Kingdom of Cambodia
Nation Religion King

Ministry of Health
DEPARTMENT OF DRUGS AND FOOD ESSENTIAL DRUGS BUREAU

ADVERSE DRUG REACTIONS (ADR) MONITORING AND RELATED MATTERS

Prepared by CAMBODIAN PHARMACOVIGILANCE CENTER

DKSH Cambodia Ltd

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Preface

The safe use of medicines by patients and by the population in general, is a high priority in the modern world. This implies to ensure that prescription rules are properly enforced, and that recommendations for proper use are adequately followed in order to maximize the therapeutic benefit while minimizing the risks inherent to any effective therapeutic agent.

Whilst all possible efforts should be made to prevent adverse drug reactions (ADR) to occur, it is also essential to have in place an effective Pharmacovigilance system designed to collect, compile and analyse the safety information received from ADR reports.

The quality of ADR reports and the active reporting behavior of health care professionals constitute essential factors conditioning the effectiveness of any pharmacovigilance system. Those driving factors determine the capability to detect the safety signals which should alert, pointing to the need to implement risk minimization measures aimed to ensure the safety and quality of life of the patients. ADR reporting is moreover essential for the effective prevention and control of many kinds of diseases, aiming at reducing suffering and related costs.

The *Guideline for Adverse Drug Reaction Monitoring and Related Matters* describes the Pharmacovigilance System of Cambodia. It specifies the respective roles of registration holders, medical institutions and health care professionals as well as consumers who are all expected to contribute to the system. It explains the goals, the purposes and the processes to be applied at the different levels of the system in Cambodia, as well as the importance and advantages of this initiative for our Country.

This Guideline highlights why it is essential to direct all ADRs to the Cambodian Pharmacovigilance Centre which, in addition to its national role, is collaborating with the World Health Organisation (WHO) and the WHO Collaborating Center for International Drug Monitoring (the Uppsala Monitoring Center). One of the essential roles of the WHO and its partners in supporting pharmacovigilance, is to provide countries with the necessary support and tools to carry out pharmacovigilance activities effectively and in a harmonized way in order to ensure that data collected in each setting can be used globally.

Accordingly, this guideline is designed to support undertaking pharmacovigilance in a comprehensive way in accordance to WHO guidelines and recommendations, in line with contemporary best practice. We recommend using it as a practical toolbox for conducting pharmacovigilance activities in Cambodia, describing the relevant supporting framework and processes applicable to the different levels and settings involved.

We expect this guideline to serve as general orientation and practical reference for use by registration holders, medical institutions and health care professionals who are expected to commit to ADR reporting.

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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 the 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. Purpose

The purpose of this document is to provide guidance to the monitoring and reporting of ADR and related matters by Drug Registration Holders and Health Professions in the public and private sector. The guidelines include adverse drug reactions monitoring in all national health programs.

3. LEGAL BASIS

In accordance with the Ministry of Health (MoH) Announcement number 0973 dated on 23rd of November 2011 it is mandatory for registration holders of all products registered by the Department of Drugs and Food (DDF) to submit reports of all ADRs encountered to the DDF.

Although, ADR reporting by health professionals and consumers are on a voluntary basis, submission of reports of all adverse reactions encountered to the DDF is highly encouraged.

4. CONFIDENTIALITY

THE DEPARTMENT OF DRUG AND FOOD WILL MAINTAIN STRICT CONFIDENTIALITY WITH REGARDS TO THE IDENTITY OF PATIENTS AND

REPORTERS. However, reporters need to identify patients, at least with initials, in order enable retrieving complementary and follow-up information (e.g. the outcome of the reported ADR).

5. SCOPE OF ADR REPORTING

Suspected ADRs encountered should be reported for all products registered by the DDF i.e. pharmaceutical products as well as traditional medicines

An Adverse Drug Reaction is suspected if either the reporting health-care professional or the registration holder believes there is a plausible causal relationship between the untoward event and the suspected drug or therapeutic agent. The usual reason for suspecting a causal relationship is the observation of a temporal relationship. Spontaneous reports of suspected ADRs 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.

Product registration holders should validate and follow-up on 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 suspected ADRs 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.

6. OBJECTIVES OF ADR MONITORING

The primary objectives of ADR monitoring are as follows:

- To detect ADRs as early as possible especially if serious, unexpected or rare.
- To further specify the incidence of well recognized ADRs and determine the incidence newly discovered ones.
- To identify the risk factors that may predispose, induce or influence the development, severity and incidence of adverse reactions e.g. demographic, ethnic and genetic factors, drug interactions, underlying conditions etc.
- To maintain a database for compiling, analysing and sharing information relative to the safety of the medicinal products used in Cambodia.

7. 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, the information leaflets and labels in order to create awareness on these findings
- Regulatory authority can take appropriate action in the interest of public health to minimise the risk of occurrence or the severity 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.

8. PROCEDURES FOR REPORTING

8.1. GENERAL PRINCIPLES

8.1.1 All ADR reports should be sent to:

The Cambodian Pharmacovigilance Centre
Department of Drug and Food
Ministry of Health of Cambodia
#151-153 Kampucheakrom Bvl Phnom Penh, Cambodia

Tel/Fax: 023 990 499

E-mail: pv.center@ezecom.com.kh

Web site: www.ddfcambodia.gov

8.1.2 Reporting Forms

The Cambodian Pharmacovigilance Centre has a preferred format which are supplied free of charge by the DDF for reporting of suspected ADRs. The International CIOMs-1 form made available by the WHO is also acceptable. The contents may be submitted in Khmer or in English.

If several suspected ADRs occur in a same episode, those several ADRs should be reported as part of the same Individual Case Safety Report (ICSR) on the same Report Form (possibly including additional pages).

8.1.3 Content of suspected serious ADR reports

When aware of suspected ADR, HCP and registration holders should strive to collect at least the minimum criteria required for assessing the corresponding ICSR objectively and enabling entering it into the National Safety Database of Cambodia. Those criteria include:

- The name of the suspected drug
- A medical term reflecting the suspected ADR
- A parameter making the patient identifiable patient (e.g. patient's initials)
- Information enabling to identify and contact the reporter.

However, registration holders should not wait for having all above 4 criteria available to submit the Initial ICSR report to the DDF.

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 provided. The terms used to

describe the suspected ADR should be based upon standard medical terminology and the use of vague terms should be avoided.

Once informed of the occurrence of a suspected ADR, the Registration Holder is expected to follow-up and on the case and strive to obtain comprehensive information as far as available. Additional information not available at the time of the initial report should be provided to the DDF in a subsequent follow-up reports.

Registration holders shall strive to obtain from the reporting HCP an assessment of the causal relationship between the suspect drug and the suspected ADR. As far as possible, the criteria used by the Reporter for making the causality assessment should be specified. Registration holders have the obligation to report the causality assessment provided by the HCP. However, the registration holder is entitled to include into the ICSR submitted to the DDF, a distinct causality assessment. In such a case, the ICSR should clearly distinguish the opinion of the registration holder from the causality assessment made by the HCP reporting the case.

8.1.4 Route of Notification

All reports could be sealed and directly sent, mailed, faxed, or phoned to DDF.

ICSRs are to be submitted via the E-mail: pv.center@ezecom.com.kh, or via a phone call to 023 990 499 or by connecting to the web site of the DDF: WWW.ddfcambodia.com.

8.1.5 Time-lines for Reporting

Refer to Appendix 2

8.1.6 Follow-up reports

After the Initial submission of a suspected ADR, a letter or e-mail of acknowledgement will be sent by the Cambodian Pharmacovigilance Center (CPC) to the HCP and/or the registration holder who submitted the case. The letter (or e-mail) sent by the CPC will specify the reference number assigned to this ICSR in the National Safety Database of Cambodia.

Any follow-up correspondence relating to a previously submitted ICSR should specify the reference number assigned to this ICSR in the National Safety Database of Cambodia.

Additional ICSR reference numbers assigned by the registration holder or by the reporter's medical institution should be provided as far as possible at it is the only reliable way to minimise the duplication of reports submitted to the DDF by the applicant.

8.2 REPORTING REQUIREMENTS IN SPECIAL SITUATIONS

8.2.1 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 DDF 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.

8.2.2 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 inspection of quality of drugs used in these groups.

Registration holders must report suspected ADRs 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 fetus 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 fetus 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 DDF should be informed immediately.

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

A Registration Holder may be involved in post-marketing initiatives, which result in the structured collection of information related to its products. Only those suspected ADRs which are specifically reported as Serious and related to the registration holder's product must be reported.

The above ICSR submission obligation applies to post-approval interventional studies, post-approval non-interventional studies (NIS), patient's support programs (PSP) and more

generally to ICSR reported from any post-marketing initiative implying a condition of solicited or stimulated collection of safety information.

The above obligation applies also to ADRs occurring in investigators sponsored-studies whenever reaching the awareness of the registration holder.

8.2.4 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 to the DDF and to the registration holder, any suspected ADR related to use of the product. Registration Holders should continuously monitor the balance of benefit and risk of drugs used under such conditions.

The prescriber of the product must report any serious suspected ADR occurring with the use of the product in the specified patients within 15 calendar days of first awareness by such prescriber.

8.2.5 Lack of efficacy

Reports of lack of efficacy should also be reported to the DDF. 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.

8.2.6 Reporting of medication errors including over dose, sensitive reaction, contraindication, unclear prescription script, follow prescription of other patient, etc…)

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 ADR should be reported however specifying that no ADR was observed. Reports of overdose 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.

8.2.7. Consumer Reports

If a registration holder receives a report from a consumer, the consumer should be advised to report this reaction directly to DDF or via the phone call or e-mail to Cambodian

Pharmacovigilance Center or to retail pharmacist or physician. 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.

9. *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 Cambodian Pharmacovigilance Center 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 DDF. A comprehensive report evaluating the issue and the risks in the context of the benefits should be submitted as soon as possible.

9.1 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.

9.1.1 Assessment of risks

Risk assessment 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:

- ICSRs originating from Cambodia as well as ICRSs reported from Foreign countries
- Safety data from post-marketing clinical investigations company-sponsored or not

- In vitro and in vivo laboratory investigations
- World-wide scientific literature
- Investigations on pharmaceutical quality
- Data on sales and product usage

Whenever a safety hazard is identified which may impact or influence the overall benefits/risk ratio of the medicinal product, the registration holder should propose appropriate measures such as supplementary investigation(s) to further explore the nature of the hazard(s) and its incidence, provided such investigation(s) would not cause unacceptable risk to the patients involved.

The overall benefit/risk assessments should be established using the whole 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

9.1.2 Assessment of benefits

Whenever 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.

9.1.3 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 otherwise 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.

9.2 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 DDF.

- Making changes to the indications, dosage recommendations, contra-indications, 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.

9.3 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 upon request from the DDF.

9.4 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 DDF.

PART 2

10. GUIDELINES FOR REGISTRATION HOLDERS

10.1 REPORTING OBLIGATIONS

The MoH announcement number 0973 regarding the Pharmacovigilance activities dated on the 23rd of November 2011 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".

10.2 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 required that the registration holder have permanently and continuously at its disposal in Cambodia, a qualified person responsible for pharmacovigilance. This person should have experience in all aspects of pharmacovigilance.

Registration holders should inform the Cambodian Pharmacovigilance center, Essential Drug Bureau, Department of Drug and Food, 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 reports of suspected ADR from Cambodia are submitted to the DDF in a timely manner
- To submit Periodic Safety Updated Reports (PSUR), company-sponsored post-registration study reports, etc to the DDF
- To ensure that any request for additional risk-benefit information from the DDF is reported to the DDF promptly and completely.

10.3 REPORTING ADRS TO THE DDF

10.3.1 Adverse Drug Reactions Occurring Within Cambodia

i. Applicable to all marketed drugs: ALL reports of suspected ADR associated with the use of registered products occurring in Cambodia must be reported to the DDF within the timelines stipulated in Appendix 2.
ii. Applicable to New Chemical Entities (NCE): Registration holders of NCE are required to actively monitor suspected ADRs occurring as a result of the use of the registered product. Registration holders are required to report all ADRs in accordance to the timelines stipulated in Appendix-2. The registration holder is also obliged to submit a "NULL" ICSR report at six-monthly intervals for the first two years should there be no ADR reports submitted to them.

10.3.2 Adverse Drug Reactions Occurring Outside Cambodia

i. ADR reports originating from outside Cambodia need not be submitted to the DDF on a routine basis but only in the context of a specific safety issue or upon specific request by the DDF.
ii. Registration holders are expected to inform the DDF within 3 calendar days of any posting and/or action taken by foreign Health Authorities relative to the safety or benefit/risk of a medicinal product marketed in Cambodia. Health Authorities to be monitored for safety-related posting and actions are listed in Appendix 3.
iii. Information on withdrawal of the registration status in any country must be notified to the DDF within 24 hours of first awareness by the registration holder.

10.4 PERIODIC SAFETY UPDATE REVIEWS (PSUR)

i. Registration holders who have registered a product containing a NCE after 1 January 2013 must routinely submit PSURs on that product 6 monthly for the first 2 years after approval in Cambodia and annually for the subsequent 3 years. *"Recommended formats include the international PSUR format as defined by CIOMS guidelines and the Periodic Benefit Risk Evaluation Report (PBRER) defined by the European Pharmacovigilance Legislation. Translation into Khmer is not required".*
ii. The period of interest covered by individual PSURs may be varied in order to harmonize with the date of release of PSURs generated internationally. However, the first PSUR should be submitted no later than 6 months after the date of approval. The last PSUR released prior to approval may be submitted in order to meet the above timeline.
iii. The registration holders should inform the DDF of any steps which are to be taken with regards to any safety concern 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, new dosage form, new route of administration, combination of previously marketed products into a common formulation, or use in populations beyond the registration for the active ingredient.

10.5 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 DDF.
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.

10.6 REPORTS FROM POST-REGISTRATION STUDIES

i. Adverse reactions from post-registration studies taking place in Cambodia must be reported to the DDF 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 systematically solicited. In cases where the causality of the suspected drug is difficult to determine, it is better to report the case as a suspected ADR. Events that are clearly unrelated to the product should not be reported.

10.7 ON-GOING PHARMACOVIGILANCE EVALUATION

i. Registration holders must inform the DDF 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 pharmaco-epidemiology studies, pre-clinical studies or significant product quality data may be requested by the DDF as the situation warrants. This must be submitted within a time period specified by the DDF.

PART 3

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 recommended to report adverse reactions encountered to the Department of Drug and Food (DDF). 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 DDF 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 DDF.

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 DDF.

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,
- is medically important..

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/Unlabeled 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 DDF are treated as being confidential and reporters are not required to divulge the identity of the involved patients excepted with initial report. Identify of reporters must remain confidential. 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 DDF or to the relevant Registration Holders.

Reports may be submitted by using the ADR forms which are supplied free of charge by the DDF or by letter. Reporting may also be done through the E-mail: pv.center@ezecom.com.kh or Phone call: 023 990 499 or Web site: www.ddfcambodia.com

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 or Prescribers 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 Department of Drug and Food. The hospital pharmacy is the obvious central point for this work. In this arrangement, the pharmacy can also play the role of providing the DDF with information on the brand name of the product used, the outcome of the patients and to provide feedback received from the DDF back to the reporter.

11.5.2 Hospital 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 DDF.

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 DDF.

11.7 PRIVATE CLINICS

The General Practitioners and Private Specialist Clinics should report the adverse reactions encountered directly to the DDF or relevant Registration Holders by completing the ADR forms and sending it through the post or by using the on-line reporting form available on the DDF website.

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 DDF or via the product registration holders.

11.9 PATIENTS

All Patients or relatives are highly encouraged to report any adverse reactions either directly to either the DDF by phone or by e-mail to Cambodian Pharmacovigilance Center or to retail pharmacist or physician.

PART 4

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. an 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.

PART 5: System supporting the ICSR handling workflow in Cambodia

The Pharmacovigilance Center of Cambodia may receive ICSRs from multiple sources including:

1. Major Hospitals where qualified persons (e.g. hospital pharmacists) are to be assigned to inquire at regular interval in medical departments searching for suspected ADRs.
2. Health Care Professional in any category of medical institution, including not only medical doctors, but also nurses, dentists, physiotherapists, etc..
3. Pharmacists delivering medicinal products to users in general population
4. Users who are encouraged to report suspected ADRs directly or via their treating physician or pharmacist.

Safety information from the above sources is to be directed to the Pharmacovigilance Center of Cambodia by e.g. e-mail, telefax, letter or phone call. Additional communication channels may be added as technologies are further evolving.

Once received at the Pharmacovigilance Center of Cambodia, the safety information is to be checked for completeness and entered into the National Pharmacovigilance Database of Cambodia. Whenever necessary, the Pharmacovigilance Center of Cambodia may request re reporting source to provide complementary and/or Follow-up information.

Subsequently, one recognized as ICSRs, cases including suspected ADR(s) are to be entered into the National Safety Database of Cambodia and evaluated for the causality of the suspected drug(s).

Once the evaluation and causality assessment are completed, the ICSRs stored into the National Safety Database are eligible for transfer into the WHO safety database (Vigibase) maintained by the Uppsala Monitoring Center. Forwarding ICSRs from the National Safety Database of Cambodia to the WHO database is operated under the responsibility of the head of the Pharmacovigilance Center of Cambodia.

The IT system supporting the National Safety Database of Cambodia is a Vigiflow application provided by the WHO Collaborating Center for International Drug Monitoring referred to as *The Uppsala Monitoring Center* (UMC). Vigiflow is a safety database following the E2B (M2) standard established by the International Conference of Harmonisation (ICH).

ICSR data entered at the Pharmacovigilance Center of Cambodia are to be routed via internet to an encrypted country-specific data container maintained under the responsibility of the UMC. ICSRs entered into the Vigiflow Country-specific ICSR container are subsequently transferred to the WHO safety database (Vigibase), however the transfer those data remains controlled at the Country level.

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.

A response to a medicinal product which is noxious and unintended. This includes adverse reactions which arise from:

- The use of a medicinal product within the terms of the marketing authorization;

- The use outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors;

- Occupational exposure

- Use of medicines during pregnancy

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 hospitalization 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

CAMBODIAN GUIDELINE FOR REPORTING & MONITORING

TABULATED SUMMARY OF REPORTING REQUIREMENTS FOR REGISTRATION HOLDERS POST-REPORTING ADR REPORTING.

	TYPE OF ADVERSE REACTION	TIME FRAME FOR REPORTING
Domestic ADR Reports	Life-threatening or fatal	As soon as possible but no later than 7 calendar days after first awareness by registration holder, follow by as complete a report as soon as possible within 8 additional calendar days. This report should include an assessment of the importance and complications of the finding including relevant previous experience with the same or similar products.
	Serious however non-life threatening or fatal	As soon as possible but no later than 15 calendar days after first awareness by registration holder.
	Non-serious non-solicited (spontaneous)	within 90 calendar days
	Non-serious Solicited from post-marketing experience	Not reportable unless specific request
Foreign ADR Reports	Not required on a routine basic	
Domestic or Foreign Safety Information	Notification of changes in nature severity or frequency or risk factor	Within 15 days after first knowledge by registration holder
	New information impacting on risk - benefit profile of product including international regulatory decisions	3 calendar days
	Withdrawal of registration in any country	24 hours after first knowledge by registration holder
Periodic Safety Update Reviews (PSUR)	All NCEs approved from 2013.01.01 Upon request for older products if • new indications • new dosage form • new route of administration	6 monthly for first two years Annually for subsequent 3 years

APPENDIX 3

List of Health Authorities to be monitored for the posting of safety-related contents and actions relative to medicinal products marketed in Cambodia:

ASEAN Ministry of Health and/or national pharmacovigilance center of:	Indonesia Malaysia Philippine Singapore Thailand Vietnam
Asia-Pacific (non-ASEAN)	PMDA (Japan) SFDA (China) KFDA (Korea) Taiwan FDA TGA (Australia)
America	US-FDA (United Stated of America) Health Canada
Europe	EMA (European Union) MHRA (United kingdom) BfArM (Germany) ANSM (France) Swissmedic (Switzerland)