an increased frequency of a given reaction is suspected this is also a reason for reporting.

Although pharmacovigilance is primarily concerned with pharmaceutical products (including vaccines), adverse reactions associated with medicines used in traditional/alternative medicines (e.g. herbal remedies) should also be considered. Special fields of interest include drug abuse and drug use in pregnancy (teratogenicity) and lactation.

In addition, the reporting of lack of efficacy and suspected pharmaceutical defects is recommended, especially when there is the possibility of manufacturing problems, counterfeit pharmaceuticals or of the development of resistance (e.g. antibiotics). Pharmacovigilance and poison control are closely related activities, since the problems encountered with accidental or intentional overdose may cast doubt on the safety of a product.

Also, adverse reactions to cosmetics need to be reported, especially when they contain obsolete, toxic or undisclosed proprietary ingredients (e.g. mercury compounds or corticoids in bleaching creams).

The Pharmacovigilance centre also monitor adverse reactions related to medical, surgical devices, equipment and consumables until an institution or body specifically takes this role. The spontaneous reporting system of adverse reactions is by far the most effective method of gathering such information. It is fairly efficient in detecting truly serious reactions. It appears that serious problems are reported early and that warnings are issued timely. When there is an adverse reaction to drugs the reporting form should be completed by the concerned health professional and sent to the ADR monitoring division.

Note: The reporter does not need to prove that there is a casual association between drug and adverse reaction. Therefore, uncertainty of the cause and effect relationship should not be reason for not reporting.
WHAT TO REPORT?
- All suspected reactions
- Lack of effect
- Counterfeiting
- Resistance to treatment
- Interaction with food, other medications or Herbal products
- Dependence and abuse

OF WHICH TO REPORT?
- Allopathic medicines including OTC
- Traditional Medicines
- Biologicals like vaccines and sera
- Cosmetics
- Medical, Surgical, Equipment and consumables

REPORT EVEN IF
- You’re not certain the product caused adverse event
- You don’t have all the details as soon as possible

SEND REPORT TO
Drug Regulatory Unit
Ministry of Health
P/Bag 0038, Gaborone
Botswana
Tel: +267-3632381
Fax: +267-3170169

Table 1: Quick Reference for Reporting

Over Dosage:
Reports of overdose should be submitted only when an adverse reaction was associated with the overdose. Suspected adverse reactions associated with an overdose should be reported as other reactions. This should include reports that indicate that taking of the suspected medicine led to suicidal intention and subsequent overdose of the suspected medicine or other medications.

Teratogenicity and Congenital Anomalies:
For reports on Teratogenicity and congenital anomalies:
- Indicate age and sex of the infant
- Follow-up reports for the infant should be considered - a follow-up to the initial report
- The birth date or the date pregnancy was terminated should be the event onset date
- Include date and or duration of in utero exposure where possible
- Any adverse reaction experienced by the mother must be considered a new initial case report on a separate report form

Product Details:
If an adverse event is suspected to be related to a product defect, it should be reported in the same manner as a suspected adverse reaction. The lot number of the suspected medicine should be included in the report. Applicants should inform whether the implicated products have been tested for product quality and what (if any) corrective actions are being/have been taken.

Drug Interactions:
Any drug interaction which results in an adverse reaction should be reported as an adverse reaction in the prescribed manner.

Another Applicant’s Product:
If the pharmaceutical company receives a report of a suspected adverse reaction to a medicine marketed by another applicant, such a report should promptly be forwarded to the applicant. Such
reports should not be reported to the Authority by the applicant to whom the event was originally reported. When serious, unexpected reactions are observed for another applicant’s medicine, used during the conduct of clinical trial, reports should be submitted directly to the authority by the applicant conducting the study.

Confidentiality:
Strict confidentiality will be maintained by the Authority regarding the identities of the patient and the reporter.

Lack of Efficacy Reports:
Lack of Efficacy applies to the medicines registered in the country. The lot number of the suspected medicine should be included in the report. If the report of “Lack of Efficiency” is for an unapproved indication, the event is still reportable.

5. REPORTING DURATION OF AN ADR
Applicant should report all non-serious, suspected and unexpected adverse reactions to the ADR monitoring division as soon as possible within 15 calendar days after first knowledge by the applicant. Delay in reporting will make reporting inaccurate and unreliable. Reporting while the patient is still in the health institution will give chance to the reporter to clear any ambiguity by re-questioning or examining the patient.

REPORTING REQUIREMENTS FOR APPLICANTS:

Table 2: Post-Registration ADR Reports (registered medicinal products and exempted complementary medicines and products)

<table>
<thead>
<tr>
<th>Type of ADR report</th>
<th>Time frame for reporting</th>
<th>Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Reports (spontaneous/published/study):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serious (expected and unexpected)</td>
<td>15 days</td>
<td>ADR form or other internationally accepted format</td>
</tr>
<tr>
<td>• Non serious (unexpected)</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>• Non serious (expected)</td>
<td>As above</td>
<td>As above (more so for HIV/AIDS, malaria and TB)</td>
</tr>
<tr>
<td>Foreign Reports (spontaneous/published/study):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serious</td>
<td>30 days</td>
<td>As appropriate</td>
</tr>
<tr>
<td>Notification of Change in Nature, Severity or Frequency or Risk factors</td>
<td>15 days</td>
<td>Detailed report (including publications)</td>
</tr>
<tr>
<td>New information impacting on benefit-risk profile of product including international regulatory decisions</td>
<td>3 days</td>
<td>Detailed report (including publications)</td>
</tr>
</tbody>
</table>
Table 3: Pre-Registration ADR/ADE reports (i.e. unregistered medicines being used approved clinical trials)

<table>
<thead>
<tr>
<th>TYPE OF ADR REPORT</th>
<th>TIME FRAME FOR REPORTING</th>
<th>FORMAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Reports:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fatal or life-threatening (unexpected)</td>
<td>7 days</td>
<td>ADR form or other internationally accepted format</td>
</tr>
<tr>
<td>• Other serious (unexpected)</td>
<td>15 days</td>
<td>As above</td>
</tr>
<tr>
<td>All (local &amp; foreign) reports:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serious (unexpected and expected) events</td>
<td>15 days</td>
<td>ADR form or other internationally accepted format</td>
</tr>
<tr>
<td>• Non-serious unexpected and expected reactions</td>
<td>15 days</td>
<td>ADR form or other internationally accepted format</td>
</tr>
<tr>
<td>Notification of Change in Nature, Severity or Frequency of Risk factors</td>
<td>15 days</td>
<td>Detailed report</td>
</tr>
<tr>
<td>New information impacting on risk-benefit profile of product or conduct of trial</td>
<td>3 days</td>
<td>Detailed report</td>
</tr>
</tbody>
</table>

6. PERIODIC SAFETY UPDATE REPORTS (PSURs):

PSURs are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product. They are submitted by marketing-authorisation holders at defined time points during the post-authorisation phase.

Periodic Safety Update Reports: General principles
A PSUR is intended to provide an update of the worldwide safety experience of a medicinal product to Competent Authorities at defined time points post-authorisation. At these times, marketing authorisation (MA) holders are expected to provide succinct summary information together with a critical evaluation of the risk-benefit balance of the product in the light of new or changing information. This evaluation should ascertain whether further investigations need to be carried out and whether changes should be made to the marketing authorisation and product information.

PSURs must be submitted for all registered products regardless of marketing status. A single report may cover all products containing the same active substance(s) licensed by one MA holder. The report will usually include all dosage forms and formulations, as well as all indications, associated with such an active. Within the PSUR, separate presentations of data for different dosage forms, indications or populations (for example, children vs. adults) may be appropriate, however an overview of the combined data should also be provided.

For combinations of substances which are also registered individually, safety information for the fixed combination may be reported either in a separate PSUR or be included as a separate
Frequency of PSUR reporting requirements
PSURs should be submitted at the following times from the time of authorisation, for all medicinal products unless the marketing authorisation makes different provisions:

- Immediately upon request
- At least 6 monthly after authorisation and until the placing on the market
- At least 6 monthly for the first two years after being placed on the market
- Annually for the subsequent two years
- Thereafter at three-yearly intervals

PSURs should only be submitted in the following situations:

- Whenever requested by the authority
- When the submission of PSURs is a condition of registration for a new medicinal product. These PSURs must be submitted within 30 calendar days of initial receipt by the applicant from the parent company.
- As part of a part of a submission for a package insert amendment when the PSUR contains information supporting the amendment.
- When a new medicinal product is submitted to the Authority for registration and where the product has already been marketed elsewhere, PSURs should be submitted to the Authority within 30 calendar days during the evaluation period prior to registration.

The table below shows the PSUR submissions for a product that is marketed immediately after approval. If the product is not marketed at approval then there will be extra six monthly PSURs before marketing.

<table>
<thead>
<tr>
<th>PSUR</th>
<th>Time covered by PSUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 month</td>
</tr>
<tr>
<td>2</td>
<td>6 month</td>
</tr>
<tr>
<td>3</td>
<td>6 month</td>
</tr>
<tr>
<td>4</td>
<td>6 month</td>
</tr>
<tr>
<td>5</td>
<td>12 month</td>
</tr>
<tr>
<td>6</td>
<td>12 month</td>
</tr>
<tr>
<td>7</td>
<td>3 year</td>
</tr>
<tr>
<td>8, 9 etc.</td>
<td>3 year</td>
</tr>
</tbody>
</table>

Please note the renewal is no longer part of the actual PSUR cycle. The PSUR cycle continues regardless of any communication from competent authorities, therefore you should maintain your PSUR cycle.

The PSURs must be submitted in a CD form.

7. FOLLOW-UP OF REPORTS:
After initial receipt of an adverse reaction report, a notice of acknowledgement will be sent to the applicant quoting the number assigned to the case report. Any follow-up correspondence from the applicant, relating to the same case report should be cross-referenced to the assigned database number or to an appropriate unique number assigned by the applicant (relating specifically to the initial notification). This is the only reliable way to minimize the duplication of reports submitted by applicants.
8. COMMUNICATIONS:

DO NOT HESITSTE TO CONTACT THE DRUG REGULATORY UNIT (contact person detailed below) IF YOU HAVE ANY SUGGESTION OR IMPROVEMENT OR NEED CLARIFICATION ON THE GUIDELINES OR ON THE FORM FOR REPORTING ADR’s.

Mr. Tau G Mahupu  
Drugs Regulatory Unit- Pharmacovigilance Office  
Ministry of Health Enclave  
P/Bag 0038, Gaborone, Botswana

Or

Mrs Tebogo Mokotedi

Ph: +267-363-2381  
+267 363 2376  
Fax: +267-317-0169  
Email: dunit@gov.bw